Synthesis of (+/-) - Oxohexahydrofuro[3,2-*b*]pyrroles (Pyrrolidine-*trans*-lactones) Using Acyl-Iminium Chemistry

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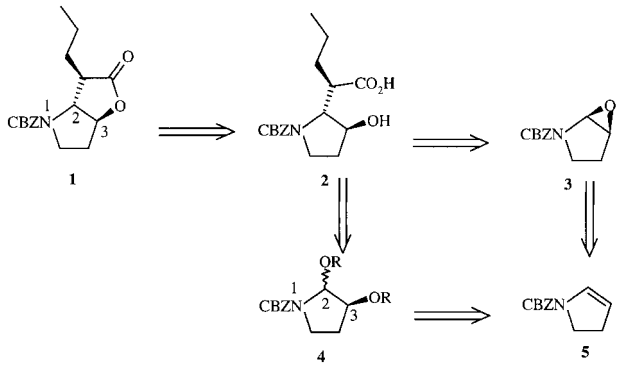
Abstract: In a new synthesis of pyrrolidine-*trans*-lactones, an acyl-iminium pyrrolidine reacts with silyl ketene acetals. This reaction selectively generates C2, C3 *trans* stereochemistry.

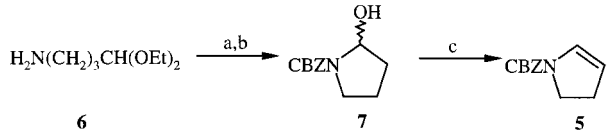
Serine protease inhibition is a field of enormous importance to the pharmaceutical industry in the search for new therapies for, amongst others, respiratory[1] and cardiovascular[2] diseases. Therefore our introduction of a new scaffold known as pyrrolidine *trans*-lactones[3,4] **1** (and lactams),[4] which are strained 5,5-*trans* fused bicycles, is both timely and significant. We have studied these systems during a programme to develop inhibitors of human neutrophil elastase (HNE) for respiratory diseases and which has led to development candidates. We required a flexible approach allowing stereocontrol and facile introduction of substituents α to the lactone carbonyl (eg *n*-propyl in **1**). Our previous synthesis[4a] featured the creation of the pyrrolidine ring and a stereocentre *via* an intramolecular Michael reaction. However it lacked stereoselectivity and as inhibition of HNE requires specific relative stereochemistry (as in **1**) it was inefficient. This letter describes a new route which generates the stereocentres on a preformed pyrrolidine. It addresses some of the stereochemical issues, uses chemistry suitable for larger scale work and avoids, for example, low temperature alkylations.[4a]

In our retrosynthesis, concern for the potential lability of the highly strained *trans*-lactone meant that its creation was deferred to the end of the synthesis: hence the initial disconnection to the hydroxy-acid **2** (Scheme 1). This in turn was disconnected to either the epoxide **3** or the diol **4** – a convenient acyl-iminium precursor. Both compounds may be derived from the benzyl carbamate of 2-pyrroline **5**.



Scheme 1

Although Thaning and Wistrand[5] have described preparations of analogues of **4** an alternative procedure was developed from the 2-pyrroline **5**. This would allow access to **3** or **4** and is also potentially a precursor for asymmetric oxidations which have just recently been described for these substrates.[6] Our synthesis (Scheme 2) started from commercially available 4-aminobutanal diethylacetal **6** which was protected as its benzyl carbamate and then treated with pyridinium tosylate in aqueous acetone. The resultant aldehyde spontaneously

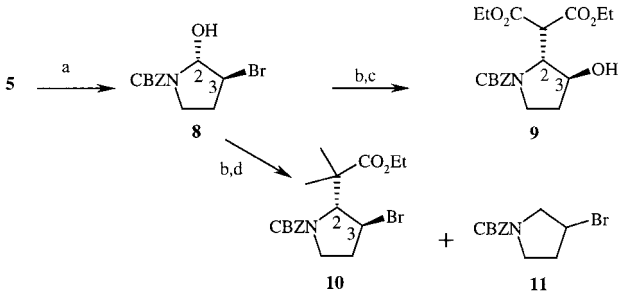


(a) CBZCl, Na_2CO_3 (aq), CH_2Cl_2. (b) pyridinium tosylate, aqueous acetone. (c) reflux, PhMe, 62% for 3 steps

Scheme 2

cyclised to give the protected cyclic aminal **7**. Heating a toluene solution of **7** at reflux gave the 2-pyrroline **5** in 62% yield over the 3 steps.

We then examined the potential of the pyrroline **5** to act as an epoxide precursor. Although oxidations of 2-pyrrolines are now known,[6,7] at the time of this work we were unable to find precedent for such

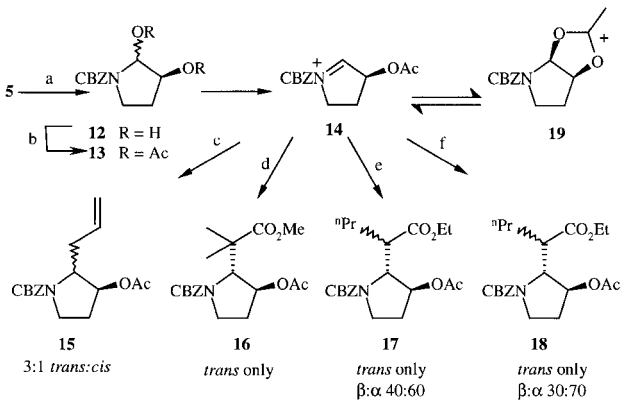


(a) *N*-bromosuccinimide, H_2O, dioxan, 96% crude. (b) NaH, THF. (c) $(EtO_2C)_2CHNa$, THF, 10% for 2 steps. (d) $Me_2CC(OMe)OSiMe_3$, $BF_3.OEt_2$, 19% of **10**, 8% of **11**

Scheme 3

transformations. Whilst conventional peracid epoxidation in dichloromethane failed to provide identifiable products,[6b] treatment with *N*-bromosuccinimide in aqueous dioxan gave the bromohydrin **8** as a single diastereomer (Scheme 3). ^{1}H-NMR studies[8] confirmed the regio- and stereo-selectivity across C2 and C3 which suggested that the reactivity profile of the epoxide **3** might provide the required control to access the products of interest (such as 2). If pure pyrroline **5** is used the crude bromohydrin **8** is stable when stored below room temperature. After treatment of the bromohydrin with sodium hydride in THF (-70°C to RT), (which produced a precipitate - presumed to be NaBr), addition of the sodium salt of diethyl malonate gave a low yield of the alcohol **9** as the only isolated product;[9] the hydroxyl had been transposed from C2 to C3 suggestive of an epoxide-like intermediate. In a separate experiment, after treatment of **8** with NaH, dimethylketene acetal and $BF_3{\cdot}OEt_2$ were added. This gave the bromo-ester **10** (19%) and the reduced bromide **11** (8%)[10] suggesting that an acyl-iminium intermediate rather than an epoxide intermediate was more likely. Whilst unoptimised, the poor yields of these processes led us to focus on the diol 4 (R = H) as an acyl-iminium precursor. There is precedent for such reactions on pyrrolidine derivatives.[11]

Dihydroxylation of **5** under standard conditions gave a mixture of the *cis* and *trans* diols **12** in 91% crude yield (Scheme 4).[12] Acetylation gave a mixture of di-acetates **13** in 32-49% yield after

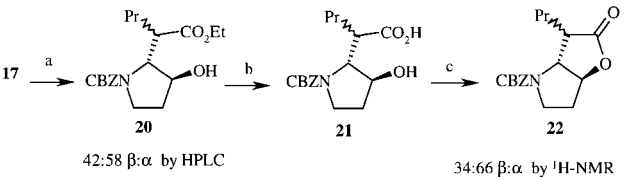


(a) OsO_4 (cat), *N*-methyl morpholine-*N*-oxide, ^tBuOH, Me_2CO, H_2O, 91%. (b) DMAP, Ac_2O, pyridine, CH_2Cl_2, 32-49%. (c) $CH_2CHCH_2SiMe_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 80%. (d) $Me_2CC(OMe)OSiMe_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 63%. (e) (*E*)-$^nPrCHC(OEt)OSiMe_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 77%. (f) (*E*)-$^nPrCHC(OEt)OSi^tBuMe_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 68%

Scheme 4

chromatography[13] which, as expected, proved to be ideal acyl-iminium ion precursors.

Reaction of **13** with trimethylallylsilane and $BF_3{\cdot}OEt_2$ gave the 2-allylpyrrolidine **15** in 80% yield as a 3:1 mixture of *trans:cis* isomers as previously described in the literature.[5a] Treatment of the di-acetate **13** with substituted ketene acetals and $BF_3{\cdot}OEt_2$ gave good yields of all *trans* products across C2-C3 of the pyrrolidine **16**, **17** and **18** and β and α mixtures of the *n*-propyl group for **17** and **18**. No *cis*-products across C2-C3 were detected. We believe the *trans* stereoselectivity is attributable to the greater steric bulk of the ketene acetals and the conformation of the cations **14** and **19** which preferentially allow nucleophilic attack from the less hindered *exo* face. It is interesting to note the improved α-product selectivity when the bulk of the silyl group of the ketene acetal group is increased. Further variation of the *O*-substituents and/or the geometry of the ketene acetal and the Lewis acid may affect the selectivity further.[14] The stereochemical ratios of the β:α propyl groups in **17** and **18** were established by analytical HPLC.[15] This was subsequently confirmed by conversion of **17** into the *trans*-lactone **22** (Scheme 5).



(a) K_2CO_3, MeOH, 75%. (b) LiOH, H_2O, THF, 92%. (c) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, PhMe, 53%

Scheme 5

Removal of the acetate from **17**[16] and saponification under standard conditions gave efficiently the hydroxy-acid **21**. Yamaguchi cyclisation[17] at 0.025mM in toluene gave a 53% yield of 1:2 β:α propyl-*trans*-lactones **22** (ratio determined by ^{1}H-NMR).[18,19] Analysis of the ^{1}H-NMR spectra was aided by comparison with the spectra of pure samples of α and β analogues prepared by other routes.[2]

NB. All new compounds gave satisfactory ^{1}H-NMR, IR and microanalytical data.

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(8) Data for **8**: ^{1}H-NMR (250MHz, $CDCl_3$) δ 7.40-7.25 (m, 5H, C_6H_5), 5.67 (d, J = 3Hz, 0.67H, major rotamer C<u>H</u>OH), 5.61 (d, J = 3Hz, 0.33H, minor rotamer C<u>H</u>OH), 5.22-5.10 (m, 2H, PhC<u>H</u>$_2$), 4.22 (m, 1H, C<u>H</u>Br), 3.73-3.62 (m, 2.67H, NC<u>H</u>$_2$ + major rotamer CHO<u>H</u>), 3.33 (d, J = 3Hz, 0.33H, minor rotamer CHO<u>H</u>), 2.74-2.56 (m, 1H, NCH$_2$HC<u>H</u>), 2.24-2.13 (m, 1H, NCH$_2$<u>H</u>CH); assignments were supported by decoupling experiments and warming to 55°C coalesced the signals at δ 5.67 and 5.61, the OH's. The other signals simplify.

(9) ^{1}H-NMR at 55°C, decouplings and ^{13}C-NMR studies support the regiochemistry of **9**. The key H2 proton is masked by the CH_2's of the malonate. Spectroscopic correlation with **20**, and the fact that *cis*-hydroxyester affords spontaneously *cis*-lactone, supports the *trans* assignment.

(10) Data for **10**: ^{1}H-NMR (400MHz, $CDCl_3$, 50°C), δ 7.38-7.23 (m, 5H, C_6H_5), 5.19 (s, 2H, PhC<u>H</u>$_2$), 4.62 (s, 1H, NC<u>H</u>CMe$_2$), 4.50 (broad d, J = 3Hz, 1H, C<u>H</u>Br), 3.96 (m, 1H, N<u>H</u>CH), 3.66 (s, 3H, CO_2CH_3), 3.45 (m, 1H, NHC<u>H</u>), 2.38 (m, 1H, NCH$_2$<u>H</u>CH), 2.26 (m, 1H, NCH$_2$HC<u>H</u>); assignments supported by decoupling and HMQC experiments.

(11) On pyrrolidones: (a) Dai, W-M.; Nagao, Y.; Fujita, E. *Heterocycles* **1990**, *30*, 1231 and references therein. (b) Bernadi, A.; Micheli, F.; Potenza, D.; Scolastic, C.; Villa, R. *Tetrahedron Lett.* **1990**, *31*, 4949. (c) Koot, W-J.; Ginkel, R.; Kranenburg, M.; Hiemstra, H.; Louwrier, S.; Moolenaar, M.J.; Speckamp, W.N. *Tetrahedron Lett*. **1991**, *32*, 401; (d) Pilli, R.A.; Russowsky, D. *J. Org.Chem.* **1996**, *61*, 3187. On carbamates of pyrrolidines: (f) Kraus, G.A.; Neueschwander, K. *J. Chem. Soc., Chem. Commun.*, **1982**, 134. (g) Asada, S.; Kato, M.; Asai, K.; Ineyama, T.; Nishi, S.; Izawa, K.; Shono, T. *J. Chem. Soc., Chem. Commun.* **1989**, 486; (h) David, M.; Dhimane, H.; Vanucci-Bacque, C.; Llommet, G. *Synlett* **1998**, 206.

(12) The mixture of *cis* and *trans* diols may indicate the facile formation of an acyl-iminium ion from the *cis* diol which reacts

with water from the less hindered face to give the *trans* diol, or ring opening of the cyclic aminal and reclosing.

(13) The yield was dependent on the mode of work-up and/or the stability of the product to chromatography on silica gel.

(14) We are exploring such variation with the 3-aminopyrrolidine series to access *trans*-lactams.[4]

The experimental procedure for the preparation of **18** is representative. To 2,3-diacetoxy-1-benzyloxycarbonylpyrrolidine **13** (0.049g, 0.153mmol) and the ketene acetal - (*E*)-(1,1-dimethylethyl)[(1-ethoxy-1-butenyl)oxy]dimethylsilane - (0.161g, 0.659mmol) in dry dichloromethane (5mL) at –70^{o}C was added boron trifluoride etherate (37.6μL, 0.306mmol) dropwise over 5min. After 2h at –70^{o}C, tlc showed absence of starting material so water (10mL) was added and the aqueous layer separated. After extraction with dichloromethane (2 x 7mL), the combined organic layers were washed with brine (7mL), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography on silica (Merck 9385) eluting with 7:3 hexane:ethyl acetate afforded **18** (β:α 30:70) (0.041g, 68%).

Analytical HPLC data was obtained on an Inertsil ODS2 column at 215nm with gradient elution, solvent A (H_2O + 0.1% H_3PO_4) and solvent B (95% MeCN + 5% H_2O 0.1% H_3PO_4) 0 to 100% B over 40min with a flow rate of 1mL/min. The α-isomer of **17** and **18** retained at 31.61min and the β-isomer at 31.94min.

(16) After removal of the acetate there was no evidence for the *cis*-hydroxyester or the corresponding *cis*-lactone. The selective hydrolysis of the acetate was carried out to correlate **20** with material available from a different route (unpublished results).

The HPLC data for **20** was obtained on an ABZ column at 215nm with isochratic elution (30% MeCN in H_2O + 0.12% trifluoroacetic acid) with a flow rate of 1mL/min. The α-isomer of **20** retained at 32.31min and the β-isomer at 36.26min. Data for **20**: ^{1}H-NMR (250MHz, $CDCl_3$, 55^{o}C) δ 7.40-7.28 (m, 5H), 5.15 (s, 2H), 4.46-4.37 (m, 1H), 4.18-4.05 (m, 2H), 3.99-3.90 (m, 1H), 3.83-3.63 (m, 1H), 3.43-3.30 (m, 1H), 3.15-2.97 (bm, 0.6H), 2.84-2.62 (bm, 0.4H), 2.28-1.13 (m, 10H), 0.85 (t, J = 7Hz, 3H).

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(18) Data for **22**: ^{1}H-NMR (250MHz, $CDCl_3$, 55^{o}C) δ 7.39-7.26 (m, 5H), 5.23-5.03 (m, 2H), 4.26-4.13 (m, 0.6H), 3.98-3.47 (m, 3H), 3.29-3.18 (m, 0.4H), 3.03-2.88 (m, 0.6H), 2.83-2.73 (m, 0.4H), 2.41-2.28 (m, 1H), 2.13-1.15 (m, 5H), 0.91-0.78 (m, 3H). This data correlates with material available by a different route (unpublished results); IR (KBr diffuse reflectance) $\nu_{C=O}$ 1796, 1715 cm^{-1}.

(19) The dimethyl analogue **16** was processed in an identical manner to **17** with yields of 93% for the hydrolyses and 61% for the *trans*-lactonisation. Data for the dimethyl *trans*-lactone: ^{1}H-NMR (250MHz, $CDCl_3$, 55^{o}C) δ 7.38-7.28 (m, 5H, $C_6\underline{H}_5$), 5.16 (d, J = 12Hz, 1H, Ph$\underline{H}$CH), 5.10 (d, J = 12 Hz, 1H, PhHC$\underline{H}$), 4.06 (ddd, J = 10, 10, 5.5Hz, 1H, H3), 3.89 (t, J = 10Hz, 1H, H5α), 3.68 (ddd, J= 10, 10, 5.5Hz, 1H, H5β), 3.23 (d, J = 10Hz, 1H, H2), 2.38-2.28 (m, 1H, H4β), 2.10-1.92 (m, 1H, H4α), 1.45 (s, 3H, Me), 1.17 (s, 3H, Me) assignments confirmed by decoupling experiments; IR ($CHCl_3$ solution) $\nu_{C=O}$ 1791, 1705 cm^{-1}.