Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 4, pp. 511–514, 1997

Printed in Great Britain
PII: S0957-4166(97)00001-3
0957-4166/97 $17.00 + 0.00

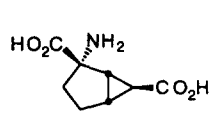
Asymmetric synthesis of (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740)

Carmen Domínguez,[a,*] Jesús Ezquerra,[a] Lourdes Prieto,[b] Modesta Espada[b] and Carmen Pedregal[b]

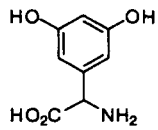
[a] Centro de Investigación Lilly, S. A. Paraje de la Cruz S/N, 28130 Valdeolmos, Madrid, Spain
[b] Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain

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.

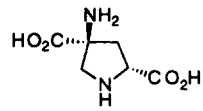
Excitatory amino acid (EAA) receptors are generally accepted as the main transmitter receptors mediating synaptic excitation in the mammalian central nervous system (CNS),[1] being implicated in the pathogenesis of many CNS disorders.[2] L-Glutamic acid is the endogenous neurotransmitter activating two 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]



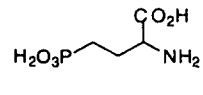
(±)-1 LY314582
(+)-1 LY354740



3,5-DHPG



2*R*,4*R*-APDC

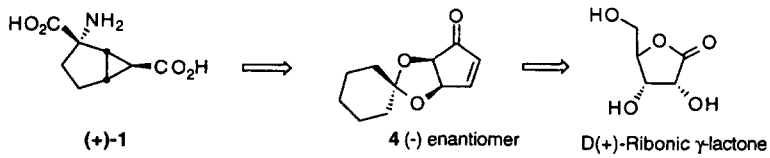


L-AP4

Figure 1.

* Corresponding author. Email: dominguez_carmen@lilly.com

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.



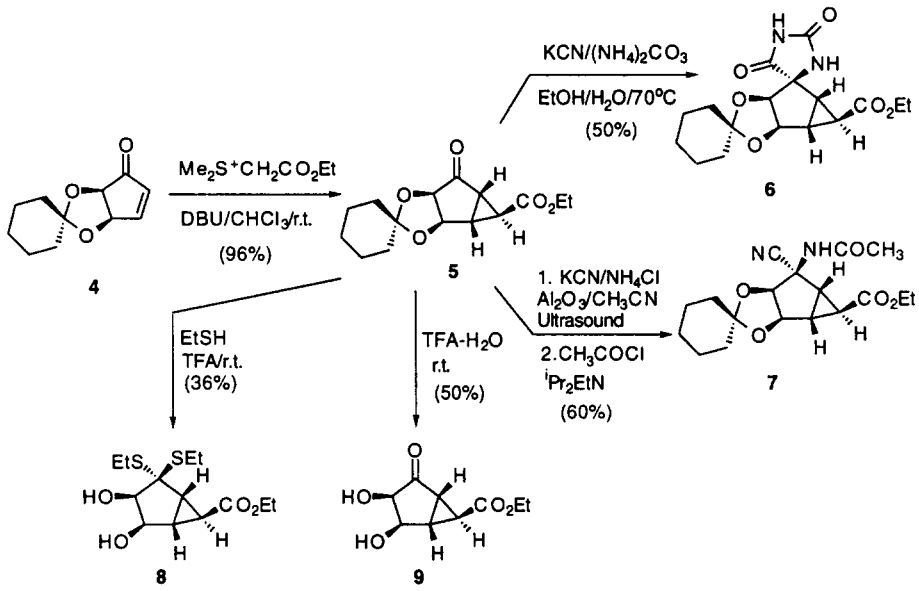
Scheme 1.

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.

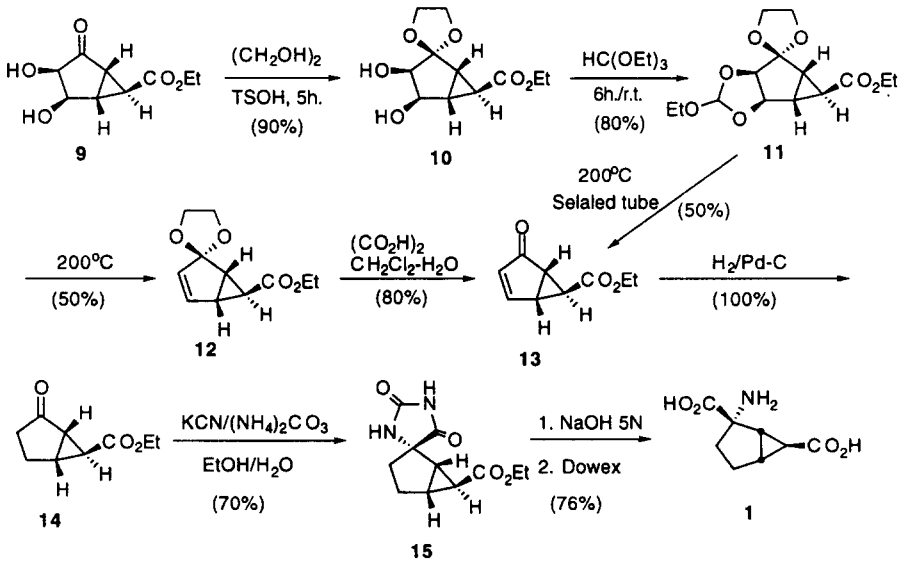
A way to avoid this problem was to direct the synthesis to the generation of the chiral bicyclopentanone **14**, a substrate for which the Bucherer–Bergs reaction is known to produce the hydantoin with the desired relative stereochemical configuration.[7b] Thus, ketal hydrolysis of **5** was accomplished 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*.

Acknowledgements

This research was supported by a **CDTI** programme (Plan concertado 94/0036) and the Spanish **FARMA III** programme (Ministerio de Industria y Ministerio de Sanidad). L. P. thanks Lilly, S. A. for

a fellowship. We are also grateful to Dr James A. Monn (Lilly Research Laboratories, Indianapolis, USA) for useful suggestions and Dr William Prowse (Lilly Research Laboratories, Erl Wood, UK) for helpful assistance in the structural assignments.

References

1. (a) Monaghan, D. T.; Bridges, R. T.; Cotman, C. W. *Ann. Rev. Pharmacol. Toxicol.* **1989**, *29*, 365. (b) Watkins, J. C.; Krogsgaard-Larsen, P.; Honoré, T. *TiPS* **1990**, *11*, 25.
2. (a) Kozikowski, A. P. in *Neurobiology of the NMDA Receptor from Chemistry to the Clinic* Alan P. Kozikowski, Editor. VCH Publishers, Inc., New York, **1991**. (b) Lodge, D. in *Excitatory Amino Acids in Health and Disease* John Wiley & Sons, Inc., New York, **1988**.
3. (a) Nakanishi, S. *Science* **1992**, *258*, 597–603. (b) Nakanishi, S.; Masu, M. *Annu. Rev. Biophys. Biomol. Struct.* **1994**, *23*, 319–348. (c) Hollmann, M.; Heinemann, S. *Annu. Rev. Neurosci.* **1994**, *17*, 31–108. (d) Schoepp, D. D.; Conn, P. J. *TiPS* **1993**, *14*, 13–20. (e) Pin, J.-P.; Duvoisin, R. *Neuropharmacol.* **1995**, *34*, 1–26.
4. (a) Ito, I.; Kohda, A.; Tanabe, S.; Hirose, E.; Hayashi, M.; Mitsunaga, S.; Sugiyama, H. *NeuroReport* **1992**, *3*, 1013–1016. (b) Birse, E. F.; Eaton, S. A.; Jane, D. E.; Jones, P. L. St. J.; Porter, R. H. P.; Pook, P. C.-K.; Sunter, D. C.; Udvarhelyi, P. M.; Wharton, B.; Roberts, P. J.; Salt, T. E.; Watkins, J. C. *Neurosci.* **1993**, *52*, 481–488. (c) Schoepp, D. D.; Goldsworthy, J.; Johnson, B. G.; Salhoff, C. R.; Baker, S. R. *J. Neurochem.* **1994**, *63*, 769–772.
5. (a) Schoepp, D. D.; Johnson, B. G.; Salhoff, C. R.; Valli, M. J.; Desai, M. A.; Burnett, J. P.; Mayne, N. G.; Monn, J. A. *Neuropharmacol.* **1995**, *34*, 843–850. (b) Monn, J. A.; Valli, M. J.; Johnson, B. G.; Salhoff, C. R.; Wright, R. A.; Howe, T.; Bond, A.; Lodge, D.; Griffey, K; Tizzano, J. P.; Schoepp, D. D. *J. Med. Chem.* **1996**, *39*, 2990–3000.
6. (a) Kristensen, P.; Suzdak, P. D.; Thomsen, C. *Neurosci. Lett.* **1993**, *155*, 159–162. (b) Tanabe, Y.; Nomura, A.; Masu, M.; Shigemoto, R.; Mizuno, N.; Nakanishi, S. *J. Neurosci.* **1993**, *13*, 1372–1378. (c) Nakajima, Y.; Iwakabe, H.; Akazawa, C.; Nawa, H.; Shigemoto, R.; Mizuno, N.; Nakanishi, S. *J. Biol. Chem.* **1993**, *268*, 11868–11873.
7. (a) Schoepp, D. D.; Johnson, B. G.; Wright, R. A.; Salhoff, C. R.; Mayne, N. G.; Wu, S.; Cockerham, S. L.; Burnett, J. P.; Belagaje, R.; Bleakman, D.; Monn, J. A. *Neuropharmacology* **1996**, *in press*. (b) Monn, J. A.; Valli, M. J.; Massey, S. M.; Wright, R. A.; Salhoff, C. R.; Johnson, B. R.; Howe, T.; Alt, C. A.; Rhodes, Gç A.; Robey, R. L.; Griffey, K. R.; Tizzano, J. P.; Kallman, M. J.; Helton, D. R.; Schoepp, D. D. *J. Med. Chem.* (in review).
8. Wolfe, M. S.; Borcherding, D. R.; Borchardt, R. T. *Tetrahedron Lett.* **1989**, *30*, 1453–1456.
9. Borcherding, D. R.; Scholtz, S. A.; Borchardt, R. T. *J. Org. Chem.* **1987**, *52*, 5457–5461.
10. Collado, I.; Dominguez, C.; Ezquerra, J.; Pedregal, C.; Monn, J. A. (unpublished results).
11. Edward, J. T.; Jitrangsri, C. *Can. J. Chem.* **1975**, *53*, 3339–3350.
12. Avendaño, C.; Trigo, G. G., 'The Chemistry of Hydantoins', in *Advances in Heterocyclic Chemistry* Academic Press, New York, **1985**, *38*, 177–228.
13. Hanafusa, T.; Ichihara, J.; Ashida, T. *Chem. Lett.* **1987**, 687–690.
14. For study dealing with the stereoelectronic effects on the reduction of 2-(methylthio) and 2-(methylsulfonyl)cyclohexanones see: Carreño, M. C.; Domínguez, E.; García-Ruano, J. L.; Rubio, A. *J. Org. Chem.* **1987**, *52*, 3619–3625.
15. Cook, S. L.; Secrift III, J. A. *J. Am. Chem. Soc.* **1979**, *101*, 1554–1564.
16. Ulibarri, G.; Nadler, W.; Skrydstrup, T.; Audrain, H.; Chiaroni, A.; Riche, C.; Crierson, D. S. *J. Org. Chem.* **1995**, *60*, 2753–2761.
17. (+)-**13** {$[\alpha]_D$=+251 (c=1.12, CH_3OH)} has recently been described. Moher, E. *Tetrahedron Lett.* **1996**, *37*, 8637–8640.
18. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.

(Received in UK 16 December 1996)