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Synthesis of *Trans*-Fused [5,5] Bicyclic Lactones / Lactams as Templates for Serine Protease Inhibition

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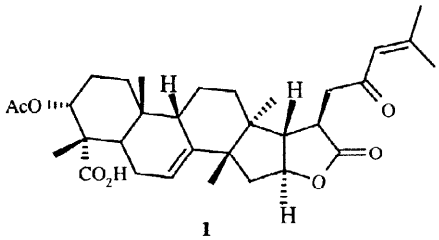
Abstract: Efficient routes have been developed for the synthesis of the *trans*-lactone **2**, the *trans*-lactam **3** and their 3-substituted analogues based upon cyclisation strategies using Mukaiyama's reagent. 3β-Allyl, thiophenyl and propyl lactones **5** inhibit chymotrypsin and human leucocyte elastase and are representative of a novel class of serine protease inhibitors. © 1998 Elsevier Science Ltd. All rights reserved.

The natural product **1**, extracted from *Lantana camara*, is a potent inhibitor of several serine proteases[1] and the [5,5] *trans*-lactone moiety is necessary for potent inhibitory action involving cleavage of the lactone ring by the active site serine with concomitant enzyme acylation.[1] Following these findings, we wished to access the parent *trans*-lactone **2** and its 3-substituted analogues to assess whether biological activity would be retained in simpler molecules. Furthermore, the *trans*-lactam **3** represented a novel template which might behave in an analogous manner. This paper describes efficient methodology for the generation of these systems.



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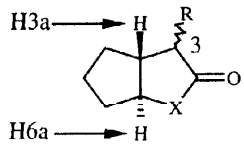

2 R=H, X=O
3 R=H, X=NH
4 α–R, X=O
5 β–R, X=O
6 β–R, X=NH

In contrast to *cis*-fused bicyclic lactones/lactams which are widely described in the chemical literature,[2] there are only a few isolated reports of the corresponding *trans*-lactone **2**[3] and no reports of the lactam **3**. Our approach to the parent *trans*-lactone **2** was *via* a simple lactonisation strategy. Thus, treatment of *trans*-2-hydroxycyclopentaneacetic acid **7**[4] with Mukaiyama's reagent[5] under high-dilution conditions (*ca.*1mg/ml) afforded **2** in 64% yield (Scheme 1);[6] the strained nature of this system was evident from the IR spectrum which showed a carbonyl stretching frequency of 1782 cm^{-1}, significantly higher from that reported for the corresponding *cis*-lactone (1740 cm^{-1}). Access to the novel *trans*-lactam **3** was accomplished using a similar strategy. Thus, reductive amination of the racemic keto ester **8** with benzylamine gave the *trans* benzyl derivative **9**. Catalytic hydrogenation afforded the intermediate *trans* amino ester which was hydrolysed under basic conditions to give the *trans* amino acid **10**. Cyclisation, using Mukaiyama's reagent, gave **3** in good yield (64%), the *trans*-fused geometry of which was confirmed by X-ray crystal structure analysis[7] [mp. 99 °C, ν_{max}(Nujol) 1701 cm^{-1} *cf.* 1690 cm^{-1} for the corresponding *cis*-lactam[2c]].

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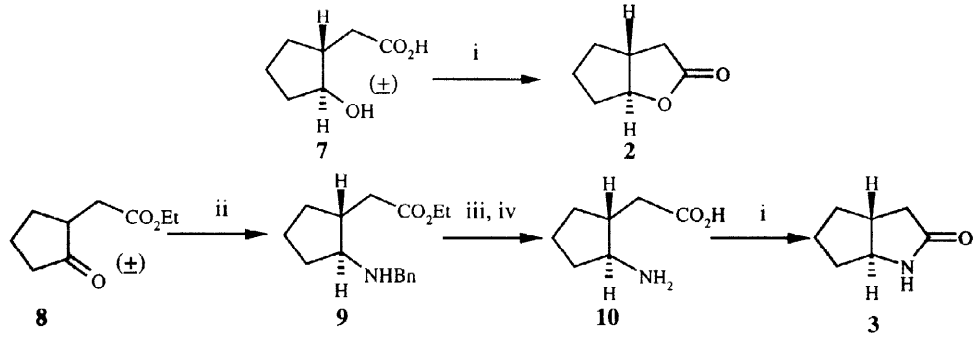
Scheme 1



Reagents and conditions: i, 2-chloro-1-methylpyridinium iodide 4eqs, Et_3N 8eqs, DCM, 40 °C, 18h, 64% **2**, 64% **3**; ii, $BnNH_2$, $NaBH(OAc)_3$, AcOH, DCM, 43%; iii, H_2, Pd/C, EtOH, 78%; iv, NaOH, MeOH; HCl, 55%.

Although lactone **2** showed weak enzyme inhibitory activity (e.g. IC_{50} 250 μM *vs* thrombin), we believed introduction of substituents proximate to the carbonyl functionality, designed to access the primary specificity pockets of enzymes of interest, would increase potency and provide selectivity of inhibition. 3α-Alkyl-, 3α-benzyl- and 3α-allyl analogues were readily prepared when alkylations of lactone **2** were performed at -90 °C and with extended reaction times [LHMDS, THF, >16 h] (Table 1). The diastereoselectivity in these reactions presumably arises from the electrophile approaching the enolate from the molecular face opposite to the proximate angular hydrogen H3a, in what is an essentially planar molecule.

Table 1. Alkylation of *trans*-Lactone **2**

2 → 4 + 5

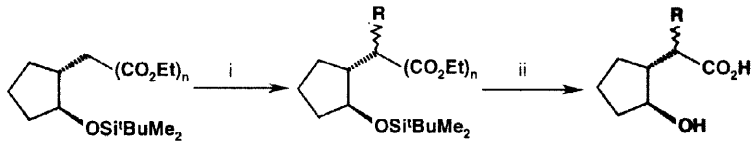
ENTRY	RX	RATIO 4:5[a]	YIELD %
1	$PhCH_2Br$[b]	>99:1	53
2	MeI	>99:1	69
3	Allyl iodide	>99:1	79
4	MeOCOCl	17:83	53

[a]Measured by integration of the signal for H6a in ^1H NMR. Detection limits of minor isomer *ca.* 1%. [b]LDA, THF, HMPA, -78 °C, 20%.

This is similar to that observed for 5,6-*trans*-γ-lactones,[8] but is in contrast to findings for the 5,5-*cis*-system in which the β-isomer is produced due to its folded conformation.[2b] Electrophiles which, when introduced, result in enhanced H3 acidity, afford mainly β-orientated analogues (e.g. entry 4, Table 1), presumably *via* enolisation/reprotonation of the initially formed product **4**.

These facile epimerisations in derivatives possessing electron-withdrawing 3-substituents contrasts with the failure to epimerise the corresponding α-methyl or α-allyl analogues (LDA, -90 °C; quench with aq. NH_4Cl, 25 °C), whereas, similar epimerisations have been observed in 5,6-*trans*-γ-lactones[8] and in a related 5,5-*cis*-lactone.[2b] However, β-isomers **5** not bearing an activating 3-substituent were prepared by alkylation of ester **11** or malonate **12**, prepared by silylation (TBDMSCl, imidazole, DMF, 25 °C) of the corresponding hydroxy esters,[4] followed by appropriate deprotection/hydrolysis which gave the precursor hydroxy acids **13**, usually as an inseparable 1:1 mixture of diastereoisomers (Scheme 2). Lactonisation using Mukaiyama's reagent gave the desired lactones as mixtures of α- and β- isomers (Table 2).

Scheme 2



11 n = 1
12 n = 2

13

Reagents and conditions: i, n=1, LDA, -78 °C, THF, allyl bromide; 87%: n=2, NaH, DMF, MeI, EtBr, PrBr or BnBr; 81-93%. ii, n=1; R=allyl, NaOH, aq. EtOH; 67%; n=2, R=Me, Et, Pr, Bn a. KOH/EtOH, 54-100%; b. Cu_2O/MeCN; 40-76%; c. KOH/EtOH; 81-100%.

Table 2. Lactonisation of Substituted Hydroxy Acids

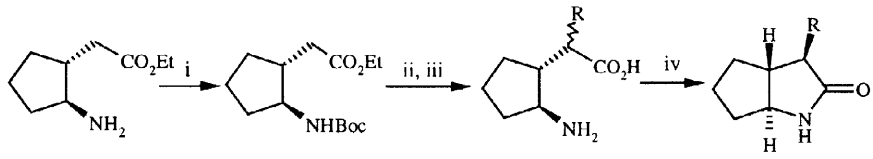
13 → 4 + 5

Entry	R	RATIO 13[a]	RATIO 4:5[b]	% YIELD
1	Me	50:50	50:50	90
2	Et	50:50	50:50	84
3	^{n}Pr [c]	90:10	90:10	77
4	^{n}Pr [c]	10:90	10:90	92
5	Allyl[d]	50:50[e]	13:87	89
6	Bn[d]	50:50[e]	33:77	82

[a] Ratio of diastereoisomers. [b] Ratio measured by ^{1}H NMR, see Table 1. [c] Diastereoisomers partially separated by flash chromatography. [d] β-Substituted lactones were isolated following chromatography. [e] Diastereoisomeric ratio measured at the hydroxy ester stage.

Unfortunately, it was not possible to assign the stereochemistry of the diastereoisomeric hydroxy acids **13**, or their precursor hydroxy esters. Since the ratio of the α- and β-propyl substituted lactones **4** and **5** reflects the diastereoisomeric ratio of the partially separated substituted hydroxy acids, we assume that the substituent is configurationally stable during the lactonisation process. However, that predominantly β-substituted lactones arise from the allyl and benzyl compounds suggests that side-chain epimerisation can occur at some stage during the hydrolysis/lactonisation process. The reasons for these differences are not currently understood.

Scheme 3



14

15 R= $CH_2CH=CH_2$
16 R= Bn

17 R= $CH_2CH=CH_2$
18 R= Bn

Reagents and conditions: i, $(Boc)_2O$, MeCN, 64%; ii, Either, LHMDS, THF, allyl iodide, -75 °C, 64% or LHMDS, THF, benzyl bromide, -75 °C, 55%; iii, NaOH, MeOH; HCl, 53% **15**, 58% **16**; iv, 2-chloro-1-methylpyridinium iodide, Et_3N, DCM, 62% **17**, 65% **18**.

Extending these findings to the *trans*-lactam system, 3-substituted analogues were accessed from the protected amino ester **14** by initial alkylation of its enolate with either allyl iodide or benzyl bromide under standard conditions. The 1:1 diastereoisomeric mixtures were deprotected to give their respective amino acids **15** and **16** and then lactamised to afford only the 3β-alkylated lactams **17** and **18** in 62% and 65%, respectively (Scheme 3), indicating that epimerisation also occurs during the hydrolysis/lactamisation process.[9]

Several of the substituted *trans*-lactones were shown to be serine protease inhibitors. For example, the α- and β-phenylthio compounds **4** and **5** (R= PhS) are potent inhibitors of chymotrypsin (IC_{50} 120 and 20 nM, respectively). Furthermore, the β-allyl (R= $CH_2CH{=}CH_2$) and propyl (R= ^nPr) lactones **5**, in addition to inhibiting chymotrypsin (IC_{50} 26 and 19 μM, respectively), inhibit human leucocyte elastase (IC_{50} 7.0 and 23 μM) and kinetic and mass spectrometry studies have shown that compounds of this type are time-dependent acylating inhibitors of serine proteases.[10] In contrast, *trans*-fused lactams **17** and **18**, were without significant enzyme inhibitory activity when tested against selected serine proteases (thrombin, Factor Xa), which we believe reflects the decreased reactivity of this template.

In summary, efficient routes to *trans*-lactone **2**, the novel *trans*-lactam **3** and their 3-substituted derivatives have been developed, providing access to novel classes of serine protease inhibitors. The further manipulation of both systems, leading to the identification of potent inhibitors of serine proteases, will be reported in future communications.

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REFERENCES AND NOTES

1. Weir, M. P.; Bethell, S. S.; Cleasby, A.; Campbell, C. J.; Dennis, R. J.; Dix, C. J.; Finch, H.; Jhoti, H.; Mooney, C. J.; Patel, S.; Tang, C-M.; Ward, M.; Wonacott, A. J.; Wharton, C. W. *Biochemistry* **1998**, *37*, 6645-6657; O'Neill, M. J.; Lewis, J. A.; Noble, H. M.; Holland, S.; Mansat, C.; Farthing, J. E.; Foster, G.; Noble, D.; Lane, S. J.; Sidebottom, P. J.; Lynn, S. M.; Hayes, M. V.; Dix, C. J. *J. Nat. Prod.*, submitted for publication.
2. a. For example, Ali, S. M.; Chapleo, C. B.; Roberts, S. M. *J. Chem. Soc. Perkin Trans. 1* **1979**, 126-129 and references therein; b. Carnell, A. J.; Roberts, S. M.; Sik, V.; Willets, A. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2385-2389; c. Knapp, S.; Lerose, A. T. *J. Org. Chem.* **1988**, *53*, 4006-4014.
3. Fukazawa, S.; Iida, M.; Nakanishi, A.; Fujiinami, T.; Sakai, S. *J. Chem. Soc., Chem Commun.* **1987**, 920-921; Shultz, N.; Totenberg-Kaulen, S.; Dapperheld, S.; Heyer, J.; Platen, M.; Schumader, K.; Steckhan, E. *Stud. Org. Chem. (Amsterdam), (Recent Adv. Electroorg. Synth.)* **1987**, *30*, 127-135; Tanaka, T. *Bull. Chem. Soc. Jpn.* **1959**, 1320-1324; for natural products containing this system see Ma, K. W.; Chang, F. C.; Clardy, J. C. *J. Chem. Soc., Chem. Commun.* **1971**, 424-425 and references therein; Marco, J. A.; Sanz-Cervera, F.; Pareja, J. M; Sancenon, F.; Valles-Xirau, J. *Phytochemistry* **1994**, 477-485.
4. Grigsby, W. E.; Hind, J.; Chanley, J.; Westheimer, F. H. *J. Am. Chem. Soc.* **1942**, *64*, 2606-2610.
5. Mukaiyama, T.; Usui, M.; Shimada, E.; Saigo, K. *Chem. Lett.* **1976**, 49-50.
6. All new compounds, which are racemic, exhibited satisfactory spectra (^1H NMR, IR) and/or mass spectral or combustion analytical data. Data for **2:** ^1H NMR δ_H ($CDCl_3$) 1.44 - 1.26 (2H, m), 1.85-2.20 (5H, m), 2.26 (1H, dd, ***J*** 16 and 13), 2.63 (1H, dd ***J*** 16 and 6) and 3.79 (1H, dt, ***J*** 10, 10 and 6). Data for **3:** δ_H ($CDCl_3$) 1.36 (2H, m, 5-H_2), 1.77-2.12 (6H, m, 3a-H, one of 3-H_2, 4-H_2, 6-H_2), 2.42 (1H, dd, ***J*** 15,6, one of 3-H_2), 3.04 (1H, dt, ***J*** 12,12,6, 6a-H) and 5.81 (1H, br s, NH).
7. Crystal data, atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.
8. Nishizawa, M.; Greico, P. A.; Burke, S. D.; Metz, W. *J. Chem. Soc., Chem. Commun.* **1978**, 76-78.
9. Early investigations indicate that stereoselective 3α-alkylation in the *trans*-lactam series is possible e.g. **3** → (3α-Bn) **3** by the following sequence of reactions: (i) TBDMSCl, Et_3N, DMF, 74%; (ii) LDA, BnBr, -78 °C, THF, 12%; (iii) TBAF, 67%.
10. Finch, H. manuscript in preparation.