Tetrahedron Letters,Vol.30,No.9 pp 1071-1072,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ENANTIOSELECTIVE SYNTHESIS OF β-HYDROXY-α-AMINOPHOSPHONIC ACID PRECURSORS

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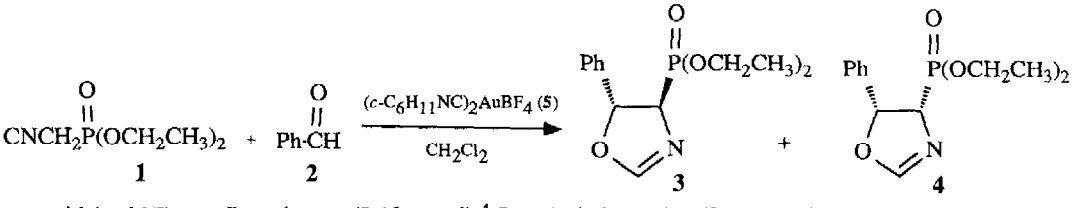
Summary: The gold(I) catalyzed aldol reaction of diethyl α-isocyanomethylphosphonate with benzaldeyde gave the oxazoline **3**, a β-hydroxy-α-aminophosphonic acid precursor, with high enantio- and diastereoselectivity (98 % *trans*, 85 % ee) by employing a chiral ferrocenylamine ligand. The use of ^{31}P NMR spectroscopy with the chiral solvating agent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol was found to be a powerful tool for determination of optical purity.

The biological activity of α-aminophosphonic acid analogues of the naturally occurring amino acids[1,2] has resulted in a considerable research effort directed towards developing suitable synthetic methodologies for their preparation. Despite the importance of α-aminophosphonic acid derivatives, few general enantioselective procedures exist for their preparation.

Schöllkopf *et al.* reported the preparation of the substituted 2-oxazoline-4-ylphosphonate **3** by the sodium cyanide-catalyzed reaction of diethyl isocyanomethylphosphonate, **1**, with **2**.[2] Quite recently, Hayashi and co-workers have described an elegant diastereo- and enantioselective synthesis of oxazolines by the gold(I)-catalyzed reaction of alkyl α-isocyanoacetates with aldehydes utilizing chiral ferrocenylamine ligands.[3] These results suggested that an asymmetric synthesis of oxazoline-4-ylphosphonates could be developed that would provide a facile route to enantiomerically pure β-hydroxy-α-aminophosphonic acids upon hydrolysis.

A 1,2-dichloroethane solution (10 mL) of **1** (10 mmol) and **2** (10 mmol) in the presence of bis(cyclohexyl



isocyanide)gold(I) tetrafluoroborate (0.13 mmol),[4] **5**, and triethylamine (0.13 mmol), which was heated at 60 °C for three days, gave a 89:11 mixture (GLC) of **3** and **4**, respectively (44 % distilled). In the $^{31}P\{^1H\}$ NMR spectrum of the reaction mixture, two singlets were observed at δ 22.2 and δ 18.6, which were assigned to the *trans* and *cis* isomers, respectively. Repeating the reaction of **1** (10 mmol) with **2** (10 mmol) using **5** (0.13 mmol) and the chiral ligand (*R*)-N-methyl-N-[2-(dimethylamino)ethyl]-1-[(*S*)-1',2-bis(diphenylphosphino)-ferrocenyl]ethylamine[3] (0.13 mmol), (*R*)-(*S*)-**6**, gave a 98:2 ratio (GLC) of the *trans*:*cis* isomers **3** and **4** (54 % distilled).[5,6] The assignment of the *trans* geometry to the major product obtained was based upon the

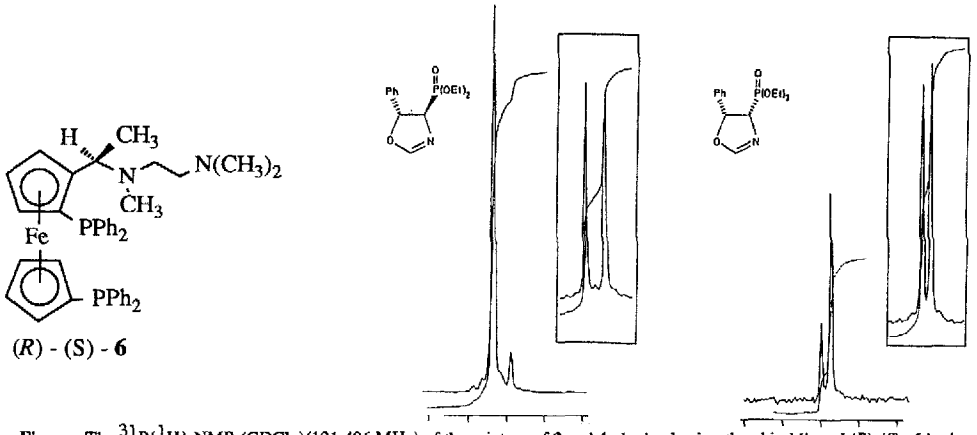


Figure. The $^{31}P\{^1H\}$ NMR ($CDCl_3$)(121.496 MHz) of the mixture of **3** and **4** obtained using the chiral ligand (*R*)-(*S*)- **6** in the presence of (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol. The spectrum of the corresponding racemic product is shown within the boxed inserts.

observation of identical J_{HP} and J_{HH} phosphorus-proton and proton-proton coupling constants to those reported by Schöllkopf.[2]

Although Pirkle and co-workers have demonstrated the use of chiral 1-aryl-2,2,2-trifluoroethanol solvating agents with ^1H NMR for the determination of enantiomeric purity, their use in combination with ^{31}P NMR has not been exploited.[7] In the $^{31}P\{^1H\}$ NMR (121.496 MHz) spectrum of the reaction mixture upon addition of (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol, four distinct resonances were observed that were assigned to the enantiomers of the *trans* and *cis* isomers. The resonances for the enantiomers of the *trans* and *cis* isomers were separated by 0.05 and 0.03 ppm, respectively. An enantiomeric excess (ee) of 85 % for **3** and 51 % for **4** was determined by integration of the peak areas. In a control experiment, the addition of (*S*)-(+)-2,2,2-trifluoro-1- (9-anthryl)ethanol to the racemic modification made without a chiral catalyst gave four resonances in the $^{31}P\{^1H\}$ NMR spectrum with the peak areas expected for a mixture of racemic **3** and **4**. In another experiment, the use of (*S*)-(*R*)-**6** led to the formation of the opposite *trans* and *cis* oxazoline isomers in identical diastereoselectivity and enantiomeric excess to those obtained with (*R*)-(*S*)-**6**.

REFERENCES AND NOTES

ACKNOWLEDGMENT: The authors wish to thank CIBA-GEIGY Ltd. for support and permission to publish this work, and Miss G. Puleo for the synthetic laboratory work.

1. (a) Maier, L.; Lea, P. J. *Phosphorus Sulfur*, **1983**, *17*, 1. (b) Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc. Perkin Trans. I* **1984**, 2845 and references therein. (c) For a review, see Dhawan, B.; Redmore, D. *Phosphorus Sulfur* **1987**, *32*, 119.
2. Schöllkopf, U.; Schröder, R.; Stafforst, D. *Liebigs Ann. Chem.* **1974**, 44.
3. (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405.
4. Bonati, F.; Minghetti, G. *Gazz. Chim. Ital.* **1973**, *103*, 373.
5. (a) Only one enantiomer of both the *cis* and *trans* isomer is illustrated. (b) GLC analysis was performed on a 50 m Chirasil-L-valine column (Carlo Erba model HRGC 5300 GLC). The diastereomers were cleanly separated. The peaks for the individual enantiomers, although observable for **3**, could not be completely resolved.
6. (a) Spectral data for *trans*-**3** from the 98:2 3:4 mixture obtained, ^1H NMR ($CDCl_3$)(300.133 MHz) δ 1.35 (m, CH_3, 6 H), 4.23 (overlapping m, OCH_2 and C(4)-H, 5 H), 5.71 (dd, C(5)-H, $^3J_{HCCP}$ = 19.6 Hz, $^3J_{HCCH}$ = 7.6 Hz, 1 H), 7.11 (dd, $^4J_{HC=NCH}$ = 2.2 Hz, $^4J_{HP}$ = 4.2 Hz, 1 H), 7.36 (complex m, 5 H); MS (DI) m/e 283^+. (b) Although the absolute stereochemistry of **3** is unknown, the enantiomer illustrated is the one expected based upon the work of Hayashi.[3]
7. (a) Pirkle, W. H.; Beare, S. D.; Muntz, R. L. *Tetrahedron Lett.* **1974**, *26*, 2295. (b) Pirkle, W. H.; Hoekstra, M. S. *J. Am. Chem. Soc.* **1976**, *98*, 1832. (c) Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem.* **1977**, *42*, 384. (d) Pirkle, W. H.; Rinaldi, P. L. *J. Org. Chem.* **1977**, *42*, 3217. (e) Pirkle, W. H.; Beare, S. D.; Muntz, R. L. *J. Am. Chem. Soc.* **1969**, *91*, 4575.

(Received in Germany 14 November 1988)