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TETRAHEDRON: *ASYMMETRY*

Synthesis of enantiomerically pure (3*R*,4*R*,5*R*)-4-hydroxy isoleucine lactone

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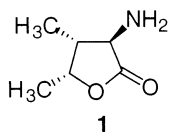
Abstract—A short four-step synthesis of (3*R*,4*R*,5*R*)-4-hydroxyisoleucine lactone with total control of stereochemistry is reported, the key intermediate being the didehydroamino acid derivative arising from an aldol dehydration reaction between a glycine anion equivalent and butan-2,3-dione. © 2001 Published by Elsevier Science Ltd.

1. Introduction

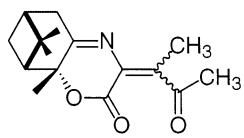
4-Hydroxyisoleucine was first isolated as a new amino acid lactone from γ-aminitin hydrolysate[1] and later from ε-amanitin.[2] In 1973, Fowden et al.[3] reported the isolation and identification of free 4-hydroxyisoleucine from the seeds of fenugreck, *Trigonella foenum-graecum* L (Leguminosae). Their results suggested that the 4-hydroxyisoleucine in fenugreck and in γ-amanitin have the same absolute configurations at the three stereogenic centers. Gieren et al.[4] had correctly determined the configurations which were (2*S*,3*R*,4*S*); this result was confirmed by Alcock[5] who carried out an X-ray crystal structure of 4-hydroxyisoleucine. In fenugreck (2*R*,3*R*,4*S*)-4-hydroxyisoleucine is also present as a minor component. Dardenne et al.[6] reported the presence of the same isomer in fruit bodies of *Lactarius camphoratus*. Ribes et al.[7] showed that (2*S*,3*R*,4*S*)-4-hydroxy isoleucine extracted from fenugreck seeds known for its anti-diabetic properties in traditional medicine was an insulinostimulant compound which could be used in diabetes mellitus treatment. Few stereoselective synthesis of 4-hydroxy isoleucine have been reported in the literature, including the enantioselective synthesis of the (3*R*,4*R*,5*R*)- and the (3*R*,4*S*,5*S*)-lactone diastereomers by Schöllkopf[8] using a reaction between a chiral glycine anion equivalent and epoxybutane. However the stereochemical assignment of the (3*R*,4*R*,5*R*)-lactone was erroneous as demonstrated by Fredj et al.,[9] who achieved the enantiospecific synthesis of the (3*R*,4*R*,5*R*)- and (3*S*,4*R*,5*R*)-diastereomers starting from benzyl-2,3-anhydro-4-*O*-(*tert*-butyldimethylsilyl)-β-L-ribopyranoside.

2. Results

We report here a new approach to the enantioselective synthesis of (3*R*,4*R*,5*R*)-4-hydroxy isoleucine lactone **1** via the chiral didehydroamino acid **2**, whose hydrogenation of the double bond will allow the control of the stereochemistry at carbons 3 and 4; configuration of the C-4 induced control of the stereochemistry at C-5, after reduction of the corresponding ketone.



1



2

We have prepared numerous enantiomerically pure α-amino acids[10] using 2-hydroxypinan-3-one[11] or the derived oxazinone as the chiral auxiliary.[12] We have found that the potassium enolate prepared from this oxazinone rapidly reacted with aldehydes to afford the didehydro compound directly in excellent yields.

The first step of this strategy was the reaction of the potassium enolate prepared from **3**, using KHMDS as base, with butan-2,3-dione which afforded the alcohol **4** in 51% yield after purification on silica gel and not the

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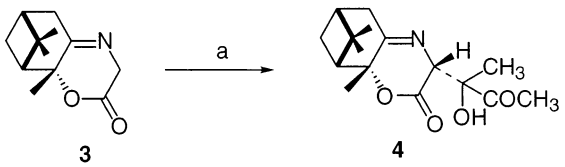
didehydro compound **2** as expected (Scheme 1). It is well known that secondary alcohols are much more prone to E_2 elimination than tertiary alcohols. Two diastereomers (d.r. 60/40) were detected by ^1H NMR (possibility of four isomers) and separated by chromatography on silica gel.

The major isomer **4a** was crystallized, its structure established by X-ray crystal structure determination[13] and the configurations (2*R*,3*S*) were assigned. As expected, the electrophile approaches the enolate on the face opposite to the *gem* dimethyl group inducing the *R* configuration on the C-2. For C-3, the symmetry of the diketone explains the poor stereoselectivity, the major isomer **4a** arising from the (*Re*,*Si*) approach, the minor **4b** from the (*Re*,*Re*) approach. The dehydration step afforded the didehydro compound **2** in 75% yield using di-*tert*-butyl dicarbonate in the presence of dimethylaminopyridine[14] (Scheme 2).

Two isomers *E*/*Z* (80/20) were obtained; interconversion of these two compounds was easy at room temperature under irradiation, but we were unable to transform completely and cleanly the *E* isomer into the *Z* isomer or vice versa. The dehydro compound **2** was obtained in 36% yield directly by reaction of the potassium enolate prepared from **3** in the presence of $TiCl(O^iPr)_3$ on butan-2,3-dione.

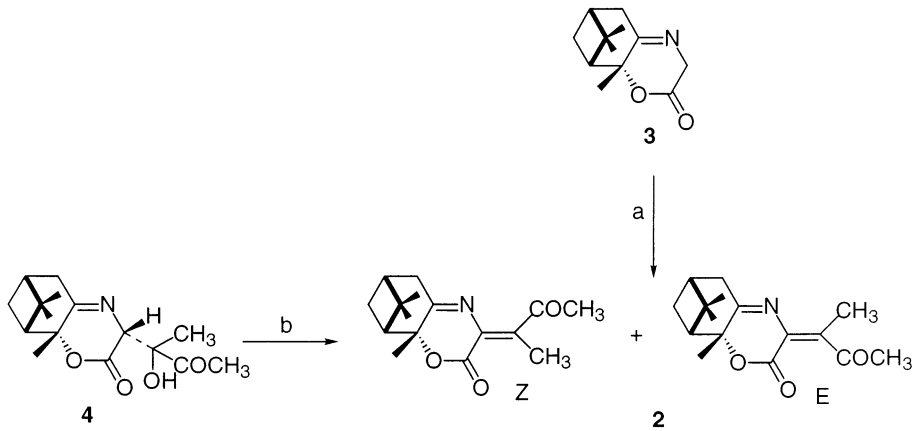


Scheme 1. *Reagents and conditions*: (a) (1) KHMDS (1.1 equiv., 0.5 M in toluene), THF, −78°C, 30 min, (2) $CH_3COCOCH_3$ (1.1 equiv.), **4**, d.r. 60/40, 51%.

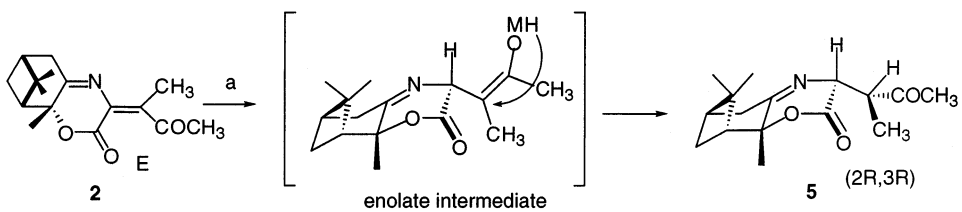
Catalytic reduction of the double bond of the *Z*/*E* isomer mixture was performed at atmospheric pressure of H_2 in ethanol, using 10% $Pd(OH)_2/C$ as catalyst providing compound **5** in 64% yield; only one diastereomer was detected whose configurations (2*R*,3*R*) were assigned after an X-ray crystal structure determination[13] (Scheme 3). The two diastereoisomers were separated by column chromatography and hydrogenated. The major *E* isomer afforded after purification the (2*R*,3*R*)-isomer **5** in 75% yield and the over-hydrogenated product arising from the hydrogenation of the two double bonds C=C and C=N in 12% yield. Starting from minor *Z* isomer, the reaction was more sluggish and led to the (2*R*,3*R*)-isomer in 45% yield and the over-hydrogenated product in 9% yield.

In such catalytic reductions, a stereoselective *syn* hydrogenation process is generally expected. However only the minor *Z* stereoisomer would lead to the (2*R*,3*R*) isomer **5** by a *syn* addition.[15] The production of the (2*R*,3*R*)-isomer **5** from the *E* isomer could be explained by a *syn* addition if the *E* isomer is transformed into the *Z* isomer during the reduction or by an *anti* addition.

An attractive hypothesis has sometimes been advanced to explain such results (*anti* addition) with diester



Scheme 2. *Reagents and conditions*: (a) (1) KHMDS (1.1 equiv., 0.5 M in toluene), THF, −78°C, 30 min, (2) $TiCl(O^iPr)_3$ (1.1 equiv.), −78°C, (3) $CH_3COCOCH_3$ (1.1 equiv.), **2**, 36%; (b) BOC_2O (2.5 equiv.), DMAP (1.3 equiv.), CH_2Cl_2, rt, 12 h, **2**, 75%.



Scheme 3. *Reagents and conditions*: (a) $Pd(OH)_2/C$, EtOH, rt, **5**, 64%.

substrates[16] and enaminoesters.[17] In our case it would involve the formation of an enolate intermediate by addition of an MH_2 equivalent on the enone double bond. The chiral auxiliary would favor the addition on the face of the *gem* dimethyl group leading to an *R* configuration for this center. Scheme 3 represents the more-favored transition-state structure; stereoselective protonation on the less-crowded face would lead to the *R* configuration. It should be noted that the hydrogen atom for the last protonation may arise from the catalyst surface or protic solvent.

Reduction of the ketone using L-Selectride® afforded, quantitatively, alcohol **6** in a diastereomerically pure form; the *R* configuration was assigned to C-4 after an X-ray crystallographic study. This result could be explained by assuming a chelation of the metal with the two carbonyl groups or more probably with the ketone and the sp^2-hybridized nitrogen and attack of the hydride on the opposite side of the methyl group on C-3. Cleavage of the chiral auxiliary using anhydrous HF yielded (3*R*,4*R*,5*R*)-lactone hydrofluoride in 55% yield (Scheme 4).

3. Conclusion

We have described a new enantioselective synthesis of (3*R*,4*R*,5*R*)-4-hydroxy isoleucine lactone in five (or four steps) and 14% overall yield starting from the oxazinone **3**. This strategy could be applied to the obtention of the (3*S*,4*S*,5*S*)-enantiomer starting from *S* oxazinone. Further, various structural analogues of **1** can be prepared by simple variation of the electrophile (α-diketones or α-ketoesters).

4. Experimental

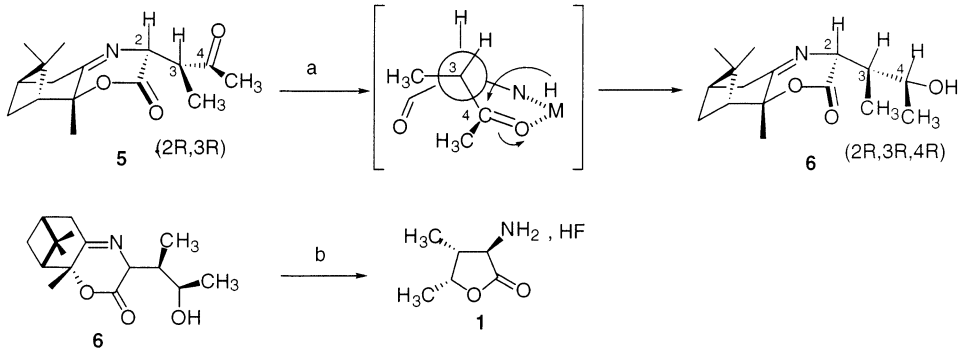
Melting points were obtained using a Büchi 510 capillary apparatus and are uncorrected. Infrared spectra were recorded using a Perkin–Elmer Fourier-transform spectrometer. ^{1}H NMR spectra were recorded at 250 MHz using a Brüker AC250 instrument. For ^{1}H NMR spectra recorded in $CDCl_3$ chemical shifts are quoted in parts per million and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Coupling constants are reported in Hertz (Hz). Diastereoisomeric ratio (d.r.) were determined by ^{1}H NMR on the crude product. Low resolution mass spectra were recorded on micromass electrospray instrument with only molecular ion and other major peaks being reported. Flash chromatography was carried out using E. Merck Silica Gel (Kieselgel 60, 230–400 mesh) as stationary phase. Thin layer chromatography was carried out on aluminium plates pre-coated with Merck Silicagel 60F254 and were visualized by quenching of UV fluorescence or by staining with a 10% methanol phosphomolybdic acid solution followed by heat. THF was distilled from sodium/benzophenone ketyl. Reagents were supplied from commercial sources (ALDRICH, FLUKA). The oxazinone **3** was prepared as previously described.[3]

4.1. Reaction of the oxazinone with butan-2,3-dione

The oxazinone (0.2 g, 0.97 mmol) was added to a magnetically stirred solution of potassium bis(trimethylsilyl)amide (KHMDS) 0.5 M in toluene (2.12 ml, 1.06 mmol) in dry THF (5 ml), under argon at −78°C. The mixture was stirred for 30 min at −78°C. After addition of butane-2,3-dione (1.06 mmol, 1.1 equiv.), the mixture was stirred at −78°C the reaction being monitored by TLC. The mixture was poured into a solution of NH_4Cl (5 ml) and extracted with Et_2O (3×15 ml). The extracts were dried over $MgSO_4$. After filtration and removal of the solvent under reduced pressure the residue was purified by flash column chromatography to afford the desired product. Elution with petroleum ether/AcOEt: 60/40 gave two diastereoisomers **4a** and **4b** (0.146 g, 51%) as an oil. Compound **4a** crystallized in ether at rt. MS ESI >0: 294 (M+H), 316 (M+Na); IR (film): 2931, 1740, 1703, 1616.

4a (major diastereoisomer): R_f=0.61 (hexane/AcOEt: 60/40); mp 102–104°C; ^{1}H NMR ($CDCl_3$): δ 4.60 (dd, 1H, J=3.6 Hz, J=2.8 Hz), 3.45 (br, 1H, OH), 2.92–2.85 (m, 2H), 2.43 (s), 2.41–2.10 (m, 3H), 1.67 (s, 3H), 1.58 (s, 3H), 1.42 (s, 3H), 1.18 (d, 1H, J=11.2 Hz), 1.08 (s, 3H).

4b (minor diastereoisomer): R_f=0.68 (hexane/AcOEt: 60/40); ^{1}H NMR ($CDCl_3$): δ 4.15 (dd, 1H, J=3.9 Hz,



Scheme 4. *Reagents and conditions*: (a) L-Selectride® (1.1 equiv.)=M: [B(CH(CH$_3$)C$_2$H$_5$)$_3$]Li, −78°C, 1 h, **6**, quant.; (b) HF, 0°C, 1 h, **1**, 55%.

$J=2.5$ Hz), 2.92–2.74 (m, 2H), 2.28 (s, 3H), 2.41–2.10 (m, 3H), 1.69 (s, 3H), 1.62 (s, 3H), 1.42 (s, 3H), 1.18 (d, 1H, $J=11.2$ Hz), 1.08 (s, 3H).

4.2. α,β-Didehydroamino acid derivative 2

To a solution of a mixture of alcohol **4** (0.68 mmol) in dry dichloromethane (700 μl) was added DMAP (0.88 mmol) followed by di-*tert*-butydicarbonate (1.70 mmol) under rapid stirring at rt. The reaction monitored by TLC was left for 12 h. Evaporation under reduced pressure gave a residue that was partitioned between ethyl ether 20 ml and citric acid 15% (10 ml). The organic phase was dried over $MgSO_4$. Removal of the solvent followed by purification by flash chromatography afforded product **2**. Elution with petroleum ether/AcOEt: 80/20 gave two isomers **2a** and **2b** (0.140 g, 74%) as an oil. Compound **2a** crystallized in ether at rt. E/Z: 80/20. MS ESI >0: 276 (M+H), 298 (M+Na).

2a (major isomer): $R_f=0.47$ (hexane/AcOEt: 70/30), mp 130–132°C; ^{1}H NMR ($CDCl_3$): δ 2.81 (AB syst., 2H, $J=18.4$ Hz), 2.36 (s, 3H), 2.35–2.32 (m, 1H), 2.15–2.09 (m, 2H), 2.08 (s, 3H), 1.52 (s, 3H), 1.31 (s, 3H), 1.14 (d, 1H, $J=11.3$ Hz), 1.02 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 205.2, 173.7, 164.0, 145.1, 85.2, 49.7, 40.1, 39.5, 37.5, 28.9, 28.4, 27.8, 24.5, 23.4, 15.7.

2b (minor isomer): $R_f=0.65$ (hexane/AcOEt: 70/30); ^{1}H NMR ($CDCl_3$): δ 2.81 (AB syst., 2H, $J=18.4$ Hz), 2.51 (s, 3H), 2.50–2.39 (m, 1H), 2.25 (s, 3H), 2.24–2.19 (m, 2H), 1.50 (s, 3H), 1.31 (s, 3H), 1.14 (d, 1H, $J=11.3$ Hz), 1.01 (s, 3H).

4.3. Hydrogenation of the α,β-didehydroamino acid derivative 2

A solution of compound **2** (0.24 mmol) in ethanol (9 ml) was hydrogenated with 10% palladium hydroxide on charcoal (90 mg) and the reaction followed by TLC. When the reaction was finished, the catalyst was removed by filtration and the filtrate was evaporated to dryness to afford the corresponding α-amino acid derivative **5** as a single diastereoisomer (^{1}H NMR). Purification of the residue by flash chromatography (eluent: petroleum ether/AcOEt: 80/20) gave an analytically pure sample of compound **5** (0.130 g, 64%) which crystallized in ether at rt. MS ESI >0: 278 (M+H), 300 (M+Na); $R_f=0.42$ (petroleum ether/AcOEt: 7/3); mp 109–111°C; ^{1}H NMR ($CDCl_3$): δ 4.43 (ddd, 1H, $J=7.6$ Hz, 4.1 Hz, 2.5 Hz), 3.10 (q, 1H, $J=7.3$ Hz), 2.72 (AB syst., 2H, $J=17.6$ Hz), 2.27–2.08 (m, 3H), 2.25 (s, 3H), 1.58 (s, 3H), 1.32 (s, 3H), 1.23 (d, 3H, $J=7.3$ Hz), 1.05 (d, 1H, $J=11.2$ Hz), 0.98 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 211.4, 173.2, 172.8, 86.2, 61.7, 50.7, 48.7, 38.9, 37.5, 29.9, 27.5, 27.4, 23.3, 22.1, 14.2.

4.4. Reduction of compound 5 promoted by L-Selectride®

To a magnetically stirred solution of compound **5** (0.23 mmol) in dry THF (5 ml) was added 1.0 M solution of L-Selectride® in dry THF (0.25 mmol, 0.25 ml) under argon at −78°C. After 1 h at −78°C the mixture was quenched with saturated aqueous NH_4Cl solution (5 ml) and the mixture extracted with diethylether (20 ml). The combined organic layers were washed with H_2O and dried ($MgSO_4$). The ether was evaporated under reduced pressure to give an oil which crystallized in diethylether. MS ESI >0: 280 (M+H); $R_f=0.22$ (petroleum ether/AcOEt: 7/3); mp 144–146°C; ^{1}H NMR ($CDCl_3$): δ 4.79–4.67 (br, 1H), 4.18–4.11 (m, 2H), 2.72 (AB syst., 2H, $J=17.7$ Hz), 2.39–2.28 (m, 2H), 2.15–2.13 (m, 1H), 2.11–2.03 (m, 1H), 1.51 (s, 3H), 1.32 (s, 3H), 1.17 (d, 3H, $J=6.4$ Hz), 1.08 (d, 1H, $J=11.3$ Hz), 0.99 (s, 3H), 0.83 (d, 3H, $J=6.9$ Hz); ^{13}C NMR ($CDCl_3$): δ 174.1, 170.9, 85.3, 72.0, 64.8, 50.6, 40.2, 39.6, 39.5, 37.4, 30.1, 28.2, 27.8, 23.4, 27.7, 21.6, 6.9.

4.5. (3*R*,4*R*,5*R*)-4-Hydroxyisoleucine lactone

To compound **6** (0.28 mmol) was added anhydrous HF (2–3 ml) at 0°C. The mixture was stirred at 0°C for 1 h. The solution was extracted with ether and the amino acid lactone **1** partially precipitated (0.023 g, 55%). MS ESI >0: 130 (M−HF+H); mp 214–216°C; $[\alpha]_{20}^{D}=+51.2$ (*c* 0.43, MeOH); ^{1}H NMR (D_2O): δ 4.87 (dq, $J=7.0$ Hz, 6.8 Hz), 4.09 (d, 1H, $J=11.8$ Hz), 2.79 (ddq, $J=11.8$ Hz, 7.0 Hz, 6.9 Hz), 1.28 (d, 3H, $J=6.8$ Hz), 1.11 (d, 3H, $J=6.9$ Hz); ^{13}C NMR (D_2O): δ 173.9, 80.6, 53.7, 37.7, 15.0, 11.3.

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