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Synthesis of Quaternary Amino Acids Bearing a (2′*Z*)-Fluorovinyl α-Branch: Potential PLP Enzyme Inactivators

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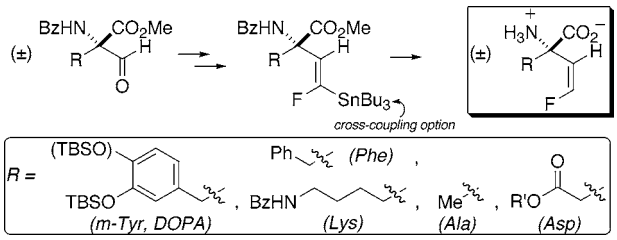
ABSTRACT



Protected α-formyl amino acids, themselves available from the corresponding α-vinyl amino acids, are stereoselectively transformed into the (*Z*)-configured α-(2′-fluoro)vinyl amino acids via a three-step sequence. The route employs McCarthy's reagent, diethyl α-fluoro-α-(phenylsulfonyl)-methyl phosphonate, and proceeds via the intermediate (*E*)-α-fluorovinyl sulfones and (*E*)-α-fluorovinylstannanes. The latter may either be exploited as novel cross-coupling partners for fluorovinyl branch extension or be globally deprotected, to provide the title compounds.

Quaternary, α-vinyl amino acids (AA's) are potential mechanism-based inactivators of pyridoxal phosphate (PLP) dependent enzymes, particularly amino acid decarboxylases (AADC's).[1,2] The "vinylic trigger" is also found in the naturally occurring PLP-enzyme inactivator vinylglycine[3] and in the anti-epileptic drug vigabatrin (γ-vinyl-GABA),[4] which has gained attention more recently for its potential application in the treatment of substance abuse.[5] Elegant work by Silverman and John has elucidated the mechanism by which the vinylic trigger in vigabatrin functions to inactivate GABA transaminase.[6,7] Both electrophilic (Michael addition) and nucleophilic (Metzler-type enamine-PLP aldimine condensation[8]) pathways are operative, each of which follows from the normal first two enzymatic steps (transaldimination/γ-proton abstraction).

Introduction of a 2′-fluorine atom into this trigger might lead to an alternative, potentially more electrophilic,[9] Michael acceptor, on one hand, and might divert the Metzler enamine pathway into a second Michael addition pathway, on the other. Indeed, in the one case in which such a trigger has been reported, for γ-(2′-fluoro)-γ-vinyl-GABA inactivation of GABA transaminase, such changes in mechanism are evident, though multiple pathways are operative.[10] Interestingly, in that case, the (*Z*)- and (*E*)-(2′-fluoro)vinyl triggers

(1) Berkowitz, D. B.; Jahng, W.-J.; Pedersen, M. L. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2151−2156 and references therein.

(2) Note that the "quaternary" AA design, in and of itself, should provide some specificity, as classes of PLP enzymes that act by α-deprotonation should be incapable of actuating these triggers.

(3) (a) *ACC Synthase*: Liang, F.; Kirsch, J. F. *Biochemistry* **2000**, *39*, 2436−2444. (b) *Cysteine desulfurase*: Zheng, L.; White, R. H.; Cash, V. L.; Dean, D. R. *Biochemistry* **1994**, *33*, 4714−20. (c) *Kynurenine aminotransferase*: Asada, Y.; Tanizawa, K.; Yonaha, K.; Soda, K. *Agric. Biol. Chem.* **1988**, *52*, 2873−2878. (d) *Asp aminotransferase*: Gehring, H.; Rando, R. R.; Christen, P. *Biochemistry* **1977**, *16*, 4832−4836. (e) *D-AA transaminase*: Soper, T. S.; Manning, J. M.; Marcotte, P. A.; Walsh, C. T. *J. Biol. Chem.* **1977**, *252*, 1571−1575.

(4) Jung, M. J.; Palfreyman, M. G. Vigabatrin. In *Antiepileptic Drugs*, 4th ed.; Levy, R. H., Mattson, R. H., Eds.; Raven: New York, 1995.

(5) (a) Brodie, J. D.; Figueroa, E.; Dewey, S. L. *Synapse* **2003**, *50*, 261−265. (b) Gerasimov, M. R.; Dewey, S. L. *Drug Dev. Res.* **2003**, *59*, 240−248.

(6) Mechanistic studies: (a) Nanavati, S. M.; Silverman, R. B. *J. Am. Chem. Soc.* **1991**, *113*, 9341−9349. (b) De Biase, D.; Barra, D.; Bossa, F.; Pucci, P.; John, R. A. *J. Biol. Chem.* **1991**, *266*, 20056−20061.

(7) X-ray studies: Storici, P.; De Biase, D.; Bossa, F.; Bruno, S.; Mozzarelli, A.; Peneff, C.; Silverman, R. B.; Schirmer, T. *J. Biol. Chem.* **2004**, *279*, 363−373.

(8) Ueno, H.; Likos, J. J.; Metzler, D. E. *Biochemistry* **1982**, *21*, 4387−4393.

(9) Zhou, H.; Schmidt, D. M. Z.; Gerlt, J. A.; van der Donk, W. A. *ChemBioChem* **2003**, *4*, 1206−1215..

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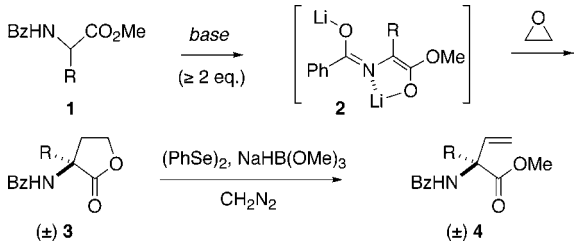
give different profiles, highlighting the importance of accessing single geometric isomers.[11]

Given this, it would be interesting to install such a trigger *at the* α-*carbon* to probe its effectiveness in an AADC active site. Yet, to our knowledge, no syntheses of quaternary, α-(2′-fluoro)vinyl AA's have yet been reported, though (*E*)- and (*Z*)-α-(2′-fluoro)vinylglycine have been described by McCarthy.[12]

A fluoromethylenation route related to McCarthy's[13] was attractive, as protected α-formyl AA's might be obtained ozonolytically, from the corresponding quaternary, α-vinyl AA's. The latter were available, with appropriate protecting groups, via a formal α-vinylation sequence that had been developed earlier (Scheme 1).[14] Furthermore, success in the

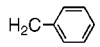
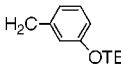
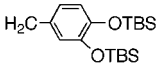
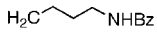
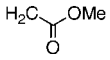
Scheme 1. Formal α-Vinylation of Amino Acids



racemic series here would map onto an enantioselective variant, starting from either L- or D-α-vinyl AA's.[15] Pleasingly, the ozonolysis of vinylic AA's (**4**) to formyl AA's (**5**) proceeded in good to excellent yield, across an array of functionalized side chains (Table 1).

McCarthy had taken a Horner Wadsworth Emmons (HWE) approach, condensing lithio diethyl α-fluoro-α-(phenylsulfonyl)methylphosphonate (**6**) with the Garner aldehyde to obtain an (*E*)/(*Z*) mixture of α-(2′-fluoro)vinylglycinol

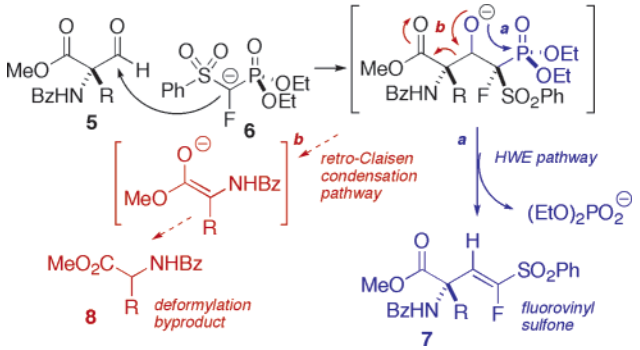
Table 1. From Vinyl AA's to Formyl AA's[a]

entry	R	AA	reduction method[b]	yield of **5**[c]
a	Me	Ala	A1	87%
b		Phe	A2	93%
c		*m*-Tyr	A2	66%
d		DOPA	A2	99%
e		Lys	A2	84%
f		Asp	A1	65%

[a] Procedure: Ozone was bubbled into a solution of the protected vinyl-AA (**4a**−**f**) in CH_2Cl_2 at −78 °C, until a light blue color persisted. After several minutes, oxygen was then bubbled through to remove excess ozone (decolorizes). [b] Method A1: The crude ozonide was reduced with Me_2S at room temperature. Method A2: Ozonide reduction was carried out with Zn, AcOH. [c] Isolated yields.

isomers.[12] In considering the application of this chemistry here, several key issues arose at the outset: (i) Would such sterically encumbered aldehydes (**5**) be amenable to nucleophilic attack by **6**? (ii) If so, would the intermediate *β*-alkoxyphosphonates follow the desired HWE reaction mode or fragment along a competing "retro-Claisen" mode (Scheme 2)? (iii) Would any such HWE products be formed as an *E*/*Z* mixture as is typical for this chemistry?[12]

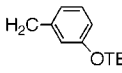
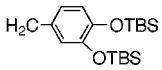
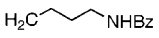
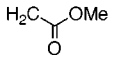
Scheme 2. Competition between HWE and "Retro-Claisen" Condensation Manifolds



Should these issues be addressable, this synthetic strategy would be redox-efficient in that the α-carboxyl group oxidation state would be preserved throughout. This route would also have the attractive feature of providing intermediate α-fluorovinylstannanes as potential vehicles for fluorovinyl branch extension. Indeed, as can be seen from Table

(10) Silverman, R. B.; Bichler, K. A.; Leon, A. J. *J. Am. Chem. Soc.* **1996**, *118*, 1253−1261.
(11) For a related trigger bearing both *E*- and *Z*-configured fluorines, see: Pan, Y.; Qiu, J.; Silverman, R. B. *J. Med. Chem.* **2003**, *46*, 5292−5293.
(12) McCarthy, J. R.; Huber, E. W.; Le, T.-B.; Laskovics, F. M.; Matthews, D. P. *Tetrahedron* **1996**, *52*, 45−58.
(13) For other examples of HWE-type condensations with **6**, see: (a) McCarthy, J. R.; Matthews, D. P.; Paolini, J. P. *Org. Synth.* **1995**, *72*, 216−24. (b) Gross, R. S.; Mehdi, S.; McCarthy, J. R. *Tetrahedron Lett.* **1993**, *34*, 7197−7200. (c) McCarthy, J. R.; Matthews, D. P.; Stemerick, D. M.; Huber, E. W.; Bey, P.; Lippert, B. J.; Snyder, R. D.; Sunkara, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 7439−7440
(14) (a) Pedersen, M. L.; Berkowitz, D. B. *J. Org. Chem.* **1993**, *58*, 6966−6975. (b) Pedersen, M. L.; Berkowitz, D. B. *Tetrahedron Lett.* **1992**, *33*, 7315−7318. See also: (c) Columbo, L.; Di Giacomo, M.; Vinci, V.; Columbo, M.; Manzoni, L.; Scolastico, C. *Tetrahedron* **2003**, *59*, 4501−4513.
(15) For enantioselective syntheses of quaternary, α-vinyl AA's, see: (a) Ma, D.; Zhu, W. *J. Org. Chem.* **2001**, *66*, 348−350. (b) Berkowitz, D. B.; McFadden, J. M.; Chisowa, E.; Semerad, C. L. *J. Am. Chem. Soc.* **2000**, *122*, 11031−11032. (c) Berkowitz, D. B.; McFadden, J. M.; Sloss, M. K. *J. Org. Chem.* **2000**, *65*, 2907−2918. (d) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *J. Org. Chem.* **1999**, *64*, 8220−8225. (e) Berkowitz, D. B.; Pumphrey, J. A.; Shen, Q. *Tetrahedron Lett.* **1994**, *35*, 8743−8747 (f) Colson, P.-J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 5918−5924. (g) Seebach, D.; Bürger, H. M.; Schickli, C. P. *Liebigs Ann. Chim.* **1991**, 669−684. (h) Weber, T.; Aeschimann, R.; Maetzke, T.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1365−1377. (i) Groth, U.; Schöllkopf, U.; Chiang, Y.-C. *Synthesis* **1982**, 864−866.

Table 2. A Stereoselective McCarthy-Type HWE Reaction[a]

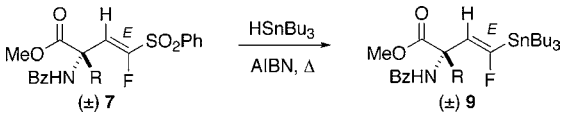
entry	R	AA	yield of **7**[b]	yield of **8**[c]
a	Me	Ala	74%	trace
b		Phe	44%	nd
c		*m*-Tyr	55%	5%
d		DOPA	57%	17%
e		Lys	61%	24%
f		Asp	41%	41%

[a] Procedure: To a solution of McCarthy's reagent (1.2. equiv) in THF at −78 °C was added LiHMDS (1.4 equiv, 1 M in hexanes) and stirring was continued for 20 min. Then, a solution of α-formyl AA (**5**) in THF at −78 °C was added via cannula. The reaction was allowed to warm to room temperature, and quenched with NH_4Cl (aq) once **5** had been consumed and a predominant spot for **7** was visible on TLC. [b] Isolated yields of purified HWE products **7** [assigned as *E* as $J_{1,2}$(H−F) = 33−34 Hz, as opposed to ≈22 Hz for *Z*, see ref 12]. [c] The "retro-Claisen" byproducts were not generally isolated. The estimated yields given are based on the ratio of **7**:**8** from the crude NMR spectra and the isolated yields of **7**.

2, the targeted fluorovinyl sulfones were obtained in each case and *as single geometric isomers*. This level of diastereoselectivity is unusual for carbonyl condensation reactions of **6**, and presumably is a reflection of the steric demand of the quaternary α-center. Furthermore, though the competing "retro-Claisen" manifold is observed, the HWE pathway predominates for all AA's but aspartate.

The subsequent tin−sulfone exchange proceeded smoothly under the agency of Bu_3SnH, generally in very high yield (Table 3). *Surprisingly, only the (E)-stereoisomers were*

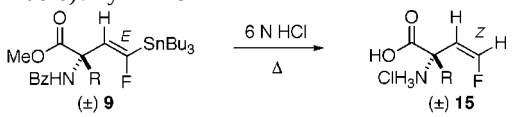
Table 3. Sulfone/Stannane Interchange with Retention of Configuration[a]

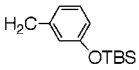
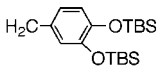
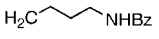
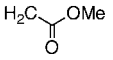


entry	R	AA	yield of **9**,[b] %
a	Me	Ala	80
b	CH_2Ph	Phe	91
c	CH_2(3′-OTBS)C_6H_4	*m*-Tyr	97
d	CH_2(3′,4′-bis-OTBS)C_6H_3	DOPA	79
e	$(CH_2)_4NHBz$	Lys	76
f	CH_2CO_2Me	Asp	50

[a] Procedure: An Ar-purged solution of **7** in benzene containing AIBN (glovebag) and Bu_3SnH (1 equiv) was heated at reflux, until complete conversion to **9** was evident by TLC. [b] Isolated yields of purified substitution products **9** [assigned as *E* as $J_{1,2}$(H−F) = 55−58 Hz, as opposed to ≈37 Hz for *Z*, see ref 12].

Table 4. Global Deprotection to the Target α-(2′*Z*-Fluoro)vinyl-AA's[a]



entry	R[b]	AA	yield
a	Me	Ala	89%[d]
b		Phe	85%[d]
c		m-Tyr	88%[d]
d		DOPA	93%[d]
e		Lys	63%[e]
f		Asp	52%[e]

[a] Procedure: The fully protected stannylvinyl amino acid (**9**) was suspended in 6 N HCl and refluxed for 12−30 h. [b] R groups are given as they are found in the educts **9**. Under the reaction conditions, the side chain of aspartate is de-esterified, that of lysine is debenzoylated, and those of *m*-Tyr and DOPA are desilylated. Geometry is assigned as *Z* as $J_{1,2}$(H−F) = 43−46 Hz, as opposed to ≈17 Hz for *E*, see ref 10]. [d] These fluorovinyl AA's were isolated as their hydrochloride salts. [e] Further purified by Dowex 50 cation exchange chromatography.

observed in the crude NMR spectra of these reactions. Previously, McCarthy had observed *E*/*Z* equilibration in such transformations for fluorovinyl sulfones bearing a single *β*-substituent.[12] Thus, the transformations **7a**−**f** → **9a**−**f** may be the first examples of stereospecific tin−sulfonyl exchange for *β*-monosubstituted, α-fluorovinyl phenyl sulfones.[16] Once again, attachment of a hindered quaternary center directly to the *β*-vinylic position appears to confer an unexpectedly high degree of stereocontrol.

At this juncture, we selected stannane **9a** as a model compound to examine its potential for chain extension to AA's bearing side chains with embedded fluorovinyl groups (Scheme 3).[17] Stille-type couplings[18] with aryl halides produced α-methylated and homologated analogues of phenylalanine (**11**) and *m*-tyrosine (**13**). A similar Pd-mediated coupling with ethyl chloroformate[19] yielded the α-methylglutamate analogue **10**.

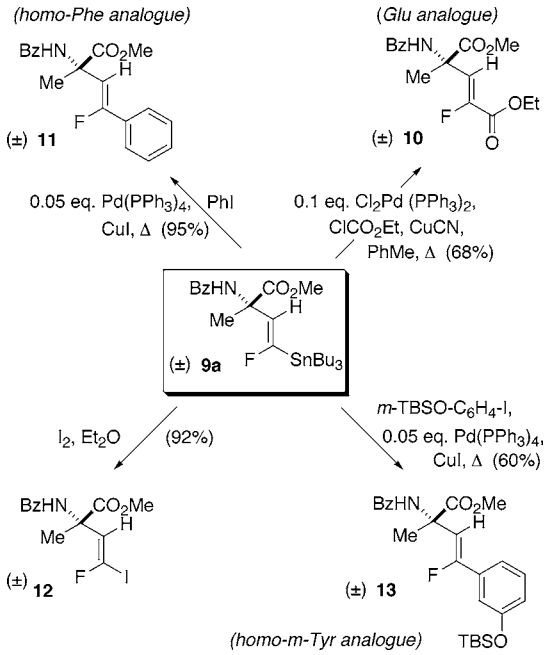
(16) In support of this, McCarthy does observe a stereospecific conversion of *β*,*β*-disubstituted fluorovinyl phenyl sulfones to the corresponding stannanes (ref 11). However, in the absence of data for the stannylation of the (*Z*)-isomers of **7**, one cannot rigorously rule out an equilibration mechanism here. In this context, it is well to note that vinyl stannanes are known to isomerize upon heating in the presence of tin hydrides: Leusink, A. J.; Budding, H. A. *J. Organomet. Chem.* **1968**, *11*, 541−547.

(17) For a related cross-coupling approach to α-branch extension for nonfluorinated quaternary AA's, see: Berkowitz, D. B.; Chisowa, E.; McFadden, J. M. *Tetrahedron* **2001**, *57*, 6329−6343.

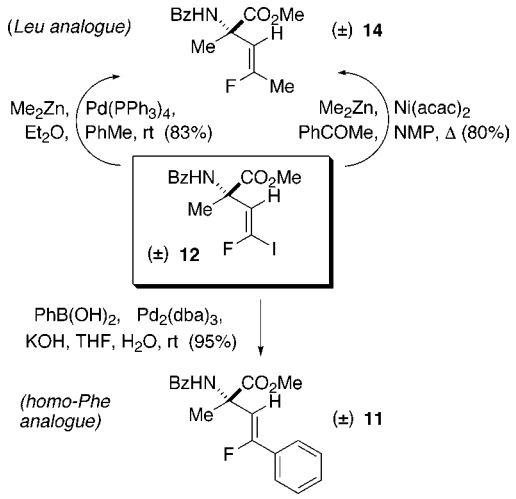
(18) (a) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833−4840. (b) Chen, C.; Wilcoxen, K.; Zhu, Y.-F.; Kim, K.; McCarthy, J. R. *J. Org. Chem.* **1999**, *64*, 3476−3482.

(19) (a) Soderquist, J. A.; Rosado, I.; Marrero, I.; Burgos, C. *ARKIVOC* **2001** *4*, 12−19. (b) Jeong, I. H.; Park, Y. S.; Kim, M. S.; Song, Y. S. *J. Fluorine Chem.* **2003**, *120*, 195−209.

Scheme 3. Introduction of Fluoroalkene-Embedded Side Chain Functionality via Stille-Type Coupling



Scheme 4. Negishi and Suzuki-Type Couplings on α-Fluorovinyl Iodide **12**



Alternatively, tin−iodine exchange could be effected smoothly to **12**, which could subsequently be engaged in a "ligandless" Suzuki coupling[20] with $PhB(OH)_2$, as an alternative route to **11** (Scheme 4). Pd-mediated Negishi-type coupling[21] with Me_2Zn or the analogous Ni-mediated procedure of Knochel[22] could be applied to the synthesis of **14**, an unusual analogue of α-methylleucine in which a fluorine atom takes the place of a methyl group.

Finally, upon refluxing in 6 N HCl, **7a**−**f** could be protodestannylated with concomitant ester, ether, and amide hydrolysis to **15a**−**f**, the free, quaternary, α-(2′*Z*-fluoro)-vinyl AA's, bearing side chains relevant to target PLP enzymes. Studies of this new class of potential AADC inactivators are now underway.

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Supporting Information Available: Complete set of ^1H NMR and selected ^{19}F NMR spectra, as well as experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) For other examples and a discussion of "ligandless" Suzuki conditions, see: (a) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *Org. Synth.* **1998**, *75*, 61−68. See also: (b) Chen, C.; Wilcoxen, K.; Strack, N.; McCarthy, J. R. *Tetrahedron Lett.* **1999**, *40*, 827−830.

(21) Negishi, E.-I. In *Organozinc Reagents*; Knochel, P., Jones, P., Eds.; Oxford University: Oxford, UK, 1999; pp 213−243.

(22) Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2387−2390.