Palladium-catalyzed cyclization of bromoenynamides to tricyclic azacycles: synthesis of trikentrin-like frameworks†

Craig D. Campbell, Rebecca L. Greenaway, Oliver T. Holton, Helen A. Chapman and Edward A. Anderson†

In recent work, we have developed a number of routes to azabicycles from ynamides, including via ynamide carbopalladation. We have also reported a strategy to access the tricyclic 7,6,5-CDE ring cores of rubriflordilactones A and B, which contain penta- and tetrasubstituted arenes respectively, through palladium-catalyzed cascade cyclization of bromoenedynes. We noted that the combination of these two methodologies could provide access to the tricyclic indole core of the trikentris, via cyclization of a bromoenamide equipped with a remote alkyne (Scheme 1). The construction of fused ring arenes in this manner has rarely been employed in synthetic endeavours, and in the context of ynamides offers a useful alternative to the elegant cyclotrimerization methodology pioneered by Witusli, which has recently been applied to the herbindole systems. This sequenced carbopalladation strategy offers advantages over intramolecular cyclotrimerization, where long tethers restrict the formation of larger rings, presumably due to competing intermolecular reactions. Here we describe the development of this novel ynamide chemistry, and its application to a number of azatricyclic systems, including aza- and benzazepine trikentrin analogues. Elaboration to the bis-desmethyltrikentrin B framework is also described.

We first set about the synthesis of a series of bromoenamide alkynes suitable for cyclization, through the preparation of appropriate sulfonamide and bromoalkyne precursors (Scheme 2). The bromoalkenyl sulfonamides 3a and 3b were prepared from alkynes 4a and 4b via bromonoboration/protodeborylation (with simultaneous Boc deprotection), whilst bromoalkynes 5a and 5b were synthesized from 1,6-heptadiyne by monosilylation then bromination. Both trimethylsilyl and benzylidemethylsilyl groups were installed, which we anticipated would enable various strategies for the attachment of trikentrin-like sidechains following cyclization. These building blocks were coupled using Hsung's copper-catalyzed methodology for ynamide formation, which provided ynamides 1a-c in moderate to good yield, albeit accompanied by a degree of desilylation in the case of TMS-substituted dyne 5a. To further extend the cyclization methodology, we targeted a substrate featuring two ynamides, which would lead to an aza-trikentrin (pyrroloindoline) framework. The bisynamide 1d was readily prepared in four steps from 4a by bromination/carbamate deprotection (to afford the sulfonamide 6), followed by...
sequential Hsung couplings – firstly with 1-bromo-oct-1-yn e (used in excess to minimize intermolecular homocoupling of 6), then with sulfonamide 3a.

With a selection of substrates in hand, the cascade cyclizations were investigated (Table 1). Using our previously reported conditions (10 mol% Pd[PPh3]4, Et3N, 0.017 M in MeCN, 80 °C),6 we were pleased to obtain the 5,6,5-tricyclic trikentrin frameworks 2a and 2b in excellent yields (90%, entries 1 and 4). The catalyst loading could be lowered to 5 mol% with a slight reduction in yield (entries 2 and 5); however, by increasing the concentration (to 0.16 M), catalytic efficiency was restored, with 2a isolated in 88% yield (entry 3).

Cyclization to the challenging 7,6,5-tricyclic analogue of the trikentrin framework was next attempted. At higher catalyst loading and dilution, the desired tricycle 6 was obtained as a component of a complex mixture (entry 6). However, by performing this reaction at higher concentration, 2c was formed as the sole product in excellent yield (entry 7), a result that highlights the advantages of the sequenced carbopalladation strategy. Finally, dyynamide 1d was subjected to the range of reaction conditions (entries 8–10). To our delight, dyynamide 2d, which represents the first example of such a pyrroloindoline framework, was isolated in high yield when reacted at the higher concentration (70%, entry 10).

With efficient access to azatricycles established, we aimed to demonstrate the utility of the methodology by preparing a natural product analogue – bis-desmethyl-trikentrin B 13 (see Scheme 3) – from the 5,6,5-indolines 2a or 2b. This required installation of the requisite butenyl sidechain, and conversion of the protected indoline to the free indole. For the former of these tasks, we recognised the synthetic value of the silane present in 3a and is an attractive alternative to other coupling methods (e.g. Stille, Suzuki) due to the low toxicity of silicon and its stability to multistep synthesis.6 To our knowledge, no Hiyama couplings between aryl-benzyl dimethylsilanes and alkenyl halides have been reported, with only the reverse process being described (i.e. the coupling of alkenylbenzyl dimethylsilanes with aryl halides).6

Standard conditions for the coupling of alkenyl benzyl dimethylsilanes (TBAF, Pd(dba)3·CHCl3 or Pd(dba)3)10 using either β-styrenyl iodide 7a or butenyl iodide 7b as the halide partner, afforded no cross-coupling product (Table 2, entries 1 and 2). As benzylsilanes are ‘safety-catch’ silanols, and indeed are hydrolysed to the latter on treatment with TBAF, alternative conditions for the coupling of alkylsilanol-s11 were also investigated, without success (entry 3). In all of these trials, mixtures of silanol, disiloxane, and desilylated arene were recovered,12 suggesting that the aryl silanol revealed on unmasking of the benzylsilane was resistant to transmetallation. The addition of Ag2O has been reported by Hiyama to accelerate transmetallation,13 and we were delighted to find that the coupling of styrenyl iodide 7a under these conditions smoothly afforded the styrenyl trikentrin framework 8a (68%). Disappointingly, only desilylated arene was returned on attempted coupling with butenyl iodide 7b, which for this study presented an insurmountable limitation.

A more classical route to install the butenyl sidechain was thus developed (Scheme 3).14 Aryltrimethylsilane 2a was subjected to a Friedel-Crafts acylation, which proceeded with exclusive ipso-selectivity to give ketone 9 (79%). This ketone then underwent a high-yielding reduction–dehydration sequence to deliver the targeted butenyl sidechain 8b. Completion of the synthesis now required indoline detosylation and oxidation to reveal the indole moiety. However, all attempts to oxidise 8b to the corresponding sulfonyl indole were unsuccessful, leading mainly to degradation.15 Inverting this sequence of events resolved this issue; although Mg/MEOH/sonication (which is usually effective for such detosylations)16,16 effected partial deprotection...
(25%), treatment of 8b with sodium naphthalenide gave the deprotected indole 11 with high efficiency. Somewhat surprisingly, 11 underwent rapid aerobic decomposition, presumably due to the indole-enhanced reactivity of the electron-rich styrene,17 and isolation of the pure indole proved difficult. However, we were pleased to find that direct dehydrogenation of the crude indole using Pd/C in degassed toluene completed the synthesis, giving bis-desmethyl-trikentrin 12 in good yield over the two steps.

In conclusion, we have developed a facile method for the preparation of azatricycles from bromoalkenyl ynamides. The reaction enables formation of five- to seven-membered rings, and offers an alternative approach to cyclotrimerization strategies. The utility of this chemistry is demonstrated by installation of the trikentrin B alkanyl sidechain in a further four steps using Friedel–Crafts ipso-substitution of the arylsilane cyclization products. As an alternative, we report the first example of an alkyl iodide/arylbenzylsilane Hiyama cross-coupling, which affords a styrenyl-trikentrin analogue.

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Notes and references


6 For a recent review, see: S. Kotha, E. Brahmachary and K. Lahiri, Eur. J. Org. Chem., 2005, 4741. See also ref. 3b.


12 See the ESf for details.


14 Alternative strategies, such as the use of ynamides already featuring the trikentrin B sidechain, were not investigated in this study, which targeted a system enabling skeletal diversification at a late stage.

15 Oxidation using MnO4−, Mn(OAc)3, DDO, or AIBN/NBS led to complete degradation of material, Co(salen)2O2 led to no reaction.


17 Aldehyde-containing byproducts, presumably arising from cleavage of the alkene sidechain, were noted in this decomposition process.