Total Synthesis of (+)-Papuamine: Determination of the Absolute Stereochemistry of the Natural Product

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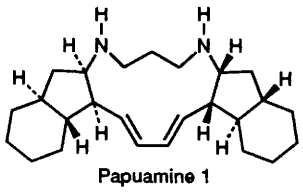
The total synthesis of (+)-papuamine has been completed using an intramolecular Pd^0 catalysed (Stille) coupling reaction to close the central diazadiene macrocycle unit.

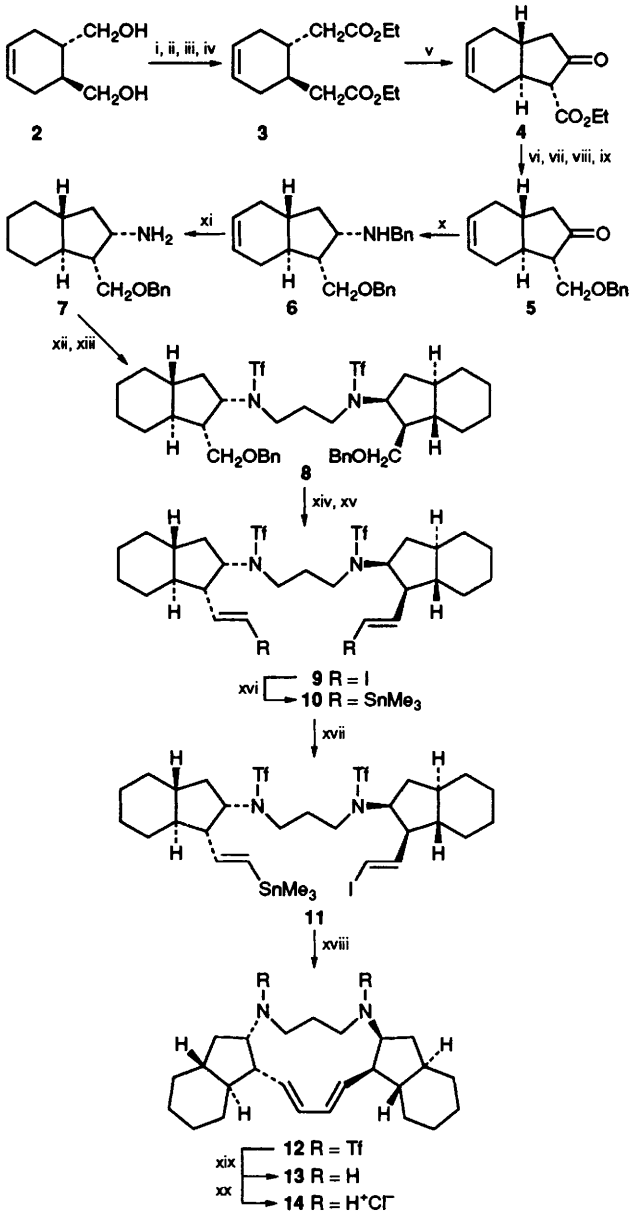
Papuamine **1**, is a C_2 symmetric, optically active pentacyclic diamine initially isolated by Scheuer and coworkers from the marine sponge *Haliclona*[1] collected in Papua New Guinea. Subsequently, Faulkner and Clardy *et al.* reported the isolation of a specimen of *Haliclona* from Palau[2] in which papuamine was the minor constituent. The major component of this specimen, haliclonadiamine, is an unsymmetrical diastereoisomer of papuamine. The structure of the diacetate derivative of haliclonadiamine was confirmed by an X-ray crystallographic analysis, however the absolute stereochemistry of this material and papuamine were not determined. Papuamine was shown to inhibit the growth of the fungus *Trichophyton mentagrophytes*[1] and to have antimicrobial activity.[2] Owing to the lack of absolute stereochemical detail, its unique structure, and biological activity, papuamine represents an important synthetic target.

Herein we report a total synthesis of (+)-papuamine, the antipode of the natural product. Our approach to this intriguing alkaloid is based upon an intramolecular palladium (0) catalysed coupling reaction between a vinyl tin and vinyl iodide, as reported by Stille.[3] Recently, this strategy has been applied to the total synthesis of rapamycin[4] and by Pattenden and Thom for the construction of polyene macrolactams.[5] (+)-Papuamine was synthesised starting from the known chiral diol **2**,§ which is readily available from butadiene *via* an asymmetric Diels–Alder reaction.[6] At this point we arbitarily set the sterochemistry of the target synthetic papuamine, The diol was further homologated to the diester **3** using procedures previously reported for the racemic modification[7] and Dieckmann cyclised to reveal the ketoester **4**.[8] This transformation was subject to thermodynamic control thereby giving the isomer **4** with the correct relative stereochemistry at C-7 (ds 11 : 1). Sequential reaction of ketone **4** with ethylene glycol and toluene-4-sulfonic acid,† lithium aluminium hydride in ether, benzyl bromide and sodium hydride and finally 0.2 mol dm^{-3} HCl gave the ketone **5** (88%). Reductive amination of **5** under mild conditions[9] using benzylamine gave the secondary amine **6** in 70% isolated yield. The diastereoselectivity in this transformation was biased, 4.5 : 1 in favour of the required *cis*-diastereoisomer.[10] Selective catalytic transfer hydrogenolysis[11] of the *N*-benzyl group with concurrent reduction of the alkene unit gave amine **7**. All the stereochemical assignments in these transformations required substantiation. Fortunately, reaction of amine **7** with sodium hydroxide and di-*tert*-butyl dicarbonate gave the crystalline carbamate **15** (93%), and the stereochemistry of this substance was unequivocally established by X-ray crystallography.‡

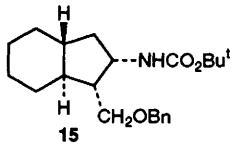
Diamine **7** was converted to the trifluoromethanesulfonamide and cleanly doubly alkylated with 1,3-dibromopropane and potassium carbonate catalysed by potassium iodide[12] to provide the bis-benzyl ether **8**. Deprotection *via* hydrogenolysis gave the corresponding diol which was subjected to a



Papuamine 1



Scheme 1 *Reagents and conditions*: i, TsCl, pyridine, 83%; ii, NaCN, EtOH, 86%; iii, KOH, H_2O, heat, 95%; iv, EtOH, H_2SO_4, 99%; v, NaH, THF, heat, 95%; vi, ethylene glycol, TsOH, Ph–H, molecular sieves (4Å), heat, 100%; vii, $LiAlH_4$, Et_2O, 99%; viii, NaH, BnBr, DMF, 92%; ix, 0.2 mol dm^{-3} HCl, THF 25–60 °C, 97%; x, benzylamine, AcOH, $NaBH(OAc)_3$, THF, 85%; xi, NH_4O_2CH, 10% Pd/C, MeOH, heat, 86%; xii, $(CF_3SO_2)_2O$, Et_3N, CH_2Cl_2, −78 °C, 97%; xiii, 1,3-dibromopropane, K_2CO_3, KI (cat), MeCN, heat, 90%; xiv, H_2, 10% Pd/C, EtOH, 95%; xv, (*a*) Swern oxidation, (*b*) CHI_3, $CrCl_2$, 1,4-dioxane/THF (6 : 1), 71%; xvi, hexamethylditin, Li_2CO_3, $PdCl_2(PPh_3)_2$, THF, 60 °C, 51%; xvii, I_2 (1 equiv.), Et_2O, 44%; xviii, $Pd(PPh_3)_4$, (30 mol%), $PhCH_3$, 100 °C, 39%; xix, $LiAlH_4$, Et_2O, heat, 42%; xx, MeOH, H_2O, HCl



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Swern oxidation and the resulting bis-aldehyde, which proved to be delicate and particularly unstable, was converted directly into the bis-vinyl iodide **9** using the Takai method.[13] Conversion of diiodide **9** into the stannane **10** was effected, under $PdCl_2(PPh_3)_2$ catalysis, with excess hexamethylditin and lithium carbonate in THF at 60 °C.[14] Much to our chagrin, all our initial attempts to macrocyclise either diiodide **9** or stannane **10** to reveal the papuamine framework met with unmitigated failure. Thus we sought refuge in desymmetrisation. Treatment of the bis-vinylstannane **10** with iodide (1 equiv.) provided **11** in 44% yield along with recovered starting material **10** (24%) and **9** (24%) which were dutifully recycled. Reaction of iodostannane **11** with $Pd(PPh_3)_4$ in toluene at 100 °C provided the required macrocycle **12** in 39% yield. Finally, treatment of **12** with lithium aluminium hydride resulted in clean deprotection to reveal the target diamine **13**. Our synthetic (+)-papuamine **13** and its dihydrochloride **14** showed spectral characteristics (^1H NMR, ^{13}C NMR, HRMS, and IR) that were identical with those reported for the natural material.[1] Additionally, our synthetic sample of the dihydrochloride **14** was identical with an authentic sample. Synthetic papuamine dihydrochloride **14** exhibited an optical rotation {$[\alpha]_D$ + 138.6, (c 0.34, MeOH)} which corresponds exactly, albeit antipodally, with the natural product {$[\alpha]_D$ −140 (c 1.3, MeOH)}[1] and an [UV λ_{max} = 236 (MeOH); lit.[1] UV λ_{max} = 241 nm (MeOH)].

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Footnotes

† Fortuitously, reaction of ketone **4** with ethylene glycol resulted in an enhancement of the desired C-7α-epimer: undesired C-7β-epimer ratio from 11 : 1 to 22 : 1.

‡ The X-ray crystallographic structure determination established the relative stereochemistry of carbamate **15**. Since diol **2** is of known absolute stereochemistry, the absolute stereochemistry of **15** is thereby unequivocally established. Details of the crystal structure will be published elsewhere: M. A. Miller, O. P. Anderson, to be submitted for publication.

§ C. H. Heathcock is presently independently working on the synthesis of papuamine using a strategically identical approach to that reported here.

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