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A concise total synthesis of (+)-okaramine C

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The first total synthesis of (+)-okaramine C is described. Our previously described selenocyclisation-oxidative deselenation sequence was used to establish a 3a-hydroxy-pyrrolo[2,3-*b*]-indole core, which was modified by selective epimerisation to the common pyrrolo[2,3-*b*]indole of the okaramines.

The okaramines are a family of natural products isolated by Hayashi *et al.*[1] from fermentation extracts of *Penicillium simplicissimum* and *Aspergillus aculeatus* cultured on okara (the soybean residue from soymilk production).[2] The okaramines have been found to have insecticidal properties; okaramine C **1** itself has an LD_{50} of 7 μg g^{-1} towards the larvae of silkworm on oral administration,[3] and as such is one of the most potent within the series. Synthetic efforts have recently led to the total synthesis of two members of the family, okaramine N **2**, by Corey *et al.*[4] and okaramine J **3**, by Ganesan *et al.* (Fig. 1).[5]

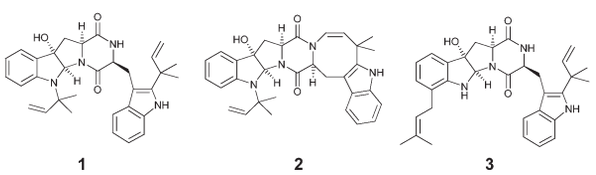
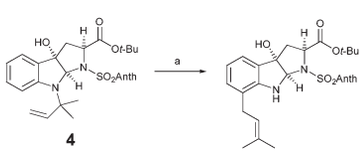


Fig. 1 Okaramines C (**1**), N (**2**) and J (**3**).

Although okaramine C appears to be the simplest target within the series, it has so far proven to be synthetically inaccessible. Indeed, during the aforementioned okaramine J synthesis, the initial target was okaramine C. Unfortunately when advanced intermediate **4** was treated with acid, a facile aza-Claisen rearrangement was observed. This however allowed a neat synthetic entry to okaramine J (Scheme 1).[5]

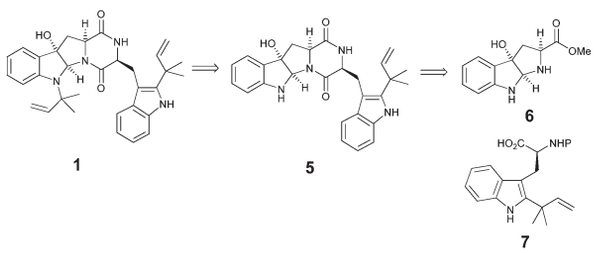


Scheme 1 *Reagents and conditions*: a) CF_3CO_2H (5 eq.), CH_2Cl_2, 16 h, 84%. Anth = 9-anthracenyl.

In order to suppress this aza-Claisen rearrangement we decided to install the *N*-reverse-prenyl appendage at a late stage. This led to diketopiperazine **5** as an advanced intermediate, which in turn could be assembled from key fragments **6** and **7** (Scheme 2).

The synthesis of 3a-hydroxy-pyrrolo[2,3-*b*]indole **6** began from unnatural D-tryptophan **8**. Benzyloxycarbonyl (Z)-protection of **8** followed by formation of the methyl ester and *t*-butyloxycarbonyl (Boc) protection of the indolic nitrogen afforded **9** in 71% yield over three steps. Treatment of **9** with *N*-(phenylseleno)phthalimide (*N*-PSP)[6] resulted in cyclisation in accord with our previously reported work with the corresponding L-tryptophan derivative.[7] This gave the selenocyclised product **10** as a single diastereomer in an excellent 89% yield.

Oxidative deselenation of **10** was effected on addition of wet *meta*-chloroperbenzoic acid (*m*-CPBA) giving the corresponding



Scheme 2 Synthetic strategy for okaramine C synthesis.

alcohol **11** in 92% yield. Having used the D-tryptophan stereocentre to induce selectively the correct stereochemistry at the [5,5]-ring junction, we needed to epimerise this centre to complete the pyrroloindole core of okaramine C. Systems similar to **11** have been shown to be sterically crowded due to the all *syn* relationship around the [5,5]-ring junction.[8] We hoped to exploit this sterically demanding environment to facilitate the desired epimerisation. Unfortunately, whilst the desired epimerised alcohol **12** could be produced under various conditions, it was formed only as a mixture along with the starting alcohol **11**.

In order to increase the steric bulk for this epimerisation the same reaction was attempted on the precursor selenide **10**. Pleasingly, when **10** was treated with one equivalent of LiHMDS at −10 °C in THF, followed by quenching with methanol at −78 °C, the desired ester **13** was formed as a single epimer in quantitative yield (Scheme 3). As before, treatment of **13** with wet *m*-CPBA resulted in oxidative deselenation giving tertiary alcohol **14** in 85% yield.

Unfortunately a problem was encountered with the deprotection steps. We had previously observed that the Boc group in the enantiomer of **11** was removed rapidly in the presence of trifluoroacetic acid (TFA).[7] However, the relief of steric strain achieved by epimerising the ester functionality led to **14** being destroyed by these harsh conditions. Fortunately, a newly described milder alternative for Boc deprotections was found to be effective for this transformation.[9] Thus treatment of **14** with 1 : 1 phosphoric acid : CH_2Cl_2 gave deprotected aniline **15**.

Finally, removal of the Z group was achieved upon hydrogenolysis in methanol to give 3a-hydroxy-pyrroloindole **6** as a single enantiomer in 93% yield over two steps, and overall the left hand fragment in eight steps and 50% yield.

The synthesis of a reverse-prenylated tryptophan derivative **16** has been previously described by Danishefsky *et al.*[10] Starting from phthalimide protected L-tryptophan methyl ester, treatment with *tert*-butyl hypochlorite followed by nucleophilic attack of prenyl-9-BBN on the resulting chloroimine gave the corresponding reverse prenylated tryptophan **16**. Saponification of the methyl ester with lithium hydroxide in THF/H_2O gave the desired carboxylic acid **7** in quantitative yield (Scheme 4).

Coupling of fragments **6** and **7** was carried out by treating acid **7** with HATU followed by pyrroloindole **6**. The crude product from this coupling was then deprotected with hydrazine in methanol at 60 °C. As expected under these conditions cyclisation also occurred as indicated by HPLC-MS. Unfortunately attempts to isolate the desired product from this mixture failed.

In order to perform the deprotection-cyclisation under milder conditions, a different *N*-protecting group was required.

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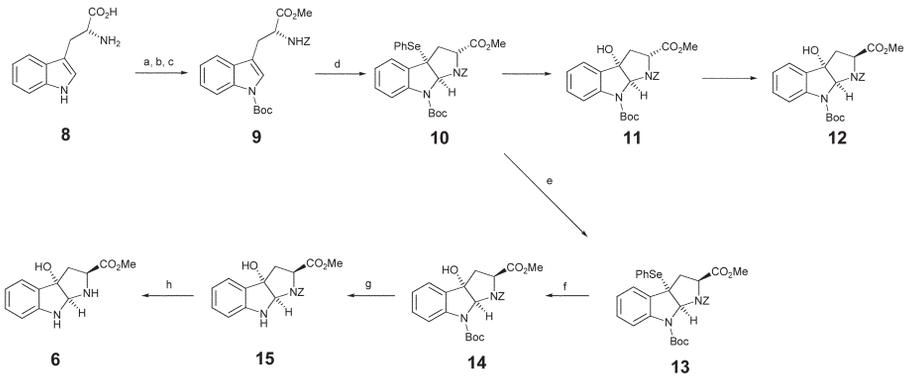
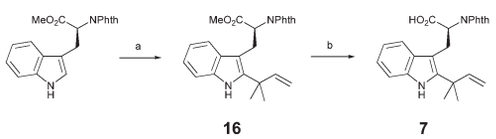


Scheme 3 *Reagents and conditions*: a) Z–Cl, H_2O, NaOH, 88%. b) $SOCl_2$, MeOH, 90%. c) Boc_2O, NaOH, DCM, Bu_4NHSO_4, 90%. d) *N*-PSP, DCM, PPTS, Na_2SO_4, 89%. e) LiHMDS, THF, −10 °C, 10 min, then MeOH, −78 °C → rt, 100%. f) wet *m*-CPBA 5 eq., K_2CO_3, DCM, 0 → 25 °C, 85%. g) H_3PO_4 (aq.), CH_2Cl_2. h) H_2, Pd/C, MeOH, 93% over two steps.

Accordingly, the phthalimide group was removed from ester **16** in moderate yield, as reported by Danishefsky,[10] and subsequent ester hydrolysis using barium hydroxide afforded the corresponding free amino acid. After considerable experimentation, conditions were found which facilitated the desired coupling and cyclisation. Protection of the amine as its 2-trimethylsilylethoxycarbonyl (Teoc) derivative gave acid **17** in good yield. Coupling of this fragment with amine **6** mediated by *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU), followed by deprotection with tris(dimethylamino)sulfur(trimethylsilyl) difluoride (TAS-F) and concomitant cyclisation, gave the diketopiperazine **5** in excellent yield (Scheme 5). Problems were encountered using a variety of other protecting groups, for example Z removal *via* hydrogenation resulted in over-reduction and removal of Fmoc with base also caused epimerisation of **5** to yield a mixture of diastereomers.



Scheme 4 *Reagents and conditions*: a) *t*-BuOCl, THF, NEt_3, prenyl-9-BBN, 51%. b) LiOH, 1 : 1 THF : H_2O, rt, 100%.

With the advanced intermediate **5** in hand, all that remained was the installation of the reverse prenyl fragment on the anilinic nitrogen. Our initial attempts at this transformation utilised the two-step procedure described by Corey *et al.* during their okaramine N synthesis, namely treatment of a propargylic acetate with copper(I) chloride in refluxing THF. Unfortunately, in our system these conditions did not afford any of the alkylated product.

However, subjecting **5** to the corresponding alkynyl bromide in the presence of copper(I) chloride[11] effected the transformation smoothly. Under these conditions the desired alkyne **18** could be isolated in a 70% yield along with 20% unreacted starting material (88% yield at 80% conversion). The recovered starting material could efficiently be recycled in the alkylation step.

Finally, partial reduction of the alkyne **18** completed the synthesis of okaramine C **1**. After attempting to perform this transformation under a number of conditions, it was found that careful hydrogenation using Lindlar's catalyst poisoned with 1% pyridine in methanol gave **1** in 95% yield.

All the data for synthetic okaramine C[12] are in accordance with those published for natural okaramine C.[3]

In summary, we have completed the first synthesis of okaramine C **1**, using the recently described selenocyclization-oxidative deselenation protocol developed in our laboratory to furnish the hydroxypyrroloindole skeleton. In addition, a totally selective epimerisation of the C2 position of the initial selenide is reported, allowing this method to be adapted to the total synthesis of the okaramine family of natural products. We will report the synthesis of more complex members of this family in due course.

Acknowledgements

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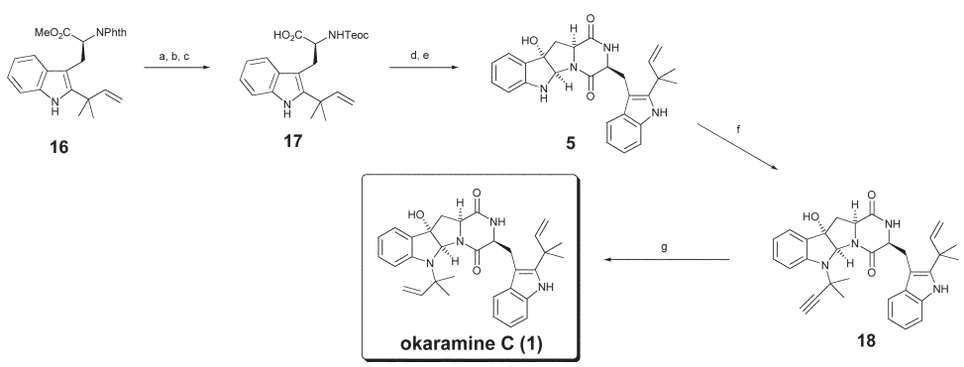

Scheme 5 *Reagents and conditions*: a) H_2NNH_2, MeOH, rt, 51%. b) $Ba(OH)_2 \cdot 8H_2O$, MeOH, rt, 100%. c) TeocOSu, H_2O, NEt_3, dioxane, 95%. d) HATU, DMF, **6**, NEt_3, rt, 16 h, 95%. e) TAS-F, DMF, rt, 8 h, 97%. f) 2-bromo-2-methyl-but-3-yne, CuCl, THF, DIPEA, rt, 4 days, 88% at 80% conversion. g) Lindlar's catalyst, H_2, 99 : 1 methanol : pyridine, 95%.

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12 Data for synthetic okaramine C: $[\alpha]_d^{25}$ +4 (0.1, MeOH); ^{1}H NMR (500 MHz, acetone-d_6). δ 1.51, s C13 Me; δ 1.53, s, C13′ and C14′ Me; δ 1.72 C14 Me; δ 2.48, dd, J = 13.4 and 10.0 Hz; C3 H_β; δ 3.00, dd, J = 13.4 and 5.5 Hz, C3 H_α; δ 3.04, dd, J = 15.2 and 11.0 Hz, C1′H; δ 3.68, dd, J = 11.0 and 4.5 Hz, C1′; δ 4.38 dd, J = 11.0 and 4.3 Hz, C2′H; δ 4.48, dd, J = 10.0 and 5.5 Hz, C2 H; δ 4.61, s, O*H*; δ 4.97, d, J = 10.6 Hz, C4′ H; δ 5.05, d, J = 17.6 Hz, C4′ H; δ 5.07, d, J = 10.7 Hz, C12 H, δ 5.20, d, J = 17.7 Hz, C12 H; δ 5.44, s, $C8_\alpha$ H; δ 5.46, br s N*H*; δ 6.16, dd, J = 17.5 and 10.6 Hz, C5′ H, δ 6.48, dd, J = 17.8 and 10.8 Hz, C11 H; δ 6.73, t, J = 7.4 Hz, C5 H; δ 6.94, d, J = 7.9 Hz, C7 H; δ 6.95, m C9′ H; δ 7.07, m, C6 H and C10′ H; δ 7.23, d, J = 7.3 Hz, C4 H, δ 7.32, d, J = 8.0 H, C8′ H; δ 7.45, d, J = 7.8 Hz, C11′ H; δ 9.97, br s, C7′ H. ^{13}C (125 MHz acetone-d_6) ppm 170.2, 170.1, 150.0, 149.7, 145.6, 142.8, 136.5, 135.1, 130.4, 130.0, 124.8, 122.5, 120.4, 120.3, 118.8, 115.6, 112.5, 112.3, 111.9, 106.1, 86.0, 84.9, 60.1, 58.7, 56.9, 40.2, 35.3, 28.7, 28.6, 28.5, 26.7, 25.9. The numbering system is the same as appears in reference 3. The table of ^{13}C chemical shifts in reference 3 contains an error; the correct values are in agreement with the above.