Pergamon

Tetrahedron Letters 42 (2001) 2957–2960

TETRAHEDRON LETTERS

Synthesis of chiral and geometrically defined 5,5-diaryl-2-amino-4-pentenoates: novel amino acid derivatives

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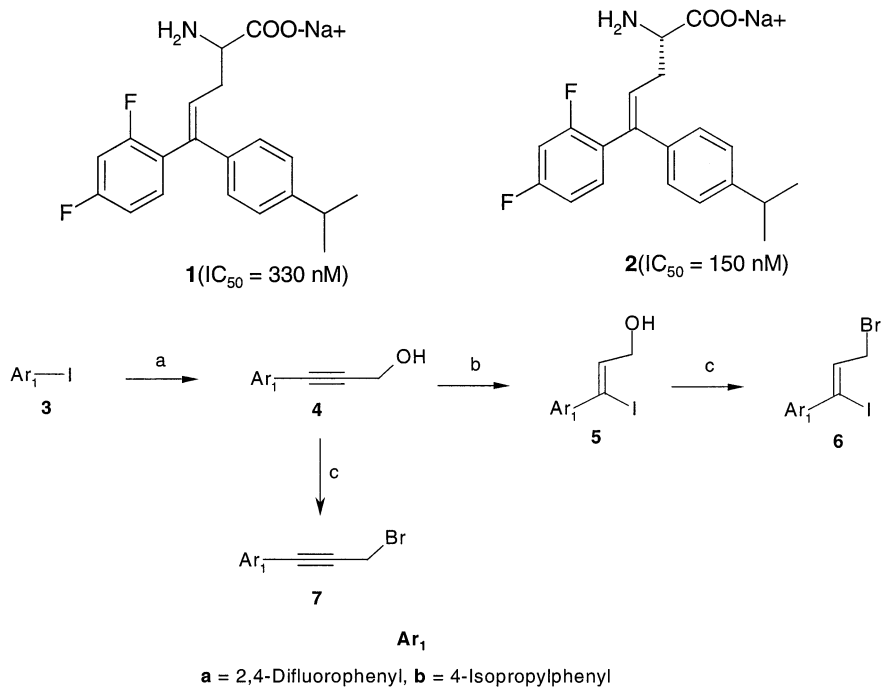
Received 27 January 2001; revised 23 February 2001; accepted 1 March 2001

Abstract—A novel series of 5,5-diaryl-2-amino-4-pentenoates were synthesized. Chirally defined substrates were obtained efficiently using Oppolzer's sultam as a chiral auxiliary and a palladium-catalyzed stereoselective hydrostannylation.

The 5,5-diaryl-2-amino-4-pentenoate series was developed as a novel class of biologically active molecules targeted towards the recently cloned glycine reuptake transport system, specifically the glycine transporter type-2 (GlyT-2) system. This system is prevalent in the central nervous system and is thought to be involved in the treatment of pain and spasticity.[1] Of particular interest from this series is the sodium derivative of *E*-2-amino-5-[2,4-difluorophenyl]-5-[4-isopropylphenyl]-4-pentenoic acid (**1**), which was found to be a potent GlyT-2 reuptake inhibitor ($IC_{50}=330$ nM) as a racemic mixture. Resolving the racemate indicated that the *S*-enantiomer **2** was the active component of the mixture with an IC_{50} of 150 nM.



Scheme 1. (a) $Pd(PPh_3)_4$, CuI, propargyl alcohol, Et_3N; (b) Red-Al, I_2, ether; (c) PBr_3, CH_2Cl_2, 0°C.

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0040-4039/01/$ - see front matter
PII: S0040-4039(01)00353-7

We wish to report on the synthesis of **1**, highlighting the various regio- and stereoselective control elements utilized.

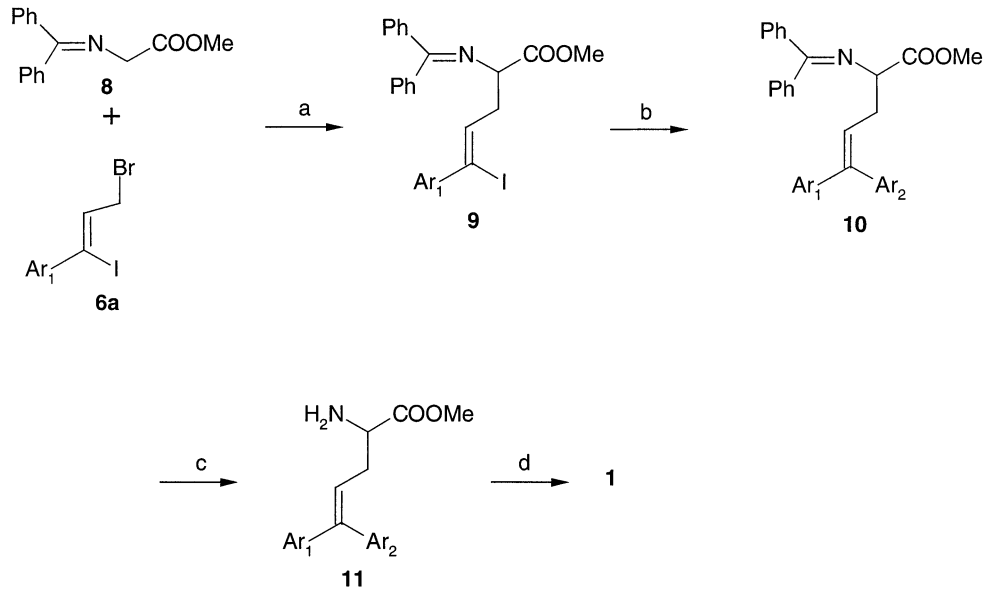
2,4-Difluoroiodobenzene **3a** was subjected to the Sonogashira coupling condition[2] with propargyl alcohol giving the alcohol **4a** (Scheme 1). Treatment of **4a** with Red-Al, followed by quenching with iodine, afforded **5a** in good yield and in a regio- and stereospecific manner.[3] The alcohol functionality of intermediate **4a** was then transformed cleanly into the corresponding bromide **6** using phosphorus tribromide.[4]

The allyl bromide **6a** was used in the allylation of **8**,[5] with LDA as base, to afford the versatile intermediate **9**, which can be reacted with a variety of boronic acids (Scheme 2). Compound **9** was then coupled to 4-isopropylbenzeneboronic acid under the Suzuki-coupling conditions furnishing **10** in good yield. Trifluoroacetic acid-mediated deprotection, followed by hydrolysis, furnished **1** in good overall yield.[6]

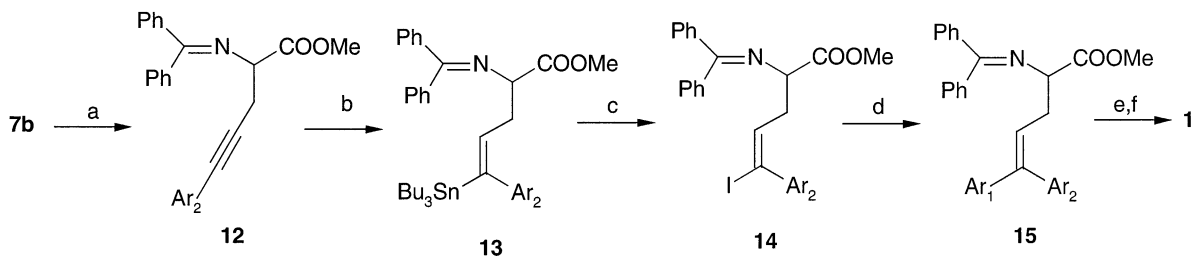
An alternative route to **1** is illustrated in Scheme 3. The propargyl bromide **7b**, prepared according to Scheme 1, was reacted with **8** giving the highly functionalized intermediate **12**. The palladium-catalyzed stereoselective hydrostannylation[7] of **12** provided **13** in 55% yield, which was subsequently treated with iodine to effect a tin to iodine exchange to afford **14** (Scheme 3). The vinyl iodide **13** was immediately treated with 2,4-difluorobenzeneboronic acid to give the Suzuki-coupled product **15**. Deprotection of **15**, followed by base-mediated hydrolysis, provided **1**.

To further determine the effect of the chirality on activity, **1** was resolved using a chiral column of an analytical HPLC and the resolved components were separated (Fig. 1).[8] The absolute stereochemistry of the active enantiomer **2** was confirmed using chemical correlation methods.[9]

Utilizing Oppolzer's bornane-10,2-sultam as a chiral auxiliary, treatment of the sultam-derived *N*-(diphenyl-



Scheme 2. (a) LDA, THF, HMPA, −78°C to rt; (b) Ar_2-$B(OH)_2$, $Pd(PPh_3)_4$, DME/Na_2CO_3, 110°C; (c) TFA, H_2O, CH_2Cl_2, rt; (d) 1N NaOH, MeOH.



Scheme 3. (a) **8**, LDA, THF, HMPA, −78°C to rt; (b) Bu_3SnH, $PdCl_2(PPh_3)_2$, THF; (c) I_2, CH_2Cl_2; (d) Ar_1-$B(OH)_2$, $Pd(PPh_3)_4$, DME/Na_2CO_3, 110°C; (e) TFA, H_2O, CH_2Cl_2, rt; (f) 1N NaOH, MeOH.

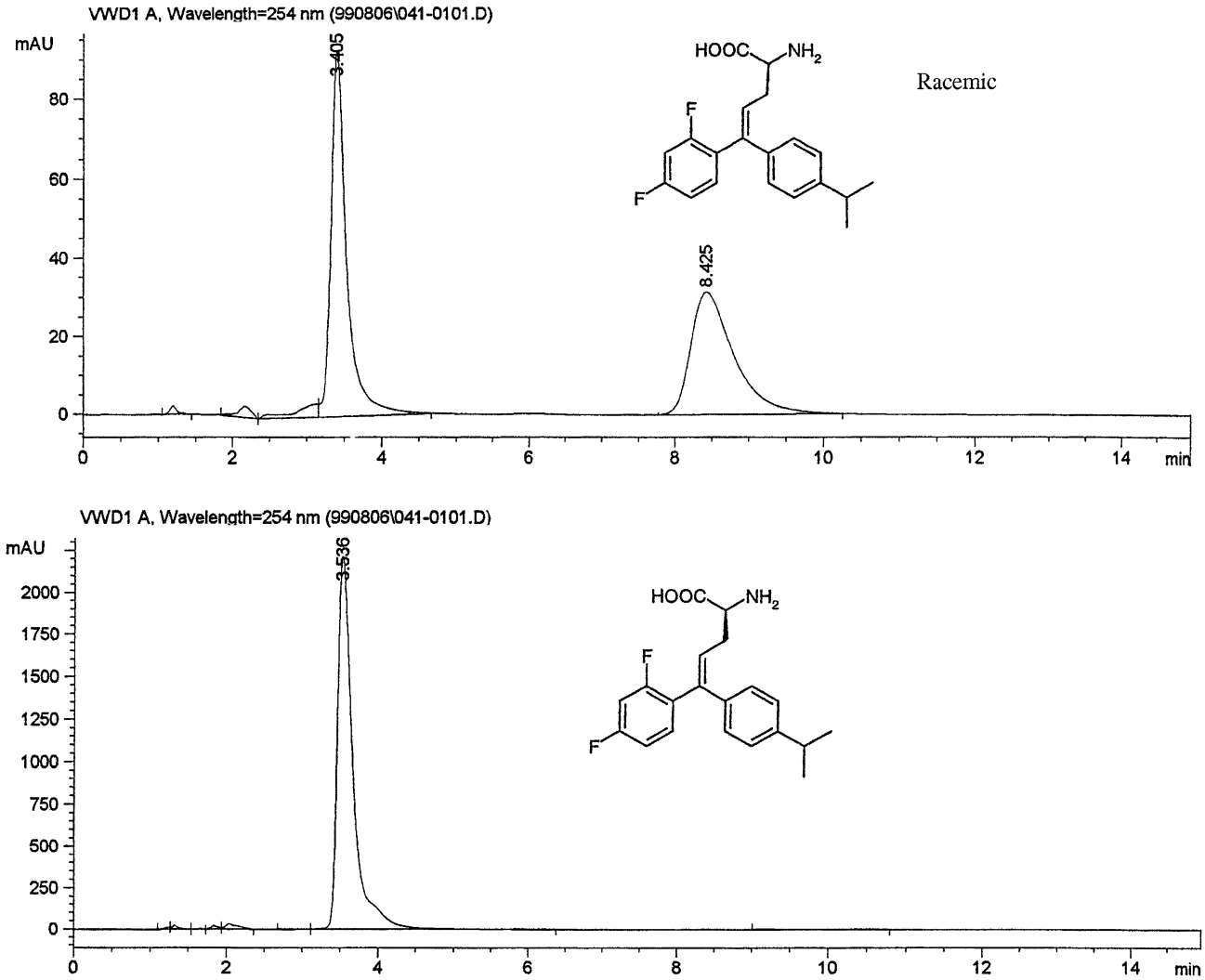
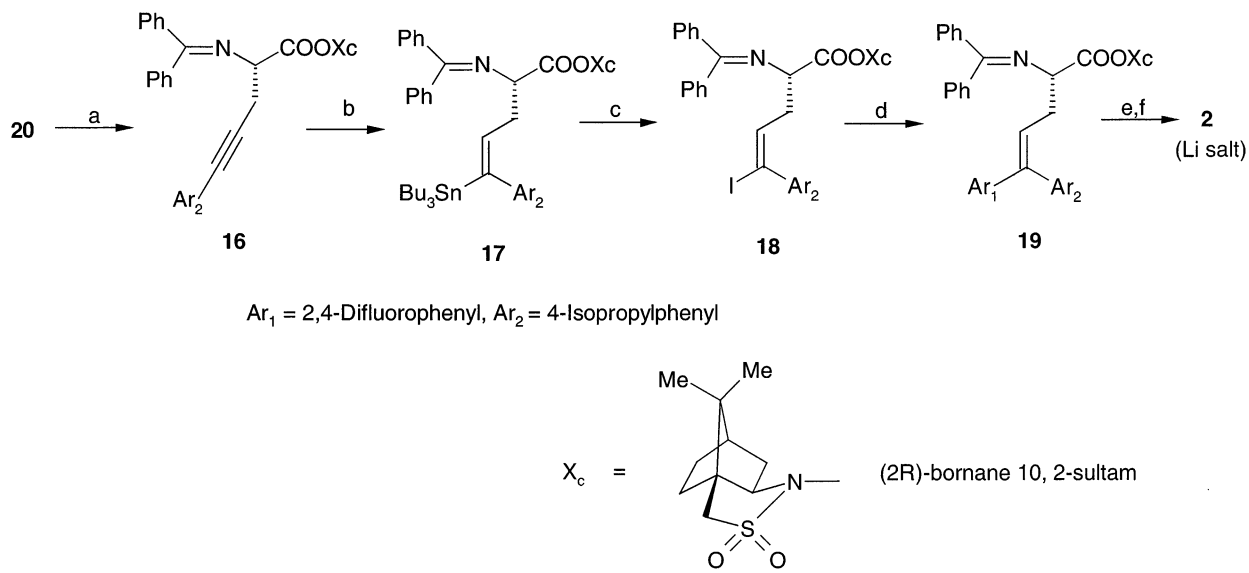


Figure 1.



Scheme 4. (a) (i) LDA, THF, HMPA, −78°C, (ii) **7b**, −78°C to rt; (b) Bu_3SnH, $PdCl_2(PPh_3)_2$, THF; (c) I_2, CH_2Cl_2; (d) Ar_1-$B(OH)_2$, $Pd(PPh_3)_4$, DME/Na_2CO_3, 110°C; (e) TFA, H_2O, CH_2Cl_2, rt; (f) 2.5N LiOH, H_2O/THF.

methylene)glycinate **20**[10] with the activated organic bromide **7b** affords the monoalkylated intermediate **16** with high diastereoselectivity (only one isomer was observed) (Scheme 4). Regioselective hydrostannation of **15**, followed by tin–iodine, afforded the intermediate **17**, which was then subjected to Suzuki coupling, trifluoroacetic acid-mediated deprotection, followed by lithium hydroxide-mediated hydrolysis of the chiral auxiliary, to give the lithium salt of **2** as the pure *S*-enantiomer.

In conclusion, we have successfully synthesized a novel amino acid **1** from *N*-(diphenylmethylene)glycinate precursors. The synthesis was carried out in a highly regio- and stereodefined fashion, as illustrated by the asymmetric synthesis of **2**. The key highlight of the synthetic strategy is the palladium-catalyzed stereoselective hydrostannylation of the highly functionalized intermediates affording products **1** and **2** in good overall yield.

Acknowledgements

The authors would like to thank Dr. Shawn Maddaford for his valuable discussions and suggestions.

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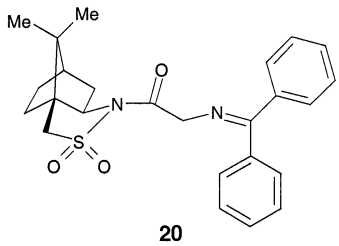
10. 

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For the synthesis of **20**, see: (a) Josien, H.; Lavielle, S.; Brunissen, A.; Saffroy, M.; Torrens, Y.; et al. *J. Med. Chem.* **1994**, *37*, 1586; (b) Josien, H.; Martin, A.; Chassing, G. *Tetrahedron Lett.* **1991**, *32*, 6547.