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Amino Acid Based Diastereoselective Synthesis of Elsaminose

María Ruiz, Vicente Ojea and José Mª Quintela*

Departamento de Química Fundamental e Industrial, Facultade de Ciencias, Universidade da Coruña. Campus A Zapateira, A Coruña 15071. Spain

Abstract: Optically pure (+)-elsaminose (**2**), the amino sugar contained in the antitumour antibiotic elsamicin A, has been synthesized in eight steps (26% overall yield) from known building blocks derived from glycine, L-valine, and L-threonine. Direct and selective construction of the key intermediate **6**, with the complete backbone and the proper stereochemical configuration, is accomplished by a *syn*-aldol type reaction between lithiated Schöllkopf's bislactime ether **5** and a 1,3-dioxolane-4-carboxaldehyde (-)-**3**. Copyright © 1996 Elsevier Science Ltd

Elsamicin A (**1**) is an antitumour antibiotic structurally related to chartreusin[1]. It contains chartarin as aglycone and possesses two sugars, 6-deoxy-3-*C*-methyl-D-galactose and 2-amino-2,6-dideoxy-3-*O*-methyl-D-galactose (**2**). The presence of the amino sugar (elsaminose) makes elsamicin A remarkably water soluble and more bioactive than chartreusin.[2] In addition, elsaminose seems to play a critical role in the regulation of the biological activity of elsamicine A.[3]

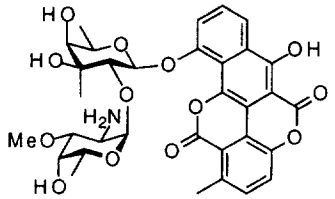
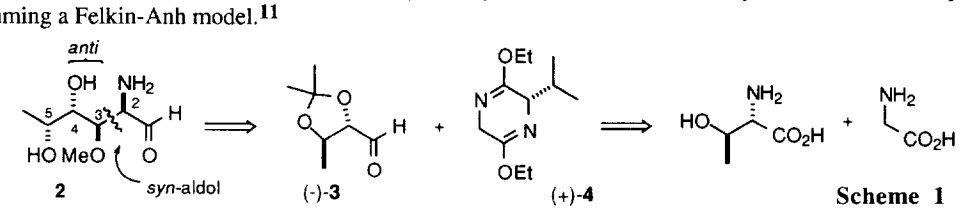


Fig. 1. Elsamicin A (**1**)

Asymmetric syntheses of several amino sugars with the 2-amino-2,6-dideoxy-D-galactose backbone have been described in the literature,[4] but, to the best of our knowledge, only a multistep, carbohydrate based synthesis of elsaminose has been reported.[5] In this communication we introduce the first convergent approach to elsaminose, based on the use of natural amino acids as chiral auxiliaries and building blocks. Thus, the amino acids glycine and L-threonine were sought as starting materials which would enable a disconnection at C2-C3 bond of elsaminose (scheme 1).[6] In this way, a direct and stereocontrolled formation of the target carbon skeleton could involve in the key step a *syn* aldol reaction [7] between a chiral glycine equivalent and a C_4-building block with the required absolute configuration at positions 4 and 5. Among various chiral glycine equivalents,[8] we found Schöllkopf's bislactim ethers [9] to be very attractive, due to the high *syn* selectivity shown by these reagents in aldol-type reactions.[10] On the other hand, the additions of nucleophiles to 1,3-dioxolane-4-carboxaldehyde systems, like **3**, generally occur with *anti* selectivity, which has been explained assuming a Felkin-Anh model.[11]

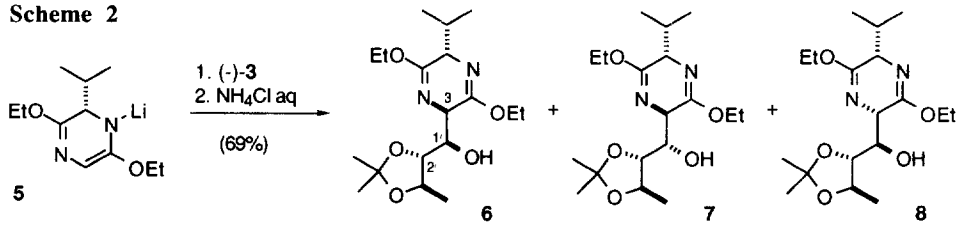


2 *syn*-aldol (-)-**3** (+)-**4** **Scheme 1**

As substrate (-)-**3** and reagent (+)-**4** would form a matched-pair, we expected the reaction of the more accessible but usually less selective lithium anion [10] to proceed with enough diasteroselection for our synthetic purpose.

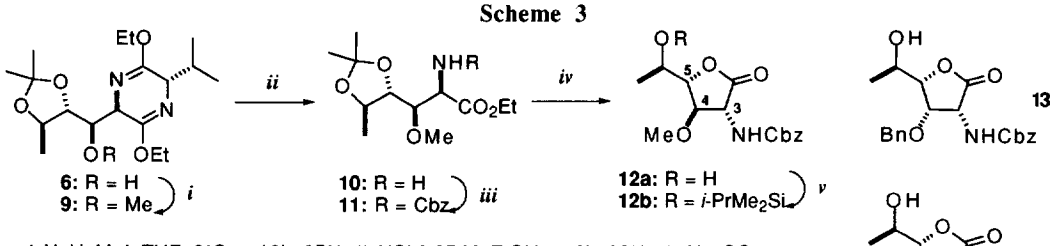
To this end, L-threonine was converted into the (4*S*)-*trans*-2,2,5-trimethyl-1,3-dioxolane-4-carboxaldehyde ((-)-**3**) according to the literature,[12] while (3*S*)-2,5-diethoxy-3-isopropyl-3,6-dihydropyrazine ((+)-**4**) was prepared from glycine and L-valine, by a slight modification of a recently reported procedure.[13] Slow addition of freshly distilled (-)-**3** [14] over a solution of 1.2 equivalents of lithium salt **5** at -78°C led (after quenching, aqueous work-up and removal of excess of (+)-**4** [15] and side products by flash chromatography) to a mixture of aldol adducts **6+7+8**, in a combined yield of 69% (see scheme 2).[16] Integration of the pairs of doublets corresponding to the isopropyl groups in the ^{1}H NMR spectrum of this mixture revealed a high asymmetric induction in the formation of both new chiral centers (the ratio **6** : **7** : **8** being *ca.* 50 : 3.3 : <1). Thus, the diastereomeric excess (*de*) of the adduct **6** over its epimers **7** and **8** was greater than 85%. However, the stereoselectivity of this reaction was found to be markedly dependent on the reaction temperature. When the addition was carried out at 0 °C a mixture of aldol products was also obtained with similar yield. Nevertheless, at this temperature, the adduct **6** was only obtained with a *de* of 50% over the adduct **8**, the secondary isomer in this case. Separation of the components of the mixtures could be achieved by medium pressure chromatography to provide products of high purity (*de* > 98%) on a multigram scale.[17]

Scheme 2



Once we had the desired adduct in our hands, it was necessary to form the methyl ether on the free hydroxy group and a partial reduction of the carboxylate group to complete the synthesis (schemes 3 and 4). Methylation was accomplished in high yield by treatment of **6** with sodium hydride and methyl iodide (THF, 0°C to rt).[18] Selective hydrolysis of the pyrazino moiety of **9** in the presence of the isopropylidene ketal yielded, after removal of the auxiliary valine ester by simple chromatography, the amino ester **10** in good yield.[19] Protection of the amino group of **10** as benzyloxycarbonyl was accomplished in almost quantitative yield under standard conditions. Hydrolysis of the isopropylidene ketal of **11** in acidic media (THF/TFA/H_2O 6:6:1, rt), led to the simultaneous formation of the desired γ-lactone **12a** in high yields. In an analogous fashion, but using benzyl ether as protecting group for the hydroxy group, the adducts **7** and **8** were transformed into the cyclic derivatives **13** and **14** with similar yields. Treatment of lactone **12a** with dimethylisopropylsilyl chloride (imidazole, THF, rt) afforded the corresponding silyl ether **12b** in excellent yield.

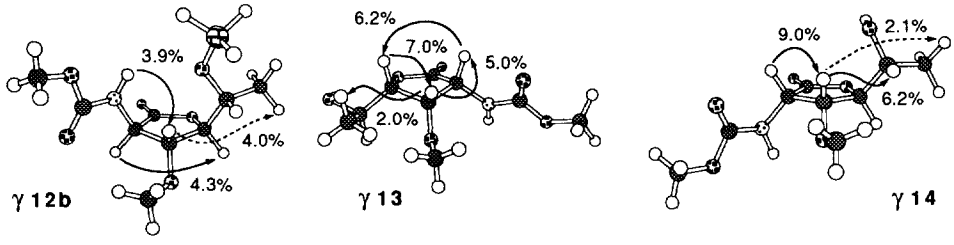
Scheme 3



i: NaH, MeI, THF, 0°C-rt, 12h, 95%. *ii*: HCl 0.25 M, EtOH, rt, 6h, 80%. *iii*: Na_2CO_3, $NaHCO_3$, BnOCOCl, dioxane:H_2O 1:1, rt, 2h, 99%. *iv*: TFA:THF:H_2O 6:6:1, rt, 3h, 87%. *v*: 1.25 eq *i*-$PrMe_2SiCl$, 2eq imidazole, THF, rt, 1h, 99%.

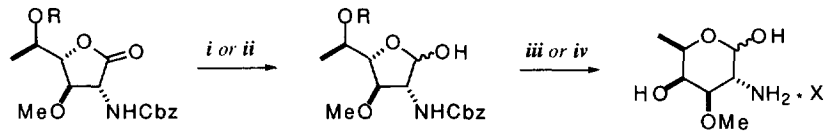
With difference to **12a**, lactones **12b**, **13** and **14** showed in the ^1H NMR spectra a pattern of signals suitable for the study of their conformation and relative stereochemistry by NOE difference spectroscopy.[20] After corroborating the ^1H NMR assignments by COSY experiments, the analysis of the sets of observed NOEs confirmed the formation of γ-lactones. In addition, the stereochemistry of lactone **12b** derived from the major aldol adduct **6**, was determined as 3,4-*trans*-4,5-*trans*, while lactones **13** and **14** showed an 3,4-*cis*-4,5-*cis* and 3,4-*cis*-4,5-*trans* configuration, respectively. These results were supported by force field and semiempirical calculations (see figure 2).[21]

Fig. 2. Chem3D [25] drawings of the PM3-optimized minimum energy conformations (MMX force field) found for models of γ-lactones **12b**, **13** and **14**, showing characteristic NOEs.[21]



Although partial reduction of **12a** followed by hydrogenation of the galactofuranoses **15a** gave rise to elsaminose with acceptable efficiency (16% yield for the seven steps), better yields were obtained starting from the fully protected lactone (scheme 4). Thus, treatment of **12b** with DIBAL-H at low temperature led to a mixture 2:1 of lactols **15b** within a combined yield of 85%. Finally, deprotection of **15b** by catalytic hydrogenation in acidic media (THF:HCl 0.25N 2:1) allowed, after ion-exchange chromatography, the isolation of the free amino sugar in excellent yield. Treatment of **2** with HCl and purification by reverse phase flash chromatography afforded elsaminose as its hydrochloride salt (**16**) in almost quantitative yield.[26]

Scheme 4



12a: R = H
12b: R = *i*-PrMe$_2$Si

15a: R = H
15b: R = *i*-PrMe$_2$Si

2: X = -
16: X = HCl

i. 2.5 eq DIBAL-H, **12a**, -78°C, toluene:THF 2:1, 6h, 43%. *ii.* 2.1 eq DIBAL-H, **12b**, -78°C, toluene:THF 2:1, 6h, 85%. *iii.* Pd/C 10%, **15a**, MeOH, Patm, rt, 6h, 86%. *iv. (a)* Pd/C 10%, **15b**, Patm, MeOH:HCl 0.25N 2:1, rt, 6h. *(b)* Dowex 50x8-200, 1% aq. NH_3. *(c)* HCl 0.25 M (pH = 2), 86%.

The present asymmetric synthesis of **2** in eight steps with 26% overall yield from easily accessible building blocks is much more efficient than the previous one,[5] and has the potential for modification to produce 2-amino-2-deoxy sugars derived from galactose and altrose in either D and L series. Attempts to extend this new methodology for the synthesis of other natural amino sugars and of bioactive 1-deoxyazasugars are currently in progress.

ACKNOWLEDGEMENTS

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13. *Cyclo*[(2*S*)-val-gly] was obtained as described by Rose *et al.* Treatment of this compound with triethyloxonium tetrafluorborate allowed the preparation of the 2,5-diethoxy pyrazine derivative. See Rose, J.E., Leeson, P.D.; Gani, D. *J. Chem. Soc. Perkin Trans 1* **1995**, 157.
14. Pure aldehyde (-)-**3** is elusive, probably due to hydration or polymerization.
15. The excess of Schöllkopf's reagent could be recovered, and showed no racemization.
16. Part of this work was presented as a poster communication to the *8th European Carbohydrate Symposium*, Sevilla, Spain. 2-7 July 1995.
17. Evidence supporting the stereochemical assignments was obtained by NMR analysis (^{1}H, ^{13}C, COSY and ^{1}H NOE difference spectroscopy) of cyclic derivatives (compounds **12b**, **13** and **14**). Absolute configurations follow from the use of (-)-**3**, as there is precedent.[12]
18. Attempts to obtain **9** by quenching the aldol reaction with methyl iodide were unsuccessful. After 24 h at rt and aqueous work-up, only traces of methylated adduct were isolated, along with the adduct **6**.
19. Prolonged reaction times or the use of ethers as solvent resulted in a complete hydrolysis to the corresponding 2-amino-4,5-dihydroxy acid, isolated in low yields. Lactonization of this compound was not efficiently achieved.
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21. Minimum energy conformations for models of all possible γ- and δ-lactones derived from adducts **6**, **7** and **8** (with the alkyl chain of the alcoxy and silyl ether groups reduced to methyl and proton, respectively) were located using MMX force field as implemented in PCModel v5.[22] The geometries of the most important conformers were fully optimized by semiempirical molecular orbital calculations, using the MNDO, AM1 and PM3 Hamiltonians [23] included in MOPAC 93.[24] The refined geometries in the gas phase were in agreement with the conformations in solution deduced from ^{1}H NOE spectroscopy. All models of γ-lactones showed lower heats of formation than the corresponding δ-isomers (the differences in ΔH^0(PM3) being higher than 3 Kcal/mol). For lactones **12b** and **14**, rotamers (within 0.7 and 1.1 Kcal/mol of the global minimum, according to PM3 method) can better account for the observed NOEs between methyl groups and protons on C4, showed with dashed arrows in figure 2 and characteristic for the γ-lactones.
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26. Spectral data for hydrochloride sat of elsaminose (**16**): $[\alpha]^{22}_D$ + 92.1 (c 0.6, H_2O) (lit.[5] $[\alpha]_D$ + 85.3 (c 1.1, H_2O). α-anomer: ^{1}H NMR (500 MHz, D_2O) δ 1.01 (d, 3H, *J* = 6.6 Hz, C<u>H</u>$_3$CH), 3.21 (dd, 1H, *J* = 11.0, 3.8 Hz, H-2), 3.22 (s, 3H, OCH_3), 3.54 (dd, 1H, *J* = 11.0, 3.0 Hz, H-3), 3.91 (d, 1H, *J* = 3.0 Hz, H-4), 4.00 (q, 1H, *J* = 6.6 Hz, H-5), 5.17 (d, 1H, *J* = 3.8 Hz, H-1); ^{13}C NMR (125 MHz, D_2O) δ 16.6 (C-6), 50.9 (C-2), 56.8 (OCH_3), 67.0 (C-4), 67.4 (C-3), 76.5 (C-3), 90.2 (C-1). β-anomer: ^{1}H NMR (500 MHz, D_2O) δ 1.06 (d, 3H, *J* = 6.4 Hz, C<u>H</u>$_3$CH), 2.90 (dd, 1H, *J* = 11.0, 8.6 Hz, H-2), 3.22 (s, 3H, OCH_3), 3.35 (dd, 1H, *J* = 11.0, 3.0 Hz, H-3), 3.60 (q, 1H, *J* = 6.4 Hz, H-5), 3.87 (d, 1H, *J* = 3.0 Hz, H-4), 4.63 (d, 1H, *J* = 8.6 Hz, H-1); ^{13}C NMR (125 MHz, D_2O) δ 16.7 (C-6), 54.1 (C-2), 57.1 (OCH_3), 66.4 (C-4), 72.3 (C-5), 79.4 (C-3), 94.0 (C-1).

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