A Versatile Asymmetric Synthesis of β-Branched α-Amino Acids

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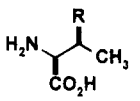
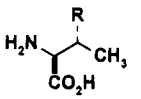
Unnatural β-branched α-amino acids are important tools which have been used successfully to construct conformationally biased peptide ligands with the ultimate goal of achieving novel, desirable biological properties.[1] Therefore, it is of considerable importance to establish efficient, general, and flexible methods for the preparation of all diastereomers of this important class of compounds in enantiomerically pure form. Herein, we report the development of such a method which has been applied to the asymmetric synthesis of L-β-methylphenylalanines, *threo*-(2*S*,3*R*)-**1a** and *erythro*-(2*S*,3*S*)-**1b**, and



1a



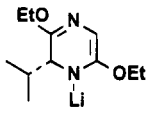
1b

R = Ph

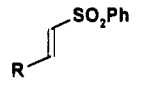
R = 3-indolyl 2a

allowed the asymmetric synthesis of unprotected *threo*-(2*S*,3*R*)-L-β-methyltryptophan, **2a**, as well as a precursor of *threo*-L-β-ethylphenylalanine, compound (2*S*,1′*S*)-**13a**.

Previously, the asymmetric synthesis of chiral β-alkyl-branched α-amino acids had been achieved via conjugate addition of an organometallic species to an α,β unsaturated acceptor bearing a chiral auxiliary followed by trapping the adduct with a functional group suitable for conversion to the α-amino functionality. Organocuprates have been used successfully by Hruby in the case where the auxiliary is an Evans oxazolidinone with the stereoselectivity being somewhat variable.[2] The Oppolzer group has demonstrated that alkyl Grignard reagents add with high selectivity to enoylsultams.[3] However, for the conjugate addition of a phenyl group a cuprate was also required. Although clearly useful, there are sometimes drawbacks or limitations of these methods regarding either reagents or generality. We have conceived an alternative strategy for the asymmetric synthesis of β-alkyl-branched α-amino acids based on the conjugate addition reaction of a chiral glycine synthon, **3**, to an (*E*)-vinyl sulfone, **4**, or (*Z*)-vinyl sulfone, **5**. Although the conjugate addition of the lithium salt of the Schöllkopf bis-lactim ether,[4] to phenyl vinyl sulfone, **4a**, had been

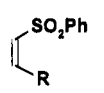


(-)-3

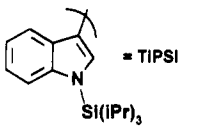


4a R = H

4b = Ph



5b R = Ph



4c = = TIPSI

demonstrated to result in polymerization,[5] we anticipated that the conjugate addition of **3** to β-substituted vinyl sulfones would be uncomplicated.[6] Furthermore, it seemed likely that the stereochemical course of addition of the D-valine derived, (−)-**3**, to (*E*)-vinyl sulfones, **4**, would preferentially furnish adducts with the (2*S*,1′*R*) absolute stereochemistry while the addition to (*Z*)-vinyl sulfones **5** would yield adducts of (2*S*,1′*S*) configuration.[7] After reductive desulfonation and hydrolysis, stereochemically homogeneous L-α-amino acids with β-methyl branching could be obtained.

As targets for this synthetic strategy we have chosen optically active L-β-methylphenylalanines[2a,3,8] *threo*-(2*S*,3*R*)-**1a** and *erythro*-(2*S*,3*S*)-**1b**, as well as the more challenging *threo*-L-β-methyltryptophan,[2c,9] (2*S*,3*R*)-**2a**, all of which are known characterized compounds. For our method to be useful simple access to stereochemically homogeneous (*E*)- and (*Z*)-vinyl sulfones was a prerequisite. We have slightly modified a published "one pot" method for the preparation of (*E*)-vinyl sulfones, ((*E*)-RCH=CHSO$_2$Ph), allowing easy, reliable access to these compounds starting from an aldehyde RCHO in a single step.[10] The Cu(BF$_4$)$_2$-mediated R$_3$SiH reduction[11] of sulfonyl acetylenes[12] is satisfactory[13] for the preparation of (*Z*)-vinyl sulfones, making them also available.

Addition of **4b** to 3 equiv of the bislactim ether lithium salt, (−)-**3**,[14] in Et$_2$O–THF (90:10)[15] at −70 °C under argon gave a spontaneous reaction which was quenched after 15 min with acetic acid. HPLC analysis[16] of the crude reaction mixture indicated a 90:10 ratio of **6a:6b**,

(1) (a) For a review article on the use of conformationally biased amino acids to influence the biological activity of peptide ligands see: Hruby, V. J.; Al-Obeidi, F.; Kazmierski, W. *Biochem. J.* **1990**, *268*, 249. (b) For examples with β-methyl-Phe and β-methyl-Trp containing somatostatin analogs see: Huang, Z.; He, Y. B.; Raynor, K.; Tallent, M.; Reisine, T.; Goodman, M. *J. Am. Chem. Soc.* **1992**, *114*, 9390.

(2) (a) Li, G.; Jarosinski, M. A.; Hruby, V. J. *Tetrahedron Lett.* **1993**, *34*, 2561. (b) Li, G.; Russell, K. C.; Jarosinski, M. A.; Hruby, V. J. *Tetrahedron Lett.* **1993**, *34*, 2565. (c) Boteju, L. W.; Wegner, K.; Qian, X.; Hruby, V. J. *Tetrahedron* **1994**, 2391.

(3) Oppolzer, W.; Tamura, O.; Deerberg, J. *Helv. Chim. Acta* **1992**, *75*, 1965 and references therein.

(4) For reviews wherein the use of **3** is described see: (a) Williams, R. *Synthesis of Optically Active α-Amino Acids;* Pergamon: Oxford, 1989. (b) Duthaler, R. O. *Tetrahedron* **1994**, 1539.

(5) Schöllkopf, U.; Pettig, D.; Schulze, E.; Klinge, M.; Egert, E.; Benecke, B.; Noltemeyer, M. *Angew. Chem.* **1988**, *100*, 1238.

(6) We have demonstrated that addition of **3** to unsubstituted vinyl phosphonic acid esters also results in polymerization and that this can be overcome by using a mixture of a 2-bromoethyl phosphonate and a catalytic amount of vinyl phosphonate: Shapiro, G.; Buechler, D.; Ojea, V.; Pombo-Villar, E.; Ruiz, M.; Weber, H. P. *Tetrahedron Lett.* **1993**, *34*, 6255. No polymerization was observed in the conjugate addition of **3** to 2-substituted vinyl phosphonates.[7]

(7) Conjugate additions of **3** to vinylphosphonates have shown this stereochemical preference for the β center. Ojea, V.; Ruiz, M.; Shapiro, G.; Pombo-Villar, E. *Tetrahedron Lett.* **1994**, *35*, 3273.

(8) Dharanipragada, R.; VanHulle, K.; Bannister, A.; Bear, S.; Kennedy, L.; Hruby, V. J. *Tetrahedron* **1992**, *48*, 4733.

(9) Spöndlin, C.; Tamm, C. *Heterocycles* **1989**, *28*, 453. The preparation of *erythro*-(2S,3S)-**2b** from tryptophan has been recently reported: Bruncko, M.; Crich, D. *J. Org. Chem.* **1994**, *59*, 4239.

(10) Lee, J. W.; Oh, D. Y. *Synth. Commun.* **1989**, *19*, 2209. We have found that the reaction is more reliable and gives higher yields when 2 equiv of lithium diisopropylamide are used in place of *n*-BuLi.

(11) Ryn, I.; Kusumoto, N.; Ogawa, A.; Kambe, N.; Sonoda, N. *Organometallics* **1989**, *8*, 2279.

(12) Lee, J.; Oh, D. Y. *Synlett* **1990**, 290.

(13) Although the chemical yield of this reaction[11] is quite good we obtained ca. 10% of the (*E*)-vinyl sulfones which require careful chromatographic separation from the desired *Z*-isomers.

(14) Prepared in the Sandoz kilolaboratory.

(15) Use of diethyl ether as the reaction solvent was found to be important for obtaining good stereoselection at the β-center. Since the lithium salt of the Schöllkopf bis-lactim ether is poorly soluble in ether a small amount of THF is necessary to ensure a homogeneous solution.

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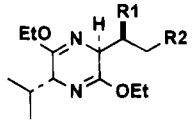
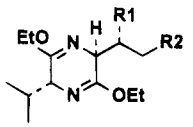
the diastereomeric adducts. Isomerism at the α-center was not observed.[17] This mixture was separated by flash chromatography[18] to give a 74% isolated yield of isomerically pure **6a**. Standard sodium amalgam-mediated





6a R_1 = Ph R_2 = SO_2Ph **6b** R_1 = Ph R_2 = SO_2Ph

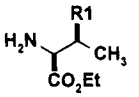
7a = Ph = H **7b** = Ph = H

9a = 3-(TIPSI) = SO_2Ph **9b** = 3-(TIPSI) = SO_2Ph

10a = 3-(TIPSI) = H

13a = Ph = CH_3

reductive cleavage of the sulfonyl group[19] cleanly afforded **7a** (82% after chromatography). Mild acid hydrolysis (0.5 N HCl–Et_2O) gave amino ester **8a** which was readily



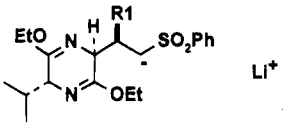
8a R_1 = Ph

11a R_1 = 3-(TIPSI)

separated from the concommitantly formed D-valine ethyl ester by simple chromatography (90%). Final conversion of **8a** to *threo* (+)-(2*S*,3*R*)-**1a** as its amino acid hydrochloride was achieved under standard conditions (6 N HCl–reflux).[20] Thus, the stereochemical outcome of the conjugate addition reaction was as predicted. In the addition of (−)-**3** to (*Z*)-phenyl vinyl sulfone **5b**[21] the degree of stereoselectivity was comparable to that observed with **4b** the sense of β-stereoselection, however, being reversed. Thus, a mixture of **6a:6b** in 10:90 ratio was obtained again with apparent complete selectivity with regard to the α-center. Compound **6b** was purified and converted to **7b** as above.

To establish the generality and scope of this method, we have used it to prepare the biologically important isomer[22] of L-β-methyltryptophan, *threo*-(2*S*,3*R*)-**2a**. Addition of **3** to *N*-(triisopropylsilyl)-(*E*)-(vinylsulfonyl)-indole, **4c**,[23] as above afforded pure **9a** with <5% of an isomeric product, presumably (2*S*,3*S*)-**9b**. After purification,[24] standard desulfonation and hydrolysis (1 N HCl–THF) of **9a** gave **11a** with only slight loss of the silyl protecting group.[25] Then, *threo* (2*S*,3*R*)-**2a** was prepared directly in moderate yield (54%) by standard acid hydrolysis of **11a** (6 N HCl–dioxane reflux) or in a milder two-step procedure in which the triisopropylsilyl group was first removed[26] (NBu_4F/THF/rt) and then the described[9] chymotrypsin-mediated hydrolysis performed.[27]

A powerful feature of this method is the potential for trapping the α-sulfonyl anion, **12**, generated by the conjugate addition with an electrophile, "in situ". To



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demonstrate this extension of scope, the addition of **3** to **4b** was quenched with MeI. After chromatography of the reaction mixture one major isomer was obtained (ca. 90% of the diastereomeric mixture) indicating that the alkylation of the intermediate sulfonyl anion was highly stereoselective. Desulfonation of this compound gave **13a**, to which the (2*S*,1′*R*) configuration is assigned by analogy. Thus, optically pure isomers of β-ethylphenylalanine are also readily available, and the possibility for trapping with a wide variety of other electrophiles is evident as the synthetic utility of α-sulfonyl anions is well established.[28]

In summary, a versatile new method for the asymmetric synthesis of optically pure β-alkyl-branched amino acids of defined absolute configuration has been achieved whose scope is under investigation. In this study *threo* isomers are readily available. For the *erythro* series one is limited by the somewhat more difficult access to (*Z*)-vinyl sulfones. A careful analysis of the conformationally accessible lithium chelate transition states remains to be performed to account for the stereoselectivity observed in the conjugate addition.

Acknowledgment. B.G.L. thanks the Xunta de Galicia and the Ministerio de Educacion y Ciencia of Spain for financial support.

Supporting Information Available: Optical rotations and high field ^1H NMR and ^{13}C NMR spectra have been provided for compounds **1a, 2a, 6a,b, 7a,b, 8a, 9a, 10a, 11a,** and **13a** along with a general procedure for **6a** (26 pages).

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(16) HPLC, RP-2 (Brownlee column, 100 × 4.6 mm, Speri-10 μm), gradient 50 A:50 B to 100% B solution in 20 min [A = 1000 H_2O, 20 tetramethylammonium hydroxie, 2 H_3PO_4 (85%); B = 700 CH_3CN, 300 H_2O, 20 tetramethylammonium hydroxide, 2 H_3PO_4(85%)], 1.5 mL $min,^{-1}$ detection 254 nm.

(17) No other isomer was observed in the HPLC or in the 360 MHz ^1H NMR analysis of the crude reaction mixture or purified components indicating that such an isomer if formed would be present to an extent of ca. 2% or less.

(18) Solvent system hexane–isopropyl acetate 80:20.

(19) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, *11*, 3477.

(20) The analytical data for the hydrochloride of **1a** were consistent with those reported. Optical rotation and ^1H NMR data for the hydrochloride of **1a** are reported by: Kataoka, Y.; Seto, Y.; Yamamoto, M.; Yamada, T.; Kuwata, S.; Watanabe, H. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1081. The D_2O chemical shifts reported for **1a** in ref 8 are off by 0.2 ppm due to the misreferencing of the shift of the dioxane internal standard at δ = 3.55 ppm instead of δ = 3.75 ppm. Roberts, G. C. K. *NMR of Macromolecules*; IRL Press: Oxford, 1993; p 31.

(21) After chromatography **5b** still contained ca. 3% of **4b**.

(22) **2a** is the biosynthetic precursor of streptonigrin, and lavendomycin is a component of the antibiotic telomycin.

(23) This material was prepared with our modified method[10] in 55% yield from 1-(triisopropylsilyl)-3-formylindole which was readily prepared according to: Mercedes, A.; Hadida, S.; Sathyanarayana, S.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 10.

(24) Compound **9a** was obtained in 82% yield after MPLC chromatography (hexane–ethyl acetate 90:10).

(25) MPLC chromatography (90:10 ethyl acetate–hexane) was performed after the two steps to give **11a** in 79% overall yield. Ca. 5% cleavage of the triisopropylsilyl group was observed; this product coelutes with the valine ethyl ester.

(26) Interestingly, the silyl group was not cleaved with dilute (5%) HF in CH_3CN.

(27) To prepare salt free material the reaction product was purified by semipreparative RP-18 HPLC eluting with water. After lyophilizing, **2a** was obtained having analytical data (optical rotation, ^{13}C, ^1H-NMR) consistent with those reported.[9]

(28) Simpkins, N. S. *Sulphones in Organic Synthesis;* Pergamon Press: Oxford, 1993.