Pergamon

Tetrahedron Letters 43 (2002) 3919–3922

TETRAHEDRON LETTERS

Memory of chirality effects in aldol cyclisations of 1-(3-oxobutyryl) derivatives of L-4-oxaproline and L-proline isopropyl esters

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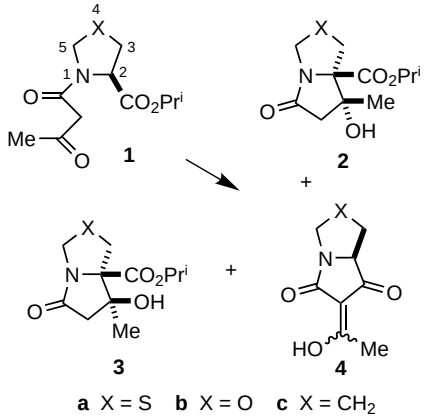
Received 7 March 2002; accepted 28 March 2002

Abstract—Stereoretentive C–C bond formations are features of the aldol cyclisations of the 1-(3-oxobutyryl) derivatives of L-4-oxaproline and L-proline isopropyl esters, consistent with the involvement of axially chiral enolate intermediates. © 2002 Elsevier Science Ltd. All rights reserved.

Because of the wide-ranging biological properties of both natural and unnatural representatives, α-*C*-substituted α-amino acids have attracted a great deal of synthetic attention.[1–5] A powerful route, pioneered by Seebach and referred to as the self-regeneration of stereocentres,[1] enables enantiopure α-*C*-substituted α-amino acids to be elaborated from readily available enantiopure α-amino acids. The process requires four operations. Initially, the α-amino acid substrate is modified with the formation of a second stereogenic centre (in a directed manner) within a new ring. In the next operation, the original α-amino acid stereocentre is destroyed in a deprotonation reaction leading to an enolate intermediate. In the third operation, a new α-amino acid stereocentre is generated by interception of the enolate with a *C*-electrophile (in a directed manner). Finally, the initially established stereocentre and ring are destructively removed. The Seebach methodology has been applied to numerous α-amino acids; although there are a few examples of intramolecular interception reactions (involving L-serine scaffolds),[6,7] the vast majority involve intermolecular processes.[1]

The possibility that the self-generation of stereocentres could be streamlined (obviating the need to generate a second stereogenic centre within a new ring) was foreshadowed by Seebach when a 'chiral memory effect' was observed in the α-alkylation of an L-aspartic acid derivative.[8] Subsequently, Fuji's group and that of the senior author noted further examples. Fuji's effects were observed in intermolecular α-*C*-substitution reactions.[9,10] Our effects were encountered in intramolecular α-*C*-substitution reactions[11] (although they were first noted in intramolecular α-*N*-substitution processes[12,13]).



Scheme 1.

Keywords: aldol reactions; amino acid derivatives; asymmetric induction; oxazolidines; pyrrolidines; pyrrolinones.

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PII: S0040-4039(02)00632-9

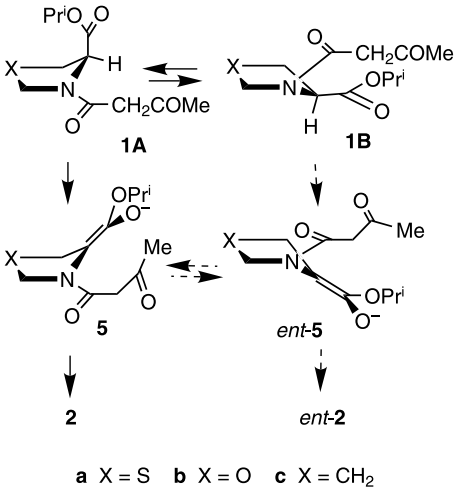
We had found[11] (Scheme 1) that the L-thiaproline **1a** was converted [KCN (150 mol%), MeOH, 2 h] into a 72:28 mixture of the aldol products **2a** and **3a** (68% yield; e.e.s 99%); a small amount of the acylation product **4a** was also formed. To account for the stereoselection, we postulated that planar ester enolate intermediates possessing chiral axes intervened; for example, the species **5a** (arbitrary enolate geometry) was considered to be involved in the **1a**→**2a** cyclisation (Scheme 2). The marked kinetic preference for the generation of the enolate **5a** was attributed to the ease with which the reactant **1a** could adopt the geometry **1Aa** required for the deprotonation reaction (the generation of *ent*-**5a** and thence *ent*-**2a** would require taking up the geometry **1Ba**, possessing a severe $A^{1,3}$ interaction between the *N*-acyl and CO_2Pr^i groups).[14] In the hope of broadening the scope of such stereoinductions, we have studied the reactivities of the L-oxaproline **1b** and the L-proline **1c**. We now present our findings.

Initially, the L-oxaproline **1b** was synthesised as outlined in Scheme 3. Thus, L-serine **6** was transformed into its isopropyl ester hydrochloride **7**[15] (93% yield) which, under conditions described by Schöllkopf,[16] gave L-oxaproline isopropyl ester **8**. Without purification, the last-cited material was subjected to *N*-acetoacetylation conditions; following chromatography, compound **1b**,[17] $[\alpha]_D$ −94 (*c* 2.4, CH_2Cl_2), was isolated in 24% yield (based on **7**).

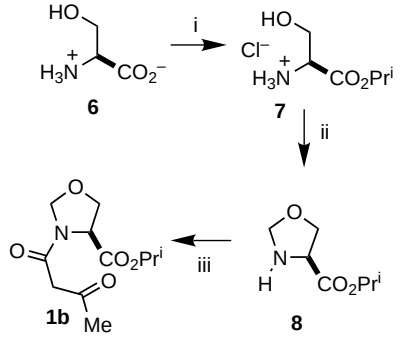
Under basic conditions [KCN (150 mol%), MeOH, 2 h], compound **1b** was transformed into mainly a 75:25 mixture of the aldol products **2b** and **3b** (Scheme 1); none of the acylation product **4b** was detected. After chromatography, a 75:25 mixture of compounds **2b** and **3b**, $[\alpha]_D$ −27 (*c* 0.62, CH_2Cl_2), was isolated in 27% yield.

Since efforts to determine the e.e.s of the aldols **2b** and **3b** by HPLC were unproductive, derivatisation studies were undertaken (Scheme 4). Based on the earlier observation that the alcohols **2a** and **3a** could be transformed into a common dehydration product **9a**,[11] attention was directed at the generation of the alkene **9b**. An acetylation–elimination sequence delivered the alkene **9b**[18] (84% yield after chromatography), mp 33°C, $[\alpha]_D$ +184 (*c* 0.52, CH_2Cl_2). The enantiomers of *rac*-**9b** (prepared from *rac*-**6**) were readily separated by HPLC,[19] enabling the e.e. of the optically active material to be assessed at 96%. Clearly, the C–C bond-forming reactions involved in the **1b**→**2b**/**3b** conversion display selectivities of ~98:2. The specific rotation of the alkene **9b** was similar in sign and magnitude to that of its thia analogue **9a** {$[\alpha]_D$ +215 (*c* 0.41, CH_2Cl_2)}, supporting the notion that the compounds shared a common absolute configuration. Since the absolute stereochemistry of the aldol **2a** had been established by X-ray crystallography,[11] we infer that a retention of configuration is involved in the **1b**→**2b**/**3b** transformation.

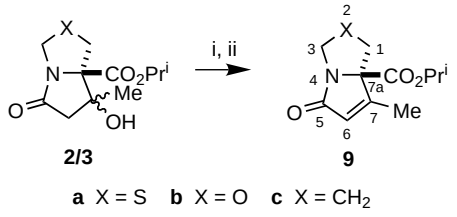
An improvement in the overall yield of the **7**→**2b**/**3b** transformation was sought. When the reaction of the serine isopropyl ester **7** with formaldehyde was conducted under neutral conditions and the crude product was subjected to the *N*-acetoacetylation reaction, the oxaproline **1b** was isolated in 50% yield after chromatography; in the presence of aqueous potassium carbonate, compound **1b** was cleanly converted into the aldols **2b**/**3b** in 63% yield.[20] The derived alkene **9b** showed an e.e. of 95%, indicating that the modified conditions had resulted in no significant loss in stereoselectivity.



Scheme 2.



Scheme 3. *Reagents and conditions*: (i) Pr^iOH, HCl, reflux, 12 h; (ii) 37% H_2CO (100 mol%), CH_2Cl_2–0.1 M aq. CF_3CO_2H (1:1), 0°C, 5 h; (iii) diketene (100 mol%), Et_3N (catalytic amount), CH_2Cl_2, reflux, 6 h.



Scheme 4. *Reagents and conditions*: (i) Ac_2O–pyridine (1:1), 4-dimethylaminopyridine (catalytic amount), 15 h (for X = O) and Ac_2O–60% aq. $HClO_4$ (3:1), 4 h (for X = CH_2); (ii) 1,5-diazabicyclo[4.3.0]non-5-ene (200 mol%), CH_2Cl_2, reflux, 6 h.

Subjection of L-proline to the action of diketene (100 mol%) and triethylamine (catalytic amount) in dichloromethane (reflux, 12 h) and esterification of the product (Pr^iOH, HCl, reflux, 4 h) gave compound **1c**[17] (75% yield after chromatography), $[\alpha]_D$ −88 (*c* 0.8, CH_2Cl_2). Under the usual basic conditions [KCN (150 mol%), MeOH], the proline **1c** was converted into its transesterification product which slowly cyclised to give, after acidification, mainly the acylation product **4c** (earlier, the acylation product **4a** predominated in the corresponding reaction of the methyl ester counterpart of **1a**[11]). However, when heated under reflux for 24 h with isopropyl alcohol and potassium cyanide (300 mol%), cyclisation occurred to give mainly a 55:19:26 mixture of compounds **2c**, **3c** and **4c** (Scheme 1). After chromatography, a 75:25 mixture of the aldols **2c** and **3c**, $[\alpha]_D$ −37 (*c* 0.38, CH_2Cl_2), with e.e.s of 87%[21] was isolated in 35% yield.

The alcohols **2c**/**3c** were transformed into the bicyclic alkene **9c**[22] (51% yield after chromatography), $[\alpha]_D$ +124 (*c* 0.52, CH_2Cl_2), by an acetylation–elimination sequence (Scheme 4). Again, the reasonably high positive specific rotation of the alkene **9c** provided support for the absolute stereochemical assignment. Once more, it is inferred that the C–C bond formations involved in the **1c**→**2c**/**3c** conversion, which display selectivities of ~94:6, occur with predominant retention of configuration.

Clearly, the enolate intermediates involved in the **1b**→**2b**/**3b** and **1c**→**2c**/**3c** conversions are imprinted with stereochemical memories of the reactants. We attribute the imprints to the axially chiral nature of the enolates, e.g. **5b** and **5c** (Scheme 2). The greater loss in stereochemical integrity noted in the L-proline-derived aldols **2c** and **3c** may be ascribed to the harsher conditions needed to effect the cyclisations; presumably, this is a reflection of the reduced acidity of the 2-proton of the precursor **1c** (caused by the S/O→CH_2 replacement).

The aforecited results are of note in the following respects. The finding that stereoretentive aldol cyclisations can be conducted on oxaproline and proline scaffolds significantly extends the scope of stereoinductions attributable to axially chiral enolate intermediates. Compounds **2b**/**3b** and **2c**/**3c** are interesting examples of enantioenriched α-*C*-substituted α-amino units embedded in heterocyclic frameworks.

During the course of the work, memory of chirality effects involving α-amino acid derivatives have been observed in photocylisations,[23,24] oxidative decarboxylations[25] and enolate alkylations.[26,27] With other substrates, they have been noted in electron-transfer[28] and radical reactions.[29]

Acknowledgements

Research grants from the EPSRC (GR/L52246, GR/L3439 and GR/M16054/01) and the Link Asymmetric Synthesis Programme are gratefully acknowledged. Thanks are also due to Dr. C. M. Raynor (UMIST) for carrying out the HPLC analyses.

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17. Like the methyl ester relative of compound **1a** (see Ref. 12), this compound existed (in $CDCl_3$ at ~25°C) as a mixture of keto and enol tautomers, each as a mixture of rotamers.
18. Data for compound **9b**: ν_{max} (film)/cm^{-1} inter alia 1725 (ester and pyrrolinone C=O) and 1635 (C=C); δ_H (400 MHz; $CDCl_3$) 1.30 and 1.31 (each 3H, d, *J* 6.5 Hz, Me_2CH), 2.12 (3H, d, *J* 1.5 Hz, 7-Me), 3.67 and 4.37 (each 1H, d, *J* 8.5 Hz, 1-H_2), 4.54 and 5.24 (each 1H, d, *J* 5.5 Hz, 3-H_2), 5.14 (1H, sept, *J* 6.5 Hz, $CHMe_2$) and 5.84 (1H, apparent d, separation 1 Hz, 6-H); δ_C (100 MHz; $CDCl_3$) 14.6 (CH_3), 20.4 and 21.3 [$(CH_3)_2CH$], 69.4 (1-CH_2), 70.1 (OCH), 77.6 (3-CH_2), 123.5 (6-C), 161.5 (7-C), 167.9 (ester CO) and 177.9 (5-CO) [presumably, the 7a-C signal was masked by either the 3-CH_2 signal or one of the $CDCl_3$ signals (in the case of **9a**, the 7a-C signal appeared at δ 83.3)]; *m*/*z* (FAB) 226 (MH^+,

45%), 73 (80), 55 (90) and 43 (100). Found: C, 58.9; H, 6.8; N, 6.2. $C_{11}H_{15}NO_4$ requires C, 58.7; H, 6.7; N, 6.2%.

19. The enantiomers were separated on a Chiralpak AD column, using hexanes–ethanol (9:1) as eluent (flow rate: 1 cm^3 min^{-1}; retention times: 12.3 min for **2b** and 15.0 min for *ent*-**2b**).
20. Aqueous sodium hydroxide [prepared by dissolving NaOH (1.42 g, 35.4 mmol) in H_2O (200 cm^3)] was ice cooled and added in one portion to a stirred ice-cooled slurry of L-serine isopropyl ester hydrochloride **7** (6.50 g, 35.4 mmol) in dichloromethane (350 cm^3). Ice-cooled aq. formaldehyde [prepared by diluting 37% HCHO (2.88 cm^3, 35.4 mmol) with H_2O (150 cm^3)] was then added in drops over 15 min to the stirred ice-cooled mixture. The mixture was stirred for 1.5 h and the phases separated. The organic phase and extracts from the aq. phase [obtained by extraction (3×) with CH_2Cl_2] were combined, dried ($MgSO_4$) and concentrated to leave a syrup (4.65 g, ~83%) which was predominantly the oxaproline **8** by ^1H NMR spectroscopy. Diketene (2.46 g, 29.3 mmol) and triethylamine (five drops) were added to a solution of the oxaproline **8** in dichloromethane (150 cm^3), which was then heated under reflux for 6 h. After having been cooled and washed with dilute hydrochloric acid followed by water, the mixture was dried ($MgSO_4$) and concentrated. Subjection of the residue to silica gel chromatography [hexanes–EtOAc (3:2→1:1) as eluent] gave the 3-oxobutyryl derivative **1b** (4.34 g, 50%) as a yellow oil. The oil was dissolved in water (80 cm^3) and potassium carbonate (7.59 g, 17.8 mmol) was added to the stirred solution. After 2 h, the solution was saturated with sodium chloride and extracted (4×) with dichloromethane. Evaporation of the dried ($MgSO_4$) organic phase gave a colourless solid (2.73 g, 63%) that comprised a 70:30 mixture of the alcohols **2b** and **3b** by ^1H NMR spectroscopy.
21. The enantiomers of each diastereomer were separated on a Chiralpak AD column, using hexanes–isopropyl alcohol (9:1) as eluent (flow rate: 0.5 cm^3 min^{-1}; retention times: 16.2 min for *ent*-**2c** and 19.1 min for **2c**, 23.0 min for **3c** and 24.4 min for *ent*-**3c**).
22. Data for compound **9c**: ν_{max} (film)/cm^{-1} inter alia 1735 (ester C=O), 1710 (pyrroline C=O) and 1635 (C=C) λ_{max} (EtOH)/nm 208 (ε 10 700); δ_H (400 MHz; $CDCl_3$) 1.23 and 1.25 (each 3H, d, *J* 6 Hz, Me_2CH), 1.44 (1H, ddd, *J* 8.5, 11 and 12 Hz, 1-H), 2.04 (3H, d, *J* 1.5 Hz, 7-Me), 2.13–2.28 (2H, m, 2-H_2), 2.51 (1H, ddd *J* 2.5, 6.5 and 12 Hz, 1-H), 3.26 and 3.59 [each 1H, 7 lines (*J* 4, 8.5 and 11.5 Hz) and dt (*J* 11.5 and 8.5 Hz), 3-H_2], 5.04 (1H, sept, *J* 6 Hz, C*H*Me_2) and 5.71 (1H, q, *J* 1.5 Hz, 6-H); δ_C (100 MHz; $CDCl_3$) 14.4 (CH_3), 21.5 and 21.6 [(CH_3)$_2$CH], 28.1 (2-CH_2), 32.0 (1-CH_2), 42.3 (3-CH_2), 69.7 (OCH), 80.1 (7a-C), 123.4 (6-C), 160.3 (7-C), 169.4 (ester CO) and 175.8 (5-CO); *m*/*z* (FAB) 447 (M_2H^+, 80%) and 224 (MH^+, 100). Found: C, 64.3; H, 7.9; N, 6.6. $C_{12}H_{17}NO_3$ requires C, 64.6; H, 7.7; N, 6.3%.
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