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Macrocyclic polyenynes: A stereoselective route to vinyl-ether-containing skipped diene systems

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The stereoselective synthesis of a challenging macrocyclic polyene scaffold, containing a sensitive vinyl ether motif, has been accomplished using *O*,*C*-dilithiation/selective *C*-alkylation, Pd-catalysed etherification and Wittig reactions as key steps. An end-game macrocyclisation strategy employed a regio- and stereoselective Stille cross-coupling using Pd(Br)(*N*-Succ)($AsPh_3$)$_2$ (AsCat) as the precatalyst.

Skipped diene (1,4-diene) motifs are synthetically valuable sub-components found in an eclectic array of bioactive natural products. Examples include macrocyclic compounds such as phacelocarpus 2-pyrone A,[1] labillaride C,[2] ripostatin B[3] and neurymenolide A[4] (Fig. 1). These chemical structures provide a stiff examination of any synthetic methodology that facilitates the construction of isolated or multiply bonded 1,4-diene systems embedded within these types of macrocycles.[5] For ripostatin B two synthetic approaches to the 1,4-diene motif were simultaneously reported by Christmann[6] and Prusov[7] employing alkene metathesis. Fürstner[8] employed alkyne metathesis, and a variety of organometallic cross-coupling methods, to access the 1,4-dienes embedded within neurymenolide A, where he also applied an Au-catalysed process to reveal the core 2-pyrone motif. Related to the ripostatin family, Sigman developed a Pd-catalysed 1,4-vinylvinylation methodology using 1,3-butadiene, vinyl triflates and vinyl boronates.[9] Despite these successes there are still many challenges associated with the selective synthesis of 1,4-diene containing products.

Macrocycle **1** (Scheme 1) is a structural mimetic of phacelocarpus 2-pyrone A, a target in which we have been interested for some time.[10] Only one model study towards this natural product, exploring a ring-closing alkyne methathesis route, has previously been carried out.[11] We wished to synthesise **1** for the following reasons: (a) it contains four skipped centres of unsaturation (two with *Z*-stereochemistry) and a novel embedded skipped 1,4-diene motif containing an (*E*)-vinyl ether; (b) formation of a polyene/yne macrocyclic structure, using Stille cross-coupling in the final step, was particularly appealing as we have previously developed catalysts for this purpose;[10c,10d] (c) an arene mimetic could increase the intrinsic stability of the macrocycle, allowing new synthetic analogues to be identified for drug discovery.[10e]

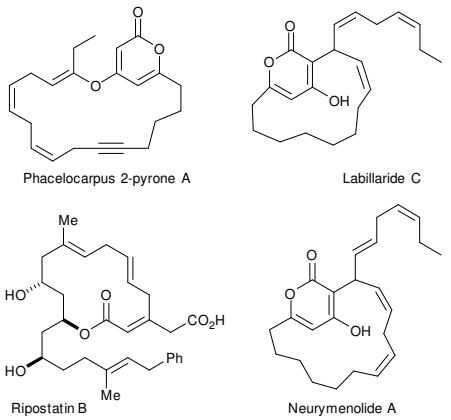
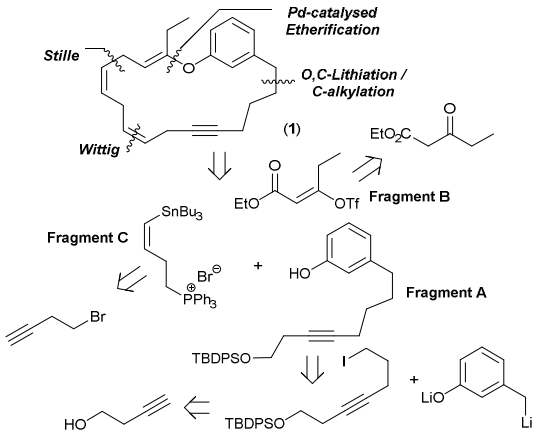


Fig. 1 Exemplar macrocyclic natural products containing 1,4-diene motifs.

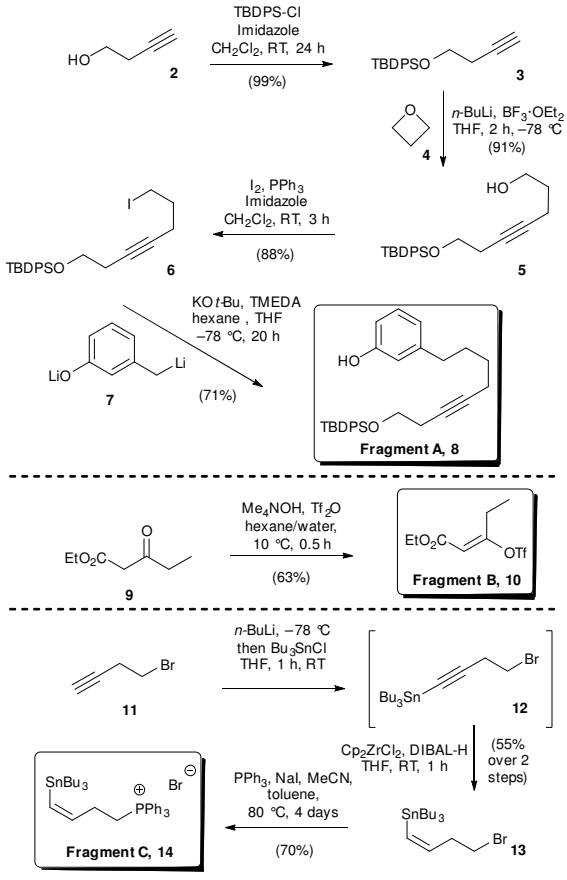


Scheme 1 Proposed retrosynthetic analysis of macrocyclic target compound **1**.

A retrosynthetic analysis to macrocycle **1** is shown in Scheme 1. We identified four key disconnections, revealing three synthetic fragments A–C. We recognised that the non-trivial trisubstituted vinyl ether could be accessed by a Pd-catalysed etherification reaction, allowing fragments A and B to be connected.[12] The synthesis of the fragment A could be achieved by selective *C*-alkylation of the dilithium salt derived from *m*-cresol.[13] The adventurous branch within the retrosynthetic route exploits the dual nucleophilic reactivity of (*Z*)-1-tributylstannyl-but-1-en-4-triphenylphosphonium bromide (the key vinylstannyl–phosphonium salt, fragment C), allowing sequential Wittig reaction[14] and Stille cross-coupling[15] to be assessed, along with any associated regio- and stereoselectivity. We postulated that the Stille cross-coupling was best suited to the last step, to deliver the macrocyclic target compound **1**.[16]

The forward synthetic route began with the synthesis of fragments A–C (Scheme 2). Fragment A was prepared from the homopropargylic alcohol **2**, by silyl protection to give **3**, then alkylation of the terminal alkyne with oxetane **4**, giving **5** in high yield. Iodination to give **6**, and then subsequent alkylation of the dilithium salt of *m*-cresol **7** with the primary iodide, gave compound **8** (fragment A) in good overall yield.

Fragment B was efficiently prepared using Frantz's method,[17] by reaction of commercially available β-ketoester **9** with Me_4NOH and Tf_2O, giving (*E*)-enol triflate **10** (fragment B) selectively in 63% yield.

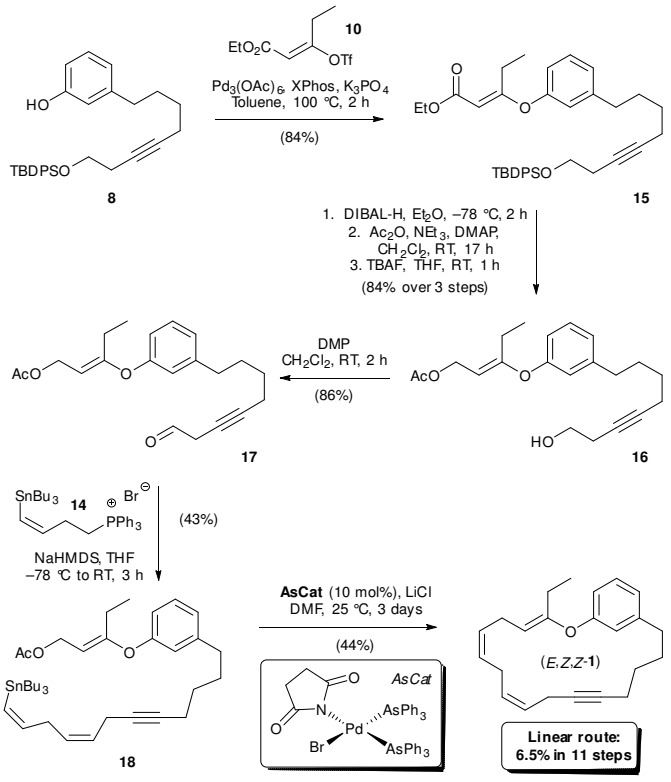


Scheme 2 Synthesis of fragments A–C.

Fragment C was synthesised starting from homopropargylic bromide **11**, which was lithiated on the terminal alkyne and then trapped with *n*-Bu_3SnCl to give alkynyl stannane **12** in good yield. The synthesis of (*Z*)-stannane **13** was accomplished using *in-situ* generated Schwartz reagent, $Cp_2Zr(H)Cl$,[18] giving **13** which was reacted directly with PPh_3 to give phosphonium salt **14** (fragment C) in good yield.

The end-game synthetic route is described in Scheme 3. Phenolic compound **8** (fragment A) was subjected to a highly novel Buchwald–Hartwig type etherification[12] by reaction with (*E*)-enol triflate **10**, mediated by a precatalyst consisting of $Pd_3(OAc)_6$ (>99% purity) and the XPhos ligand (Pd:XPhos = 1:2), which gave (*E*)-enol ether product **15** in 84% yield. The vinyl ester functionality within **15** was then reduced to the alcohol with DIBAL-H and acetylated under standard conditions. Subsequent silyl deprotection with TBAF afforded compound **16** in 84% yield (over 3 steps). A mild and neutral protocol for the Dess–Martin perodinane (DMP) oxidation[19] of **16** afforded aldehyde **17** in 86% yield.

The final sequence for the synthetic route involved reaction of Wittig reagent **14** (fragment C) with aldehyde **17** to give **18** in 43% yield.[20,21] Only the *Z* stereoisomer was formed, and the (*Z*)-vinyl stannane was also retained. The last step unites the (*Z*)-vinyl stannane and allylic vinyl ether components. The allylic centre creates the potential for S_N2 and S_N2' products being formed from $Pd^{II}(\pi\text{-allyl})(OAc)L_n$ or $Pd^{II}(\pi\text{-allyl})(R)L_n$ intermediates; any π-σ-π equilibration could influence the alkene stereochemistry. The Stille cross-coupling macrocyclisation reaction was run at low concentration (0.02 M). We initially evaluated the established and widely used catalyst system $Pd_2(dba)_3$•$CHCl_3$/$AsPh_3$ (Pd:$AsPh_3$ = 1:2),[22] which gave the target compound **1** in 28% yield (isolated product).



Scheme 3 End-game synthesis of macrocycle **1**.

Whilst the preliminary result encouraged us, we were pleased to establish that our in-house developed precatalyst for Stille cross-couplings of benzyl halides with organostannanes,[23] Pd(Br)(*N*-Succ)($AsPh_3$)$_2$ ('AsCat'), worked well for this particular macrocyclisation Stille cross-coupling, affording **1** in 44% yield (*E*:*Z* ratio = 5:1 about the vinyl ether bond, determined by ^{1}H NMR spectroscopy) after preparatory thin layer chromatography.

The structural connectivity of **1** was confirmed by NMR spectroscopic analysis. The ^{1}H NMR data is collated in Fig. 2 (complete ^{1}H/^{13}C correlations are collated in the E.S.I.). The location of the methylene protons (H-1') allowed us to track the connectivity through to H-5. A clear nOe contact between H-1' and H-5 was observed by a NOESY experiment, confirming the stereochemistry of the vinyl ether as *E* in the major isomer.

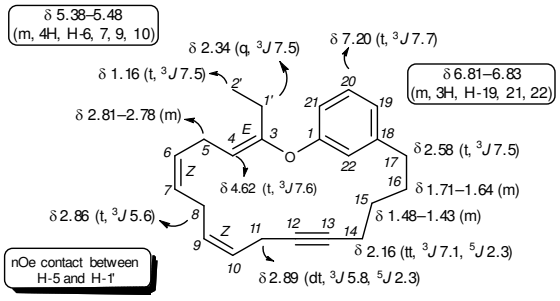


Fig. 2 Key ^{1}H NMR spectroscopic data for (*E*,*Z*,*Z*)-**1** (major stereoisomer).

In summary, we have described the stereoselective synthesis of a challenging macrocyclic polyene scaffold **1**, containing a sensitive vinyl ether motif. A series of key steps, namely selective *O*,*C*-dilithiation/*C*-alkylation, Pd-catalysed etherification, Wittig and Stille cross-coupling reactions were needed to ensure success. A highlight of the synthetic route is the first use of a vinyl stannane containing an alkyl phosphonium bromide,[21] where its intrinsic dual nucleophilic character has been used in sequential Wittig and Stille cross-coupling reactions. The utility of Pd(Br)(*N*-Succ)($AsPh_3$)$_2$, 'AsCat', as a Stille cross-coupling precatalyst,[23] has been demonstrated, holding much promise for its wider application in cross-coupling catalysis and target-orientated synthesis.[16]

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Notes and references

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† Electronic supplementary information (ESI) available: Experimental and full characterisation details are provided, see DOI: 10.1039/c000000x/

Abbreviations: XPhos = (2-dicyclohexylphosphino-2′,4′,6′-triisopropyl biphenyl); DMP = Dess–Martin perodinane; DIBAL-H = diisobutylaluminium hydride; TBAF = tetra-*n*-butyl ammonium fluoride; DMAP = dimethyl aminopyridine; TBDPS = *tert*-butyldiphenylsilyl; TMEDA = tetramethylethyldiamine.

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