Pergamon

Tetrahedron Letters 42 (2001) 3831–3834

TETRAHEDRON LETTERS

Enantioselective synthesis of α,β-unsaturated γ- and δ-lactams

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Received 15 February 2001; accepted 3 April 2001

Abstract—An enantioselective synthesis of α,β-unsaturated γ- and δ-lactams was proposed based on a simple strategy using the initial preparation of *cis* vinylogous aminoesters by the Horner reaction followed by a mild intramolecular cyclisation.

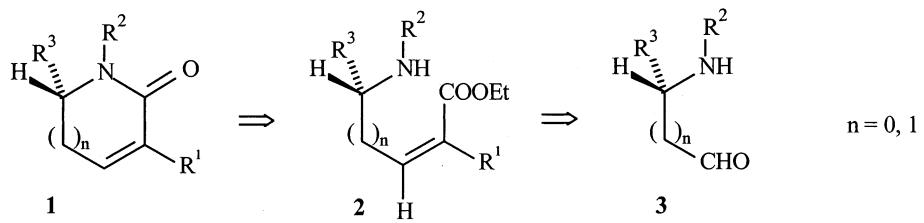
In recent years an increasing number of α,β-unsaturated γ-lactams have been isolated and characterised. 3,4-Dihydro-2*H*-pyrrolidin-2-ones and structurally related alkaloids are also of a great interest due to their antitumour or platelet aggregation inhibition activities.[1] Pyrrolams, bicyclic lactams such as 3,4-dihydro-2*H*-pyrrolizidin-2-ones, have been recently reported. They exhibit hepatotoxic, mutagenic and carcinogenic activities.[2] Likewise, optically active α,β-unsaturated γ-lactams have been shown to be versatile starting materials for the asymmetric synthesis of a wide range of biologically active compounds.[3]

The development of general methods for the preparation of these heterocycles or synthetic analogues is of increasing interest. Many syntheses have been reported, often in connection with a particular structure with a sophisticated method that needs numerous steps.[4,5] In this paper, we describe a new, short, convenient and enantioselective synthesis of substituted α,β-unsaturated γ- and δ-lactams **1** based on a relatively classical, but efficient strategy.

In this approach the construction of the heterocycle is based on the intramolecular reaction of *cis* vinylogous aminoesters **2** obtained from a *cis* olefination of aminoaldehydes.†

We have previously reported that the insertion of a *cis* ethenyl CH=CR[1] group between the α-carbon and the carboxyl group into a proline induced the formation of a very stable closed conformation.[6] As a result, the ester group of this *cis* vinylogous aminoester was found to be positioned near to the amino moiety and a possible cyclisation was clearly a favoured transformation that deserved to be studied. In this letter we describe the preparation of *cis* vinylogous aminoesters with the intention of studying their possible subsequent intramolecular cyclisation into unsaturated γ- or δ-lactams **1** in optically pure form.

cis Vinylogous aminoesters **2** were prepared using a Horner reaction between the suitable phosphonate anions **4** and α- or β-*N*-(*t*-butoxycarbonylamino)-aldehydes **3** (Scheme 1). The *cis* and *trans* relative configurations of the diastereomers were deduced from their ^{1}H NMR spectra. Mainly *cis* vinylogous aminoesters were easily obtained with the lithium anion **4a** derived from ethyl(bis-ethoxyphosphinyl)-2-alcanoate. The formation of the esters proceeded with a good *cis* stereose-



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† A *cis* vinylogous aminoester is an aminoester where R[1] and H present a *cis* relationship on the double bond.

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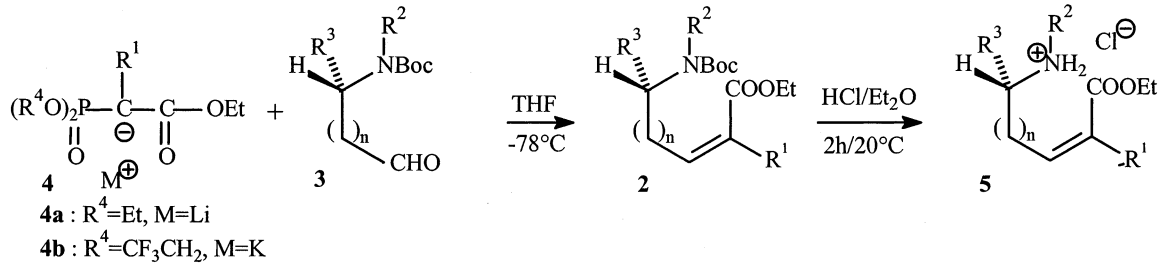
PII: S0040-4039(01)00561-5



Scheme 1.

Table 1. Results of the Horner reaction with **4** and aminoaldehydes **3** and removal of the N-Boc group to give **5**

n	R^1	R^2	R^3	**4**	**2** (yield %)	**5** (yield %)	*trans*/*cis*[a]
0	CH_3	H	CH_3	**4a**	**2a** (82)	**5a** (97)	10/90
0	Cl	H	CH_3	**4a**	**2b** (88)	**5b** (89)	2/98
0	F	H	CH_3	**4a**	**2c** (95)	**5c** (95)	<2/98[b]
1	CH_3	H	H	**4a**	**2d** (60)	**5d** (94)	40/60
1	Cl	H	H	**4a**	**2e** (90)	**5e** (90)	16/84
1	F	H	H	**4a**	**2f** (97)	**5f** (97)	<2/98[b]
0	CH_3	$-(CH_2)_3-$		**4b**	**2g** (79)	**5g** (90)	10/90
0	Cl	$-(CH_2)_3-$		**4a**	**2h** (95)	**5h** (95)	33/67
0	F	$-(CH_2)_3-$		**4a**	**2i** (92)	**5i** (92)	<2/98[b]

[a] *trans*/*cis* determined by ^1H NMR of the crude product.
[b] Only one isomer observed by ^1H and ^{13}C NMR.

lectivity. To our knowledge this olefination reactant has not yet been applied to the preparation of *cis* vinylogous aminoesters, because it was well-known to result in mostly *trans* unsaturated compounds.[7] In the case of **2g**, the steric hindrance of the pyrrolidine moiety into **3** combined with the methyl α-C substituent into **4a** (R^1 = Me) promoted the formation of the major *trans* ester. Consequently, the preparation of **2g** was accomplished with Still's reagent, potassium ethyl [bis(1,1,1-trifluoroethoxy)phosphinyl]-2-propanoate **4b** (R^1 = Me),[8] that led to the major *cis* isomer. The separation of the *cis* and *trans* stereomers was not necessary at this step to continue the strategy.[9]

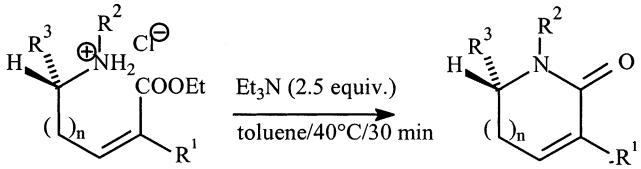
Removal of the *N*-*t*-butoxycarbonyl protecting group in vinylogous aminoesters **2** with HCl/ether yielded the corresponding chlorohydrate salts **5** without affecting the double bond, whereas we have noted that the usual conditions TFA/CH_2Cl_2 promoted the partial decomposition of the vinylogous residue (Table 1).

Addition of triethylamine (2.5 equiv.) to **5** over 30 min at 40°C in toluene provided cyclised material **1** in excellent yield (Table 2). The sole *cis* isomer **5** was converted selectively to γ- or δ-lactam **1**, whereas the minor *trans* isomer was not transformed and was entirely recovered.

The strategy allowed the obtention of unsaturated γ- and δ-lactams **1** with different substituents at the 3 or 5 positions and also allowed the preparation of unsaturated five- or six-membered lactams and bicyclic lactams with high yields.[10] No trace of intermolecular reaction products was detected, even in the case $n=2$. The mild cyclisation conditions, and the enhanced reactivity of vinylogous aminoesters **5** compared to saturated aminoesters[11,12] could be explained by the folded structure of **5**, and as a consequence, by a most favourable entropic factor.

The optical purity was determined for **1g**, the sole compound of Table 2 for which the absolute configuration was known.[5b] If it is assumed that this lactam **1g** described in Reference 5b was enantiopure, the enantiomeric excess of **1g** obtained by us from **5g** was 92% (lit.:[5b] $[\alpha]_D^{20}=+12$, $c=0.51$, $CHCl_3$, found: $[\alpha]_D^{20}=+11$, $c=1.9$, $CHCl_3$). As a consequence, the method gave the α,β-unsaturated γ-lactam **1g** in high enantiomeric

Table 2.



5 **1**

1	*n*	R^1	R^2	R^3	Yield (%)[a]	$[\alpha]_D$
1a	0	CH_3	H	CH_3	89	+132
1b	0	Cl	H	CH_3	91	+139
1c	0	F	H	CH_3	87	+141
1d	1	CH_3	H	H	94	–
1e	1	Cl	H	H	87	–
1f	1	F	H	H	90	–
1g	0	CH_3	$-(CH_2)_3-$		85	+11
1h	0	Cl	$-(CH_2)_3-$		92	–[b]
1i	0	F	$-(CH_2)_3-$		90	+6

[a] Calculated from *cis* isomer **5**.
[b] Unstable compound.

purity. This result was important because the stereochemical instability of such unsaturated γ-lactams under most reaction conditions was recently mentioned.[2,5b]

In summary, we have developed a simple enantioselective access to α,β-unsaturated lactams via a facile cyclisation of *cis* vinylogous aminoesters, which provides a versatile route to the construction of five- and six-membered ring heterocycles and substituted pyrrolams. This route can be advantageously compared to that previously described with more sophisticated methods and numerous steps.

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9. Typical procedure for the preparation of the *cis* vinylogous aminoesters **2** with the ethyl 2-diethylphosphonoalcanoate **4a**: 1.6 mL of *n*-butyllithium (2.46 mmol, 1.54 M in hexane) were added dropwise to the phosphonate **4a** (550 mg, 2.37 mmol) in THF (10 mL) with stirring at room temperature. After 20 minutes, the mixture was cooled at −78°C with stirring and aminoaldehyde **3** (2.26 mmol) in THF (10 mL) was added dropwise. After 3 hours stirring, the reaction was quenched with an aqueous saturated ammonium chloride solution (12 mL) at −78°C. The aqueous phase was extracted with diethyl ether (3×30 mL) and the combined organic phases were washed with water (2×5 mL). The organic layer was then dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford a crude product, which was purified by column chromatography on silica gel. Selected spectral data for ethyl [L-(*trans*)- and [L-(*cis*)]-4-[(*t*-butoxycarbonyl)amino]-2-methyl-2-pentenoate, **2a**: *cis* isomer: colourless oil; $R_f = 0.54$ (ethyl acetate/hexane: 1/4); $[\alpha]_D = +47$ ($c = 1.0$, $CHCl_3$). IR (KBr film) $\nu_{max} = 3360$, 1715, 1695, 1650 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.25$ (d, 3H, $^3J_{H\text{-}H} = 6.8$ Hz, CH-CH_3); 1.32 (t, 3H, $^3J_{H\text{-}H} = 7.1$ Hz, O-CH_2-CH_3); 1.43 (s, 9H, C(CH_3)$_3$); 1.90 (d, 3H, $^4J_{H\text{-}H} = 1$ Hz, CH=C-CH_3); 4.22 (q, 2H, $^3J_{H\text{-}H} = 7.1$ Hz, O-CH_2-CH_3), 4.53 (m, 1H, N*H*), 4.94 (m, 1H, -C*H*-NH-), 5.79 (d, 1H, $^3J_{H\text{-}H} = 8.6$ Hz, C*H*=C-CH_3). ^{13}C NMR

(62.9 MHz, $CDCl_3$): 14.0 (-O-CH_2-CH_3), 20.1 (CH=C-CH_3), 20.6 (CH-CH_3), 28.2 ($C(CH_3)_3$), 45.7 (NH-CH-), 60.2 (-O-CH_2-CH_3), 78.9 (-$C(CH_3)_3$), 126.7 (-CH=C-(CH_3)-, 144.5 (-CH=C(CH_3)-, 154.9 (COBoc), 167.1 (COOEt): *trans* isomer: colourless oil; $R_f = 0.50$ (ethyl acetate/hexane: 1/4); $[\alpha]_D = -12$ ($c = 0.8$, $CHCl_3$), IR (KBr film) $\nu_{max} = 3360$, 1700, 1680, 1655 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.17$ (d, 3H, $^3J_{H\text{-}H} = 6.8$ Hz, CH-CH_3); 1.24 (t, 3H, $^3J_{H\text{-}H} = 7.0$ Hz, O-CH_2-CH_3); 1.34 (s, 9H, C(CH_3)$_3$); 1.86 (s, 3H, CH=C-CH_3); 4.14 (q, 2H, $^3J_{H\text{-}H} = 6.8$ Hz, O-CH_2-CH_3), 4.46 (m, 1H, NH), 4.72 (m, 1H, -CH-NH-), 6.49 (dd, 3H, $^3J_{H\text{-}H} = 8.9$ Hz, $^4J_{H\text{-}H} = 1.3$ Hz, CH=C-CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): 12.4 (-O-CH_2-CH_3), 14.0 (CH=C-CH_3), 20.5 (CH-CH_3), 28.3 ($C(CH_3)_3$), 44.8 (NH-CH-), 60.5 (-O-CH_2-CH_3), 78.3 ($C(CH_3)_3$), 128.0 (-CH=$C(CH_3)$-), 142.7 (-CH=$C(CH_3)$-), 154.9 (COBoc), 167.9 (COOEt); MS (FAB$^+$): m/z calcd for $C_{13}H_{23}NO_4$ $[M]^+$ 257.2, found 258.2 $[[M+1]^+$, 76%], 202.2 $[[M-t\text{Bu}]^+$, 100%].

10. All new compounds exhibited spectral data consistent with their structures. Selected spectral data, 1-aza-3-cyclopentene-3-fluoro-2-one, **1c**: yellow oil; $R_f = 0.30$ (ethyl acetate); $[\alpha]_D = +141$ ($c = 0.9$, $CHCl_3$), IR (KBr) 3265, 1715, 1680, 1665 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.36$ (t, 3H, $^3J_{H\text{-}H} = 6.9$ Hz, CH_3); 4.26 (ddq, 1H, $^3J_{H\text{-}H} = 8.0$ Hz, $^3J_{H\text{-}H} = 7.9$ Hz, $^4J_{H\text{-}F} = 2.0$ Hz, -NH-CH), 6.31 (m, 1H, -CH=CF-), 7.84 (br s, 1H, -NH-). ^{13}C NMR (62.9 MHz, $CDCl_3$): 18.9 (s, -CH_3), 49.1 (d, $^3J_{C\text{-}F} = 5.8$ Hz, -NH-CH), 121.5 (d, $^2J_{C\text{-}F} = 4.5$ Hz, -CH=CF-), 152.2 (d, $^1J_{C\text{-}F} = 277.0$ Hz, -CH=CF-), 165.5 (CO). ^{19}F NMR (235.4 MHz, $CDCl_3$): −141.0 (d, $^3J_{H\text{-}F} = 4.5$ Hz). EIMS m/z 116. 04 $[MH^+]$.
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