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Synthesis of hydroxylated pyrrolidines by allenic cyclisation

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ABSTRACT

The diastereoselective gold(I) catalysed cyclisation of highly substituted aminoallene derivatives allows the synthesis of both *epi*-DAB-1 and di-*epi*-lentiginosine. While the sense of stereoselectivity observed is in line with earlier observations on analogous piperidine-forming cyclisations, different ligands and reaction conditions are required to obtain good yields.

1. Introduction

There is extensive current interest in the synthesis of hydroxylated cyclic amines due to their ability to behave as 'aza-sugars' and inhibit glycosidases.[1] This interest encompasses natural alkaloids, as well as their diastereoisomers and analogs, and covers both monocyclic and bicyclic compounds (Fig. 1). Swainsonine **1** and lentiginosine **2a** are examples of indolizidine hydroxylated alkaloids. *epi*-Fagomine **3** is an example of a hydroxylated piperidine alkaloid that has attracted interest in this context. Several years ago, we reported the stereoselective gold(III) catalysed cyclisation of α-silyloxy-δ-amino-allene **5** to give piperidine **6** in a formal synthesis of swainsonine **1**.[2,3] Subsequently, we reported the gold(I) catalysed cyclisation of the related α,β-disilyloxy-δ-amino-allene **7** with the opposite sense of diastereoselectivity to give a piperidine **8** that was carried through to *epi*-fagomine **3**.[4] In addition to the piperidine alkaloids, there is also interest in the related pyrrolidine alkaloids, such as DAB-1 **4a**.[5] It was, therefore, of interest to extend our studies to this ring system to find out how the methodology developed to date in these laboratories could be further applied to the formation of pyrrolidines and indolizidines.

2. Results and discussion

It was first necessary to prepare the α,β-disilyloxy-γ-aminoallene substrates for cyclisation studies (Scheme 1). Sonogashira coupling of propargyl alcohol with 1-iodo-2-trimethylsilylacetylene **9** gave the diyne[6] **10** which was regio- and stereoselectively reduced with lithium aluminium hydride to the ene-yne **11**.[7] The corresponding PMP ether **12** was subjected to Sharpless dihydroxylation using AD-mix-β to give diol **13** in excellent e.e. (98%).[8] Desilylation followed by Searles–Crabbé homologation[9] gave the allenic diol **15**. This was subjected to double O-silylation and oxidative removal of the PMP group, the latter reaction requiring somewhat carefully optimised conditions. Conversion of the resulting alcohol **17** to azide **19** was achieved via triflate **18**.[10] Staudinger chemistry was then used to convert azide

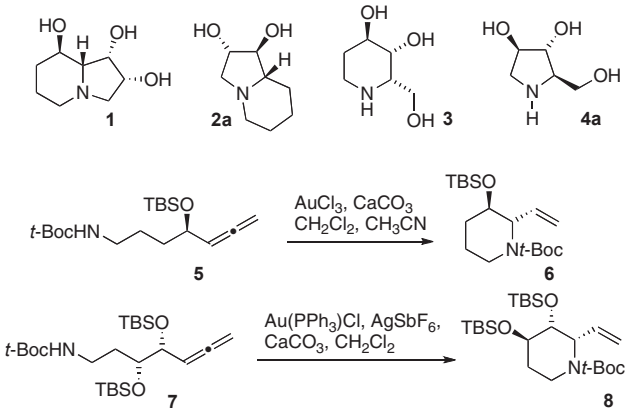

Fig. 1. Hydroxylated alkaloids and gold catalysed cyclisation.

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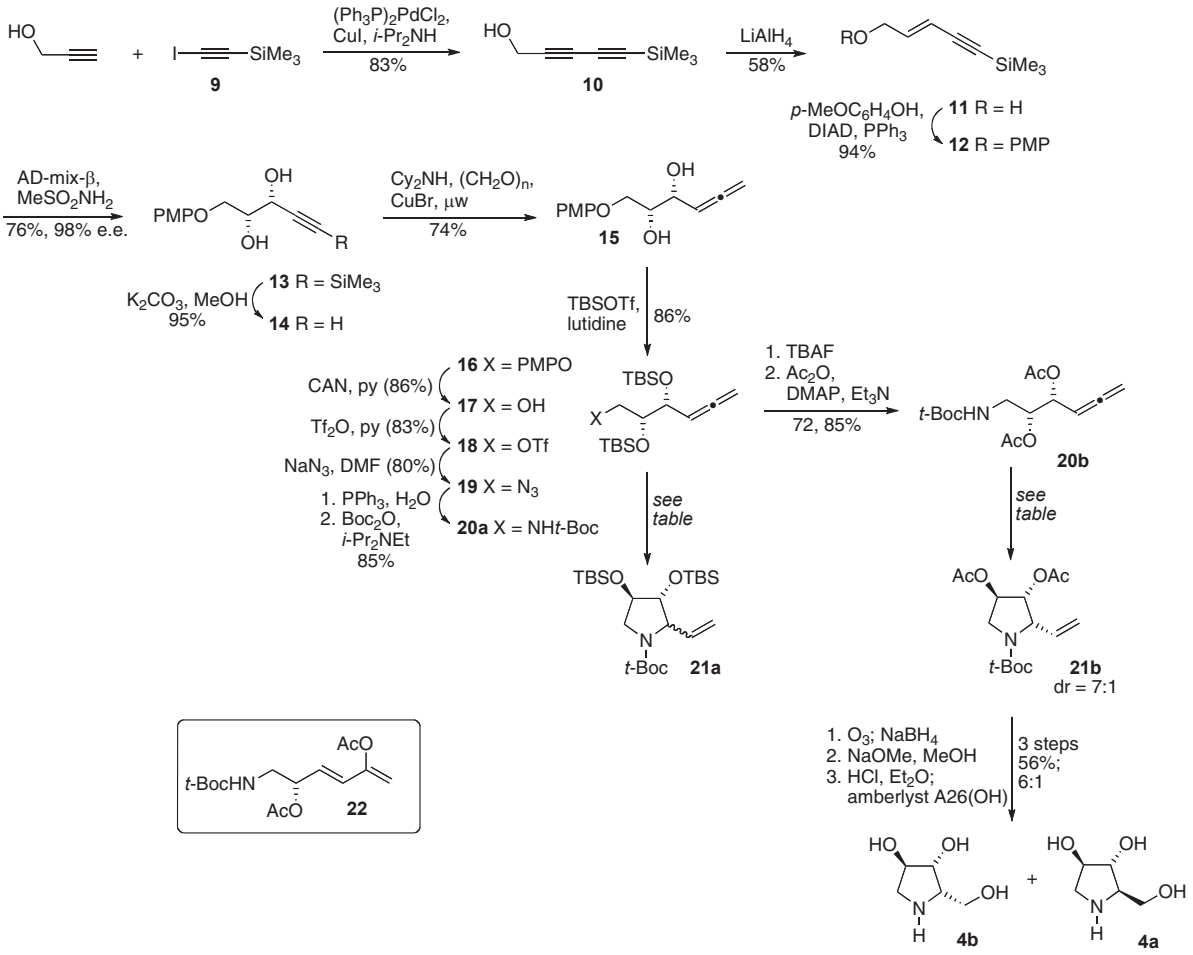

Scheme 1. Pyrrolidine Synthesis.

19 to allene **20a**, the desired substrate for gold catalysed cyclisation. Interestingly, subjecting allene **20a** to both sets of conditions employed in our earlier studies in the piperidine series gave results that were deeply disappointing in terms of both yield and diastereoselectivity (Table 1, entries 1 and 2). Use of the Echavarren catalyst[11] with the Johnphos ligand gave excellent diastereoselectivity (entry 3),[12] but the yield of pyrrolidine **21a** remained low. Suspecting that steric hindrance due to the two TBS groups was the cause, bis silyl ether **20a** was converted to diacetate **20b**, via the intermediate diol **20c**. Gratifyingly, cyclisation of diacetate **20b** could now be achieved in good yield using the Echavarren catalyst, although reaction times were long (entries 4 and 5). The diastereoselectivity was good, but the two diastereoisomers of pyrrolidine **21b** were not separable. A small amount (7%) of the Rautenstrauch rearranged product **22** was also obtained.[13]

Ozonolysis of the alkene of pyrrolidine **21b** with a reductive work up gave the corresponding primary alcohol. Removal of the protecting groups then gave a still inseparable mixture of 1,4-dideoxy-1,4-imino-L-xylitol **4b** and its diastereoisomer, DAB-1 **4a**. These were identified by comparison with the literature NMR spectroscopic data.[14] This showed that the gold catalysed cyclisation proceeds with the same sense of stereoselectivity as in the *epi*-fagomine synthesis i.e., the vinyl group is *cis* to the α-oxygen functionality.

An alkaloid in which there has been extensive interest is lentiginosine **2**. Again, this interest extends to its diastereoisomers. We felt that pyrrolidine **21b** could be employed to prepare 1,2-di-*epi*-lentiginosine **2b** by appending the missing piperidine ring (Scheme 2). Attempted cross-metathesis of the mixture of the diastereoisomeric vinyl pyrrolidines **21b** with methyl 3-butenoate using either the Grubbs II or Hoveyda-Grubbs II catalysts failed. On the other hand, the 3-butenoyl amide **24**, prepared by removal of the Boc group to give the intermediate amine **23**, followed by acylation, underwent smooth ring closing metathesis to the

Table 1
Aminoallene cyclisations

Entry	Substrate	Conditions[a]	Time/h	Yield **4ab**	d.r
1	**20a**	$AuCl_3$, $CaCO_3$, CH_2Cl_2, MeCN	24	7%	2:1
2	**20a**	$Au(PPh_3)Cl$ (6 mol %), AgOTf (6 mol %), $CaCO_3$, CH_2Cl_2	24	5%	ND
3	**20a**	Au[P*t*-Bu_2(*o*-biPh)]Cl, AgOTf, $CaCO_3$, dioxane	24 or 72	16%	>99:1
4	**20b**	Au[P*t*-Bu_2(*o*-biPh)]Cl, AgOTf, dioxane	24	50%	7:1
5	**20b**	Au[P*t*-Bu_2(*o*-biPh)]Cl, AgOTf, dioxane	96	73%	7:1

[a] 5 mol % of both the gold catalyst and AgOTf were used unless otherwise stated; 1 equiv of $CaCO_3$ was used.