

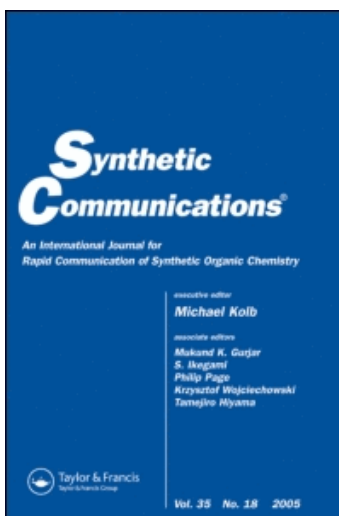
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4-Thiophenyl-2-azetidinone as Chiron: Enantiospecific Syntheses of 3R and 3S Deuteriated β -Alanines

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4-THIOPHENYL-2-AZETIDINONE AS CHIRON : ENANTIOSPECIFIC SYNTHESIS OF 3R AND 3S DEUTERIATED β -ALANINES

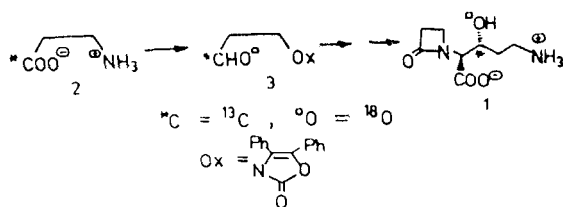
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Abstract: Stereospecific syntheses of chirally C-3 deuteriated β -alanines **6** and **7** from optically pure 4 - thiophenyl azetidinones **13** and **14** are described.

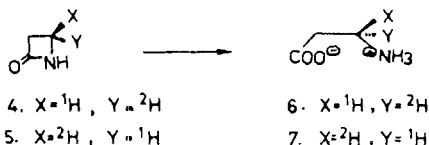
Chirally deuteriated molecules are important because of their applications in biosynthetic studies^{1,2} especially for determination of stereochemistry and kinetic isotope effects. Aminoacids, which are often involved in natural product biosyntheses³, are useful for the same reason in chirally deuteriated forms. Their simplest member β -alanine, besides being a constituent of vitamin pantothenic acid / coenzyme A, is also a synthon for biologically important molecules like 2 - azetidinone⁴. Recently⁵, it has been utilized in the synthesis of isotopically labelled proclavaminc acid **1**, the monocyclic intermediate for clavulanic acid biosynthesis (Scheme 1). In this article we describe a simple synthesis of chirally 3 - deuteriated β -alanines **6** and **7**. In principle, the method can be elaborated to synthesize β -alanine, stereospecifically substituted at C - 3 with allyl, aryl or alkynyl groups⁶.

Scheme 1



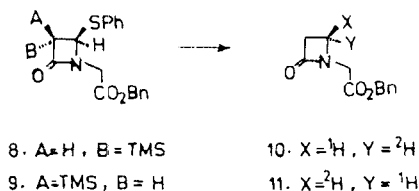
Recently, 2 - azetidinones have been utilized in the synthesis of dealanylalohopcin⁷ and α - amino phosphonic acid⁸ by ring opening in presence of base or acid. We envisioned that our problem will be solved if we can achieve a synthesis of chiral 4 - deuterioazetidinones **4** and **5** which can then be opened up to **6** and **7** (Scheme II).

Scheme II



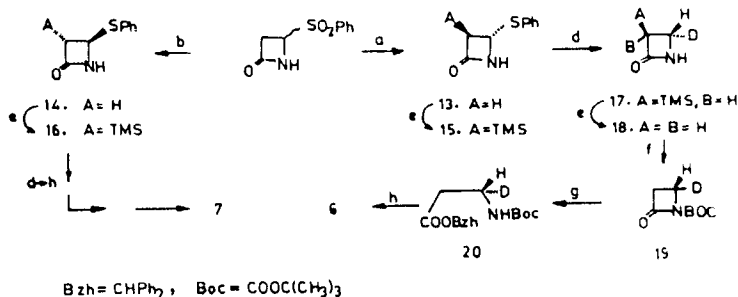
Chiral deuterated molecules are usually prepared by asymmetric reduction of deuterated aldehydes with Alpine boranes⁹. Departing from this conventional methodology, we have earlier prepared² chiral 4'-deuterated benzylazetidiny acetates **10** and **11** by tin deuteride reduction of *cis* and *trans* benzyl 3'-trimethylsilyl-4'-thiophenyl azetidiny acetates **8** and **9**, respectively, exploiting the steric effect operative during deuterium abstraction (Scheme III). We have utilized this stereospecific reduction in the synthesis of chiral β -alanines.

Scheme III



One problem in the above method is the relatively low yield for the reduction of the *cis* isomer **8** in which case the reaction is also sluggish (4 eq of tin deuteride, 24 h, 50% yield). To circumvent this problem both enantiomers of *trans* 3-trimethylsilyl-4-thiophenylazetidinyones **15** and **16** were prepared from racemic 4-phenylsulphonylazetidinyones **13** and **14**, respectively, which in turn were made from racemic 4-phenylsulphonylazetidinyone **12** via displacement with thiophenol using cinchonine or cinchonidine¹⁰ as chiral base (Scheme IV). The **3R**, **4S**-isomer **15** upon tin deuteride reduction gave **3R**-trimethylsilyl-**4S**-²H-azetidinyone **17** in 82% yield. That the deuterium was stereospecifically delivered from the opposite face of the TMS was evident in the ¹H NMR spectrum. The C-3 hydrogen appeared as a doublet at δ 3.08 with a coupling constant of 2.6 Hz (characteristic of *trans* coupling¹¹). Moreover the signal at δ 3.41 for the C-4-hydrogen was virtually absent. Careful integration in the high field NMR showed the extent of stereospecificity to be 18 : 1, while mass spectrum showed 98% deuterium incorporation. The TMS group was removed¹² (KF/acetone nitrile) and the resulting **4S**-²H-azetidinyone **18** was N-protected as *t*-butyloxycarbonyl (for easy isolation and for promoting the rate of ring opening). The resulting N-*t*-Boc-**4S**-²H-azetidinyone **19** was hydrolysed (powdered KOH, MeOH) and esterified with diphenyldiazomethane to give the fully protected

Scheme IV



a	=	PhSH/(+) Cinchonine	b	=	PhSH/(-) Cinchonidine
c	=	i) NEt ₃ /TMSCl/O ^o	ii)	LDA/TMSCl/-78°C	iii) NH ₄ Cl
d	=	Bu ₃ SnD/AIBN;	e	=	KF/CH ₃ CN;
f	=	Boc ₂ /DMAP	g	=	KOH/MeOH
h	=	TFA	ii)		Ph ₂ CN ₂ :

3S - deuterated β - alanine **20** in essentially quantitative yield. TFA deprotection finally afforded **3S** -²H - β - alanine **6**, crystallised from MeOH. The ¹H NMR showed signals for C - 3 and C - 4 hydrogens at 2.45 and 3.06 integrating in a 2 : 1 ratio, suggesting no loss of deuterium during the chemical manipulations. Definitive evidence was obtained from mass spectral analysis of **6** which showed 98% d₁ species, same as that in the tin deuteride reduction product **17**.

The **3R** -²H - β - alanine **7** was similarly prepared from **4R** - thiophenylazetidinone **14**.

Experimental section

Melting points were determined in open capillaries using a Thomas - Hoover apparatus and are uncorrected. ¹H and ¹³C spectra were recorded in XL - 400 instrument. Mass spectra were recorded on a VG 70 - S mass spectrometer, IR spectra were obtained using Perkin - Elmer 1600 series FT instrument. Experimental procedure is given for the synthesis of **3S** -²H - β - alanine **6**.

(3R) - Trimethylsilyl - (4S) -²H - 2 - azetidinone (17)

A dry degassed solution of **15**² (502 mg, 2 mmol), tri - n - butyltin deuteride (1.1 mL, 4 mmol) and AIBN (66 mg, 0.4 mmol) in benzene (15 mL) was refluxed under nitrogen for 6 h. After cooling to room temperature, the solution was evaporated, the oily residue was partitioned between acetonitrile and hexane (50 mL each) and the acetonitrile layer was evaporated. The residue was chromatographed using Si - gel. Hexane - EtOAc (2:1) elution furnished the title compound **17** as a white solid, which crystallized

(hexane-CH₂Cl₂) as needles (236 mg, 82%); m.p. 71-72°C; $[\alpha]_D^{25} = 158^\circ$ (CHCl₃, Cl) ; IR (CHCl₃) 3412, 3009, 2956, 1737, 1253, 1138, 1110, 1031, 863, 845 cm⁻¹; ¹H NMR (CDCl₃) 5.57 (1H, br, NH), 3.05 (1H, d, J = 2.6Hz, H-3), 2.83 (1H, br s, H-4), 0.14 (9H, s, TMS); ¹³C NMR (CDCl₃) δ 171.0, 43.0, 36.24(t), -3.11; MS : m/s 129 (M-CH₃, 23.1%), 116, 101, 99, 86 (100%); accurate mass : Calcd. for C₆H₁₂²HNO₃-CH₃ 129.0594 found 129.0592.

(4S) - 2H -2- azetidinone (18)

To a solution of **17** (200 mg, 1.4 mmol) in acetonitrile (10 mL), KF (568 mg, 7 eq) was added and the mixture was stirred at room temperature for 7 hours. It was filtered through a small bed of Si - gel which was thoroughly washed with EtOAc. The combined filtrate and washings were evaporated and the oily residue was chromatographed over Si - gel. The title compound **18** was isolated from the hexane : EtOAc eluates as a white solid crystallized from hexane -CH₂Cl₂ (98 mg, 97%); m.p. 73-75° C; lit¹³. 73.5-74.5° C; ¹H NMR (CDCl₃) δ 5.98(1H, br, NH), 3.28(1H, m, H-4), 3.0 (2H, m, H-3); accurate mass : Calcd. for C₃H₄²HNO 72.0433 found 72.0431.

N-t-Butyloxycarbonyl -(4S)-2H-2-azetidinone (19)

A solution of **18** (72 mg, 1 mmol), di - t - butyldicarbonate (327 mg, 1.5 mmol) and DMAP (15 mg, 0.1 mmol) in acetonitrile (10 mL) was stirred at room temperature for 10h. The solution was then partitioned between EtOAc and water (50 mL each). The EtOAc layer was washed with 0.01 N HCl, 5% NaHCO₃, brine and dried (Na₂SO₄). Filtration followed by evaporation gave an oil from which the title compound **19** was isolated as a colourless oil (165 mg, 96%); IR (CHCl₃) 2977, 2922, 1733, 1716, 1706, 1602, 1558, 1540, 1506, 1498, 1456, 1368, 1164, 1145 cm⁻¹; ¹H NMR (CDCl₃) 3.53 (1H, t, J = 5.2 Hz, H-4), 2.96 (2H, d, J = 5.2 Hz, H-3), 1.51 (9H, s, COOC(CH₃)₃) accurate mass : Calcd. for C₈H₁₂²HNO₃ 172.1092 found 172.1094.

N-t-Butyloxycarbonyl-diphenylmethyl-3S-2H-3-amino propanoate(20)

To a solution of **19** (172 mg, 1 mmol) in aqueous MeOH (1:1, 5 mL), powdered KOH (112 mg, 2 mmol) was added and stirred at room temperature for 2h. It was diluted with water (20 mL), the pH was adjusted to 2.3, then extracted with EtOAc (2 x 25 mL) and dried (Na₂SO₄). Filtration followed by removal of solvent furnished an oily residue which was dissolved in EtOAc(10 mL). Diphenyl diazomethane (291 mg, 1.5 mmol) was added and stirred at room temperature for 5h. The solution was evaporated and the residue was chromatographed over Si-gel. The title compound **20** was isolated as a white solid crystallized from hexane - CH₂Cl₂ as needles (324 mg, 91%); m.p. 63-64° C; IR (CHCl₃) 3457,2924,1732,1714,1706,1601,1506,1455,1368,1164,1146 cm⁻¹; ¹H NMR (CDCl₃) 7.38 - 7.23 (10H, m, 2 x Ph), 4.95 (1H, br, NH), 3.40 (1H, m, H-3), 2.65 (2H, d, J = 6.0 Hz, H-2), 1.43 ((OH, s, COOC(CH₃)₃); ¹³C NMR(CDCl₃) 171.57, 155.76, 139.97, 128.01, 127.01, 79.35, 77.22, 35.87(t), 34.72, 28.36; MS : m/z 300 (M - C₄H₈, 16.7%), 282, 272, 256, 185, 184, 183, 168, 167 (100%); accurate mass : Calcd. for C₂₁H₂₄²HNO₄ - C₄H₈ 300.1220 found 300.1224.

(3S)-2H - β -alanine (6)

Fully protected β - alanine **20** (50 mg, 0.14 mmol) was dissolved in ice - cold TFA (3 mL) and stirred under nitrogen at 0° C for 15 min. and then at room temperature for another 15 min. The pink solution was evaporated to dryness and the process of evaporation was repeated twice with toluene. The residue was triturated with ether, then taken up in water (5 mL) and lyophilized to give the title compound **8** as a white solid, crystallized from water - EtOH as fine needles (12mg, 96%); m.p. 200 - 202° C (dec), lit¹⁴, 195 - 200°C (dec); ¹H NMR (D₂O) 3.06 (t, 1H, J = 6.4 Hz, NCHD), 2.45 (d, 2H, J = 6.4 Hz, CH₂CO); MS (Cl, NH₃) : m/z 108 (MNH₄⁺, 0.21%), 91 (MH⁺, 100%); accurate mass : Calcd. for C₃H₆²HNO₂ 90.0540, found 90.0537.

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