Synthesis of (+/-) - Oxohexahydrofuro[3,2-*b*]pyrroles (Pyrrolidine-*trans*-lactones) *via* a Reduction - Alkylation Protocol

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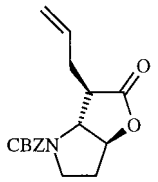
Abstract: A synthesis of pyrrolidine-*trans*-lactones is described commencing from 1-(benzyloxycarbonyl)-3-oxo-2-pyrrolidineacetic acid ethyl ester. *cis*-Reduction of the oxo-pyrrolidine followed by hydroxyl inversion with benzoic acid in a Mitsunobu reaction gave the *trans*-benzoate ester which was converted into its corresponding silyl ether. After allylation α to ethyl ester, silyl deprotection, saponification and *trans*-lactonisation gave pyrrolidine-*trans*-lactones. Stereoselective allylation of *trans*-1-(benzyloxycarbonyl)- 3-hydroxy-2-pyrrolidine-acetic acid ethyl ester is feasible to give predominantly the desired diastereomer.

Inhibitors of serine proteases are currently being explored as therapies for respiratory and cardiovascular diseases amongst others.[1] As new scaffolds for inhibitors of serine proteases are rare, our introduction of a new scaffold known as pyrrolidine *trans*-lactones **1** (and their analogous lactams)[2] is a significant and important contribution in this area. These compounds were developed during our research programme exploring inhibitors of human neutrophil elastase (HNE). Efficient and stereoselective routes to these highly unusual strained structures were critical to our progress.



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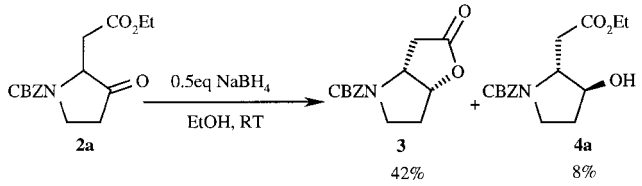
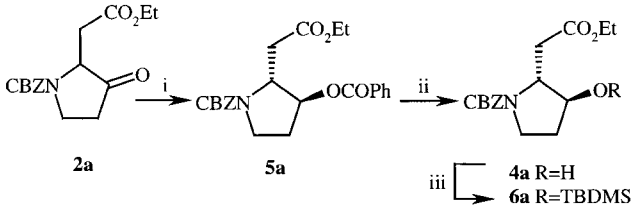
We describe here a route to racemic *trans*-lactones which addresses the lack of stereoselectivity associated with our previous route[2] and which is applicable on large scale (giving > 10g of lactone **1**). Due to the strain of the *trans*-lactone system,[2] we elected to form the lactone ring as a final synthetic step from the precursor hydroxyacid in turn prepared from the known keto-ester **2**.[3] Initially this chemistry was developed with the pyrrolidine *N* protected as its ethyl carbamate, but to facilitate the preparation of derivatives of the pyrrolidine *N* for our medicinal chemistry programme, the preferred protecting group was the benzyl carbamate (CBZ).



2a **3** 42% **4a** 8%

Scheme 1

Our initial challenge was the reduction of ketone **2a**; treatment with $NaBH_4$ gave a 5:1 ratio of *cis*-lactone **3** to *trans*-hydroxyester **4a** (Scheme 1).[4,5] After numerous attempts to reduce **2a** to **4** efficiently,[6] we used the stereochemical preference for the *cis* product to our advantage by a reduction-Mitsunobu protocol (Scheme 2). Thus reduction of **2** with $NaBH_4/CeCl_3$ (to prevent over-reduction), rapid work-up (to avoid extensive cyclisation of the intermediate *cis*-hydroxyalcohol to **3**), and treatment with benzoic acid under Mitsunobu conditions gave after chromatography, the *trans*-benzoate **5a** in 62% yield. The deprotection of the benzoate **5a** and reprotection as its TBDMS ether **6a** was easily achieved.[7,8]



2a **5a**

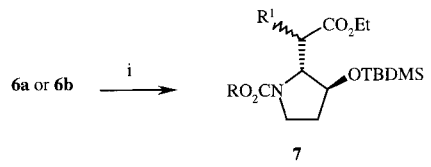
Scheme 2. (i) $NaBH_4$ (1eq), $CeCl_3$ (1eq), EtOH, RT, 2.5h; rapid work-up then $PhCO_2H$ (1.5eq), PPh_3 (1.5eq), EtO_2CNNCO_2Et (1.5eq), THF, RT,15h, 62%; (ii) K_2CO_3 (3eq), EtOH, RT, 16h, 82%; (iii) TBDMSCl (1.5eq), imidazole (2eq), DMF RT, 3 days, 90%

The silyl ether **6a** (or **6b**[7]) is readily alkylated (Scheme 3) and proved invaluable for the preparation of compounds **7** with a substituent adjacent to the ester.[9] From medicinal chemical studies the allyl group **7f** was adopted as the preferred substituent and so this chemistry was carried out on >50g scale. Deprotonation and allylation of **6a** gave an inseparable 1:1 mixture of α and β allyl diastereomers **7f**.[10,11] Standard deprotections gave the hydroxyacid **8**. *Trans*-lactonisation was achieved initially with the Mukaiyama conditions[12] but the Yamaguchi conditions[13] (shown) at *ca* 0.01M dilution gave a higher yield (62-82%) of 1:1 β:α allyl *trans*-lactones **1** and **9**, separable by flash chromatography. Their structures were confirmed by ^{1}H-NMR studies.[2,14]

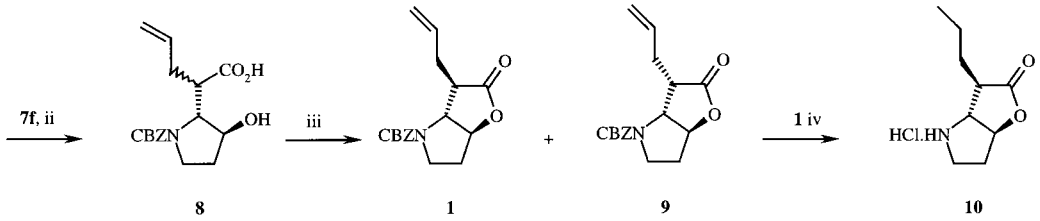
Deprotection of the benzyl carbamate **1** and allyl reduction by hydrogenation with Pearlman's catalyst followed by salt formation with ethereal hydrogen chloride gave the lactone **10** as a key intermediate in our medicinal chemical programme.[15] The free base of **10** is surprisingly stable and can be stored for several months without decomposition. However once degradation commences, it appears to be autocatalytic leading to rapid breakdown. Mass spectral evidence suggested the degradation products are the oligomeric dimers, trimers and tetramers arising from acylation of the nitrogen by the *trans*-lactone.[16] The hydrochloride is stable indefinitely.

The β-allyl/propyl lactone analogues are preferred as they are more potent HNE inhibitors *in vitro* than the α-allyl analogues.[2] We therefore attempted to epimerise the α-epimer **9**.[17] This was unsuccessful, leading to recovered **9** and/or degradation products. Presumably deprotonation of **9** gives a configurationally stable carbanion as formation of the ester enolate is disfavoured due to increased ring strain.

We then discovered a simpler introduction of the allyl group[18] which avoids TBDMS protection/deprotection and which gives a

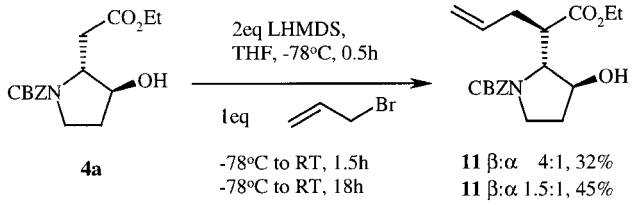


	R	R^1	Yield %	Isomer ratio
7a	Et	CH_2CN	52	2:1
7b	Et	CH_2CCH	80	2:1
7c	Et	Et	78	1:1
7d	Et	SMe	84	1:1
7e	Bn	*cis*-$CH_2CHCHCH_2$	17	-
7f	Bn	CH_2CHCH_2	60-70	1:1



Scheme 3. (All compounds racemic): (i) LHMDS (1.1-2eq), THF, -78°C, 0.5h; then add electrophile (1.1-1.5eq) ($NCCH_2Br$, $HCCCH_2Br$, EtI, MeSSMe, *cis*-$ClCH_2CHCHCH_2Cl$ or CH_2CHCH_2Br), -78°C to RT, 2h; (ii) Bu_4NF (1.2eq), THF, RT, 18h, 80-100%; then LiOH (3eq), THF:H_2O 10:1, 50°C, 7h, 70-96% (iii) 2,4,6-trichlorobenzoyl chloride (3eq), Et_3N (1.1eq), CH_2Cl_2, RT, 3h; then addition over 4h to DMAP (6eq) in refluxing PhMe, then reflux, 4h, 58-82% (iv) H_2, $Pd(OH)_2$, EtOAc, RT, 2h, then HCl, Et_2O, RT, 5min, 70-81%

stereoselective preference for the β product. Reaction of the unprotected hydroxyester **4a** with LHMDS (2eq) and allyl bromide (1eq) at –70°C for 30min and then warmed to room temperature over 1h gave a 32% yield (unoptimised) of a 4:1 ratio of β:α allyl isomers **11**[19] (Scheme 4). In an attempt to improve this yield, the reaction was allowed to warm much more slowly to room temperature over 18h. This did indeed improve the yield to 45% but also led to a decrease in stereoselectivity giving a 1.5:1 ratio of β:α allyl isomers. The stereochemical ratio of the allyl group in **11** was determined by inspection of HPLC traces of the crude products and by analysis of the crude ^{1}H-NMR spectra.[19] Assignment of the β and α isomers of **11** was determined by their conversion into the *trans*-lactones for comparison with pure samples of known α and β allyl lactones.[2] Thus a 4:1 isomer ratio of **11** was converted into a 3.6:1 ratio of β:α lactones **1** and **9**. The origins of this stereoselectivity and variability with reaction conditions are unclear, but have been observed in an analogous series.[2]



Scheme 4

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

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References and Notes

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(3) The keto-ester **2a** was prepared from the ethyl ester of β-alanine by (i) CBZCl, $NaHCO_3$, H_2O, dioxan, 98%. (ii) NaH, diethyl fumarate, PhMe, 60-80%. (iii) brine, DMSO, 65-71%. Based on Geissmann, T.A.; Waiss, A.C. *J. Org. Chem.* **1962**, *27*, 139.

(4) Reductive amination of **2a** to access precursors to the analogous pyrrolidine *trans*-lactams gave similar results; *cis*-lactams were the only products isolated.

(5) Data for **3**: ^{1}H-NMR (250MHz, $CDCl_3$) δ 7.42-7.29 (m, 5H), 5.23-5.04 (m, 3H), 4.52 (m, 1H), 3.95-3.75 (m, 1H), 3.43 (sextet, J = 5.5Hz, 1H), 2.97-2.67 (m, 2H), 2.33 (dd, J = 12.5, 5.5Hz, 1H), 2.15-1.97 (m, 1H); IR ($CHCl_3$) $\nu_{C=O}$ 1785, 1698 cm^{-1}.
Data for **4a**: ^{1}H-NMR (250MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 5.14 (bs, 2H), 4.28-4.21 (bs, 1H), 4.20-4.00 (m, 3H), 3.73-3.58 (m, 3H), 3.53-3.40 (m, 1H), 3.15-2.78 (m, 2H), 2.30-1.85 (m, 3H), 1.23 (t, J = 7Hz, 3H).

(6) Other attempts included (i) Ph_2SiH_2, $(PPh_3)_3RhCl$. (ii) Na, naphthalene. (iii) Et_3SiH, $(PPh_3)_3RhCl$. (iv) SmI_2. (v) $LiAl(O^tBu)_3H$. (vi) H_2, Pd-C. Attempts to tether a reducing agent to the corresponding acid of **2**, also failed.

(7) The CBZ series gave better yields than the ethyl carbamate series. The yields for the ethyl carbamates (**4b**, **5b** and **6b**) are: step (i) to **5b** 47%; step (ii) to **4b** 42%; step (iii) to **6b** 96%.

(8) Data for **6a**: ^{1}H-NMR (250MHz, $CDCl_3$) δ 7.40-7.29 (m, 5H), 5.18 (s, 1H), 5.15 (s, 1H), 4.25-4.22 (m, 1H), 4.21-3.99 (m, 2H), 3.68-3.45 (m, 2H), 2.94-2.66 (m, 1H), 2.27-2.13 (m, 1H), 2.02-1.87 (m, 1H), 1.86-1.72 (m, 1H), 1.31-1.21 (m, 3H), 0.87 (s, 9H), 0.07 (s, 6H).

(9) Only bis-alkylation giving **7e** proceeded in poor yield (Scheme 3). All the esters **7** were converted into the corresponding *trans*-lactones using the protocol described for **7f**. The medicinal chemistry of these compounds will be described elsewhere.

(10) Protection of the alcohol **4a** as its TBDMS ether can be replaced by protection as the TMS ether *in situ*. Thus treatment of **4a** with LHMDS followed by addition of TMSCl, then a further equivalent of LHMDS and allyl bromide, gave after work-up, the ethyl ester of **8**. This sequence proceeded in lower yield (50% yield) but avoids two extra steps.

(11) Data for **7f**: ^{1}H-NMR (250MHz, $CDCl_3$) δ 7.40-7.26 (m, 5H), 5.86-5.53 (m, 1H), 5.24-4.91 (m, 4H), 4.37-3.92 (m, 4H), 3.77-3.27 (m, 2H), 3.14-2.15 (m, 3H), 2.14-1.68 (m, 2H), 1.28-1.18 (m, 3H), 0.84 (s, 9H), 0.06 (s, 6H).

(12) Mukaiyama, T. *Angew. Chem., Int. Ed.* **1979**, *18*, 707.

(13) Inanaga, J.; Katsuki, S.; Takimoto, S.; Ouchida, S.; Inone, K.; Nakano, A.; Okukuda, N.; Yamaguchi, M. *Chem. Lett.* **1979**, 1021.

(14) *Trans*-lactone carbonyls characteristically show higher infra-red stretching frequencies when compared with the analogous *cis*-lactone carbonyls. For example the carbonyl frequencies of **1** and **3** are 1791cm^{-1} and 1785cm^{-1}.

(15) Data for **10**: ^{1}H-NMR (250MHz, d6 DMSO) δ 9.22 (s, 2H), 4.18 (ddd, J = 10.5, 10.5, 5.5Hz, 1H), 3.83-3.56 (m, 2H), 3.28-3.17 (m, 1H), 2.57-2.46 (m, 1H, hidden by DMSO peak), 2.43-2.30 (m, 1H), 2.20 (quintet, J = 9.5Hz, 1H), 1.87-1.71 (m, 1H), 1.60-1.35 (m, 3H), 0.94 (t, J = 7Hz, 3H).

(16) The mass spectum (thermospray) of a degraded sample of the free base of **10** showed ions at 170 (MH^+), 339 ($2MH^+$), 508 ($3MH^+$) and 677 ($4MH^+$).

(17) Epimerisation conditions: DBU, DMF, 45^{o}C, 3 days - degradation of **9**; Et_3N, DMF, 45^{o}C, 3 days – no change in **9**; LHMDS, THF – 85^{o}C , no change in **9**; KOH, EtOH, H_2O, 45^{o}C, 4h, α-epimer of **8**.

(18) An alternative approach to access the β-allyl products *via* the *cis*-lactone **3** was attempted. Treatment of **3** with LHMDS followed by addition of the resultant enolate to excess allyl bromide gives only the expected β-allyl *cis*-lactone in 64% yield resulting from reaction from the less hindered *exo*-face. (Addition of the allyl bromide to the enolate gave a mixture of mono- and bis-allylation.) However we were then faced with the non-trivial conversion of the *cis*-lactone into its *trans*-lactone.

(19) Preparation of **11** (β:α 4:1). To *trans*-1-(benzyloxycarbonyl)-3-hydroxy-2-pyrrolidineacetic acid ethyl ester (1.00g, 3.25mmol) in dry THF (10mL) at –70^{o}C under nitrogen, was added lithium hexamethyldisilazide (1M in THF) (6.7mL, 6.67mmol) dropwise over 5min. After 30min, allyl bromide (0.28mL, 3.25mmol) was added dropwise over 5 min. After stirring at –70^{o}C for 1h, the cooling bath was removed. After a further 1h, the reaction was quenched with 2M hydrochloric acid (25mL) and extracted with EtOAc (3 x 25mL). The combined extracts were washed with brine (25mL), dried ($MgSO_4$) and concentrated. Flash chromatography on silica (Merck 9385) eluting with 4:1 ether:hexane afforded the allylester (0.368g, 32%) as a colourless gum. Although the ^{1}H-NMR spectrum of **11** at room temperature in $CDCl_3$ is complicated by the existence of **11** as rotamers, integration of a pair of singlets at δ 4.43 (α isomer) and 4.35 (β isomer) gives the isomer ratio. Data for 4:1 β:α **11**: ^{1}H-NMR (400MHz, d6 DMSO, 100^{o}C) δ 7.39-7.28 (m, 5H β+α), 5.72 (m, 1H β+α), 5.11 (m, 2H, β+α), 5.09-4.93 (m, 2H β+α), 4.79 (s, 1Hβ), 4.74 (s, 1Hα), 4.17 (s, 1Hβ+α), 4.06 (m, 2Hβ), 4.03 (m, 2Hα), 3.93 (ddd, J = 6, 1, 1Hz, 1Hα), 3.88 (ddd, J = 7.5, 1, 1Hz, 1Hβ), 3.57 (m, 1Hβ+α), 3.33 (ddd, J = 10.5, 9, 3.5Hz, 1Hα), 3.28 (ddd, J = 9, 9, 3.5Hz, 1Hβ), 2.73 (m, 1Hβ+α), 2.36 (m, 1Hβ+α), 2.25 (m, 1Hβ), 2.16 (m, 1Hα), 1.96 (m, 1Hβ+α), 1.78 (m, 1Hβ+α), 1.17 (t, J = 7Hz, 3Hβ), 1.16 (t, J = 7Hz, 3Hα); HPLC Column ODS2-IK5 isochratic 40% MeCN in H_2O with 0.1% H_3PO_4 eluting 1mL/min at 215nm; the β isomer elutes at 19.12min and the α at 17.29min.