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Enantioselective synthesis of protected D-serine from tetrahydrooxazin-4-one via a hetero Diels–Alder reaction

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Abstract—Hetero Diels–Alder reaction between 2-aza-3-trimethylsilyloxy-1,3-diene and aldehydes gives rise to tetrahydrooxazin-4-ones, useful intermediates in the synthesis of α-amino-β-hydroxy acids. Herein we report the complete stereoselective synthesis of D-serine Cbz-methyl ester.

1. Introduction

Interest in the field of stereoselective synthesis of β-hydroxy-α-amino acids is in continuous growth because of their presence in nature as metabolites or components of biologically active compounds.[1] Moreover, due to their high degree of functionalization, they find wide use as chiral starting materials in asymmetric synthesis.[2–4]

Synthetic approaches to β-hydroxy-α-amino acids are based on condensation, possibly enzymatic,[5] of aldehydes with glycine derivatives;[6] Sharpless asymmetric epoxidation/dihydroxylation;[7] electrophilic amination of β-hydroxy esters;[8] and the use of amino acids as starting materials.[9]

In the past few years we have started a detailed study on 2-aza-3-trimethylsilyloxy-1,3-dienes, demonstrating that they can be useful intermediates in the stereoselective synthesis of nitrogen-containing biologically interesting compounds: β-lactams are accessible via electrocyclic [2+2] ring closure;[10] γ-lactams can be synthesized by a four-step one-pot process via addition of cyano groups, followed by intramolecular ring closure[11] and tetrahydrooxazin-4-ones are obtained by hetero Diels–Alder reaction with an appropriate dienophile.[12]

We have already reported on the possibility of synthesizing tetrahydrooxazin-4-ones as useful precursors of β-hydroxy-α-amino acids:[13] all stereoisomers of threonine have been obtained starting from (2*R*,5*R*,6*R*)-2-[(*S*)-1-[(triisopropyl)oxy]ethyl]-5-[(benzyloxycarbonyl)amino]-6-methylperhydro-1, 3-oxazin-4-one.

In order to demonstrate the utility of our approach in the synthesis of non-proteinogenic amino acids, we report herein the results obtained from the application of our methodology to the enantioselective synthesis of (+)-D-serine protected as *N*-Cbz-methyl ester. This target is of interest as a result of its potential pharmaceutical application: D-serine has recently been found in mammalian brain tissue, where it seems to be an endogenous modulator of the *N*-methyl-D-aspartate type (NMDA) glutamate receptors, which have well known medical implications.[14–16] Besides being a possible drug, D-serine has additionally been used as a chiral starting material for the asymmetric synthesis of a number of β-substituted-β-hydroxy-α-amino acids,[17] oxazolidinones,[18] pyrrolidines,[19] indolizidines.[20]

2. Results and discussion

The synthesis of the azadiene **4** was carried out according to the procedure previously reported, starting from the *N*-(trimethylsilyl)imine **2** of (*S*)-lactic aldehyde **1** and acyl chloride **3** (Scheme 1).[12]

Treatment of the azadiene[21] **4** with formaldehyde (obtained by thermal depolymerization of trioxymethylene) in the presence of boron trifluoride etherate in methylene chloride at −78°C followed by

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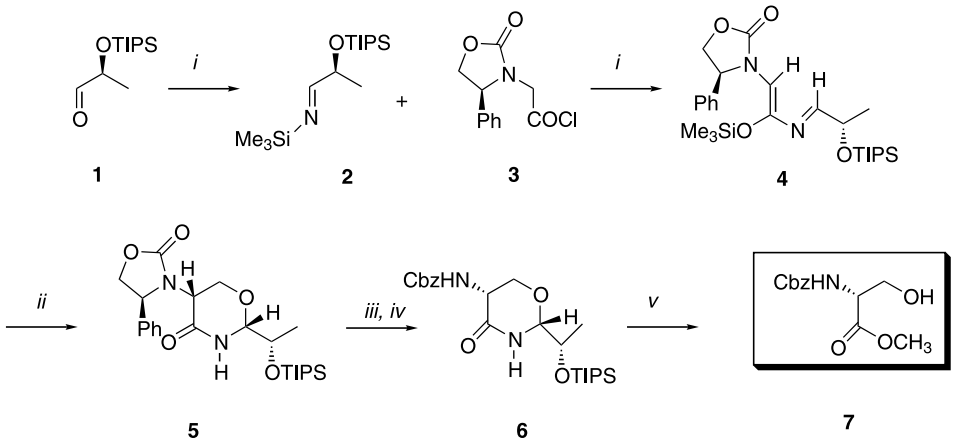

Scheme 1. *Reagents and conditions*: (i) Ref. 13; (ii) HCHO, $BF_3{\cdot}Et_2O$, −78°C, CH_2Cl_2; (iii) Li/NH_3, −78°C, THF, NH_4Cl; (iv) CbzCl, acetone/H_2O, $NaHCO_3$; (v): HCl/MeOH.

standing overnight at room temperature afforded the corresponding tetrahydro-1,3-oxazin-4-one **5** as a single diastereoisomer in 41% yield. The yield has been calculated for the whole process. It is interesting to note that the use of gaseous formaldehyde as dienophile in the hetero Diels–Alder reaction did not seem to influence the yield and diastereoselectivity of the reaction, since the expected tetrahydrooxazinone **5** is obtained in satisfactory yield. Subsequent elaboration of compound **5**, according to a published procedure (removal of the Evans' oxazolidinone and formation of the corresponding *N*-Cbz derivative), furnished the Cbz-protected compound **6**. Ring-opening of this product with methanolic HCl furnished the desired D-*N*-Cbz-serine methyl ester **7** (mp 31–33°C; $[\alpha]_D^{20}=+12.8$, *c* 0.9 MeOH; lit. $[\alpha]_D^{20}=+12.4$, *c* 1, MeOH[22]).

3. Experimental

3.1. General methods and materials

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian VXR 200, or on a Varian Mercury 400 MHz spectrometer. Chemical shifts are reported on the δ scale and coupling constants (*J*) are reported in hertz. Infrared spectra were recorded on a Nicolet 205 FT-IR spectrophotometer in $CHCl_3$. Specific rotation measurements were carried out on a Perkin–Elmer 343 polarimeter and specific rotation $[\alpha]_D^{20}$ is reported in deg per dm^3 at the specified temperature and with the concentration [*c*] given in g per 100 mL. Mass spectra were recorded on Finnigan MAT instrument.

3.2. (5*S*)-1-[(4*S*)-2-Oxo-4-phenyloxazolidin-3-yl]-2-trimethylsilyloxy-3-aza-5-triisopropylsilyloxy-hexa-1,3-diene, 4

Compound **4** was prepared according to reported procedures[13] starting from (*S*)-(+)-2-oxo-4-phenyl-3-oxazolidin-3-yl-acetyl chloride **3** and *N*-trimethylsilylimine **2**.

3.3. (5*R*)-[(4*S*)-(2-Oxo-4-phenyloxazolidin-3-yl)-2*R*-(1*S*-triisopropylsilanyloxyethyl)]-[1,3]oxazinan-4-one, 5

Crude azadiene **4** (obtained from (*S*)-triisopropyloxylactaldehyde **1** (1 mmol) and acyl chloride **3** in a one-pot two-step procedure according to Ref. 13) was dissolved in dichloromethane (10 mL). The solution was cooled to −78°C, a solution of boron trifluoride diethyl etherate (0.13 mL, 1 mmol) in dichloromethane (10 mL) was added and gaseous formaldehyde, obtained from trioxymethylene (0.5 g) by means of thermal depolymerization, was bubbled into the dichloromethane solution. The reaction was stirred at −78°C for 3 h and allowed to warm to room temperature overnight. The crude reaction mixture was diluted with dichloromethane (10 mL), poured into a saturated aqueous $NaHCO_3$ solution, and extracted further with dichloromethane. The organic layers were washed with brine, and then dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the crude reaction mixture was purified by flash chromatography on silica gel, eluting with dichloromethane/acetone, 9/1. Compounds **5** was obtained in 41% yield, calculated on the whole process starting from aldehyde **1**. Oil. $[\alpha]_D^{20}=+79.9$ (*c* 1.76, $CHCl_3$); IR: 3635, 1760, 1686. ^1H NMR: 7.35 (m, 5H); 6.36 (bs, 1H); 5.13 (t, $J=8.4$, 1H); 4.70 (d, $J=4.2$, 1H); 4.65 (t, $J=8.7$, 1H); 4.39 (dd, $J_1=3.9$, $J_2=10.8$, 1H); 4.11–3.80 (m, 4H); 1.02 (m, 24H). ^{13}C NMR: 166.5; 158.2; 137.2; 129.2; 127.4; 85.4; 70.6; 68.5; 66.1; 62.4; 52.0; 17.9; 16.4; 12.2. MS *m*/*z* 462, 419, 401, 318, 271, 209, 186, 144. Elemental analysis found: C, 62.55; H, 8.31; N, 6.03%. $C_{24}H_{38}N_2O_5Si$ requires: C, 62.30; H, 8.28; N, 6.05%.

3.4. [(2*R*,5*R*)-4-Oxo-[(1*S*)-triisopropylsilanoxyethyl)-[1,3]oxazinan-5-yl]carbamic acid benzyl ester, 6

A solution of **5** (0.26 mmol) in THF/*t*-BuOH (10:1, 3 mL) was added at −78°C to a solution of Li (11 mg, 6 mmol) in NH_3 (7 mL). The excess Li was quenched after 2 min by the addition of solid NH_4Cl (83 mg, 6 mmol), and the ammonia was allowed to distil off at −33°C under a stream of N_2. The resulting crude product was dried in vacuo, dissolved in H_2O (5 mL),

briefly acidified to pH 3 with the addition of 10% aqueous HCl, and subsequently basified (pH 8) by the addition of solid $NaHCO_3$. Acetone (2 mL) and benzylchloroformate (0.11 mL, 3 mmol) were added to the aqueous mixture. After 4 h, the reaction mixture was extracted with ethyl acetate, washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography on silica gel, eluting with dichloromethane/acetone, 9/1, afforded **6** in 65%. Oil. $[\alpha]_D^{20} = -24.8$ (*c* 0.87, $CHCl_3$); IR: 3680, 3650, 1721, 1686. ^{1}H NMR: 7.35 (s, 5H); 6.45 (bs, 1H); 5.48 (d, $J = 6.8$, 1H); 5.12 (s, 2H); 4.86 (d, $J = 3.5$, 1H); 4.36 (m, 1H); 4.06 (m, 3H); 1.14 (d, $J = 6.2$, 1H); 1.04 (s, 21H). ^{13}C NMR: 167.5; 156.2; 136.0; 128.5; 128.2; 84.5; 68.8; 68.2; 67.3; 50.7; 18.0; 17.9; 15.8; 12.1. MS *m*/*z* 450, 407, 363, 299, 273, 91. Elemental analysis found: C, 61.47; H, 8.53; N, 6.20%. $C_{23}H_{38}N_2O_5Si$ requires: C, 61.30; H, 8.50; N, 6.22%.

3.5. (2*R*)-Benzyloxycarbonylamino-3-hydroxy-propionic acid methyl ester, 7

Compound **6** (0.1 mmol) was dissolved in MeOH (3 mL). The solution was cooled at 0°C, and 5 mL of a previously prepared satured solution of HCl in MeOH was added. After 2 h the solvent was removed in vacuo, a saturated solution of $NaHCO_3$ was added, and the mixture was extracted with ethyl acetate. A simple filtration on silica gel (CH_2Cl_2/acetone, 9/1) yielded the target compound **7** in quantitative yield. Mp 31–33°C; $[\alpha]_D^{20} = +12.8$ (*c* 0.9, $CHCl_3$); ^{1}H NMR: 7.35 (s, 5H); 5.72 (bs, 1H); 5.12 (s, 2H); 4.45 (m, 1H); 3.95 (m, 2H); 3.77 (s, 3H); 2.32 (bs, 1H). ^{13}C NMR: 170.9; 156.2; 136.0; 128.6; 128.3; 128.1; 67.2; 63.3; 56.1; 52.7. MS *m*/*z* 253, 162, 150, 108, 91. Elemental analysis found: C, 57.11; H, 5.99; N, 5.51%. $C_{12}H_{15}NO_5$ requires: C, 56.91; H, 5.97; N, 5.53%.

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