Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 6, pp. 955-960, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

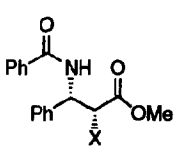
0957-4166(94)00125-1

Synthesis of (2*R*, 3*S*)-Methyl-2-fluoro-3-(N-benzoylamino)-3-phenylpropanoate: Modified Side Chain of Taxol

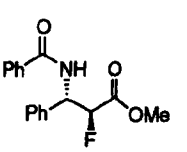
Franklin A. Davis* and Rajarathnam E. Reddy
Department of Chemistry, Drexel University, Philadelphia, PA 19104

Abstract: Methyl-2-fluoro-3-(N-benzoylamino)-3-phenylpropanoate **2** and **3**, fluorine analogs of the C-13 side chain of taxol, were synthesized by electrophilic fluorination of the dianion of methyl (*R*)-(-)-(N-benzoyl)-3-amino-3-phenylpropanoate (**4**).

Site-specific fluorination of organic molecules is of considerable current interest because of fluorine's unique ability to influence biological activity and its utility in the exploration of enzyme mechanisms.[1] Replacement of hydrogen by fluorine is usually sterically inconsequential because their van der Waals radii are similar (1.2 vs. 1.35Å). Furthermore, the high C-F bond strength generally protects fluorine from metabolic transformations. The ability of fluorine to function as a hydrogen-bond acceptor, together with the similarity of typical C-F and C-O bond lengths (1.39 vs. 1.43 Å), suggest that replacement of hydroxyl by fluorine in bioactive compounds could result in useful analogs as well as probing of hydrogen bonding. N-Benzoyl (2*R*, 3*S*)-3-phenylisoserine (**1**), the C-13 side chain of the remarkable antitumor agent taxol, is essential for its bioactivity.[2,3] In taxol, intramolecular hydrogen bonding of the 2-hydroxy group in **1** with the adjacent amino and ester functionalities has been proposed by Swindell et al. to hold the side-chain in the proper conformation for receptor binding.[4] In light of our interest in organofluorine chemistry[5] and in the synthesis of **1**[6] we describe the preparation of syn-(2*R*, 3*S*)- and anti-(2*S*, 3*S*)-methyl-2-fluoro-3-(N-benzoylamino)-3-phenylpropanoate **2** and **3**, fluorine analogs of the taxol C-13 side-chain.



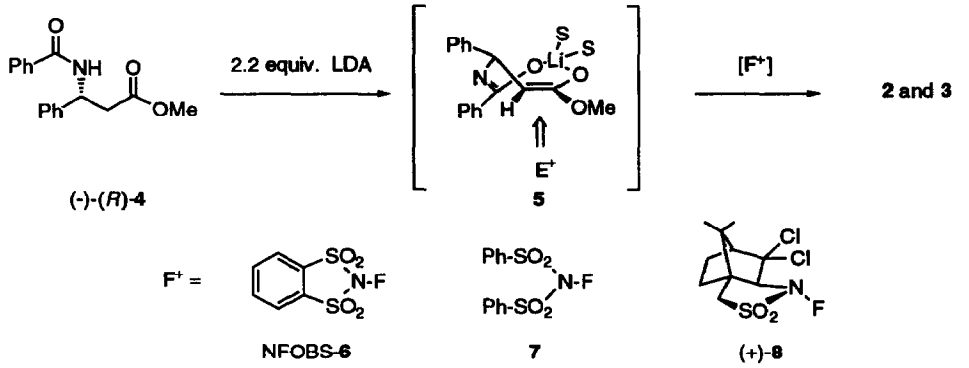
(2*R*, 3*S*)-**1**, X = OH
2, X = F



(2*S*, 3*S*)-**3**

Our earlier synthesis of (2*R*,3*S*)-**1** utilized the enolate oxidation protocol[7] to introduce the 2-hydroxy group via hydroxylation of the dianion of methyl (N-benzoyl)-3-amino-3-phenylpropanoate (**4**) with (camphorylsulfonyl)oxaziridine.[6] The remarkably good syn-selectivity (85:15) was attributed to the formation of eight-membered cyclic chelate **5** with approach of the electrophilic oxaziridine from the sterically least

Scheme 1



hindered direction. A similar strategy was employed in the synthesis of **2** and **3** using N-fluoro-*o*-benzenedisulfonimide (NFOBS) (**6**),[5] N-fluorobenzenesulfonimide (**7**)[8] and (+)-N-fluoro 2,10-(3,3-dichlorocamphorsultam) (**8**)[9] as electrophilic sources of fluorine (Scheme 1).

Accordingly, treatment of the dianion of (-)-**4**,[6] prepared from 2.2 equiv. of lithium diisopropylamide (LDA), with 1.3 equiv. of **6** at -78 °C afforded methyl-2-fluoro-3-(N-benzoylamino)-3-phenylpropanoate **2** and **3** as a 35:65 mixture of diastereoisomers in 82% yield following purification by preparative TLC (Table, entry 1). While the two isomers proved to be inseparable by TLC, they were readily separated by preparative HPLC. In our synthesis of **1** by hydroxylation of the dianion of **4** with (camphorylsulfonyl)oxaziridine we found that addition of anhydrous lithium chloride improved the yield; presumably this additive promotes the formation of **5**. Indeed addition of 2.0 equiv. of LiCl to the dianion prior to treatment with **6** had a similar effect affording **2** and **3** in 94% yield and increasing the diastereoselectivity to 44:56 (entry 2). Lowering the reaction temperature to -100 °C result in lower yields with recovery of **4** (45%) (entry 3). Addition of the enolate solution (-78 °C) of **4** to a cooled (-78 °C) solution of NFOBS **6** afforded **2** with only slightly enhanced diastereoselectivity (entry 4). Fluorination was also studied using N-fluorobenzenesulfonimide (**7**), which gave mostly the anti-isomer **3** in lower yield (entry 5) and with the optically active reagent (+)-N-fluoro 2,10-(3,3-dichlorocamphorsultam) (**8**), which failed to react (entry 6). These results are summarized in the Table.

The stereochemical assignments are based on analysis of the ^{13}C NMR and vicinal proton coupling constants ($J_{2,3}$) in **2** and **3** which are a function of the conformational populations of the two diastereoisomers. Not only will steric factors influence the equilibria of the rotational conformations, but columbic attraction and hydrogen bonding between the fluorine and NH groups may also have a role.[10] For stereoisomeric aldols, which can exist in an intermolecular hydrogen bonded conformation, proton $J_{2,3}$ for the syn isomers (2-6 Hz) are less than the anti isomers (7-10 Hz), in agreement with the Karplus correlation.[11] Pridgen and co-workers recently reported a study of the aldol reaction of α-halogenated imide enolates where they also observed lower proton $J_{2,3}$ for the syn vs. the anti fluorohydrins; e.g., 3.0 vs. 7.35 Hz, respectively.[12] Interestingly they also noted a consistent, solvent-independent, downfield shift of the ^{13}C NMR of CHF for the syn (δ 91.0 ppm) vs. the anti (δ 88.8 ppm) isomer. Based on these considerations the syn-isomer ($J_{2,3}$ = 2.0 Hz, δ 90.1 ppm) is assigned to **2** and the anti-isomer ($J_{2,3}$ = 3.75 Hz; δ 89.54 ppm) is assigned to **3**.[13]

Table: Fluorination of the Dianion of (-)-(*R*)-methyl (N-benzoyl)-3-amino-3-phenylpropanoate (**4**) with Electrophilic Fluorinating Reagents.

Entry	Reagent	Temp(°C)/ Time (h)	% Yield[a]	Ratio of **2** and **3**[b]
1	NFOBS-**6**	-78/ 6	82	35:65
2	NFOBS-**6**[c]	-78/ 6	94	44:56
3	NFOBS-**6**[c]	-100/6	41	44:56
4	NFOBS-**6**[c,d]	-78/ 6	58	48:52
5	**7**[c]	-78/ 6	65	19:81
6	(+)-**8**[c]		No Reaction	

a) Isolated yields. b) Ratio determined by ^{1}H NMR. c) 2.0 equiv. of LiCl was added. d) Addition of the enolate to NFOBS.

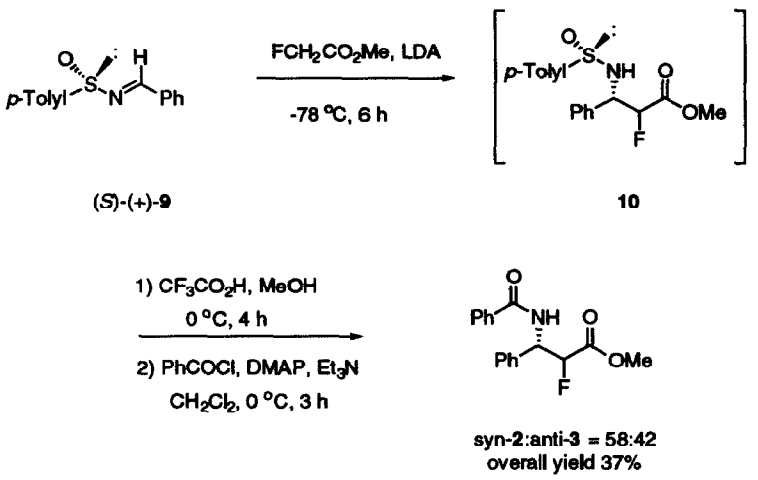
Additional support for these stereochemical assignments is the facile epimerization of **2** to the more thermodynamically **3**, discussed in the following section.

The poor selectivity observed in the electrophilic fluorination of the enolate dianion may mean that cyclic chelate **5** is not being formed and/or breaks down under the reaction conditions. This idea finds support in the observation that N-fluorobenzenesulfonimide (**7**), which is bulkier than NFOBS-**6**, give a more higher portion of the anti-isomer (entry 6) . However, a more likely scenario is that the increased acidity of the α-fluoro proton promotes base catalyzed epimerization of the syn-isomer **2** to the thermodynamically more stable anti-isomer **3**. Indeed treatment of pure anti-**3** with 2.2 equiv. of LDA at -78 °C for 2 h followed by quenching with sat. aqueous NH_4Cl afforded syn-**2**:anti-**3** in a ratio of 29:71. A similar ratio (28:72) was obtained on treatment of **2**:**3** (58:42) with LDA. Crystallization of a 44:56 mixture of **2**:**3** from *n*-hexane-ethyl acetate afforded pure **3**, with most of **2** having epimerized to **3**. Base catalyzed epimerization of α-fluorinated acids has recently been reported by Araki and Welch in studies of the Ireland-Claisen reaangement.[14]

As an alternative route to **2** is the addition of an α-fluoroenolate to the chiral ammonia-imine synthon, (*S*)-(+)-N-(benzyilidine)-*p*-toluenesulfinamide (**9**)[15] (Scheme 2). Thus treatment of methyl α-fluoroacetate with an 1.0 equiv. of LDA at -78 °C followed by addition 0.3 equiv. of (*S*)-(+)-**9** afforded β-amino acid derivative **10** which was isolated by preparative TLC.[16] This crude material was subjected to a one-pot hydrolysis-benzoylation procedure as previously described,[6] to give a 58:42 diastereomeric mixture of syn-**2** and anti-**3** in 37% overall yield. Use of excess enolate and other bases failed to better the yield. Although this is an improvement in the de (Table) the low ratio was disappointing, but not unexpected considering that the lithium enolate of methyl α-fluoroacetate exists as a 1:1 mixture of E and Z isomers.[17]

In the course of our studies we learned that Kant and co-workers[18] had prepared the fluorotaxols corresponding to **2** and **3** by treatment of baccatin III with racemic cis-3-fluoroazetidinone using methodology developed by Holton.[19] The cytotoxicity of 2'-fluorotaxol was found to be more than 100 times *less* active than taxol itself. This loss of activity was attributed to either a need for phenylisoserine side-chain to adopt a

Scheme 2



preferred conformation for effective binding and/or that the 2'-hydroxyl group participates as an intermolecular hydrogen bond donor at the receptor site.[18]

In conclusion, the present method affords both **2**-(2*R*, 3*S*) and **3**-(2*S*, 3*S*) isomers in excellent yield, but poor diastereoselectivity, due in part to base catalyzed epimerization of the α-fluoro-β-amino acid.

EXPERIMENTAL

Details concerning the recording of spectra, the determination of melting points, elemental analysis, and the purification of solvents have been previously reported.[7b] Lithium diisopropylamide 1M solution in THF was prepared by addition of *n*-butyllithium [2.5 M solution in hexanes (4.0 mL, 10.0 mmol)] to a 0 °C solution of diisopropylamine (1.47 mL, 10.5 mmol) in THF (5.0 mL) which was stirred for 20 min. prior to addition of **4**. Lithium chloride was dried in a vacuum oven at 120 °C/2 mm for 12 hr. Compounds (-)-**4**,[6] **6**,[5a] and (+)-**8**[9] were prepared as previously described. Compound **7** was provided by Allied Signal, Inc., Buffalo, NY.

(-)-(2*R*,3*S*)-Methyl-2-fluoro-3-(N-benzoylamino)-3-phenylpropanoate (2) via Electrophilic Fluorination. In a 10 mL dry single-necked round bottom flask equipped with a magnetic stir bar, argon inlet and rubber septum was placed 0.036 g (0.125 mmol) of (-)-(*R*)-methyl (N-benzoyl)-3-amino-3-phenylpropanoate (**4**) and 0.011 g (0.25 mmol, 2.0 equiv.) of anhydrous lithium chloride in 2 mL of THF. The reaction mixture was cooled to -42 °C (dry ice-acetonitrile bath) and freshly prepared lithium diisopropylamide (0.275 mmol, 2.2 equiv.; 1.0 molar soln. in THF) was added, stirred for 40 min., cooled to -78 °C and 0.039 g (0.163 mmol, 1.3 equiv.) of NFOBS **6** in 2 mL of THF was added dropwise. After stirring for 6 h the reaction mixture was quenched at -78 °C with 2 mL of sat. NH_4Cl and warmed to rt. After diluting the reaction mixture with 40 mL of ethyl acetate the solution was washed with water (10 mL) and the aqueous layer extracted with ethyl acetate (25 mL). The combined organic portions were washed with brine (20 mL), dried ($MgSO_4$) and concentrated to give the crude product which was purified by preparative TLC (silica gel) chromatography (30% ethyl acetate in *n*-hexane) to afford 0.036 g (94%) of a 44:56 mixture **2** and

3. The mixture was separated by preparative HPLC (Rainin Dynamax 6-A, 5i-83-121C, silica column, 20% 2-propanol-80% *n*-hexane, 3.0 mL/min.) to afford **2**; t_R: 50.4; mp 176-178 °C; $[\alpha]^{20}_D$ - 31.95 (c 0.77, MeOH); IR (KBr): 3343, 1752, 1636, 1530, 1489, 1090, 1070, 1057, 719, 706 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.81 (s, 3H), 5.31 (dd, 1H, J = 47.25, 2.00 Hz), 5.85 (ddd, 1H, J = 37.25, 9.00, 2.00 Hz), 6.96 (d, 1H, J = 8.25 Hz), 7.31-7.56 (m, 8H), 7.77-7.81 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 52.88, 54.12 (d, J = 79.5 Hz), 90.10 (d, J = 756.5 Hz), 126.79, 127.01, 127.65, 128.26, 128.58, 128.81, 131.82, 133.65, 136.93, 166. 62, 167. 87 (d, J = 102.5 Hz); Mass spectrum: m/z 302 (M^++1), 281, 270, 222, 210, 122, 105, 77; Anal. calcd for $C_{17}H_{16}NO_3F$. C, 67.77; H, 5.32. Found: C, 67.54; H, 5.55.

(+)-(2*S*, 3*S*)-Methyl-2-fluoro-3-(N-benzoylamino)-3-phenylpropanoate (3): t_R: 53.8 min.; mp 138-140 °C; $[\alpha]^{20}_D$ +8.09 (c 0.92, MeOH); IR (KBr): 3388, 1762, 1653, 1518, 1488, 1308, 1220, 1107, 718, 710, 690, 569 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.67 (s, 3H), 5.47 (dd, 1H, J = 48.75, 3.75 Hz), 5.75 (ddd, 1H, J = 27.00, 8.25, 3.75 Hz), 6.87 (d, 1H, 7.75 Hz), 7.30-7.53 (m, 8H), 7.79-7.82 (m, 2H) ; ^{13}C NMR ($CDCl_3$): δ 52.43, 56.42 (d, J=73.75 Hz), 89.54 (J = 760.00 Hz), 126.93, 127.62, 128.51, 128.63, 128.81, 131.77, 133.59, 135.19, 166.57, 167.25 (d, J = 95.00 Hz); Mass spectrum: m/z 302 (M^++1), 281, 222, 210, 139, 105, 77.

Synthesis of syn-2 and anti-3 via Enolate Addition. In a 25 mL dry two-necked round bottom flask fitted with a magnetic stir bar, argon inlet and rubber septum was placed 6.0 mL of THF cooled to -78 °C and 3.0 mL (3.0 mmol, 3.0 equiv.) of freshly prepared lithium diisopropylamide in THF. To this solution was slowly added 0.276 g (3.0 mmol, 3.0 equiv.) of methyl fluoroacetate in THF (2.0 mL) at -78 °C, via a double ended needle. *Caution: protective gloves were used, reaction and work-up were carried out in an efficient fumehood and extra care was taken while handling the solutions.* The mixture was stirred for 50 min. and 0.244 g, 1.0 mmol of (*S*)-(+)-**9** in THF (3 mL) was added drop wise at -78 °C. After stirring the reaction mixture for 7 h, it was quenched with sat. NH_4Cl solution (2 mL), warmed to rt and diluted with ethyl acetate (25 mL). The organic portions were washed with water (10 mL) and the aqueous layer was extracted with ethyl acetate (15 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated to give crude **10**. This material was purified by prep. TLC (40% ethyl acetate in *n*-hexane), dissolved in MeOH (10 mL), cooled to 0 °C and 0.3 mL of TFA added. After stirring the reaction mixture for 4 h the solvent was removed below 50 °C, benzene (10 mL) added to remove the residual TFA and stripped to dryness. The residue was dissolved in dry CH_2Cl_2 (5 mL), treated with 0.57 mL (10.0 equiv.) of triethylamine, a catalytic amount of 4-dimethylaminopyridine (25 mg) and 0.28 mL (8.0 equiv.) of benzoylchloride added. The resulting pale yellow precipitate was warmed to rt, stirred for 1h, cooled to 0 °C and quenched with ice. The solution was extracted with ethyl acetate (2 x 30 mL) and the combined organic layers were washed with 10% $NaHCO_3$ (3 x 10 mL), water (15 mL), brine (10 mL) and dried ($MgSO_4$). Removal of the solvent and purification by preparative TLC (silica gel) (30% ethyl acetate in *n*-hexane) afforded 0.108 g (37% overall yield from **9**) of syn-**2** and anti-**3** in a 58:42 ratio. The spectral properties were identical to **2** and **3** prepared via the electrophilic fluorination method.

Acknowledgments: We thank Dr. Joydeep Kant, Bristol-Myers Squibb, for a copy of his paper prior to publication; Dr. Lendon Pridgen, SmithKline Beecham, for discussions concerning the stereochemical assignments; and Dr. John Welch, SUNY Albany, for information on fluoroenolate geometry. We also thank Drs. Bang-Chi Chen, Bristol-Myers Squibb, and Charles Swindell (Bryn Mawr) for helpful discussions. This work was supported by a grant from the National Science Foundation.

REFERENCES AND NOTES

1. For reviews on biologically active organofluorine compounds see: (a) Welch, J. T.; Exwarakrishnan, S. *Fluorine in Bioorganic Chemistry*, John Wiley & Sons, New York, 1991. (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (c) Filler, R.; Kobayashi, Y., Eds. *Biomedicinal Aspects of Fluorine Chemistry*, Kodanasha Ltd., Elsevier Biomedical Press: Tokyo, New York 1982. (d) *Carbon-Fluorine Compounds: Chemistry, Biochemistry and Biological Activities*; Ciba Foundation Symposium, Associated Scientific Publishers; Amsterdam 1972.
2. Rowinsky, E. K.; Cazenave, L. A.; Donehower, R. J. *J. Natl. Cancer Inst.* **1990**, *82*, 1247. Parness, J.; Kingston, D. G. I.; Powell, R. G. Harracksingh, C.; Horwitz, S. B. *Biochem. Biophys. Res. Commun.* **1982**, *105*, 1082.
3. For a review on taxol chemistry see: Kingston, D. C. I., *Pharmac. Ther.* **1991**, *52*, 1.
4. Swindell, C. S.; Krauss, N. E.; Horwitz, S. B.; Ringel, I. *J. Med. Chem.*, **1991**, *34*, 1176.
5. a) Davis, F. A.; Han, W. *Tetrahedron Lett.* **1991**, *32*, 1631. b) Davis, F. A.; Han, W. *Tetrahedron Lett.* **1992**, *33*, 1153.
6. Davis, F. A.; Thimma Reddy, R.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387.
7. For a review of this protocol and recent applications see: a) Davis, F. A., Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919. b) Davis, F. A.; Weismiller, M. C.; Murphy, C. K.; Thimma Reddy, R.; Chen, B. C. *J. Org. Chem.* **1992**, *57*, 7274. c) Davis, F. A.; Chen, B.-C. *J. Org. Chem.* **1993**, *58*, 1751. d) Davis, F. A.; Kumar, A.; Reddy, R. E.; Chen, B.-C., Wade, P. A.; Shah, S. W. *J. Org. Chem.* **1993**, *58*, 7591.
8. Differding, E.; Duthale, R. O.; Krieger, A.; Ruegg, G. M.; Schmit, C. *Synlett.* **1991**, 395.
9. Davis, F. A.; Zhou, P.; Murphy, C. K. *Tetrahedron Lett.* **1993**, *33*, 3971.
10. Tsushima, T.; Kawada, K.; Nishikawa, J.; Sato, T.; Tori, K.; Tsuji, T.; Misaki, S. *J. Org. Chem.* **1984**, *49*, 1163.
11. Heathcock, C. H. in *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press; Orlando; 1984; Vol. 3, Part B, pp 111-212.
12. Pridgen, L. N.; Abdel-Magid, A. F.; Lantos, I.; Shilcrat, S.; Eggleston, D. S. *J. Org. Chem.* **1993**, *58*, 5107.
13. Caution should be exercised in considering these assignments because in syn- and anti-3-fluorophenlalanine a similar analysis of proton $J_{2,3}$ coupling constants leads to the opposite conclusion. See reference 10.
14. Araki, K.; Welch, J. T. *Tetrahedron Lett.* **1993**, *34*, 2251.
15. Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Portonovo, P. S.; *Tetrahedron Lett.* **1993**, *34*, 6229.
16. The diastereoisomer ratio of **10** was 56:44.
17. Seper, K. Ph.D. thesis, 1987, SUNY, Albany.
18. Kant, J.; Huang, S.; Wong, H.; Fairchild, C.; Vyas, D.; Farina, V. *BioMed. Chem. Lett.* **1993**, *3*, 2471.
19. Holton, R. A. *US Patent* 5,015,744 (1991); *Chem. Abstr.* **1991**, *115*, 159485.

(*Received* 8 *March* 1994)