Pergamon

Tetrahedron Letters, Vol. 35, No. 12, pp. 1821-1824, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0184-Y

Fluorinated Amino Acids

Part 3:[1] Synthesis of β-Difluoromethyl-m-tyrosine

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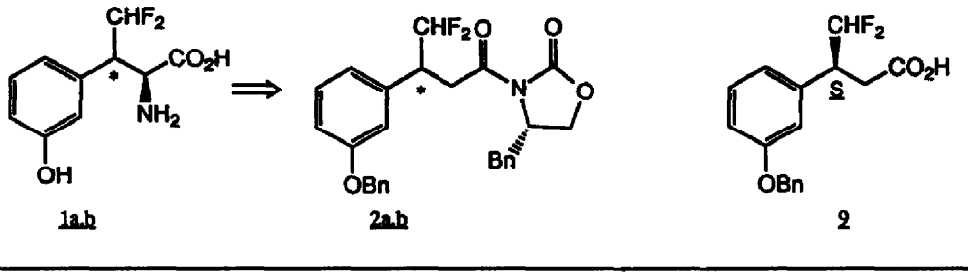
Abstract: The difluoromethyl carboxylic acid S-(+)-9 was synthesized to assign the absolute configuration of diastereomers **2a** and **2b**, and the completion of the synthesis of β-difluoromethyl-m-tyrosines **1a,b** is reported.

In the preceding letter, we detailed our approach to the synthesis of diastereomeric N-acyloxazolidinones **2a,b**, intermediates in the proposed synthesis of β-difluoromethyl-m-tyrosines **1a, b** (Scheme I). In this communication we disclose an independent asymmetric synthesis of carboxylic acid S-(+)-9 which establishes the absolute configuration of the stereocenters in **2a,b**, and we describe the completion of the synthesis of **1a,b**.

Scheme I:



A modification of our original approach[1] was used to prepare 9 (Scheme II). Commercially available aldehyde 3 was transformed through a geminal dibromoolefin to a terminal lithiated acetylide,[2] which was acylated with a Weinreb amide[3] producing ketone 4. Asymmetric reduction of 4 with R-Alpine-Borane[4] afforded R-alkynyl alcohol 5 ($[\alpha]_D^{20}$ = -3.40°(c=1.0, $CHCl_3$)) in 92% yield and 91% enantiomeric excess (ee) as determined by ^{19}F NMR analysis of the Mosher ester.[5] Reduction with lithium aluminum hydride[6] (LAH) yielded an (E)-allylic alcohol (91% ee), $[\alpha]_D^{20}$ = -5.5° (c=0.8, $CHCl_3$) which underwent an orthoester Claisen rearrangement with chirality transfer[7] to afford ester 6 ($[\alpha]_D^{20}$ = -12.1°(c=1.03, $CHCl_3$)). Ozonolysis of 6 then produced aldehyde 7; treatment of 7 with diethylaminosulfur trifluoride (DAST)[8] provided a sample of gem-difluoride S-(+)-8[9] which was saponified to acid S-9 ($[\alpha]_D^{20}$ = +23.2°(c=0.5, $CHCl_3$)).

The final phase of the synthesis of **1a,b** involves the assignment of the absolute configuration of the stereocenters of **2a,b** by correlation with **9**, and the stereoselective introduction of the amino group. The sign of rotation of S-(+)-**9** is the same as that of the previously reported carboxylic acid ($[\alpha]_D^{20}$= +39.2° (c=1.02, $CHCl_3$)),[1] obtained by removal of the chiral auxiliary from diastereomer **2a**. By correlation therefore, the absolute configuration of the stereocenter in **2a** must be S and that of **2b** is R.

For the introduction of the amino group (Scheme III), the chiral imide enolates of **2a** and **2b** were quenched by electrophilic azide transfer with 2,4,6-triisopropylbenzene sulfonyl azide (Trisyl-N_3) ; good yields of α-azido carboximides **10a** and **10b** were obtained as single diastereomers after chromatography and ^1H NMR (300 MHz, $CDCl_3$) analysis. The diagnostic -C**H**F_2 signals at δ 6.26 (td, J=2.9, 55.8 Hz) for **10a** and δ 6.04 (td, J=4.3, 56.2 Hz) for **10b** were clearly the only ones observed, and diastereoselectivity was thereby judged to be complete. The relative stereochemistry of **10a** and **10b** was assigned based on si-face delivery of the azide group.[10] Removal of the chiral auxiliary from **10a** and **10b** was effected using lithium hydroxide. Spectral analysis of the α-azido acids confirmed only single diastereomers. Catalytic hydrogenation (10% Pd/C) with concomitant hydrogenolysis of the benzyl ether completed the synthesis of **1a** and **1b**. Purification by HPLC (reverse phase)[11] afforded samples of diastereomerically pure **1a** and **1b**.[12]

In conclusion, our facile route to fluorinated amino acids **1a** and **1b** combines the synthesis and chromatographic separation of diastereomeric N-acyloxazolidinones **2a, and 2b** with the use of Evans' methodology for the electrophilic azidation of chiral imide enolates, and affords products of high diastereomeric purity for biological evaluation.

Acknowledgments: We thank Robert J. Barbuch, Dr. Edward W. Huber, and William J. Magner of our analytical chemistry department for helpful discussions and their assistance in obtaining analytical data.

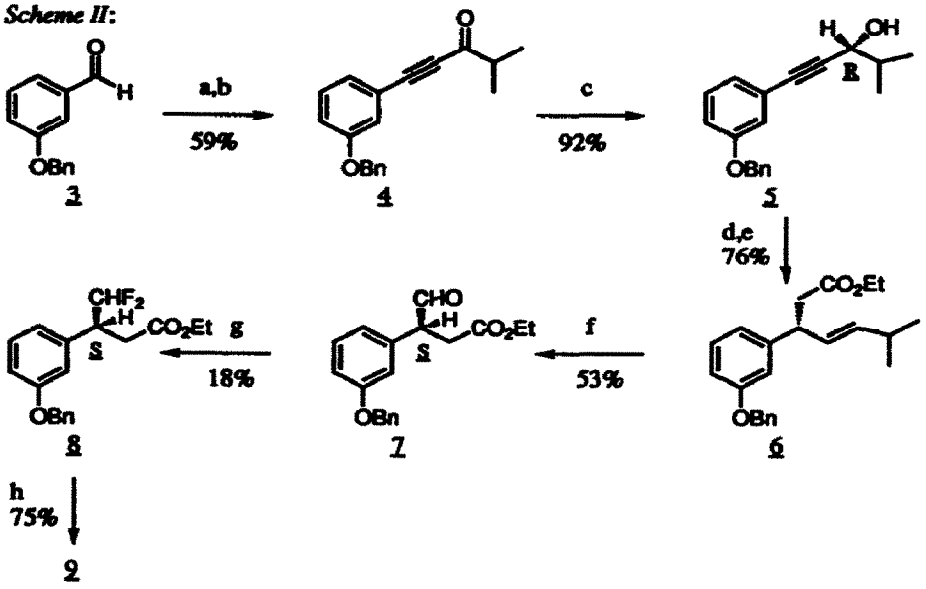
References and Notes:

1. Part 2: Sabol, J.S.; McDonald I.A. Tetrahedron Lett., preceding paper in this issue.

2. Corey, E.J.; Fuchs, P.L. . Tetrahedron Lett., **1972**, 13, 3769.

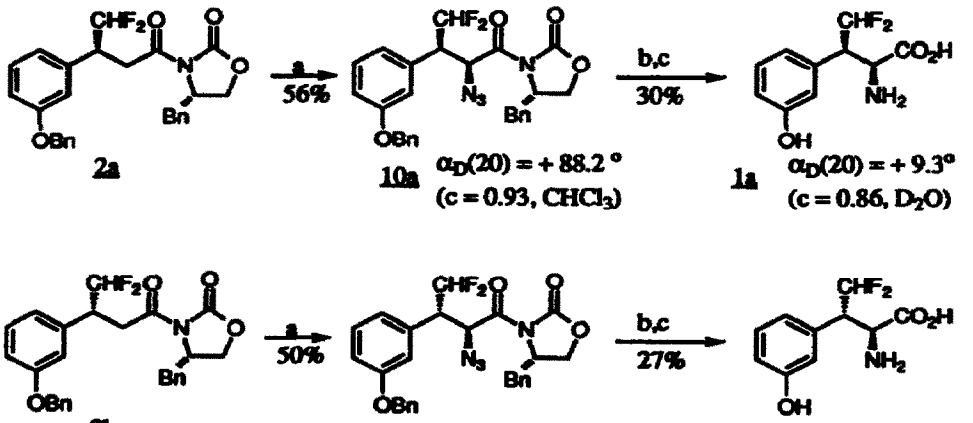
3. For a review of applications in synthesis see: Sibi, M.P. Org. Prep. Proc. Int., **1993**, 63, 57.

Scheme II:



Conditions: a) CBr_4, PPh_3, CH_2Cl_2, O °C to RT (1 h); b) n-BuLi, THF, $(CH_3)_2CHCON(OCH_3)CH_3$; c) R-Alpine Borane, THF, RT, then H_2O_2-NaOH; d) LAH, THF, reflux, (3 h); e) $CH_3C(OC_2H_5)_3$, $CH_3CH_2CO_2H$ (0.1 eq.), 135°C (2h); f) O_3, CH_2Cl_2, - 70 °C, then $(CH_3)_2S$; g) DAST, CH_2Cl_2, RT (18 h); h) LiOH, H_2O, DME, RT (2 h).

Scheme III:



2a → 10a: $\alpha_D(20) = +88.2°$ (c = 0.93, $CHCl_3$)

10a → 1a: $\alpha_D(20) = +9.3°$ (c = 0.86, D_2O)

2b → 10b: $\alpha_D(20) = +20.4°$ (c = 0.91, $CHCl_3$)

10b → 1b: $\alpha_D(20) = -45.6°$ (c = 0.86, D_2O)

Conditions: a) $[(CH_3)_3Si]_2NK$, THF, - 78 °C (0.5 h) Trisyl-N_3, then CH_3CO_2H , RT (10 h); b) LiOH, THF-H_2O; c) H_2, 10% Pd/C, EtOH-CH_3CO_2H.

4. For a discussion of the transition state leading to this enantioselectivity see: Midland, M. Organic Syntheses, **1984**, 63, 57.

5. Mosher, H.S.; Dale, J.A.; Dull, D.L. J. Org. Chem., **1969**, 34, 2543.

6. Corey, E.J.; Katzenellenbogen, J.A.; Posner, G.H. J. Am. Chem. Soc., **1967**, 89, 4245.

7. For a discussion of chirality transfer through sigmatropic rearrangements see: Hill, R.K. In Asymmetric Synthesis; Morrison, J.D.; Ed., Academic Press, Inc.: Orlando, FL 1984; Vol. III, p. 503.

8. Hudlicky, M. Org. React. (N.Y.), **1988**, 35, 513.

9. The sluggishness and poor yield for this transformation would suggest a possible erosion of chirality at this point, but for our purposes, provided an enriched sample of S-(+)-8. For a preparatively useful ,multistep alternative see 5 $\xrightarrow{\text{4 steps}}$ 7, accompanying paper in this issue.

10. For a discussion of the kinetic diastereoselection of this step see: Evans, D.A.; Britton, T.C.; Ellman, J.A. , Dorow, R.L., J. Am. Chem. Soc., **1990**, 112, 4011.

11. Purification was done using a Whatman Magnum 9 SCX (250 mm x 9.4 mm) column, with a mobile phase of 0.02M formic acid in water and a flow rate of 4 ml/min. R_T (1a)=10 min; R_T (1b)=16.5 min. Purified samples were reinjected on to a Partisil 10 SCX (250 mm x 4.6 mm.) column, same mobile phase, flow rate of 2 ml/min., and judged to be of >98% diastereomeric purity. We gratefully acknowledge the expertise of Mr. Nicholas W. Brake of our analytical chemistry department.

12. All structural assignments in the text are consistent with spectral and analytical data.

(*Received in USA* 26 *October* 1993; *revised* 21 *December* 1993; *accepted* 18 *January* 1994)