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Asymmetric synthesis of (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740)

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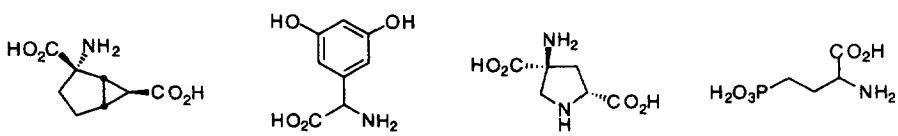
Abstract: The asymmetric synthesis of (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740) **1**, a potent and selective group 2 mGluR agonist, has been accomplished starting from the readily available enantiomerically pure cyclopentenone **4**. Thus, cyclopropanation with ethyl(dimethylsulfuranylidene)acetate generated *in situ* with DBU, followed by deketalization gave rise to the dihydroxy bicyclic ketone **9**. After protecting the ketone as 1,3-dioxolane and its transformation to the orthoformate **11**, this was pyrolytically deoxygenated in a sealed tube to the bicyclic enone **13**. The synthesis was completed after hydrogenation, stereoselective Bucherer–Bergs reaction and hydantoin hydrolysis, yielding LY354740 (+)-**1** with an e.e. ≥98%. © 1997 Elsevier Science Ltd. All rights reserved.

Excitatory amino acid (EAA) receptors are generally accepted as the main transmitter receptors mediating synaptic excitation in the mammalian central nervous system (CNS),[1] being implicated in the pathogenesis of many CNS disorders.[2] L-Glutamic acid is the endogenous neurotransmitter activating two types of EAA receptors: the ion channel-coupled or ionotropic glutamate receptors (iGluRs) and the G-protein coupled or metabotropic glutamate receptors (mGluRs). The mGluRs have been subdivided into three groups on the basis of protein sequence homology, agonist pharmacology and signal transduction mechanisms.[3] Group 1 mGluRs are coupled to phospholipase C and are selectively activated by the compound 3,5-dihydroxyphenylglycine (3,5-DHPG, Figure 1).[4] Group 2 and group 3 mGluRs are negatively coupled to adenylate cyclase. Group 2 mGluRs are selectively activated by 2*R*,4*R*-4-aminopyrrolidine-2,4-dicarboxylate (2*R*,4*R*-APDC, Figure 1),[5] while group 3 mGluRs are selectively activated by L-4-aminophosphonobutyrate (L-AP4, Figure 1).[6] LY314582 (±)-**1** has recently been discovered to be a highly potent and specific agonist for the group 2 mGluRs[7a] and to display anticonvulsant and anxiolytic properties in rodents.[7b] All the group 2 mGluR agonist-related activity of this compound has been found to reside in the (+)-enantiomer, LY354740 [(+)-**1**], obtained by classical resolution techniques.[7b]



(±)-1 LY314582
(+)-1 LY354740

3,5-DHPG

2*R*,4*R*-APDC

L-AP4

Figure 1.

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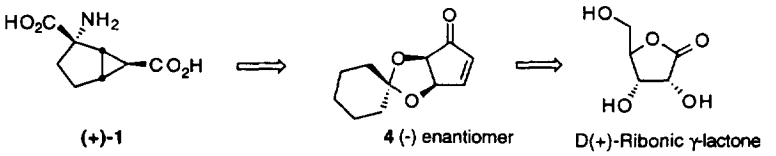
In this paper we report an asymmetric synthesis of (+)-**1** as a means to specifically access the active enantiomer and to prove its absolute configuration. The retrosynthetic analysis to obtain **1** (Scheme 1) led us to the enantiomerically pure dihydroxycyclopentenone **4**, for which its (−)-enantiomer could be obtained from D-(+)-ribonic γ-lactone[8] while the (+)-enantiomer is obtained from D-mannose.[9] For our synthetic approach we decided to start with the (−)-enantiomer of **4** which could be readily prepared in gram quantities.



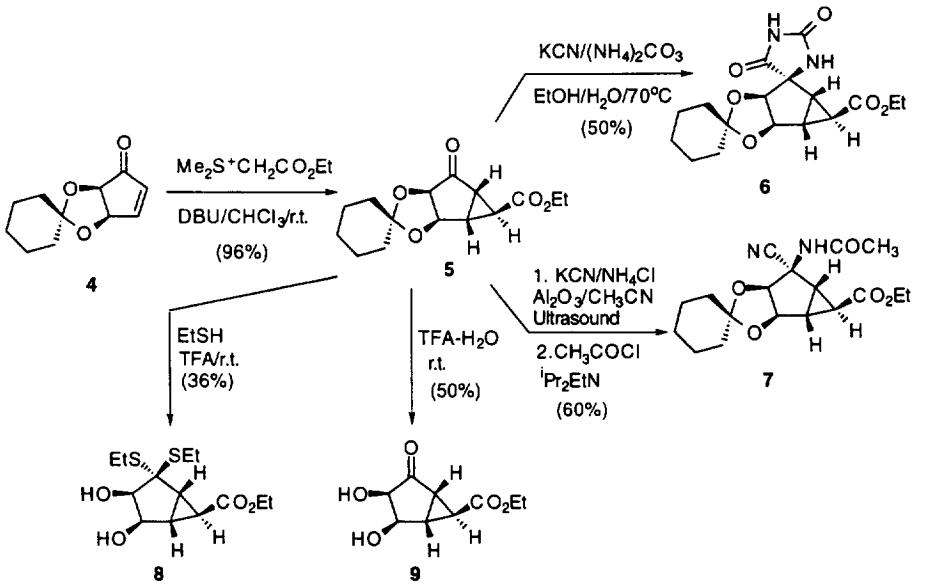
Scheme 1.

Cyclopropanation of the protected dihydroxycyclopentenone **4** was achieved using ethyl-(dimethyl sulfuranylidene)-acetate (EDSA), generated *in situ* from the corresponding sulfonium bromide and DBU in $CHCl_3$ at r.t. Under these reaction conditions,[10] the exo-adduct **5** {$[\alpha]_D=-43.2$ (c=1.0, $CHCl_3$)} was obtained exclusively in almost quantitative yield (Scheme 2). Treatment of **5** with ammonium carbonate and potassium cyanide in ethanol/water (Bucherer–Bergs reaction conditions),[11] gave rise to the single spirohydantoin **6** {$[\alpha]_D=-107.2$ (c=1.0, $CHCl_3$)} in 50% yield. The stereochemical assignment of the created quaternary carbon was made on the basis of nOe experiments, showing that the NH-1′ is β-oriented. This stereochemical result is in accordance with the general stereochemical outcome of the Bucherer–Bergs reaction,[12] the thermodynamically controlled product being the one with the C-4′ carbonyl group in the less hindered position. As the stereochemistry at the α-amino acid center was opposite to the one desired, **5** was reacted under ultrasound-promoted Strecker conditions[13] affording the corresponding amino nitrile which, without purification, was acetylated yielding **7** {$[\alpha]_D=-105.7$ (c=1.0, $CHCl_3$)} in 60% overall yield. Again, nOe experiments on **7** revealed the β-orientation of the amino group. The fact that in both experiments we did not detect any of the other diastereoisomers, led us to postulate that the stereoelectronic effect[14] of the oxygen atom at the α-position of the ketone, must drive the 1,2-nucleophilic attack to the imine intermediate of both Bucherer or Strecker reactions.

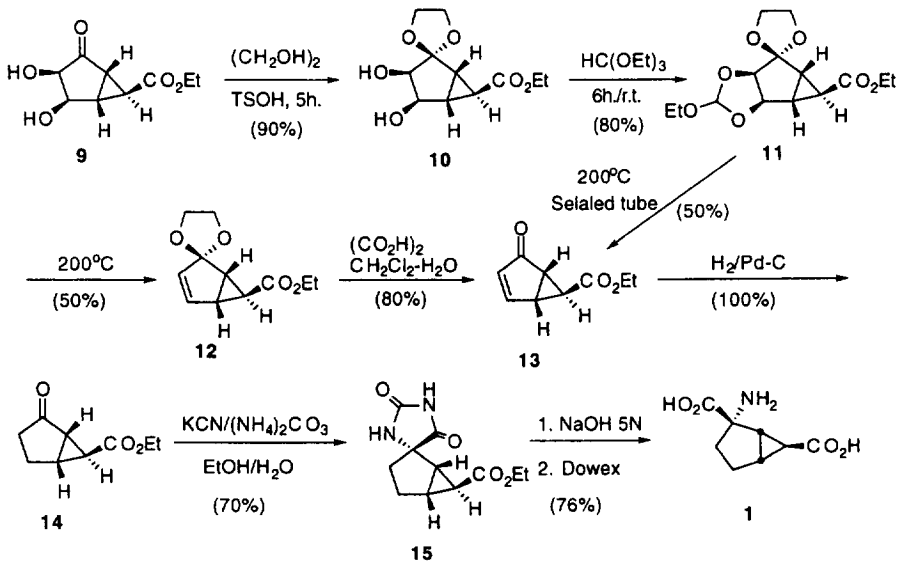
A way to avoid this problem was to direct the synthesis to the generation of the chiral bicyclopentanone **14**, a substrate for which the Bucherer–Bergs reaction is known to produce the hydantoin with the desired relative stereochemical configuration.[7b] Thus, ketal hydrolysis of **5** was accomplished using a 7:3 mixture of TFA–H_2O[15] at r.t., yielding **9** {$[\alpha]_D=+74.0$ (c=1.0, $CHCl_3$)} in 50% isolated yield. Other hydrolytic conditions tested, such as transketalization with EtSH[16] in neat TFA, gave rise to the 1,2-diol **8** in low yield, highlighting the difficulties associated with this kind of deprotection. Attempts to perform either the Bucherer–Bergs or Strecker reactions on **9** were unsuccessful. The stereoelectronic effects of the neighbouring hydroxyl functionality may be responsible for this unreactive behaviour.

The desoxygenation of the 1,2-diol **9** was accomplished by first protection of the ketone moiety as the 1,3-dioxolane **10** {$[\alpha]_D=-49.5$ (c=0.4, $CHCl_3$)} in 90% yield (Scheme 3), followed by transformation of the 1,2-diol into its O-ethoxymethylene derivative **11** as a mixture of diastereomers (80% yield). Pyrolysis of **11** gave a 50% yield of the protected cyclopentenone **12** {$[\alpha]_D=-204.6$ (c=1.15, $CHCl_3$)}, which was deketalizated to **13**[17] {$[\alpha]_D=-255$ (c=1.0, CH_3OH)} in 80% isolated yield. The cyclopentenone **13** could be also prepared directly from **11** (50% yield) by pyrolysis in a sealed tube.

Hydrogenation of **13** gave rise to the enantiomerically pure bicyclic cyclopentenone **14** {$[\alpha]_D=+64.3$ (c=1.0, CH_3OH)} in quantitative yield. Bucherer–Bergs reaction led to the single hydantoin **15** {$[\alpha]_D=-24$ (c=0.5, CH_3OH)} in 70% yield. Finally, basic hydrolysis followed by ion exchange chromatography yielded LY354740 (+)-**1** {$[\alpha]_D=+37.7$ (c=0.65, 1N HCl), lit[7b] $[\alpha]_D=+23.18$ (c=1.0,



Scheme 2.



Scheme 3.

1N HCl)} in 76% isolated yield. The enantiomeric purity of (+)-**1** was established by ^{19}F-NMR (detection limit was determined by doping experiments) of the Mosher's amides[18] of the corresponding methyl esters. Thus, esterification of (+)-**1** [$CH_3OH/HCl(g)$], followed by Mosher amide formation [(S)-(+)- and (R)-(−)-methoxy-α-(trifluoromethyl)phenylacetyl chloride in the presence of propylene oxide] gave an e.e. ≥98%. The absolute configuration of LY354740 is therefore established to be 1*S*,2*S*,5*R*,6*S*.

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