Pergamon

Tetrahedron Letters 43 (2002) 1221–1223

TETRAHEDRON LETTERS

Asymmetric synthesis of 3-alkyl substituted prolines by alkylation of a chiral sulfone

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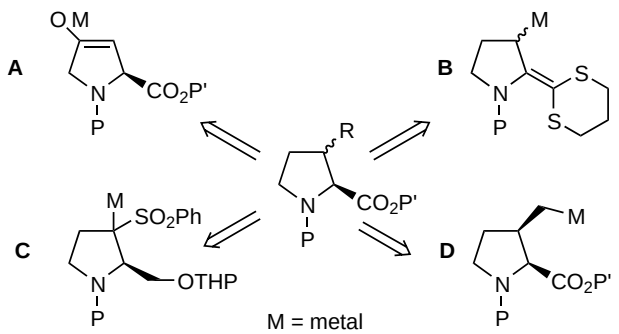
Received 19 November 2001; revised 14 December 2001; accepted 19 December 2001

Abstract—Preparation of 3-alkyl substituted prolines was achieved by alkylation of a chiral sulfone obtained from the amino–zinca-ene–enolate cyclization.

1. Introduction

Proline derivatives are used for replacing natural amino acids in peptides because their conformational rigidity allows to better understand the bioactive conformation of peptides.[1–3] Furthermore, functionalized pyrrolidine rings derived from proline have also been viewed as constrained non-peptide β-turn mimetics.[4] In this regard, 3-substituted prolines, chimeras combining amino acid side-chain functionality with proline conformational rigidity have been used as probes in structure–activity relationship studies of biologically active peptides (such as tachykinins, bradykinins, opioid peptides…)[1,5] and as scaffolds to build up low-molecular weight primary screening libraries.[6,7]

Four synthetic methodologies have been developed for the synthesis of 3-substituted prolines allowing the introduction of various chains on precursors, namely **A**, **B**, **C** and **D**.



The alkylation of 4-oxoproline enolate **A** led a mixture of *cis*/*trans* isomer and a variable amount of dialkylated product.[1,3] The alkylation of 2-amino-ketene S,S-acetals **B** provides also a mixture of racemic *cis*/*trans* isomers.[8] The alkylation of sulfonyl carbanions of pyrrolidine **C** was found to be highly diastereoselective, but the desulfonylation step provided a mixture of *cis*/*trans* isomers.[2] We have previously reported that asymmetric amino–zinc–enolate cyclization leading to precursor **D** is a powerful and straightforward method for the synthesis of *cis*-3-substituted proline derivatives.[9] This methodology was firstly applied to asymmetric syntheses of 3-prolinovaline, 3-prolinomethionine and 3-prolinoglutamic derivatives.[9–11] However, the cyclic organozinc reagent, even after transmetallation with the THF soluble copper salt CuCN–2LiCl[12] was unreactive towards non-activated alkyl-electrophiles. Thus, the introduction at the C-3 position of alkyl chain could not be directly achieved from these organometallic species. We wish to report here the synthesis of the sulfone **8** as a versatile precursor of 3-alkyl prolines. Indeed, the regioselective deprotonation in α position of the sulfone allowed alkylations with various alkyl-electrophiles as described in Scheme 1 and Table 1.

2. Results and discussion

The thioether **7** was obtained in a 'one-pot' procedure starting from the previously described olefin **1**.[9,10] This olefin was subjected to cyclization as described in Scheme 1. The lithium enolate obtained by deprotonation of **1** with LDA (1 equiv.) in THF at low temperature was transmetalated with zinc bromide (2.5 equiv. 1 M in ether). Cyclisation occurred by warming up the

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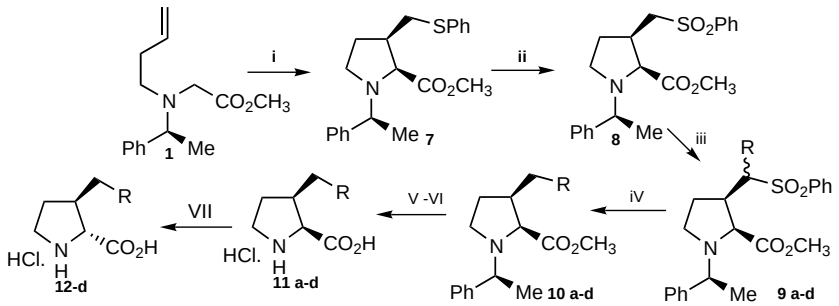
0040-4039/02/$ - see front matter
PII: S0040-4039(01)02391-7



Scheme 1. (i) THF, LDA, −78°C, $ZnBR_2$, −78°C to rt, then CuCN–2LiCl, $PhSSO_2Ph$. (ii) CH_2Cl_2, TFA (4 equiv.), *m*CpBA (2 equiv.). (iii) THF–DMPU (3:1), −78°C, LDA, RX. (iv) MeOH, Na/Hg (4 equiv.), KH_2PO_4 (3 equiv.). (v) H_2/PdC/MeOH. (vi) HCl 6N, reflux. (vii) H_2O, sealed tube, 190°C.

Table 1. 3-Alkylprolinoamino acids obtained

Entry	RX	**9** yield (%) (dr·αSO_2) [a]	**10** yield (%) [b]	**11** yield (%) [b]
a	CH_3I	92 (66/34)	84	80
b	$BrCH_2CO_2tBu$	68 (76/24)	76	73
c	$(CH_3)_2CHCH_2I$	68 (50/50)	72	76
d	$BrCH_2Ph$	69 (56/44)	73	78

[a] The diastereomeric ratios (dr) were determined by ^1H NMR spectroscopy following the integration values of the chiral auxiliary methyl group.
[b] Isolated yields of analytically pure products (^1H, ^{13}C NMR, HRMS or microanalysis).[15]

reaction mixture to room temperature. After a new transmetalation step with the THF soluble CuCN salts, the organozinccopper species were reacted with $PhSSO_2Ph$[13] leading to compound **7** as a single isomer.[15] This compound was then oxidized in sulfone **8** by *m*CpBA (2 equiv.) in the presence of TFA (4 equiv.) to avoid *N*-oxidation.[15]

This general precursor has the 2*S*,3*R* configuration as previously demonstrated by hydrolysis of the zinc derivative.[9] It was then subjected to a second deprotonation by LDA, the steric hindrance of the chiral auxiliary on the nitrogen prevented the abstraction of the proton α to the ester function.[14] The carbanion of sulfone **8** was cleanly alkylated in the position α to the sulfone group after deprotonation by LDA at low temperature in a THF–DMPU mixture (3:1) and subsequent addition of the electrophile, leading to derivative **9a–d** with formation of a new chiral center on the β′ carbon.[15] The diastereoisomeric ratios were poor but desulfonylation step by Na/Hg amalgam led in all cases to derivatives **10a–d** as single isomers.[15] Nitrogen deprotection (hydrogenolysis) and methyl ester hydrolysis by refluxing 6N HCl led to compounds **11a–d**.[15]

trans Isomers can be obtained from the *cis* isomers by inversion of the α-center in thermodynamic conditions. For example, the *trans* isomer of **11d** was obtained by heating the *cis*-derivatives at 190°C in a sealed tube.[11]

In conclusion, the combination of both amino–zinc–enolate cyclization and alkylation of the chiral sulfone allows to obtain a wide variety of *cis* 3-substituted prolines which can be epimerized in *trans* 3-substituted prolines.

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15. Experimental part for selected products: All compounds had the expected analytical and spectroscopic properties. **7**: General procedure for the cyclization–transmetallation reaction.[9,10] From amine **1** (12.25 g, 50 mmol), THF (150 ml), LDA (25 ml, 50 mmol), $ZnBr_2$ (1 M, 150 ml),

CuCN–2LiCl (1 M, 50 ml), $PhSSO_2Ph$ (12.5g, 50 mmol), yielding after purification by flash chromatography (cyclohexane–ethylacetate, 9:1) a colorless glue (13.2 g, 74%): $[\alpha]_D^{25}$ −23 (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.59–7.44 (m, 10H), 3.97–3.89 (q, 1H), 3.90 (s, 3H), 3.74–3.71 (d, 1H $J^3 = 7.5$ Hz), 3.32–3.14 (m, 3H), 3.01–2.75 (m, 2H), 2.49–2.3 (m, 1H), 2.15–1.9 (m, 1H), 1.63–1.60 (d, 3H). **8**: *m*CpBA (7.3 g, 32 mmol) was added to a cold solution (0°C) of **7** in CH_2Cl_2 (100 ml) and TFA (5 ml, 64 mmol). After 1 h stirring, the organic layer was washed with 10% $NaHCO_3$ (3×), dried over $MgSO_4$, concentrated and purified by flash chromatography (cyclohexane–ethylacetate, 7:3), yielding 9.8 g (80%) of a colorless glue. $[\alpha]_D^{25}$ −32 (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 8.14–8.11 (d, 2H), 7.94–7.79 (m, 3H), 7.55–7.44 (m, 5H), 3.94–3.91 (q, 1H), 3.85 (s, 3H), 3.69–3.66 (d, 1H $J^3 = 7.5$ Hz), 3.47–3.45 (m, 1H), 3.28–3.20 (m, 3H), 3.03–3.00 (m, 1H), 2.51–2.39 (m, 1H), 2.15–2.03 (m, 1H), 1.61–1.59 (d, 3H). General condition for alkylation: LDA (1 equiv.) was added to a dry THF–DMPU (3:1) solution of the sulfone **8** at −78°C under argon. After few seconds stirring, the electrophile (3 equiv.) was added at this temperature. The reaction mixture was stirred until complete decoloration (5–20 min) and brought to rt. Ether was added and the organic layer was washed twice with aq. satd NH_4Cl solution, dried over $MgSO_4$. Pale yellow oils were obtained after concentration. The crude materials were purified by flash chromatography. General condition for desulfonylation: KH_2PO_4 (3 equiv.) and 3% Na/Hg amalgam (4 equiv.) were added to dry solution of **9** (1 equiv.) in distilled MeOH (6 ml/mmol). The mixture was vigorously stirred for 1 h at rt. After filtration over a Celite pad, the crude material was concentrated and purified by flash chromatography. **11a**: ^1H NMR (250 MHz, D_2O): δ 4.50–4.47 (d, 1H $J^3 = 7.5$ Hz), 3.70–3.63 (m, 1H), 3.54–3.46 (m, 1H), 2.75–2.6 (m, 1H), 2.41–2.33 (m, 1H), 2.02–1.94 (m, 1H), 1.8–1.6 (m, 1H), 1.5–1.25 (m, 1H), 1.13–1.07 (tr, 3H). MH^+: Anal. calcd (found): 144 (144). **11b**: ^1H NMR (250 MHz, D_2O): δ 4.48–4.45 (d, 1H $J^3 = 7.5$ Hz), 3.75–3.60 (m, 1H), 3.55–3.40 (m, 1H), 2.85–2.55 (m, 3H), 2.48–2.33 (m, 1H), 2.1–1.85 (m, 2H), 1.8–1.7 (m, 1H). MH^+: Anal. calcd (found): 188 (188). **11c**: ^1H NMR (250 MHz, D_2O): δ 4.50–4.47 (d, 1H $J^3 = 7.5$ Hz), 3.74–3.64 (m, 1H), 3.54–3.43 (m, 1H), 2.85–2.75 (m, 1H), 2.44–2.30 (m, 1H), 2.06–1.95 (m, 1H), 1.8–1.6 (m, 2H), 1.5–1.3 (m, 3H), 1.02–1.01 (d, 3H), 0.99–0.98 (d, 3H). MH^+: Anal. calcd (found): 186 (186), $[\alpha]_D^{25}$ −19 (*c* 1, H_2O), mp: 88°C. **11d**: ^1H NMR (250 MHz, D_2O): δ 7.40–7.27 (m, 5H), 4.34–4.31 (d, 1H $J^3 = 7.5$ Hz), 3.58–3.52 (m, 1H), 3.38–3.30 (m, 1H), 2.79–2.57 (m, 3H), 2.30–2.21 (m, 1H), 1.92–1.81 (m, 2H), 1.62–1.59 (m, 1H). MH^+: Anal. calcd (found): 220 (220), $[\alpha]_D^{25}$ −6 (*c* 1, H_2O), mp: 176°C.