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Enantiospecific synthesis of (1S,2S,5R,6S)-2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid by a modified Corey-Link reaction[1]

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Abstract:

(*1S,2S,5R,6S*)-2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740) was synthesised enantiospecifically from a sugar derived enantiomerically pure cyclopentenone. The α-amino acid stereogenic centre was formed by reacting the ketone with chloroform anion and then the alcohol so formed was reacted with sodium azide/DBU in methanol to give an azido ester. Critically, this modified Corey-Link reaction gives the opposite stereochemical outcome to the traditional Bucherer-Bergs and Strecker reactions. The azide was reduced and acylated, the 1,2 diol deoxygenated and the protecting groups removed to give LY354740 with an e.e.> 98%.

Keywords: α-Amino acid synthesis; Corey-Link reaction; S_N2 reaction; cyclopropanation

L-Glutamic acid is the endogenous neurotransmitter activating two types of excitatory amino acid (EAA) receptors: the ion channel-coupled or ionotropic glutamate receptors (iGluRs) and the G-protein coupled or metabotropic glutamate receptors (mGluRs). These neurotransmitter receptors mediate or modulate synaptic transmission in the mammalian central nervous system (CNS) [2,3], and are implicated in the pathogenesis of many CNS disorders [4,5]. The mGluRs have been subdivided into three groups on the basis of protein sequence homology, pharmacology and signal transduction mechanisms [6-10]. Recently, LY354740 [(+)-**1**] (Scheme 1) has been found to be a highly potent and specific agonist for the group 2 mGluRs [11], displaying both anticonvulsant and anxiolytic properties in rodents [12]. The fact that all the group 2 mGluR agonist activity resides in a single isomer led us to report [13] the first enantiospecific synthesis of this compound.

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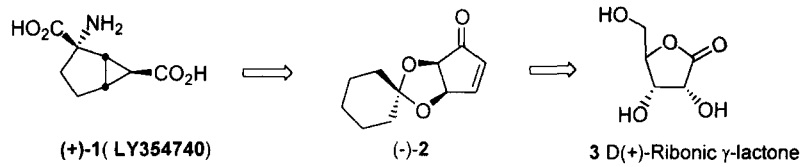
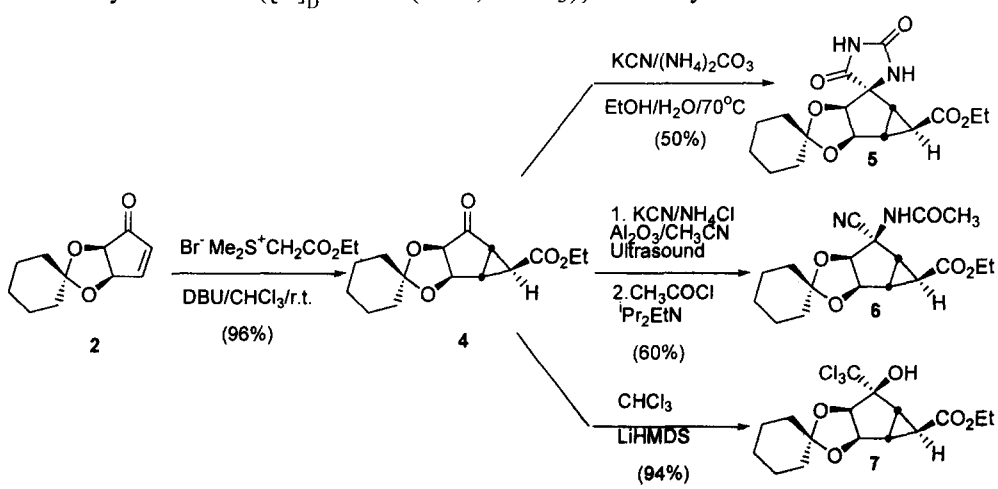
This original synthesis started with the readily available cyclopentenone **2,** obtained from commercially available *D*(+)-ribonic γ-lactone **3** [14]. The active isomer LY354740 was determined to have *1S,2S,5R,6S* stereochemistry [13]



Scheme 1

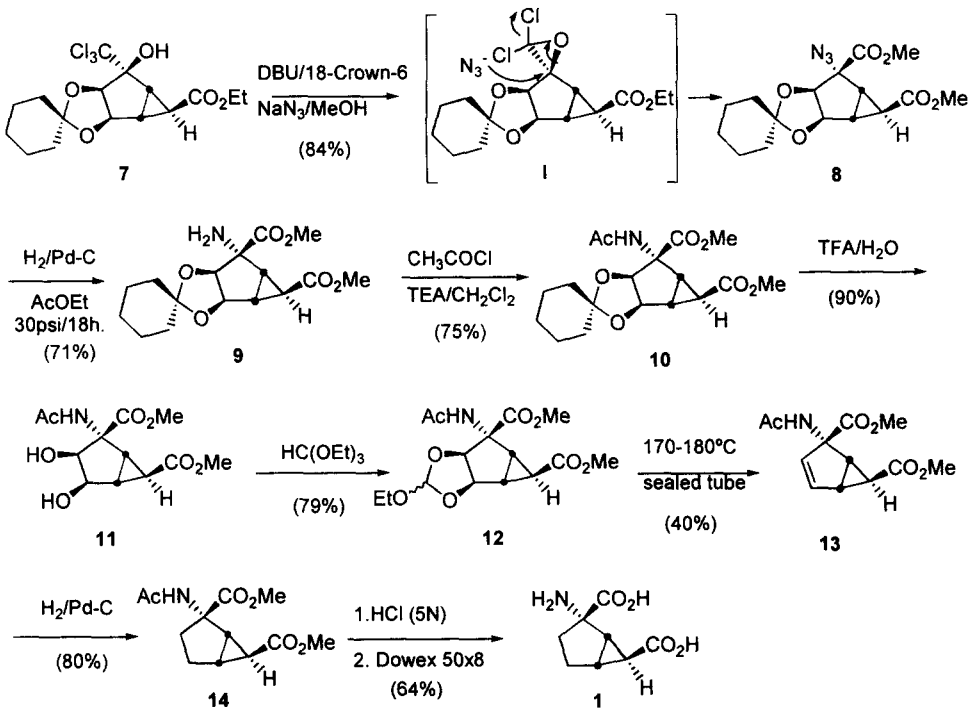
In this communication we report an alternative enantiospecific synthesis of **1**, where the α-amino acid stereogenic centre was created by a modified Corey-Link reaction [15], enabling us to access the isomer with the carboxy group on the more hindered face. The stereochemical outcome is the opposite of that observed with both the Bucherer-Bergs and Strecker reactions.

Cyclopropanation of the protected dihydroxycyclopentenone **2** was achieved using ethyl (dimethylsulfuranylidene)-acetate (EDSA), generated *in situ* from the corresponding sulfonium bromide and DBU in $CHCl_3$ at RT. Under these reaction conditions [16], the *exo* adduct **4** $\{[\alpha]_D = -43.2^\circ$ (c 1.0, $CHCl_3)\}$ was obtained exclusively in almost quantitative yield. As we previously reported [13], both Bucherer-Bergs [17] and Strecker reactions [18] gave rise to the corresponding spirohydantoin **5** or the aminonitrile **6**, where the configuration of the newly created stereogenic centre was the opposite to the one desired, due to attack of the nucleophile on the less sterically hindered face of the imine intermediate (Scheme 2). The same stereochemical outcome was observed when a solution of **4** (1 eq.) and $CHCl_3$ (2 eq.) in THF was treated with LiHMDS (2 eq.) at -78°C, giving the enantiomerically pure trichloromethylcarbinol **7** $\{[\alpha]_D = -24.7$ (c 1.5, $CHCl_3)\}$ in 94% yield.



Scheme 2

We reasoned that the Corey-Link reaction should then enable us to invert the stereochemistry of this critical stereogenic centre. Under standard conditions, using sodium azide in 1,2-dimethoxyethane and water at RT, we obtained the required α-azido acid ester contaminated with the diacid, making purification of the product difficult. In order to avoid this partial ester hydrolysis, we used DBU as a base in anhydrous methanol with 18-crown-6 as catalyst (Scheme 3). Under these reaction conditions[19], the *gem*-dichlorooxirane is probably formed and is then attacked in an S_N2 fashion by azide to give an azido acyl chloride intermediate which reacts with methanol to give the azido ester. There is also concomitant transesterification of the cyclopropyl carboxylate, to give the dimethyl diester **8** {$[\alpha]_D$ = -135.3 (c 0.45, $CHCl_3$)} in 84% yield. Hydrogenation of the azide using Pd-C catalyst gave the amino diester **9** {$[\alpha]_D$ = -79.2 (c 0.5, $CHCl_3$)} in 71% yield. The amino group was acetylated under standard conditions to give the acetamido derivative **10** {$[\alpha]_D$ = -81.2 (c 1.5, $CHCl_3$)}in 75% yield. The stereochemistry of the quaternary centre was established by nOe experiments proving that the Corey-Link reaction proceeded with complete inversion.



Scheme 3

Deoxygenation of the protected 1,2-diol **10** was accomplished by deprotection of the ketal with TFA/H_2O yielding **11** {$[\alpha]_D$ = -56.2 (c 0.5, MeOH)} in 90% yield, followed by treatment with triethyl orthoformate [20], to form the corresponding cyclic orthoformate **12** as a mixture of diastereomers in 79% yield. Finally, **12** was deoxygenated by heating in a sealed tube at

170-180°C for 5 h., to give the cycloalkene derivative **13** in 40% yield. Hydrogenation of the double bond using Pd-C catalyst provided the *N*-acetamido diester **14** {$[\alpha]_D$ = -7.0 (c 0.6, $CHCl_3$)} in 80% isolated yield, which was hydrolysed by refluxing in HCl (5N). **LY354740 [(+)-1]** {$[\alpha]_D$ = +37.6 (c 0.65, HCl 1N)} (64% yield) was finally isolated in Zwitterionic form by ion exchange chromatography (Dowex 50WX8-100) of the corresponding hydrochloride. This material had the same optical rotation as the compound obtained by us in an alternative synthesis [13].

In summary, we present here an alternative enantiospecific approach to **LY354740 [(+)-1]** starting from a readily available optically pure starting material, where the construction of the α-amino acid quaternary stereogenic centre is achieved using a modified Corey-Link reaction on the enantiomerically pure trichloromethylcarbinol **7**. This reaction is particularly valuable as it gives the opposite stereochemical outcome to the Bucherer-Bergs or Strecker reactions with the carboxy group on the more hindered face of the molecule. We believe this modified Corey-Link reaction will be of value in other syntheses where traditional methods of converting ketones to amino acids give the undesired isomer.

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References and Notes

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[19] All compounds were characterised on the basis of their IR, ^{1}H-NMR, ^{13}C-NMR spectroscopic data and combustion analysis (C, H, N). The Corey-Link reaction conditions were modified as follows: To a solution of 7 (100 mg, 0.25 mmol) in anhydrous methanol (5 mL), sodium azide (48 mg, 0.75 mmol) and a catalytic amount of 18-crown-6 (1 mg) were added under argon. To this solution DBU (0.185 mL, 1.25 mmol) was added and the reaction stirred at room temperature for 6 hours. The reaction was worked up by adding diethyl ether (15 mL) and washing with a saturated solution of NH_4Cl. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting oily residue was purified by flash chromatography (hexane:ethyl acetate, 4:1) yielding **8** (84%) as a white solid (m.p.: 111-113°C).
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