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DIASTEREOSELECTIVE ALKYLATION OF 4-METHYL-5-OXO-2-PHENYL-1,3-OXAZOLIDINE-3-CARBOXYLATE AND 2-CHLOROMETHYL-ISOINDOLE-1,3-DIONE

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Asymmetric synthesis, that is, diastereoselective alkylation of a chiral auxiliary, is an important tool in organic synthesis. In this work, an *α*-methyl, non-natural amino acid (NNAA) building block equipped with a phthalimide group tail was prepared. This work describes the generation of the lithium enolate for an oxazolidin-2-one chiral auxiliary derived from a NNAA followed by quenching this enolate with 2-chloromethyl-isoindole-1,3-dione to provide an *α*-methyl NNAA building block equipped with a phthalimide group in good yield through a multistep synthesis with no signs of any minor diastereomers. The identity of this compound was confirmed by ^{1}H NMR (Proton Nuclear Magnetic Resonance) and ^{13}C NMR (Carbon-13 Nuclear Magnetic Resonance) spectroscopy. With the availability of this building block, peptides can be produced and evaluated over a variety of therapeutic areas in drug discovery.

Keywords: asymmetric synthesis, diastereoselective alkylation, chiral auxiliary

1. Introduction

Asymmetric synthesis, namely assembling complex molecules as single enantiomers from relatively simple and readily available starting materials, is an important tool in modern organic chemistry synthesis [1]. In the pharmaceutical industry, these single enantiomers play an important rule in drug discovery since almost all newly introduced chiral drugs are marketed as single enantiomers [2]. One of the most common methods for asymmetric synthesis is the use of a chiral auxiliary. In order for the application of chiral auxiliaries to be beneficial, three important conditions must be met: first, they should mediate a highly diastereoselective transformation; second, they must be easily removed without racemization of the newly created stereogenic center(s); third, they need to be readily attached in their enantiomerically pure form to the substrate. In the literature, several chiral auxiliaries that meet these requirements have been developed [3], however, the class of chiral oxazolidinones developed by David Evans have proven to be the gold standard [4]. These chiral auxiliaries have successfully directed many diastereoselective alkylations, α-aminations, aldol additions, Diels–Alder cycloadditions and Michael additions. Most importantly, the products of these reactions can be transformed into useful enantiopure intermediates that can be used in industry to prepare drugs. Compounds with an oxazolidine ring are of great importance due to their presence in several biologically active synthetic products, for example, linezolid, an oxazolidin-2-one, which is considered to set a new antimicrobial class developed over the past 30 years (*Figure 1*) [5].

Chiral auxiliaries were first discovered and introduced by E. J. Corey in 1975 [6] using chiral 8-phenylmenthol and followed by the discovery of chiral mandelic acid by B. M. Trost [7]. As menthol is difficult to synthesize, trans-2-phenyl-1-cyclohexanol was introduced by J. K. Whitesell in 1985 as an alternative [8]. Undoubtedly, the most efficient and frequently used chiral auxiliaries with prevalent applications are the chiral oxazolidinones developed and reported by David Evans. Oxazolidinones are a class of compounds containing 2-oxazolidone, which is a heterocyclic compound containing both nitrogen and oxygen in a 5-membered ring usually prepared from chiral natural amino acids [9]-[15].

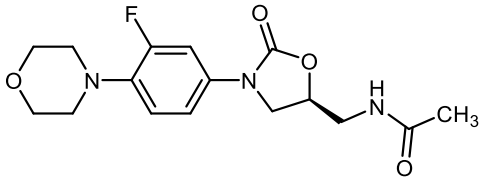

Figure 1: The structure of linezoid

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One of the most effective and popular reactions of acylated Evans' oxazolidinones is diastereoselective alkylation. In spite of the advantages realized for asymmetric catalysis, organic synthetic chemists frequently turn to Evans' methodology, especially when optically pure carboxylic acid derivatives are required as final products or as intermediates. Although it is not as graceful as asymmetric catalysis, chiral auxiliaries continue to be very significant and frequently used for asymmetric synthesis. In this regard, the total synthesis of cytovaricin by Evans et al. is considered as a classic application of oxazolidinones as chiral auxiliaries for one asymmetric alkylation and four asymmetric aldol reactions required to bring about the absolute configuration of nine stereogenic centers present in the aforementioned natural products [16].

Therapeutic programs based on peptides have closed the gap on those focused on small molecules in pharma. One modification that has extended the lifetime of peptides is backbone modification, including α-methylation using non-natural amino acids (NNAAs) [17]-[19]. However, there are very few commercially available α-methyl amino acids, and they are extremely expensive. The development of a general synthetic strategy to approach a wide variety of α-methyl NNAAs would provide a significant step forward for drug discovery by employing peptide-based candidates.

Herein, a new protocol for the introduction and diastereoselective alkylation of the Evans chiral auxiliary, namely 4-methyl-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate with 2-chloromethyl-isoindole-1,3-dione, is presented.

2. Experimental

2.1. Synthesis of 2-chloromethyl-isoindole-1,3-dione (compound **(3)**)

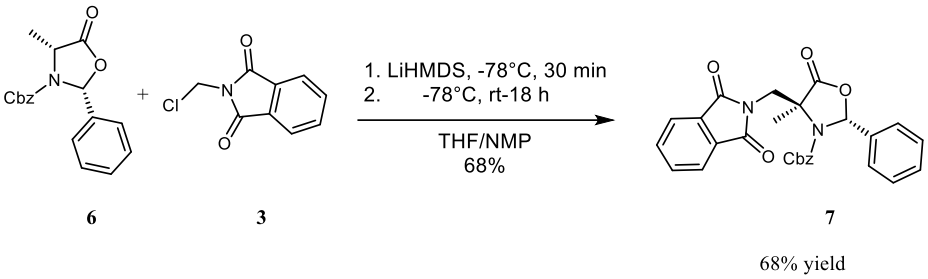
Compound **(3)**, that is, 2-chloromethyl-isoindole-1,3-dione, was prepared according to a method found in the literature [20]. A solution of phthalimide **(1)** and formaldehyde (40% M/V aqueous solution) in water (40 mL) was stirred at 100 °C for 4 h. The mixture was cooled to room temperature and filtered. The precipitate was washed several times with water and pentane before being dried to provide a quantitative yield of 2-hydroxymethyl-isoindole-1,3-dione **(2)**. In the next step, compound **(2)** and thionyl chloride ($SOCl_2$) were stirred under argon at 75 °C for 4 h before the mixture was cooled to room temperature. Thionyl chloride was removed under reduced pressure. The residue was diluted with dichloromethane (DCM) and the solvent evaporated off under reduced pressure. This procedure was repeated 5 times to afford a quantitative yield of 2-chloromethyl-isoindole-1,3-dione **(3)**.

2.2. Synthesis of (2R,4R)-4-methyl-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate (compound **(6)**)

Legend: Compound **(6)**, namely (2R,4R)-4-methyl-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate, was synthesized according to a method found in the literature [21]. Cyclization of benzyloxycarbonyl (Cbz)-protected (D) alanine **(4)** with benzaldehyde dimethyl acetal **(5)** provided compound **(6)** as a single isomer by slowly adding hexane over 6 hours to crash out the product. More specifically, in a dry flask under N_2, Cbz-D-alanine **(4)** (1.000 equiv.) and compound **(5)** (1.025 equiv.) were dissolved in dry tetrahydrofuran (THF) before being cooled to 0 °C. $SOCl_2$ (1.100 equiv.) was added dropwise and after having been stirred for 10 mins. $ZnCl_2$ (1.100 equiv.) was added then the solution further stirred for 4 h at 0°C. The reaction was quenched with the dropwise addition of ice water, followed by the addition of sodium bicarbonate ($NaHCO_3$) solution until the pH became equal to 4. The mixture was diluted in water and extracted with ether three times before the organic layers were washed with brine, dried over anhydrous sodium sulphate (Na_2SO_4) and evaporated to dryness in vacuo. The crude product was dissolved in the minimum volume of ether, cooled to room temperature and the product precipitated by the dropwise addition of hexane over 6 hours resulting in a yield of 56%.

2.3. Asymmetric alkylation between compound **(6)** and compound **(3)** to offer produce compound **(7)**

Below the synthesis of compound **(7)** is described. In a dry flask under N_2, compound **(6)** (9.2 g, 29.6 mmol, 1.000 equiv.) was dissolved in dry THF (144 mL) and N-Methyl-2-pyrrolidone (NMP) (24 ml) before the solution was cooled to -78°C. Lithium bis(trimethylsilyl)amide (LiHMDS) (1.0 M) in THF (30.8 mL, 30.8 mmol, 1.300 equiv.) was added dropwise to the solution and having been stirred for 10 mins., compound **(3)** (13.9 g, 71.1 mmol, 3.000 equiv.) was added dropwise. The reaction was allowed to warm up gradually to room temperature over 18 h and quenched with an ammonium chloride (NH_4Cl) solution before being diluted with H_2O and extracted with DCM (3X). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuo. The residue was purified by column chromatography with a gradient of 0-30% ethyl acetate in hexanes (v/v) to produce 9.5 g (20.1 mmol) with a 68% yield of compound **(7)** as a white solid.



6 **3** **7**

68% yield

Figure 2: Asymmetric alkylation between (2R,4R)-4-methyl-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate **(6)** and 2-chloromethyl-isoindole-1,3-dione **(3)** to produce compound **(7)**

3. Results and discussion

The purpose of this article is to report a new procedure regarding Evans' diastereoselective alkylation of (2R,4R)-4-methyl-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate **(6)** with 2-chloromethyl-isoindole-1,3-dione **(3)**. This alkylation is the last stage of the multistep synthesis to produce a 68% yield of compound **(7)** as a white solid as shown in *Figure 2*.

In summary, in the first case, a starting substance that was available in both its enantiomeric form and chiral as well as optically pure was envisioned. The cyclization of Cbz-protected (D) alanine with benzaldehyde dimethyl acetal yielded compound **(6)** after recrystallization as a single isomer. After the lithium enolate of compound **(6)** was generated and quenched with compound **(3)**, chirality transfer was accomplished, yielding compound **(7)** with no indication of any minor diastereomers [22].

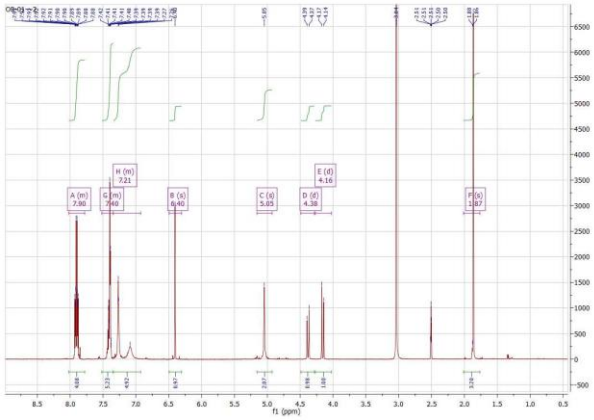
The identity of the α-methyl, non-natural amino acid (NNAA) building block equipped with a phthalimide moiety, that is, compound **(7)**, was confirmed by 500MHz NMR and HRMS spectroscopy. The experiments were carried out in dimethyl sulfoxide-d_6 (DMSO-d_6) at 100 °C.

^{1}H NMR (500 MHz, DMSO-d_6, 100 °C):
δ 8.02 – 7.78 (m, 4H), 7.52 – 7.34 (m, 5H), 7.34 – 6.93 (m, 5H), 6.40 (s, 1H), 5.05 (s, 2H), 4.38 (d, J = 14.4 Hz, 1H), 4.16 (d, J = 14.4 Hz, 1H), 1.87 (s, 3H)

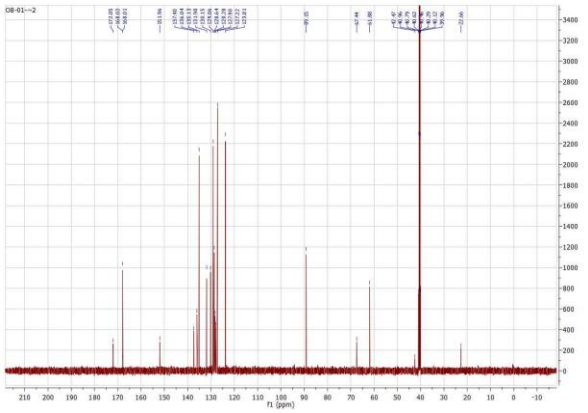
^{13}C NMR (126 MHz, DMSO-d_6, 100 °C) δ 172.05, 168.02, 151.96, 137.40, 136.04, 135.13, 131.90, 130.15, 129.06, 128.64, 128.28, 127.90, 127.22, 123.81, 89.15, 67.44, 61.88, 22.66

HRMS (ESI):
calcd. for $C_{26}H_{20}N_2O_6$ $[M+Na]^+$: 479.1219.
The peak at 479.1219 was identified as shown in *Figure 3*.

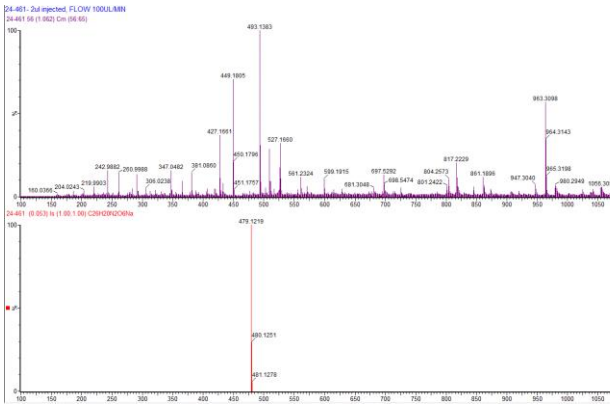
In summary, an α-methyl NNAA building block equipped with a phthalimide group tail, namely compound **(7)**, was prepared in good yield in a multistep synthesis by the generation of the lithium enolate for (2R,4R)-4-methyl-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate and quenching with 2-chloromethyl-isoindole-1,3-dione, to achieve chirality transfer, thereby providing compound **(7)** with no sign of any minor diastereomers. The α-methyl NNAA building block can



(a) ^{1}H-NMR spectra of compound **(7)** in DMSO-d_6 at 100°C



(b) ^{13}C-NMR spectra of compound **(7)** in DMSO-d_6 at 100°C



(c) HRMS spectra of compound **(7)**

Figure 3: Characterization of compound **(7)**

be used in the preparation of peptide and drug discovery processes [23]-[30].

4. Conclusions

A multistep synthesis pathway was developed to prepare an α-methyl, non-natural amino acid building block equipped with a phthalimide group tail, namely compound **(7)**, in good yield with no sign of any minor diastereomers. The power of chiral auxiliaries in asymmetric synthesis was demonstrated using the highly utilized and well-understood Evans oxazolidinone system. This α-methyl, non-natural amino acid building block could be used in the preparation of peptide and drug discovery processes in the future.

SYMBOLS

NNAA:	non-natural amino acid
^{1}H NMR:	Proton Nuclear Magnetic Resonance
^{13}C NMR:	Carbon-13 Nuclear Magnetic Resonance
NMR:	Nuclear Magnetic Resonance
DCM:	dichloromethane
Cbz:	benzyloxycarbonyl
$SOCl_2$:	thionyl chloride
THF:	tetrahydrofuran
$NaHCO_3$:	sodium bicarbonate
Na_2SO_4:	sodium sulphate
NMP:	N-Methyl-2-pyrrolidone
LiHMDS:	Lithium bis(trimethylsilyl)amide
NH_4Cl:	ammonium chloride
DMSO-d_6:	dimethyl sulfoxide-d_6

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