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A Highly Enantioselective Asymmetric Hydrogenation Route to β-(2R,3S)-Methyltryptophan

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Abstract: Asymmetric hydrogenation of a protected (Z)-dehydro-β-methyltryptophan derivative **2** with (R,R)-Me-DuPHOS-Rh catalysis was achieved in 97 % ee. Deprotection then afforded (2R,3S)-β-methyltryptophan **1**.
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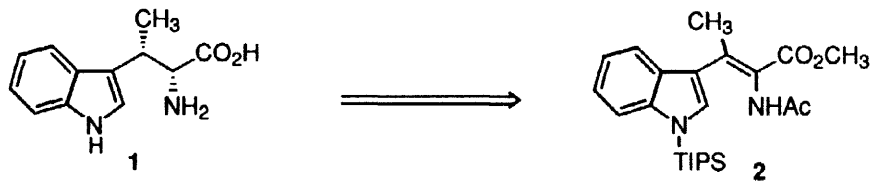
The paradigm of β-substitution of aromatic aminoacids to restrict conformational degrees of freedom or otherwise alter supramolecular architecture is well established in the design of enzyme inhibitors and modified peptide hormones. Specifically, the β-methyltryptophan motif has generated much recent attention along these lines.[1] Thus, there is interest in efficient and flexible routes to β-methyltryptophan for these purposes. Previous routes to **1** have involved resolution or intramolecular chirality transfer approaches.[2] We sought an enantioselective route which would establish both stereocenters of **1** simultaneously, and access either absolute configuration. Herein, we describe a synthesis of β-(2R,3S)-methyltryptophan **1** via a highly enantioselective asymmetric hydrogenation of suitably protected (Z)-dehydro-β-methyltryptophan derivative **2** (eq 1).



(1)

The four step synthesis of compound **2** is shown in Scheme 1. Indole **3** was silylated in nearly quantitative yield under standard conditions[3] with n-BuLi and triisopropylsilyl chloride (TIPSCl) and the silylated derivative **4** was treated with NBS/THF at -78°C to generate the *N*-TIPS-3-bromo-indole **5** (91% overall).[4] Typically, only small amounts of the isomeric *N*-TIPS-2-bromoindole (2-5 %) can be detected during the NBS bromination; furthermore, the undesired isomer is efficiently removed during crystallization of **5** in aqueous ethanol.[5] The boronic acid derivative **6** was prepared from the bromide with sec-BuLi at -60°C followed by quenching with triisopropylborate, warming to -20 °C and subequent hydrolysis (93% crude). The key Suzuki coupling of **6** and (Z)-vinyl bromide **7** was carried out in aqueous DME at 80°C with $Pd(PPh_3)_4$ in the presence of Na_2CO_3 in 86% yield. The desired olefin **2** was crystallized from ethanol/water to provide material of > 98 % purity by HPLC analysis.

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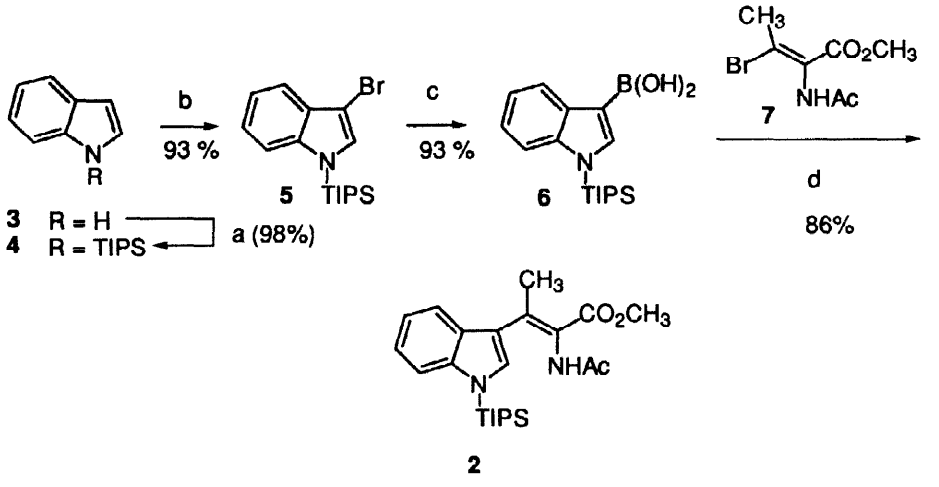
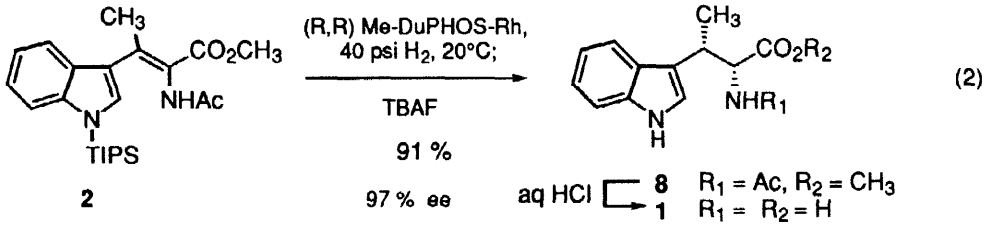
Scheme 1



(a) n-BuLi, TIPSCl, THF,- 78°C. (b) NBS, THF, -78°C. (c) i. sec-BuLi, -60°C to -20 °C; ii. $B(OiPr)_3$; iii. aqueous NH_4Cl. (d) $Pd(PPh_3)_4$, DME, aqueous Na_2CO_3, 80°C.

The hydrogenation of tetrasubstitued olefin **2** was initially performed with (R,R)-Et-DuPHOS-Rh in MeOH at 20 °C with 40 psi H_2 over 24 h (eq 2).[6] The hydrogenation product was filtered through silica gel (EtOAc) to remove the catalyst and the TIPS group was removed with TBAF/THF to yield **8**. Analysis of the crude mixture by SFC chromatography[7] indicated **8** was obtained in 91.5 % ee. *Futhermore, treatment of 2 under the same conditions with (R,R) Me-DuPHOS-Rh resulted in the formation of 8 in 97 % ee after removal of the TIPS group (91 % overall).* There is precedent for sterically congested systems where the Me-DuPHOS-Rh provides higher ee's that the Et-DuPHOS-Rh.[8]

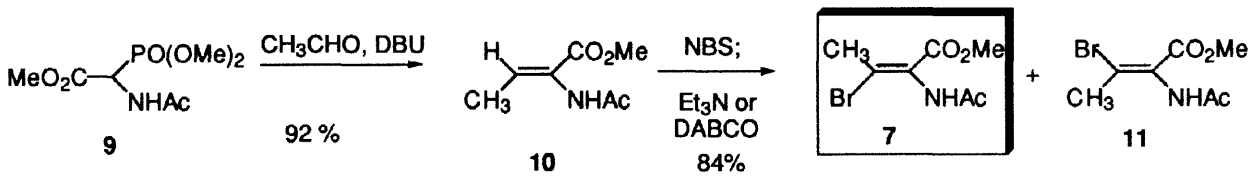


(2)

Exposure of **8** to aqueous HCl at reflux temperatures resulted in smooth hydrolysis of the acetamide and methyl ester functionalities providing the (2R,3S)-β-methyltryptophan **1** (91%), which was identical with an authentic sample.[9]

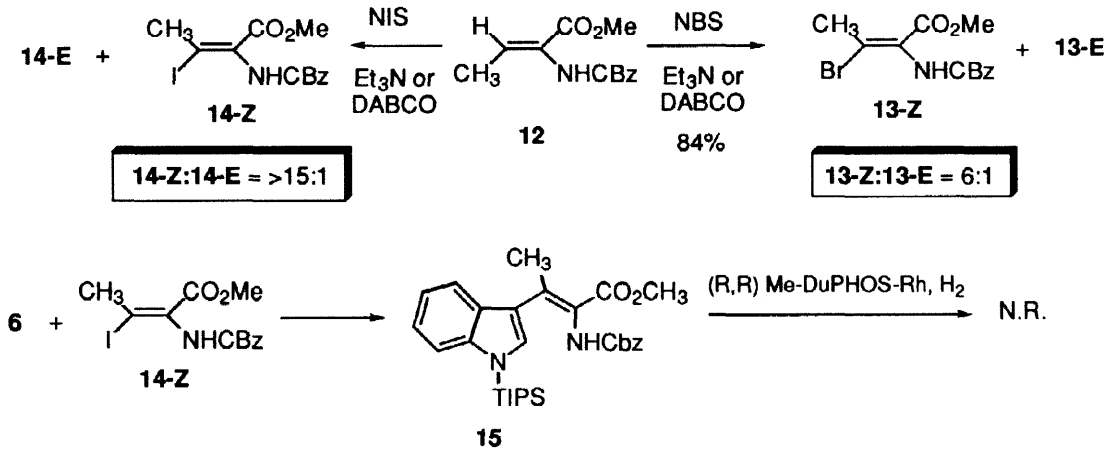
The (*Z*)-vinyl bromide **7** was prepared via the following method (Scheme 2). The *N*-Ac phosphonate **9**[10] was condensed with acetaldehyde in the presence of DBU to generate the (*Z*)-trisubstituted alkene **10**. The alkene **10** was treated with NBS to produce the intermediate β-bromo-α-imino ester which was exposed to a tertiary amine base to yield the tetra-substituted vinyl bromides 7 and **11** as a 1:1 mixture, which were readily separable by silica gel chromatography.[11,12]

Scheme 2



Interestingly, when the acetamide protecting group of **10** was replaced with an *N*-Cbz group (Scheme 3), improved selectivity in the bromination (of **12**) was obtained (ratio of **13**-*Z*/*E* vinyl bromides rose to ~6:1). More remarkably, iodination of **12** with NIS gave highly selective formation of the (*Z*) isomer (**14-Z**:**14-E** > 15:1). Compound **14-Z** could be purified by methanol crystallization thus eliminating the need for silica gel chromatography. Suzuki coupling of **14-Z** with boronic acid **6** afforded the *N*-CBz tetrasubstituted olefin derivative **15**. Unfortunately, **15** failed to undergo hydrogenation with Me-DUPHOS-Rh, even under more vigorous conditions.[13,14]

Scheme 3



In summary, a direct entry into the β-methyl tryptophan core structure is available through asymmetric hydrogenation. The products are available in high optical purity.

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5. Direct bromination of indole at the 3-position with bromine (Bocchi, V.; Palla, G. *Synthesis*, **1982**, 1096) yielded the 3-bromoindole which did not readily silylate.

6. Standard hydrogenation conditions: A solution of **2** (500 mg, 1.17 mmol) in MeOH (7.5 mL) was degassed with nitrogen for 15 min. A sample of (-)-1,2-Bis((2R, 5R)-2,5-dimethylphospholano)benzene(cyclooctadiene)rhodium (I) trifluoromethanesulfonate (7.5 mg, 0.011 mmol, purchased from STREM) was charged and the sample was hydrogenated (40 psi H_2) at 20°C for 24 h. The crude solution was filtered through silica gel (2:1 ethyl acetate/hexane) to remove the catalyst and provide **8** (482 mg, 96% yield, 97 % ee by SFC HPLC[7]).

7. SFC conditions: Hewlitt-Packard HP1205 SuperCritical Fluid chromatography instument; Chiralpak AD column (4.6 mm X 25 cm) ; 300 bar, 35°C, 1 mL/min., 4% modifier (methanol) for 4 minute ramp to 32; detection at 220 nm; retention times; **8**: 17.2 min, ent-**8**: 19.3 min.

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9. (a) Shapiro, G.; Buechler, D.; Marzi, M.; Schmidt, K.; Gomez-Lor, B. *J. Org. Chem.* **1995**, *60*, 4978. (b) Spondlin, C.; Tamm, C. *Heterocycles* **1989**, *28*, 453. (c) An authentic sample was generated via the method of Snyder and Mateson: Mateson, D.S.; Snyder, H.R. *J. Am. Chem. Soc.* **1957**, *79*, 2217; compound **1**: ^{1}H NMR (D_2O, 250 MHz) δ7.76 (d,1H), 7.53 (d,1H), 7.22-7.30 (m,2H), 7.18 (t,1H), 4.14 (d,1H), 3.91 (m,1H), 1.39 (d,3H); $[\alpha]^{25}_D$ +27.1 (water, c 0.31).

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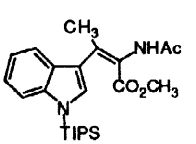
11. (a) Danion-Bougot, R.; Danion, D.; Francis, G. *Tetrahedron Lett.* **1990**, *26*, 3739. (b) Miossec, B.; Danion-Bogot, R.; Danion, D. *Synthesis*, **1994**, 1171.

12. Isomerization (*E/Z*) of similar vinyl bromides with DABCO has been reported (Coleman, R.S.; Carpenter, A.J. *J. Org. Chem.* **1993**, *58*, 4452). Extended treatment (48 h) of the (*E*)-vinyl bromide **11** with DABCO or triethylamine in hot dichloroethane did not result in isomerization to **7**.

13. The hydrogenation of **15** was carried out at 60°C (benzene) for 24 h with no reaction. The hydrogenation of **15** was attempted under high pressure (1650 psi) for 24 h with no reaction.

14. The preparation of the isomeric *N*-acetyl-*(E)*-dehydro-β-methyltryptophan derivative **16** was carried out from the (*E*)-vinyl bromide **11** under similar Pd-catalyzed Suzuki coupling with the boronic acid **6** in 65% yield. Interestingly, the (*E*)-dehydro-β-methyltryptophan derivative **16** has also been resistant to the asymmetric hydrogenation conditions.



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