Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 5, pp. 669–671, 1997

Printed in Great Britain
PII: S0957-4166(97)00028-1
0957-4166/97 $17.00 + 0.00

(*S*)-Ethyl 4,4-dimethyl pyroglutamate as a new 'quat' chiral auxiliary in aldol condensations

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Abstract: Enolates **I**, derived from the *N*-propionyl derivative of the 'quat' chiral auxiliary (*S*)-ethyl 4,4-dimethyl pyroglutamate **4** undergo highly stereoselective aldol reactions, which upon hydrolysis and removal of the chiral auxiliary yields the (2*R*,3*R*)-3-hydroxy-2-methylpropionic acid **9** in homochiral form. Remarkably, the stereogenic center of **4** was not affected during all the chemical transformations and it could be regenerated after the process in 70% yield. © 1997 Elsevier Science Ltd. All rights reserved.

Enantiomerically pure α-hydroxy acids constitute useful building blocks for natural products synthesis[1] and several methods have been developed to achieve these kinds of compounds. One of the more explored methodologies has been the use of chiral auxiliaries **1–3** (Figure 1), where it is possible to control the stereoselectivity of reactions of *N*-acyl enolates attached to these chiral auxiliaries. Thus, original Evan's oxazolidin-2-ones **1a,b**[2] or new derivatives like **1c**[3] have been used extensively. Another related auxiliary, **2a**[4] has been used successfully in stereoselective conjugate additions and Diels–Alder cycloadditions of attached α,β-unsaturated *N*-acyl fragments. However, this substrate is inappropriate for controlling the chemoselective enolate generation of attached *N*-acyl fragments to the 2-pyrrolidinone due to the competition of lactam enolate. A further modification of **2** was recently developed,[5] where the competition on the enolate generation in **3a–d** is precluded by the introduction of two methyl groups on the parent substrate. Both chiral substrates **2** and **3** are modified pyroglutamic derivatives, where the acidic moiety has been partially or fully reduced, to a protected alcohol or an alkyl group respectively, in order to ensure the asymmetric induction and to prevent the epimerization of the pyroglutamic acid stereogenic center.

In this communication, we would like to report the first successful use of the (*S*)-ethyl 4,4-dimethyl pyroglutamate **4** as a 'quat' chiral auxiliary, for which its *N*-acyl enolates undergo aldol reactions with excellent stereoselectivities without epimerization of the pyroglutamate stereogenic center.

(*S*)-Ethyl 4,4-dimethyl pyroglutamate **4** was prepared from the *N*-BOC-protected ethyl pyroglutamate[6] **5** by double alkylation of the corresponding lithium lactame enolate with CH_3I following the method recently developed by us.[7] After the urethane protecting group removal with TFA, **4** {$[\alpha]_D^{22}=-14.6$, (c 1.44, $CHCl_3$)} was obtained with a 70% overall yield from **5** (Scheme 1).

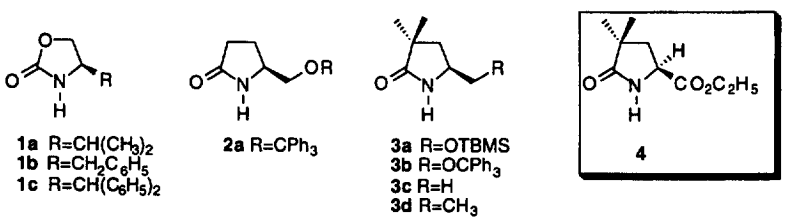

Figure 1.

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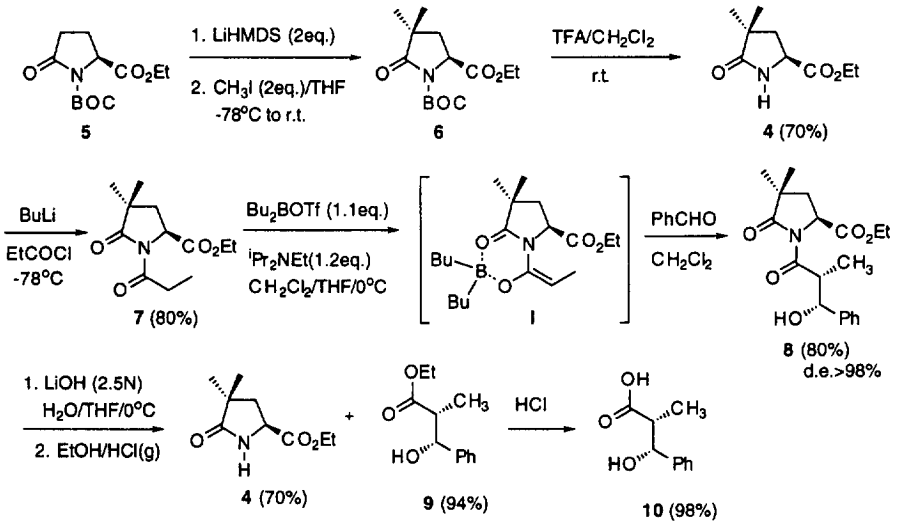
The *N*-propionyl derivative **7** {$[\alpha]_D^{22}=-31.5$, (c 1.43 CH_2Cl_2)} was achieved in 80% yield, by treatment of **4** with butyllithium and propionyl chloride. The acyl enolate of **7** was generated following the same reactions conditions as those used by S. G. Davies[8] for the asymmetric aldol reaction using the 'quat' chiral auxiliary **3c**. Thus, the reaction of the (Z)-boron enolate[9] **I** with benzaldehyde resulted in the formation of the *syn* product **8** {$[\alpha]_D^{22}=-12.8$, (c 1.25, CH_2Cl_2)} in 70% isolated yield.



Scheme 1.

The NMR analysis of the reaction crude mixture did not show any other reaction product, thus representing a diastereomeric excess (d.e.) ≥98%. The *syn* relative stereochemistry of the aldol product **8** was stabilised on the basis of ^{1}H-NMR coupling constant analysis ($J_{H2'-H3'}$=3.6 Hz). The absolute stereochemistry of the new created stereogenic centers was assigned after removal of the chiral auxiliary. Thus, hydrolysis of **8** with LiOH (2.5N) in a 1:1 mixture of THF/H_2O at 0°C resulted in a clean hydrolysis of the *N*-acyl bond which after esterification (EtOH/HCl(g)) give rise to a mixture of ethyl (2*R*,3*R*)-3-hydroxy-2-methyl-3-phenylpropionic acid **9** (94% yield) {$[\alpha]_D^{22}=-18$, (c 0.9, CH_2Cl_2)}, and the 'quat' **4** (70% yield) which were separated by flash chromatography. Finally, **9** was hydrolyzed to the (2*R*,3*R*)-3-hydroxy-2-methyl-phenylpropionic acid **10** (98% yield) {$[\alpha]_D^{22}=+25.5$, (c 0.94, CH_2Cl_2), lit.[8] $[\alpha]_D^{22}=+26.8$ (c 0.5, CH_2Cl_2)}. In none of all these transformations the pyroglutamate stereogenic center was altered,[10] showing the uselfulness of this new chiral auxiliary.

Further uses of this novel chiral auxiliary and others with different substituents at the C-4 position[7] are currently investigated in these laboratories and will be reported in due course.

Acknowledgements

This research was supported by the Spanish **FARMA III** programme (Ministerio de Industria y Ministerio de Sanidad). J. M. is grateful to Lilly, S. A. for a fellowship.

References

1. Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach.* Pergamon Press: New York, **1983**, Chapter 2.
2. For a review see: Heatcock, C. H. *Aldrichimica* **1990**, *23*, 99–111.
3. Sibi, M. P.; Deshpande, P. K.; Ji, J. *Tetrahedron Lett.* **1995**, *36*, 8965–8967.
4. (a) Tomioka, K.; Suenaga, T.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 369–372. (b) Kanai, M.; Muraoka, A.; Tanaka, T.; Sawada, T.; Ikota, N.; Tomioka, K. *Tetrahedron Lett.* **1995**, *36*, 9349–9352.

5. Davies, S. G.; Doisneau, G. J.-M.; Prodger, J. C.; Sanganee, H. J. *Tetrahedron Lett.* **1994**, *35*, 2369–2372.
6. Ethyl pyroglutamate was prepared as described by: Silverman, R. B.; Levy, M. A. *J. Org. Chem.* **1980**, *45*, 815–818. (b) The *N*-urethane protection was made as described by: Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424–2426
7. Ezquerra, J.; Pedregal, C.; Rubio, A.; Vaquero, J. J.; Matía, M. P.; Martín, J.; Diaz, A.; García Navío, J. L. *J. Org. Chem.* **1994**, *59*, 4327–4331.
8. Davies, S. G.; Doisneau, G. J.-M.; Prodger, J. C.; Sanganee, H. J. *Tetrahedron Lett.* **1994**, *35*, 2373–2376.
9. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
10. To demostrate that the optical purity of **4** was not altered, it was transformed into the corresponding ethyl 4,4-dimethyl prolinate and the ee was measured on its Mosher's amide (see ref.[7]).

(Received in UK 2 January 1997)