Enantioselective Synthesis of Renieramide

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Abstract: A highly chemo- and enantioselective PTC alkylation has been developed that allows rapid access to orthogonally protected (*S*,*S*)-isodityrosine. Utility of this material in the construction of isodityrosine-containing cyclic peptides is demonstrated by synthesis of the natural product renieramide.

Key words: amino acids, asymmetric alkylation, phase-transfer catalysis, quaternary ammonium salts

Isodityrosine (**1**) is a naturally-occurring bis-amino acid that was originally identified as a cross-linking element in plant cell wall glycoprotein.[1] This structural component has since been found in a range of natural products,[2] including a series of macrocyclic tripeptides[3–6] of which renieramide (**2**) is the most recently reported example (Figure 1).[7] These natural products have been reported to exhibit a diverse range of biological activities and hence have attracted significant attention from synthetic chemists.

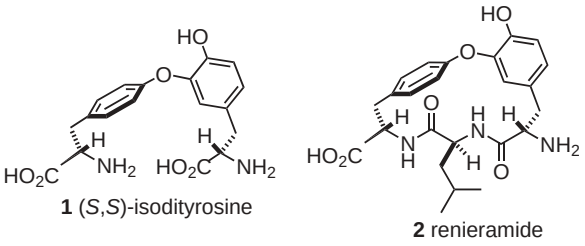


Figure 1

We have recently reported an enantioselective approach to isodityrosine (**1**), which employed a chiral phase-transfer catalyst to promote a double asymmetric alkylation involving reaction of dibromide **3a** with two molecules of glycine imine **4a**.[8] Although this approach provided rapid access to isodityrosine (**1**), it is not applicable to the synthesis of tripeptides such as **2** because it does not allow straightforward differentiation of the the two amino acid functions.

One possible solution to this problem would be to effect two separate asymmetric alkylations involving a substrate such as **3**. If a different glycine imine ester (e.g. **4a** and **4b**, Figure 2) was employed in each alkylation it would allow

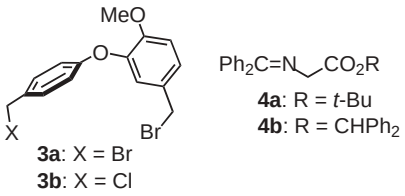
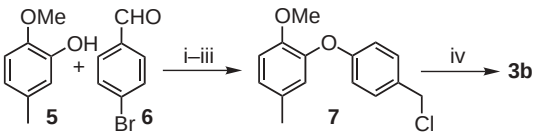


Figure 2

access to orthogonally protected isodityrosine, and hence the synthesis of targets such as renieramide (**2**) should then be possible.

Preliminary experiments involving the alkylation of glycine imines **4** with dibromide **3a** suggested that the two bromomethyl groups reacted at similar rates and so we considered the possibility of using the alternative substrate **3b**. This material was prepared in four steps from commercially available 4-bromobenzaldehyde **6** via the sequence outlined in Scheme 1. Thus, Ullmann coupling with phenol **5**, followed by reduction of the resulting aldehyde and conversion into the corresponding chloride, gave the intermediate **7** in good overall yield. Treatment of this compound with NBS in the presence of AIBN then led to selective bromination of the arylmethyl group, providing target structure **3b**.



Scheme 1 *Reagents and conditions*: (i) CuO, K_2CO_3, pyridine reflux; (ii) $NaBH_4$, MeOH, r.t.; (iii) concd HCl, EtOAc, r.t. (78% overall); (iv) NBS, AIBN, CCl_4, hν, reflux (53%).

In order to utilise bromide **3b** in the synthesis of renieramide (**2**), we needed to develop a highly regio- and enantioselective alkylation involving reaction of the bromomethyl moiety with glycine imine **4b**. Based on previous studies within the group we considered that this might be possible using phase-transfer catalyst **9** (Figure 3).[9]

This proved to be the case and, after some experimentation, we were able to establish conditions that led to the desired transformation (Scheme 2).[10] This process appears to be highly chemoselective as no alkylation involving the chloromethyl group could be detected even when larger excesses of imine **4b** were employed. We

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could also find no evidence of halogen exchange involving this function[11] even though bromide ion is generated in stoichiometric amounts during the reaction. These observations provide a powerful illustration of the chemoselectivity that can be achieved using phase-transfer conditions.

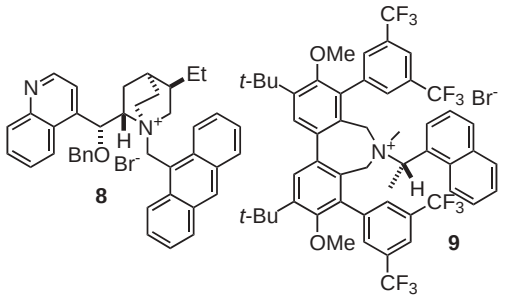
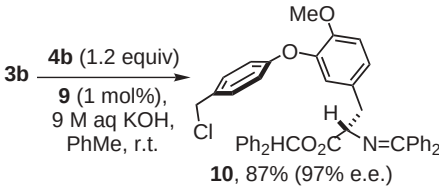


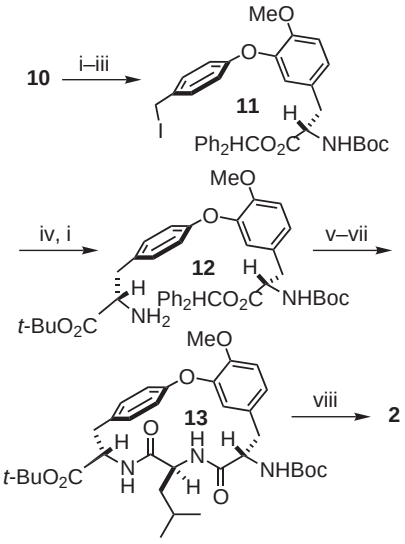
Figure 3

To complete the construction of an orthogonally protected dityrosine a second asymmetric alkylation is required. In order to achieve this, the imine function in intermediate **10** was first converted into the corresponding *tert*-butyl carbamate via hydrolysis and treatment with $(Boc)_2O$. Finklestein reaction then provided iodide **11**, which was expected to be a suitable partner for reaction with glycine imine **4a** (Scheme 3). In this case we chose to employ phase-transfer catalyst **8** in an effort to promote the asymmetric alkylation as this catalyst has proved to be highly effective for reactions involving imine **4a**.[12,13] The alkylation proceeded as anticipated and, after hydrolysis of the imine function, the orthogonally protected isodityrosine derivative **12**[14] could be isolated in good yield.[15] At this stage we were unable to accurately determine the stereochemical purity of **12**, however ^1H NMR analysis of later compounds indicated that this intermediate must have been formed with high diastereoselectivity.



Scheme 2

In order to demonstrate the utility of intermediate **12** in the synthesis of isodityrosine tripeptides we next investigated conversion into renieramide (**2**). To this end, the amino function in compound **12** was first coupled with (*Z*)-L-Leu-OSuc. This gave the corresponding dipeptide as a single diastereoisomer in good yield. Simultaneous removal of the benzyloxycarbonyl and benzhydryl functions via hydrogenolysis then provided the macrocyclisation precursor. It was found that cyclisation could be achieved in good yield by slow addition of this precursor to EDCI/HOBt at 60 °C. Using this approach, the macrocycle **13** could be obtained in 55% overall yield (from compound **12**). Deprotection using TfOH/TFA,[16] followed by purification via ion-exchange chromatography then provided synthetic renieramide (**2**) which exhibited optical rotation and $^1H/^{13}C$ NMR in reasonable agreement with that reported for the natural product.[6,17,18]



Scheme 3 *Reagents and conditions*: (i) 15% aq citric acid, THF, r.t.; (ii) Boc_2O, $NaHCO_3$, dioxane, r.t.; (iii) NaI, acetone, r.t. (45% overall); (iv) **4a** (1.2 equiv), **8** (10 mol%), 9 M aq KOH, PhMe, r.t. (83% after imine hydrolysis); (v) (*Z*)-L-Leu-OSuc, CH_2Cl_2, r.t. (85%); (vi) H_2 (1 atm), Pd/C, MeOH, r.t.; (vii) slow addition of substrate to EDCI, HOBt, NMM, PhMe, DMF, 60 °C (65% overall); (viii) TfOH, TFA, PhSMe, –5 °C, Dowex 50WX8-200 ion-exchange chromatography (54%).

In conclusion, we have established that it is possible to employ two sequential asymmetric phase-transfer alkylations for the construction of orthogonally protected (*S*,*S*)-isodityrosine. The utility of this material in the construction of isodityrosine-containing cyclic peptides has been established by the synthesis of renieramide.

Acknowledgment

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(10) The enantioselectivity of this alkylation was determined by chiral-phase HPLC comparison of the product **10** with racemic material generated using *n*-Bu_4NBr as the PTC. Use of catalyst **8** led to similar regioselectivity and yield, but gave **10** with only 50% ee.

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(14) **Representative Alkylation–Hydrolysis Procedure (Preparation of 12):** A solution of glycine imine **4a** (161 mg, 0.54 mmol) in toluene (4 mL) was placed under a nitrogen atmosphere. Iodide **11** (312 mg, 0.45 mmol), catalyst **8** (36 mg 10 mol%) and 9 M aq KOH (400 μL) were added sequentially, and the resulting mixture stirred at r.t. for 18 h. The toluene layer was then separated and the aqueous layer extracted with EtOAc (3 × 2 mL). The combined organics were dried ($MgSO_4$), and concentrated under reduced pressure. The residue was dissolved in Et_2O (10 mL), filtered (to remove catalyst), and again concentrated under reduced pressure. The residue was then dissolved in THF (5 mL) and 15% aq citric acid (1.5 mL) added. The mixture was stirred at r.t. for 18 h, then extracted with $CHCl_3$ (4 × 3 mL). The combined organics were washed with 10% aq Na_2CO_3 (2 × 4 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel ($CHCl_3$–MeOH, 50:1) to yield the orthogonally protected *iso*dityrosine **12** (269 mg, 85%) as a pale yellow oil. R_f = 0.3 ($CHCl_3$–MeOH, 25:1). $[\alpha]_D$ +1 (*c* 0.9, $CHCl_3$). IR (film): ν_{max} = 3376, 2977, 2632, 1714, 1505 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.23 (10 H, m, ArH), 7.13 (2 H, d, *J* = 8.0 Hz, ArH), 6.84 (1 H, s, $CHPh_2$), 6.81 (2 H, d, *J* = 8.0 Hz, ArH), 6.76 (1 H, d, *J* = 8.0 Hz, ArH), 6.68 (1 H, d, *J* = 8.0 Hz, ArH), 6.65 (1 H, s, ArH), 4.97 (1 H, br d, *J* = 8.0 Hz, NH), 4.68–4.60 (1 H, m, CHN), 3.78 (3 H, s, OCH_3), 3.64–3.56 (1 H, m, CHN), 3.04 (1 H, dd, *J* = 6.0, 14.0 Hz, $CHCH_aH_b$), 2.99–2.95 (2 H, m, $CHCH_aH_b$, $CHCH_aH_b$), 2.82 (1 H, dd, *J* = 8.0, 14.0 Hz, $CHCH_aH_b$), 1.44 [9 H, s, $C(CH_3)_3$], 1.40 [9 H, s, $C(CH_3)_3$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.2 (C), 170.9 (C), 156.9 (C), 155.0 (C), 150.0 (C), 144.6 (C), 139.6 (C), 139.4 (C), 131.3 (C), 130.5 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 127.5 (CH), 127.0 (CH), 125.7 (CH), 122.4 (CH), 116.9 (CH), 112.8 (CH), 81.3 (C), 80.0 (C), 78.0 (CH), 56.3 (CH), 56.0 (CH_3), 54.5 (CH), 40.3 (CH_2), 37.4 (CH_2), 28.3 (CH_3), 28.1 (CH_3). MS (ES^+): *m*/*z* (%) = 719 (28) [M + Na^+], 697 (100) [M + H^+], 641 (10) [M – *t*-Bu + H^+], 296 (68). HRMS: *m*/*z* calcd for $C_{41}H_{49}N_2O_8$ [M + H]$^+$: 697.3489. Found: 697.3528.

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(17) Selected data for synthetic renieramide (**2**): Mp 185–195 °C (decomp). $[\alpha]_D$ –32 (*c* 0.1, MeOH) (lit. $[\alpha]_D$ –30 (*c* 0.1, MeOH).[6] ^1H NMR (500 MHz, CD_3OD): δ = 7.42 (1 H, dd, *J* = 2.0, 8.0 Hz, ArH), 7.20 (1 H, dd, *J* = 2.0, 8.0 Hz, ArH), 7.01 (1 H, dd, *J* = 2.0, 8.0 Hz, ArH), 6.86 (1 H, dd, *J* = 2.5, 8.0 Hz, ArH), 6.81 (1 H, d, *J* = 8.0 Hz, ArH), 6.65 (1 H, dd, *J* = 2.0, 8.0 Hz, ArH), 5.98 (1 H, d, *J* = 2.0 Hz, ArH), 4.52 (1 H, dd, *J* = 3.5, 11.5 Hz, CHN), 4.48 (1 H, dd, *J* = 3.5, 12.5 Hz, C*H*N), 3.97 (1 H, dd, *J* = 2.0, 6.0 Hz, CHN), 3.38 (1 H, dd, *J* = 3.5, 13.0 Hz, $CHCH_aH_b$), 3.15 (1 H, dd, *J* = 2.0, 15.0 Hz, $CHCH_aH_b$), 2.91 (1 H, dd, *J* = 6.0, 15.0 Hz, $CHCH_aH_b$), 2.60 (1 H, app. t, *J* = 12.5 Hz, $CHCH_aH_b$) 1.70–1.62 [2 H, m, $CH_2CH(CH_3)_2$], 1.61–1.51 [1 H, m, $CH_2CH(CH_3)_2$], 0.95 (3 H, d, *J* = 6.0 Hz, CH_3), 0.93 (3 H, d, *J* = 6.0 Hz, CH_3). ^{13}C NMR (125 MHz, CD_3OD): δ = 178.1 (C), 172.7 (C), 169.1 (C), 154.6 (C), 149.8 (C), 147.2 (C), 137.1 (C), 133.0 (CH), 131.7 (CH), 125.0 (2 × CH), 123.1 (CH), 122.7 (CH), 117.2 (CH), 116.9 (CH), 58.1 (CH), 53.7 (CH), 52.1 (CH), 43.6 (CH_2), 40.9 (CH_2), 37.4 (CH_2), 26.0 (CH), 23.8 (CH_3), 21.6 (CH_3).

(18) There is a typographical error in the ^{13}C NMR (CD_3OD) reported for natural renieramide,[6] the CH_2 carbon of the L-DOPA fragment occurs at δ = 37.7 ppm (not 43.6). We thank Prof. R. Riccio and Dr. A. Casapullo for kindly providing this information.