# Iminophosphorane-Mediated Synthesis of Cyclic Guanidines: Application to the Synthesis of a Simplified NA22598A$_1$ Analogue

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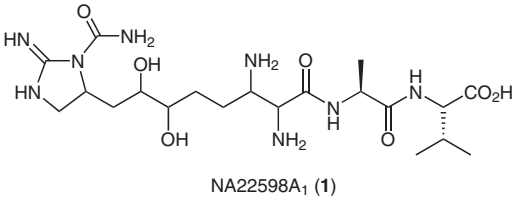
**Abstract:** Reaction of Cbz-protected β-amino azides with bis(diphenylphosphino)butane and tosyl isocyanate provides differentially substituted 2-iminoimidazolidines in good yields.

**Key words:** antitumor agents, azides, cyclizations, heterocycles, stereoselective synthesis

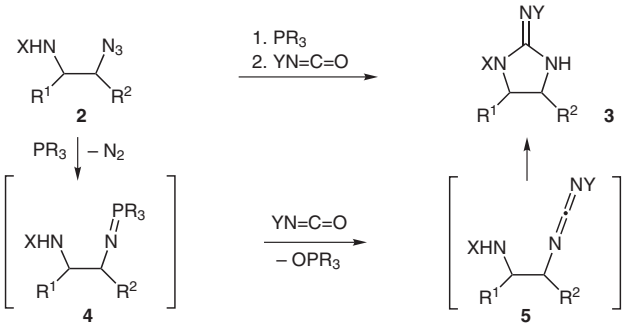
In 1997, the novel antitumour compound NA22598A$_1$ (**1**) was isolated by Kuwahara and co-workers from *Streptomyces* sp. NA22598 (FERM P-14686).[1] This molecule selectively inhibits the anchorage-independent growth of human colon cancer DLD-1 cells by arresting the cell cycle at the G1 phase and suppressing cyclin D1 synthesis.[2] The molecular structure of this natural product consists of a simple dipeptide unit linked through an amide bond to a functionalised decanoic acid. Unusually, this latter portion of the molecule contains a selectively carbamoylated cyclic guanidine (2-iminoimidazolidine) at its terminus (Figure 1).[3] The stereochemistry of NA22598A$_1$ is yet to be fully resolved. This fact, combined with its important antitumour properties, make it an attractive target for total synthesis. In this Letter, we describe studies directed towards the preparation of differentially substituted 2-iminoimidazolidines, and the application of this new methodology to the synthesis of a structurally simplified analogue of NA22598A$_1$.




NA22598A$_1$ (**1**)

**Figure 1** Structure of NA22598A$_1$

One of the key challenges associated with the preparation of NA22598A$_1$ and related structures concerns the installation of a differentially substituted 2-iminoimidazolidine.[4] Compounds of this type (e.g. **3**) might be conveniently prepared under mild conditions by reaction of a suitably substituted β-amino azide **2** with an isocyanate in the presence of a phosphine. Mechanistically, one can imagine that this process entails the following sequence of reactions: (i) Staudinger-type reaction of the azide with the phosphine to generate iminophosphorane **4**; (ii) aza-Wittig reaction of **4** with the added isocyanate to produce carbodiimide **5**; (iii) ring closure by the proximal amine to yield the 2-iminoimidazolidine ring (Scheme 1). As a number of methods exist for the synthesis of organic azides,[5] and a variety of isocyanates are commercially available, this strategy appears to offer a simple and flexible route to differentially substituted 2-iminoimidazolidines. Molina et al. have made heteroaromatic systems such as 2-aminoimidazoles using a similar approach.[6]




where R$^1$, R$^2$ = H, alkyl, aryl; X = $CO_2Bn$, $CONH_2$, etc.; Y = Ts, Bn, etc.

**Scheme 1** Planned route to 2-iminoimidazolidines

The feasibility of the approach was established using simple β-amino azide **6**.[7] Treatment of this azide with triphenylphosphine for two hours at room temperature in diethyl ether, and subsequent addition of one equivalent of tosyl isocyanate provided **7** in 40% yield after chromatography. When the reaction solvent was changed to $CH_2Cl_2$, the yield improved to 55%. $^{31}$P NMR studies conducted on closely related systems revealed that iminophosphorane formation was rather slow and incomplete after two hours. This observation led us to extend the length of time **6** was reacted with $PPh_3$ to 22 hours prior to addition of the isocyanate. Under these conditions, **7** was produced in an improved 68% yield. Although not a major issue in this particular example, the removal of triphenylphosphine oxide from the 2-iminoimidazolidine proved difficult with more highly polar products (e.g. **16**). To circumvent

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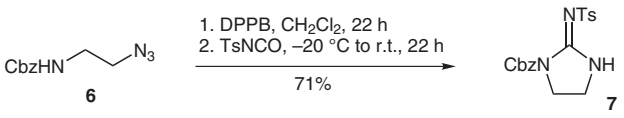
this problem, 0.5 equivalents of bis(diphenylphosphino)butane (DPPB) was used as phosphine.[8] Under these optimised conditions, **7** could be readily isolated in 71% yield (Scheme 2).[9,10]




**Scheme 2** Optimised conditions for 2-iminoimidazolidine formation

X-ray crystallography performed on a single crystal of 2-iminoimidazolidine **7** grown from $CH_2Cl_2$–$Et_2O$ confirmed its structure (Figure 2).[11] In the solid state, this cyclic guanidine exists in the depicted tautomeric form with the Cbz and the tosyl groups *anti* to one another.

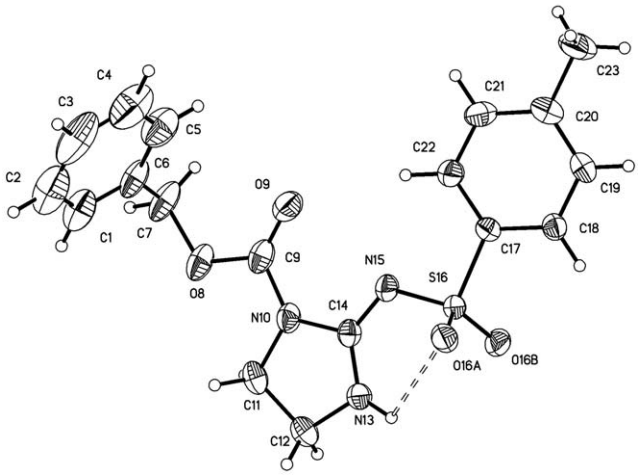
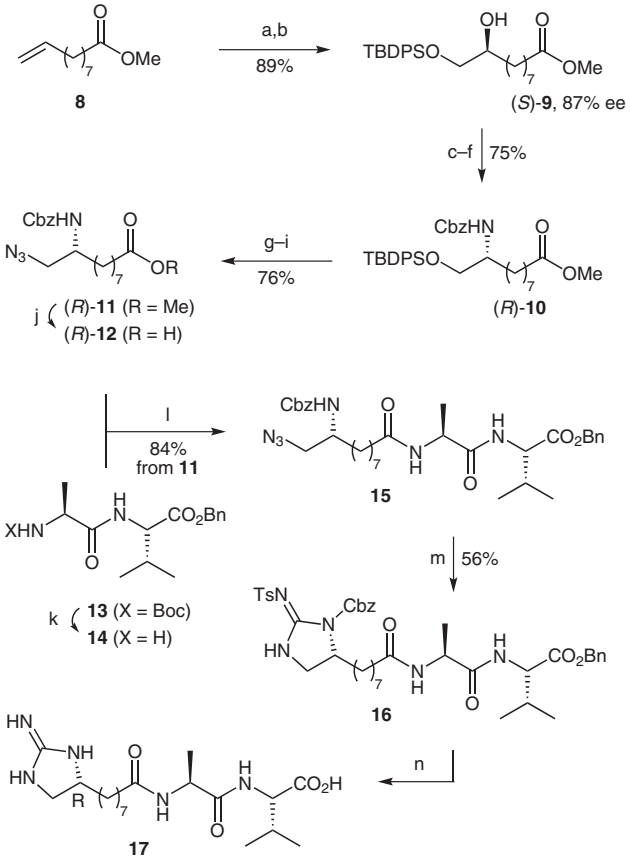



**Figure 2** Solid-state structure of **7** with thermal ellipsoids drawn at 50% probability

With suitable conditions for cyclic guanidine formation established, we sought to use it to prepare NA22598$A_1$ analogues. In the first instance, we chose to make **17**, by way of azide **15**, in which the dipeptide unit (L-ala-L-val) was retained but the diol, diamine and carbamoyl substituent were omitted. Biological evaluation of **17** might be expected to provide some initial insights into structure–activity relationships. To avoid the preparation of mixtures of stereoisomers, we arbitrarily chose to make **17** with the 9*R* stereochemistry in the first instance.

The synthesis of **17** began with Sharpless asymmetric dihydroxylation (AD) of methyl dec-9-enoate (**8**) using the hydroquinine (anthraquinone-1,4-diyl) diether [$(DHQ)_2AQN$] ligand and monosilylation of the resulting diol. This sequence provided (*S*)-**9** in 89% yield and 87% ee (Scheme 3).[12] The sense of asymmetric induction in the AD reaction was deduced by analogy to related literature examples.[13] (*S*)-**9** was transformed into (*R*)-**11** via (*R*)-**10** using a high yielding sequence of reactions that inverted the stereogenic centre. Hydrolysis of ester (*R*)-**11** by treatment with LiOH in methanol and water gave carboxylic acid (*R*)-**12**, which was then coupled with a slight excess of **14** (made by deprotection of **13**[14] using TFA) to give **15** in 84% yield from (*R*)-**11**. Gratifyingly, treatment of **15** under our optimised conditions for 2-iminoimidazolidine formation, produced differentially substituted cyclic guanidine **16** in 56% yield. Clearly, the reaction proceeds well even in the presence of a variety of other potential nucleophiles. Global deprotection of the tosyl, Cbz and benzyl ester groups of **16** was achieved by dissolving metal reduction. Although this reaction was very clean, the isolation of **17** completely free of ammonium salts was made difficult because of its zwitterionic character. After column chromatography **17** was isolated in ca. 57% yield along with small quantities of $CF_3CO_2NH_4$ arising from the workup and purification protocol.[15]




**Scheme 3** *Reagents and conditions*: (a) $K_2OsO_4{\cdot}2H_2O$, $(DHQ)_2AQN$, $K_3Fe(CN)_6$, $K_2CO_3$, $NaHCO_3$, $H_2O$–*t*-BuOH (1:1), –20 °C, 2 d, 97%; (b) TBDPSCl, imidazole, DMF, 19 h, r.t., 92%; (c) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C, 3 h, 95%; (d) $NaN_3$, DMF, 80 °C, 19 h, 88%; (e) $H_2$, 10% Pd/C, MeOH, 24 h, 96%; (f) CbzCl, $Na_2CO_3$, THF–$H_2O$ (1:1), 0 °C, 94%; (g) TBAF, THF, 0 °C → r.t., 2 h, 93%; (h) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C, 3 h, 83%; (i) $NaN_3$, DMF, 80 °C, 19 h, 99%; (j) LiOH, MeOH–$H_2O$ (1:1), 24 h, 94%; (k) TFA, $CH_2Cl_2$, 0 °C → r.t., 16 h, 99%; (l) HOBt, EDC·HCl, $Et_3N$, 19 h, r.t., 89%; (m) DPPB, $CH_2Cl_2$, 22 h then TsNCO, –20 °C → r.t., 22 h, 56%; (n) Na (40 equiv), $NH_3$–THF (5:2), –70 °C → 30 °C, 2 h, ca. 57% (see text).

Using an anchorage-independent growth assay, the effect of **17** on colon cancer DLD-1 cells was evaluated. No significant decrease in cell growth was observed against control at several time points up to 120 hours using inhibitor

concentrations up to 1 μg/mL. Since NA22598A$_1$ completely inhibits cell growth under these conditions,[2] our data indicate that one or more of the omitted functional groups on the decanoic acid chain are essential for activity. Alternatively, **17** may possess the wrong stereochemistry at C-9 in relation to the natural product.

To conclude, a new mild methodology for the synthesis of unsymmetrically substituted 2-iminoimidazolidines has been devised. It has been shown to be suitable for the preparation of simplified analogues of NA22598A$_1$. Work to fully define the scope of this reaction and to apply it to the synthesis of other NA22598A$_1$ derivatives will be the subject of future studies.

## Acknowledgment

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(9) **Representative Procedure**: To a solution of **6** (0.20 g, 0.91 mmol) in anhyd $CH_2Cl_2$ (10 mL) under nitrogen was added DPPB (0.213 g, 0.50 mmol). The reaction mixture was stirred at r.t. for 22 h, cooled to –20 °C and tosyl isocyanate (144 μL, 0.94 mmol) was slowly added. The reaction mixture was allowed to warm to r.t. and stirred for 22 h. Removal of the solvent in vacuo and subsequent column chromatography (8% EtOAc in $CH_2Cl_2$) gave **7** (0.24 g, 71%) as a white solid.

(10) **Selected Spectroscopic Data**: **7**: mp 152–153 ºC (from $CH_2Cl_2$–$Et_2O$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 8.3 Hz, 2 H, ArH), 7.71 (s, 1 H, NH), 7.29–7.37 (m, 5 H, ArH), 7.22 (d, *J* = 8.3 Hz, 2 H, ArH), 5.25 (s, 2 H, OC*H*$_2$Ph), 3.90–3.95 (m, 2 H), 3.60–3.65 (m, 2 H), 2.40 (s, 3 H, Me). $^{13}$C NMR (100.5 MHz, $CDCl_3$): δ = 154.1 (C), 150.8 (C), 142.6 (C), 139.7 (C), 135.1 (C), 129.3 (CH), 128.6 (CH), 128.3 (CH), 128.0 (CH), 126.3 (CH), 68.5 ($CH_2$), 43.9 ($CH_2$), 39.9 ($CH_2$), 21.5 (Me). IR (neat): 3315, 2919, 1753, 1621 cm$^{-1}$. MS (FAB$^+$): *m*/*z* = 374 [M + H$^+$], 330. HRMS (FAB$^+$): *m*/*z* [M + H$^+$] calcd for $C_{18}H_{20}N_3O_4S$: 374.1175; found: 374.1179. **16**: $[\alpha]_D^{24}$ 47 (*c* = 1.2, EtOH). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.69 (m, 3 H, 2 × ArH, NH), 7.27–7.33 (m, 10 H, ArH), 7.21–7.25 (m, 3 H, 2 × ArH, NH), 6.54 (br s, 1 H, NH), 5.19 (d, *J* = 12.3 Hz, 1 H, OCH*H*Ph), 5.11 (d, *J* = 12.3 Hz, 1 H, OCH*H*Ph), 5.09 (d, *J* = 12.3 Hz, 1 H, OCH*H*Ph), 5.02 (d, *J* = 12.3 Hz, 1 H, OCH*H*Ph), 4.53–4.61 (m, 1 H, α-CH Ala), 4.43 (dd, *J* = 5.0, 8.5, Hz, 1 H, α-CH Val), 4.16–4.19 (m, 1 H, H-9), 3.56 (t, *J* = 9.4 Hz, 1 H, H-10), 3.22 (d, *J* = 10.8 Hz, 1 H, H-10′), 2.28 (s, 3 H, Me), 2.03–2.10 (m, 3 H, H-2, β-CH Val), 1.58–1.70 (m, 1 H, H-8), 1.42–1.55 (m, 3 H, H-8′, 2 × H-3), 1.25 (d, *J* = 7.0 Hz, 3 H, β-Me Ala), 1.05–1.20 (m, 8 H, 2 × H-4, 2 × H-5, 2 × H-6, 2 × H-7), 0.81 (d, *J* = 6.8 Hz, 3 H, γ-Me Val), 0.78 (d, *J* = 6.8 Hz, 3 H, γ-Me Val). $^{13}$C NMR (100.5 MHz, $CDCl_3$): δ = 173.1 (C), 172.8 (C), 171.5 (C), 153.7 (C), 150.9 (C), 142.5 (C), 139.8 (C), 135.4 (C), 135.1 (C), 129.3 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 126.2 (CH), 68.4 ($CH_2$), 66.9 ($CH_2$), 57.4 (CH), 56.0 (CH), 48.6 (CH), 45.2 ($CH_2$), 36.4 ($CH_2$), 33.0 ($CH_2$), 30.9 (CH), 29.1 ($CH_2$), 29.0 ($CH_2$), 25.5 ($CH_2$), 24.2 ($CH_2$), 21.5 (Me), 19.1 (Me), 18.3 (Me), 17.7 (Me). IR (neat): 3400, 3281, 3061, 2925, 2885, 1717, 1631, 1616, 1541 cm$^{-1}$. MS (FAB$^+$): *m*/*z* = 776 [M + H$^+$], 338. HRMS (FAB$^+$): *m*/*z* [M + H$^+$] calcd for $C_{41}H_{54}N_5O_8S$: 776.3693; found: 776.3692.

(11) This data has been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. Deposition number: CCDC 679310.

(12) The enantiomers were separated by analytical HPLC on a chiralpak OD-H column (3% IPA in *n*-hexanes, flow rate = 0.5 mL/min, λ = 245 nm); $t_R$ [(*S*)-**9**] = 12.5 min, $t_R$ [(*R*)-**9**] = 14.8 min.

(13) For example, see: Hodgkinson, T. J.; Shipman, M. *Synthesis* **1998**, 1141; and references cited therein.

(14) Synthesised by coupling commercially available *N*-Boc-L-alanine with L-valine benzyl ester (EDC, HOBt, $Et_3N$, $CH_2Cl_2$, 16 h, 90%).

(15) This contamination arises from the fact that solid $NH_4Cl$ is used to quench the dissolving metal reduction and TFA is used as a co-solvent in the subsequent purification by silica gel chromatography. The effective molarity of **17** in $D_2O$, from which the yield could be estimated, was determined by adding known quantities of 1,4-dioxane to the sample and subsequent quantification of the dioxane/**17** ratio by $^1$H NMR integration.