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Synthetic Study toward Triterpenes from the Schisandraceae Family of Natural Products

Pavle Kravljanac and Edward A. Anderson *

Chemistry Research Laboratory, Department of Chemistry, University of Oxford, 12 Mansfield Road, Oxford OX1 3TA, UK
* Correspondence: edward.anderson@chem.ox.ac.uk

Abstract: Triterpenoid natural products from the Schisandraceae family have long presented a significant synthetic challenge. Lancifodilactone I, a member of the family not previously synthesized, was identified as a key natural product target, from which many other members could be synthesized. We envisaged that the core ring system of lancifodilactone I could be accessed by a strategy involving palladium-catalyzed cascade cyclization of a bromoenynamide, via carbopalladation, Suzuki coupling and 8π-electrocyclization, to synthesize the core 7,8-fused ring system. Exploration of this strategy on model systems resulted in efficient syntheses of 5,6- and 5,8-fused systems in high yields, which represent the first such cyclization where the ynamide nitrogen atom is ‘external’ to the forming ring system. The enamide functionality resident in the cascade cyclization product was found to be less nucleophilic than the accompanying tri-/tetrasubstituted alkene(s), enabling regioselective oxidations. Application of this strategy to 7,6-, and 7,8-fused systems, and ultimately the ‘real’ substrate, was ultimately thwarted by the difficulty of 7-membered ring closure, leading to side product formation. Nevertheless, a tandem bromoenynamide carbopalladation, Suzuki coupling and 6/8π-electrocyclization was shown to be a highly efficient tactic for the formation of bicyclic enamides, which may find applications in other synthetic contexts.

Keywords: natural products; total synthesis; ynamides; cascade reaction; electrocyclisation; Suzuki coupling; medium ring synthesis

1. Introduction

Triterpenes from Schisandraceae species have attracted attention from the synthetic community due to their intriguing molecular frameworks and biological activity [1,2]. Efforts by the groups of Yang [3–7], Li [8,9], Tang [10,11] and Anderson [12,13] resulted in 11 total syntheses so far. However, previously reported strategies often suffer from lengthy synthetic routes and challenges in applications to other members of the family. We aimed to develop an efficient approach to the Schisandra triterpenes in which lancifodilactone I (1, Figure 1a), a previously unconquered target, was identified as a potential common precursor to other natural products in this family. We envisioned that the key 7,8-fused ring core of lancifodilactone I could be synthesized via a palladium catalyzed cascade reaction: starting from bromoene-ynamide 2, oxidative addition followed by carbopalladation (3), Suzuki coupling (with a suitable dienyl organometallic) to give 4, and 8π electrocyclization would deliver the 7,8-fused system 5 in one step. An electron-donating ynamide functionality in 2 was proposed to enhance the nucleophilicity of the resulting enamide in 5 for further functionalisation, while the bulkiness of the ynamide nitrogen substituent should prevent cis-trans isomerisation of the intermediate vinyl palladium species 3 [14].

Previous work from our group [15,16] demonstrated that this type of cascade can indeed be used to synthesize 7,8 systems (8, Figure 1b), and indeed
carbopalladation/coupling/electrocyclisation sequences are generally well-established [17–20]. However, we aimed to avoid the use of a toxic organotin coupling partner as had been employed in our previous work [15,16] by switching to an untested Suzuki/8π strategy. We have also shown that ynamides are viable partners for intramolecular carbopalladation cascades in a carbopalladation/Suzuki/6π sequence in which the ynamide nitrogen atom is located inside the tethering ring (9→10, Figure 1b) [21]. In our planned work, we now required the nitrogen atom to be positioned at the alkyn terminus, rather than internally. At the outset of this study, several questions therefore had to be answered (Figure 1c):

1. Can carbopalladation/Suzuki/6π cascades proceed with the ynamide nitrogen atom position exocyclic to the forming ring, and how does this alkyn polarity reversal affect reactivity (11→12, Figure 1c)?
2. Can the bromoenynamide–Suzuki cascade be extended to the synthesis of 8-membered rings (13)?
3. Can the resulting 8-membered ring enamides undergo further selective functionalisation towards the carbocyclic D-ring core of lancifodilactone I (14)?

![Diagram](image.png)

**Figure 1.** (a) Retrosynthetic strategy towards lancifodilactone I. (b) Synthesis of 7,8-fused systems via alkyn carbopalladation/Stille coupling/8π-electrocyclisation tandem sequence, and synthesis of 5,6-fused systems via ynamide carbopalladation/Suzuki coupling/6π-electrocyclisation sequence. (c) Proposed synthesis of 5,6- or 5,8-fused ring systems with external nitrogen position, and subsequent selective oxidations.

**2. Results and Discussion**

**2.1. Synthesis of 5,6-Fused Systems by Bromoenynamide Carbopalladation/Suzuki Coupling/6π-Electrocyclisation Cascade**

To investigate the first of these questions, bromoenynamide 11 was synthesized in four steps from dimethyl malonate 15 (Figure 2). Malonate deprotonation by sodium hydride, followed by allylation with 2,3-dibromopropene, gave the monoallylated product. Further deprotonation by sodium hydride and treatment with excess propargyl bromide
gave bromoynamide 16. Silver catalysed alkyne bromination [22], followed by chemoselective copper catalysed ynamide formation (using the conditions developed by Hsung et al. [23]), gave the desired bromoynamide 11 in excellent yield.

To study the desired carbopalladation/Suzuki/6π cascade, three vinylboronic acid derivatives (18–20), and a vinylzinc species (21), were investigated as coupling partners. Only the potassium vinyltrifluoroborate salt 20 was found to be effective (Table 1), with other partners resulting only in degradation or no observed reaction. Further optimisation (Table 1) led to identification of tetrakis(triphenylphosphine)palladium(0) and potassium carbonate in THF/water 10:1 at 80 °C as optimal conditions to deliver the desired product 12 in 89% isolated yield.

Table 1. Optimisation of the carbopalladation/Suzuki coupling/6π-electrocyclisation cascade.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>K2CO3 (aq)</th>
<th>Cs2CO3 (s)</th>
<th>LiOH (aq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>0 (100)</td>
<td>0 (24)</td>
<td>38 (80)</td>
</tr>
<tr>
<td>THF</td>
<td>100 (100)</td>
<td>7 (100)</td>
<td>25 (66)</td>
</tr>
<tr>
<td>Dioxane</td>
<td>88 (100)</td>
<td>34 (100)</td>
<td>27 (73)</td>
</tr>
<tr>
<td>THF/H2O (10:1)</td>
<td>89 *</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Yield (%) and conversion (%), indicated in parentheses for the reaction of 11 with potassium vinyltrifluoroborate salt 20, determined by HPLC analysis after 10 h at 80 °C. * Isolated yield. Aq – aqueous solution, s – solid.

These results demonstrate that the position of the nitrogen atom on the alkyne (internal vs. external), and therefore the alkyne polarisation, does not influence the carbopalladation and subsequent Suzuki coupling reactivity, with both types of ynamide undergoing the desired cascade in excellent yields [21].

2.2. Synthesis of 5,8-Fused Systems by Bromoynamide Carbopalladation/Suzuki Coupling/8π-Electrocyclisation Cascade

To address the second question, of extending the cascade to formation of 5,8-fused systems from bromoynamides, a dienylboronic acid equivalent 23 was required (Figure 3). After examination of several different routes, this simple but synthetically challenging fragment was synthesized from 2-methyl-3-butyn-2-ol 22 in two steps. Dehydration [24], followed by rhodium catalysed trans-hydroboration developed by Miyaura [25], gave the desired pinacolboronic ester as a mixture of geometric isomers. It was possible to obtain the pure Z isomer by preparative HPLC. It is important to note that the stereochemical purity of the diene coupling partner 23 is crucial to the success of the planned cascade: any E isomer present in the mixture would preclude an 8π-electrocyclisation, therefore leading to side product formation and yield deterioration. In the event, subjection of this
dienyl pinacolboronic ester to the previously optimized conditions cleanly afforded the 5,8-fused product 13 in an excellent yield of 96% (Figure 3).

2.3. Selective Functionalisation of 5,6- and 5,8-Fused Ring Systems

To investigate selective oxidations of the 5,6- and 5,8-fused ring scaffolds, hydrolysis of enamide 12 to the corresponding ketone was attempted. Subjection of 12 to a range of strongly or weakly acidic conditions resulted in either no reaction, or decomposition of the starting material (Figure 4a). Attempts to cleave the sulfonamide under common reductive conditions (Mg, MeOH; Na, naphthalene, DME; SmI₂, pyrrolidine, THF/water) also led to either no reaction, or decomposition of the starting material. To our surprise, m-CPBA-mediated epoxidation of 12 selectively epoxidized the tetrasubstituted (non-enamide) alkene (26, 59%). Upjohn dihydroxylation of 12 gave a mixture of products, with the major product being 25 (30%). Equivalent transformations of 5,8-fused ring enamide 14 with m-CPBA or potassium osmate/NMO resulted in selective oxidation of the trisubstituted alkene (27, 28, Figure 4b), with no reaction observed at the enamide double bond.

These results stand in contrast to our anticipation that the electron donating capabilities of a sulfonamide group, through conjugation of the enamide nitrogen lone pair with its alkene, would render the enamide more nucleophilic and therefore reactive toward oxidation. It was reasoned that conjugation of the nitrogen lone pair with the double bond is reduced or even prevented due to steric congestion in systems 12 and 14, such that the lone pair may be (near) orthogonal to the alkene π system. With the mesomeric electron-donating effect removed, the inductive electron-withdrawing effects of the sulfonamide group mean the ‘enamide’ is in fact an electron poor olefin, and therefore less reactive toward oxidation.

Figure 3. Synthesis of (Z)-3-methylbutadienyl boronate ester 23 and application of the optimized cascade to synthesis of 5,8-fused system 13.

Figure 4. (a) Oxidations of the 5,6-fused ring system 12; (b) Oxidations of the 5,8-fused ring system 14.
2.4. Attempted Application of the Carbopalladation/Suzuki Coupling/8π-Electrocyclisation Cascade towards the ABCD Rings of Schisandra Triterpenes

To test if the developed cascade could be used in the synthesis of the 7,8- and 7,6-systems found in Schisandra triterpenes, model bromoenynamide 34 was synthesized in four steps from dimethyl malonate (Figure 5a). Monoallylated malonate derivative 29 was first subjected to conjugate addition to acrolein, giving aldehyde 30 (47%). Meanwhile, benzyl tosyl amine 31 was transformed to dichloroamide 32 (73%), which served as a precursor to lithiated ynamide 33 under conditions developed by our group [26]. Treatment of aldehyde 30 with 33 gave a secondary alcohol, which was protected as a tert-butylidimethylsilyl ether 34 (30% over two steps).

To our disappointment, under the previously developed conditions using potassium vinyltrifluoroborate, bromoenynamide 34 was converted to a mixture of the ‘direct’ coupling product 38, and side product 37, which derives from a formal 7-endo-trig Heck-type cyclisation [14] (Figure 5a). Similar reactions of bromoenynamide 34 with diene 23 under a range of conditions resulted only in complex mixtures of unidentifiable products (not shown). These results suggest that in the setting of a 7-membered tether, the vinylpalladium species arising from oxidative addition (35) undergoes direct Suzuki coupling at a comparable rate to carbopalladation, and that once carbopalladation has occurred, the resulting dienylpalladium intermediate 36 undergoes intramolecular Heck-type cyclisation to side product 37 much faster than the desired Suzuki coupling.

It was hoped that the more conformationally constrained nature of the ‘real’ substrate (featuring the Schisandra AB rings) would reduce the entropic penalty of seven membered ring formation, and hence favour the desired cascade over direct coupling. This substrate 39 was synthesized from aldehyde 6 [27] by addition of the lithiated ynamide derived from 32. Unfortunately, with only milligram quantities of 39 to hand, attempts to apply the developed carbopalladation, Suzuki coupling, 8π-electrocyclisation cascade resulted only in the formation of complex mixtures of unidentifiable products.

![Figure 5](image-url)

Figure 5. (a) Application of the cascade to the synthesis of 7,6-fused system; (b) application of the cascade to the “real” substrate 39.
3. Materials and Methods

3.1. General

All reactions were performed open to air and without precautions to exclude air/moisture unless specified otherwise. Reagents and solvents were purchased from commercial sources and used without further purification unless specified otherwise. NMR spectra were recorded on Bruker AVIII HD 400, NEO 400, AVIII HD 500 and AVII 500 spectrometers. Chemical shifts (δ) are quoted in parts per million (ppm). 1H and 13C NMR spectra are referenced to residual protons in chloroform-d (δH = 7.26, δC = 77.16) and acetone-d6 (δH = 2.05, δC = 28.95). Peak multiplicities are defined as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants (J) are reported to the nearest 0.1 Hz. High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific exact mass spectrometer (Waters Equity autosampler and pump) for electrospray ionisation (ESI). Flash chromatography refers to normal phase column chromatography on silica gel (Merck Si 60, 0.040–0.063 mm) under a positive pressure of nitrogen.

3.2. Experimental Procedures

Dimethyl 2-(3-((N-benzyl-4-methylphenyl)sulfonamido)prop-2-yn-1-yl)-2-(2-bromoallyl)-malonate (11). To a stirred solution of alkyne 16 (50 mg, 0.17 mmol, 1.0 eq.) in acetone (0.34 mL) at room temperature was added AgNO3 (2.9 mg, 0.10 mmol%). After stirring for 5 min, N-bromosuccinimide (34 mg, 0.19 mmol, 1.1 eq.) was added and the resulting mixture was stirred for a further 4 h at rt. The reaction mixture was concentrated, then pentane was added, and the suspension was filtered through cotton wool to remove the white precipitate. The resulting solution was concentrated to obtain the corresponding bromoalkyne 17 (58 mg, 0.16 mmol), which was of sufficient purity to be used without further purification. Note 1: Because of similar R values of reactant and product, the reaction was monitored by NMR aliquot (conversion of singlet at 5.84 to 5.80 ppm). Note 2: If acetone is not evaporated completely before trituration with pentane, some succinimide will dissolve and contaminate the product. Note 3: The product was used immediately in the next step due to its tendency to decompose on storage.

To a mixture of N-tosylbenzylamine (245 mg, 0.938 mmol, 1.0 eq.), K2PO4 (398 mg, 1.88 mmol, 2.0 eq.), CuSO4 (23 mg, 0.094 mmol, 0.1 eq.) and 1,10-phenanthroline (34 mg, 0.187 mmol, 0.2 eq.) in toluene (1 mL) was added a solution of bromoalkeyne 17 (380 mg, 1.03 mmol, 1.1 eq.) in toluene (1 mL). The vial was sealed and heated in an oil bath at 75 °C for 4 days. The reaction mixture was cooled to room temperature, diluted with EtOAc, filtered through Celite and concentrated. The product was purified via flash chromatography (pentane/EtOAc 7:3) to afford 11 (481 mg, 0.877 mmol, 93%) as a pale green gel. 1H NMR (400 MHz, CDCl3) δ 7.73 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.30–7.27 (m, 3H), 7.25–7.21 (m, 2H), 5.45 (s, 2H), 4.41 (s, 2H), 3.67 (s, 6H), 3.07 (s, 2H), 2.91 (s, 2H), 2.15 (m, 5H), 5.20 (t, J = 8.1 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.17–7.15 (m, 5H), 5.20 (t, J = 4.6 Hz, 1H), 4.46 (s, 2H), 3.66 (s, 6H), 2.91 (s, 2H), 2.87 (s, 2H), 2.46 (s, 3H), 2.22–2.13 (m, 2H), 1.27 (m, 3H), 1.13 (m, 2H), 0.96 (m, 5H). 13C NMR (101 MHz, CDCl3) δ 169.8, 144.9, 135.1, 134.8, 130.1, 128.9, 128.6, 127.9, 126.3, 123.2, 76.9, 65.6, 56.5, 55.6, 53.8, 53.3, 43.1, 22.0. HRMS (ESI) calc. for C25H25BrNO4S [M+H]+ 548.0737, found 548.0734.

Dimethyl 7-((N-benzyl-4-methylphenyl)sulfonamido)-1,3,4,5-tetrahydro-2H-indene-2,2-dicarboxylate (12). A vial loaded with potassium vinyltrifluoroborate (3.7 mg, 0.027 mmol, 1.5 eq.) was taken into the glovebox, and a solution of bromoynamide 11 (10.0 mg, 0.018 mmol, 1.0 eq. in 100 µL) and Pd(PPh3)2Cl2 (2.1 mg, 0.002 mmol, 10 mol% in 300 µL) in previously degassed THF were added. The vial was sealed, removed from the glovebox, and then a degassed solution of K2CO3 in water (7.6 mg, 0.055 mmol, 3.0 eq. in 50 µL) was quickly added under an inverted cone of nitrogen. The mixture was heated at 80 °C for 10 h. The mixture was cooled to room temperature and directly purified via flash chromatography (pentane/EtOAc 7:3) to afford 12 (8.0 mg, 0.016 mmol, 89%). 1H NMR (400 MHz, acetone) δ 7.74 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.36–7.15 (m, 5H), 5.20 (t, J = 4.6 Hz, 1H), 4.46 (s, 2H), 3.66 (s, 6H), 2.91 (s, 2H), 2.87 (s, 2H), 2.46 (s, 3H), 2.22–2.13 (m, 2H),
Dimethyl (6Z,8E)-9-((N-benzyl-4-methylphenyl)sulfonamido)-6-methyl-1,3,4,5-tetrahydro-2H-cyclopenta[8]annulene-2,2-dicarboxylate (13). To a vial loaded with bromonymadine 11 (34 mg, 0.062 mmol, 1.0 eq.) and (Z)-boronate ester 23 (18 mg, 0.093 mmol, 1.5 eq.) was added dry and degassed THF (1.3 mL, 50 mM), degassed K2CO3 solution in water (0.13 mL, 19 mg/mL, 0.19 mmol, 3.0 eq.) and Pd(PPh3)4 (7.2 mg, 0.006 mmol, 10 mol%). The mixture was further degassed by bubbling N2, then sealed and heated overnight at 80 °C. After cooling to rt, water and EtOAc were added, and the organic layer was separated and washed with brine, dried over MgSO4 and concentrated. Purification via flash chromatography (pentane/EtOAc 7:3) afforded 13 (32 mg, 0.060 mmol, 96%) of the desired product.

\[ {^1}H \text{ NMR} \ (400 \text{ MHz, CDCls}) \delta 7.76 (d, J = 8.3 \text{ Hz}, 2H), 7.37-7.13 \ (m, 7H), 5.77 (dd, J = 5.1, 1.5 \text{ Hz}, 1H), 5.51 (d, J = 4.5 \text{ Hz}, 1H), 4.55 (s, 2H), 3.71 (s, 6H), 2.91 (s, 2H), 2.61 (s, 2H), 2.44 (s, 3H), 2.02-1.96 (m, 2H), 1.84-1.78 (m, 2H), 1.65 (s, 3H). \]

\[ {^13}C \text{ NMR} \ (101 \text{ MHz, CDCls}) \delta 172.4, 143.5, 136.2, 136.1, 136.0, 134.8, 131.7, 129.6, 129.2, 128.6, 128.5, 128.3, 127.8, 127.6, 120.1, 56.9, 52.9, 52.7, 46.0, 43.4, 30.5, 27.8, 25.4, 21.7. \]

HRMS (ESI) calc. for C39H31NO6S \([M+Na]^+\) 536.2100, found 536.2101.

Dimethyl 2-(2-bromoallyl)-2-(prop-2-yn-1-yl)malonate (16). To a stirred suspension of pentane-washed NaH (162 mg, 6.26 mmol, 5.0 eq.) and solution of KHCO3 (6.26 mL, 44.9 mmol, 5.0 eq.) and HBPin (16 mg, 0.093 mmol, 1.5 eq.) in dry THF (2967 mg, 2.69 mmol, 1.0 eq.), and the mixture was stirred for 30 min. Propargyl bromide (160 mL, 5.38 mmol, 2.0 eq., 80% wt. in toluene) was slowly added and the reaction mixture was stirred overnight. Diethyl ether and NH4Cl (sat., aq.) were added and the organic layer was separated, washed with brine, dried over MgSO4 and concentrated. Purification via flash chromatography (pentane/EtOAc 9:1) afforded 16 (490 mg, 1.69 mmol, 63%) as a colourless oil.

\[ {^1}H \text{ NMR} \ (400 \text{ MHz, CDCls}) \delta 5.84 (br s, 1H), 5.63 (d, J = 1.6 \text{ Hz}, 1H), 3.77 (s, 6H), 3.31 (br s, 2H), 2.93 (d, J = 2.7 \text{ Hz}, 2H), 2.05 (t, J = 2.7 \text{ Hz}, 1H). \]

Data in agreement with literature values [15]

(Z)-4,4,5,5-Tetramethyl-2-(3-methylbuta-1,3-dien-1-yl)-1,3,2-dioxaborolane (23). A protocol for trans-selective alkyne hydroboration developed by Miyaura and co-workers [25] was applied. To a flame dried Schlenk flask was added anhydrous cyclohexane (27 mL, 0.25 M). The flask was then taken into the glovebox and [Rh(cod)Cl]2: (66 mg, 0.13 mmol, 1.5 mol%) and i-Pr3IP (86 mg, 0.54 mmol, 6.0 mol%) were added. The flask capped with a septum and removed from the glovebox, then Et3N (6.26 mL, 44.9 mmol, 5.0 eq.) and HBPin (1.15 g, 8.99 mmol, 1.0 eq.) were added and the mixture was stirred at room temperature for 30 min. 2-Methyl-1-buten-3-yne** (0.71 g, 10.8 mmol, 1.2 eq.) was added and the mixture was stirred for 3–4 h at room temperature (it could be also left overnight). The reaction was quenched by addition of MeOH (~10 mL) and evaporated (150 mbar, 30 °C). Purification via flash chromatography (pentane/EtOAc 98:2) afforded 23 (850 mg, 5.29 mmol, 49%) as a ~1:1 Z/E mixture that was separated by reversed phase HPLC (Gemini-NX C18 5 μm, 21×150 mm, H2O/MeCN 20:80, 9 mL/min, 6.6 min Z-23, 7.0 min E-23) to afford pure Z isomer.

\[ {^1}H \text{ NMR} \ (500 \text{ MHz, CDCls}) \delta 6.73 (d, J = 14.9 \text{ Hz}, 1H), 5.36 (d, J = 14.9 \text{ Hz}, 1H), 5.07-5.04 (m, 2H), 1.96 (s, 3H), 1.29 (s, 12H). \]

\[ {^13}C \text{ NMR} \ (126 \text{ MHz, CDCls}) \delta 148.6, 144.0, 119.2, 83.7, 24.9, 20.5. \]

The alkene carbon atom bonded to boron was not observed due to quadrupolar relaxation. E isomer

\[ {^1}H \text{ NMR} \ (400 \text{ MHz, CDCls}) \delta 7.11 (d, J = 18.2 \text{ Hz}, 1H), 5.56 (d, J = 18.2 \text{ Hz}, 1H), 5.16 (s, 2H), 1.85 (s, 3H), 1.29 (s, 12H). \]

**2-Methyl-1-buten-3-yne (b.p. 35 °C) could be synthesized from 2-methylbut-3-yn-2-ol according to a literature procedure [24], or purchased directly from a commercial source. Dimethyl (3aR,7aR)-7-((N-benzyl-4-methylphenyl)sulfonamido)-3a,7a-dihydroxy-1,3,3a,4,5,7a-hexahydro-2H-indene-2,2-dicarboxylate (25). To a solution of diene 12 (10.0 mg, 0.020 mmol) in acetone (0.30 mL) was added NMO/H2O (6.2 mg, 0.040 mmol, 2.0 eq.) and solution of K2Os(OH)2...
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(0.7 mg, 0.002 mmol, 10 mol%) in water (0.10 mL). The reaction mixture was stirred for 4 h at room temperature. Aqueous Na₂SO₃ and EtOAc were added, and the organic layer was washed with sat. NaHCO₃, brine, dried (MgSO₄) and concentrated. Purification via flash chromatography (pentane/EtOAc 1:1) afforded 25 (3.2 mg, 0.006 mmol, 30%). ¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, J = 8.3 Hz, 1H), 7.33–7.19 (m, 2H+5H), 5.27 (dd, J = 5.0, 3.0 Hz, 1H), 4.57 (d, J = 14.1 Hz, 1H), 4.41 (d, J = 14.1 Hz, 1H), 3.74 (s, 3H), 3.63 (s, 3H), 2.64 (d, J = 14.1 Hz, 1H), 2.50–2.44 (m, 1H), 2.44 (s, 3H), 2.31–2.19 (m, 1H+1H), 2.06–1.97 (m, 1H) 1.95–1.86 (m, 1H), 1.82–1.74 (m, 1H), 1.72–1.60 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 172.8, 144.2, 137.5, 135.7, 135.4, 134.1, 129.9, 129.6, 128.6, 128.3, 79.5, 56.7, 55.7, 53.2, 53.1, 44.6, 44.5, 30.5, 22.7, 21.7. HRMS (ESI) calc. for C₆H₃NO₅S [M+Na]+ 552.1663, found 552.1659.

Dimethyl (3aR,7aR)-7-((N-benzyl-4-methylphenyl)sulfonamido)-4,5-dihydro-1H-3a,7a-epoxyindene-2,2(3H)-dicarboxylate (26). To a solution of diene 12 (10.0 mg, 0.020 mmol) in CH₂Cl₂ (0.40 mL) was added NaHCO₃ (2.0 mg, 0.024 mmol, 1.2 eq.) and m-CPBA (70%, 5.5 mg, 0.022 mmol, 1.1 eq.) and the mixture was stirred for 30 min at rt. The colour turned from red to yellow upon addition of m-CPBA. The reaction was diluted with CH₂Cl₂, and the organic layer was washed with aqueous NaHCO₃, Na₂SO₃ and brine, dried (MgSO₄) and concentrated. Purification via flash chromatography (pentane/EtOAc 7:3 to 1:1) afforded 26 (6.1 mg, 0.012 mmol, 59%) of the epoxide product. ¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, J = 8.3 Hz, 1H), 7.35–7.21 (m, 2H+5H), 5.29 (t, J = 4.9 Hz, 1H), 4.65 (d, J = 13.5 Hz, 1H), 4.26 (d, J = 13.5 Hz, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 3.02 (d, J = 14.2 Hz, 1H), 2.96 (d, J = 14.2 Hz, 1H), 2.44 (s, 3H), 2.19–1.96 (m, 5H), 1.48 (dt, J = 14.0, 9.1 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 171.4, 171.3, 143.8, 138.5, 135.8, 135.6, 134.1, 131.9, 129.8, 129.6, 128.5, 128.1, 128.1, 68.8, 63.5, 56.6, 55.2, 53.1, 53.0, 38.9, 36.3, 22.1, 21.9, 21.7. HRMS (ESI) calc. for C₁₅H₁₃NO₅S [M+Na]+ 534.1557, found 534.1550.

Dimethyl (6R,7S,E)-9-((N-benzyl-4-methylphenyl)sulfonamido)-6,7-dihydroxy-6-methyl-1,3,4,5,6,7-hexahydro-2H-cyclopenta[8]annulene-2,2-dicarboxylate (27). To a solution of triene 14 (10.0 mg, 0.019 mmol) in acetone (0.30 mL) was added NMO.HCl (0.7 mg, 0.002 mmol, 10 mol%) in water (0.10 mL). The reaction mixture was stirred at rt, 3 h. Aqueous Na₂SO₃ and EtOAc were added, and the organic layer was washed with sat. NaHCO₃, brine, dried (MgSO₄) and concentrated. Purification via flash chromatography (pentane/EtOAc 1:1) afforded 27 (7.5 mg, 0.013 mmol, 71%). ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, J = 8.2 Hz, 1H), 7.35–7.14 (m, 2H+5H), 5.41 (d, J = 7.6 Hz, 1H), 4.95 (d, J = 14.4 Hz, 1H), 4.15 (d, J = 14.4 Hz, 1H), 3.93 (d, J = 7.6 Hz, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 3.01–2.91 (m, +1H), 2.76 (d, J = 17.1 Hz, 1H), 2.44 (s, 3H), 2.39–2.31 (m, 1H), 2.07–1.90 (m, 2H), 1.25–1.20 (m, 2H), 1.19 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 172.8, 144.2, 137.5, 135.7, 135.4, 134.1, 129.9, 129.6, 128.6, 128.3, 79.5, 56.7, 55.7, 53.2, 53.1, 44.6, 44.5, 30.5, 22.7, 21.7. HRMS (ESI) calc. for C₁₅H₁₃NO₅S [M+Na]+ 552.1663, found 552.1659.

Dimethyl (1aR,8aS,E)-7-((N-benzyl-4-methylphenyl)sulfonamido)-1a-methyl-1a,2,3,4,6,8a-hexahydro-5H-cyclopenta[5,6]cycloocta[1,2-b]oxirene-5,5-dicarboxylate (28). To a solution of triene 14 (20 mg, 0.037 mmol) in CH₂Cl₂ (0.5 mL) was added NaHCO₃ (5 mg, 0.056 mmol, 1.5 eq.) and m-CPBA (70%, 10 mg, 0.041 mmol, 1.1 eq.). The mixture was stirred overnight at rt, diluted with CH₂Cl₂ and washed with aqueous Na₂SO₃ (aq., sat.), NaHCO₃ (aq., sat.), and brine, dried (MgSO₄) and concentrated. Purification via flash chromatography (pentane/EtOAc 7:3) afforded 28 (8.7 mg, 0.016 mmol, 42%). ¹H NMR (400 MHz, CDCl₃) δ 7.76 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 7.25–7.18 (m, 3H), 7.14–7.07 (m, 2H), 5.54 (s, 1H), 4.86 (d, J = 15.0 Hz, 1H), 4.18 (d, J = 15.0 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.24 (s, 1H), 2.98–2.84 (m, 2H), 2.81 (d, J = 16.0 Hz, 1H), 2.56 (d, J = 16.0 Hz, 1H), 2.45 (s, 3H), 1.89–1.84 (m, 2H), 1.49 (dt, J = 13.8, 4.4 Hz, 1H), 1.13 (s, 3H), 1.06–0.96 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 172.3, 172.1, 143.9, 137.6, 136.3, 129.8, 128.7, 128.5, 127.9, 127.8,
To a stirred suspension of pentane-washed NaH (1.09 g pre-wash weight, 27.2 mmol, 1.2 eq., 60% in oil) in dry THF (68 mL) at room temperature under N\(_2\) was slowly added dimethyl malonate (2.61 mL, 22.7 mmol, 1.0 eq.), and the mixture was stirred for 30 min. 2,3-Dibromopropene (2.22 mL, 22.7 mmol, 1.0 eq., neat) was slowly added and the reaction mixture was stirred overnight. Diethyl ether and NH\(_4\)Cl (sat., aq.) were added. The organic layer was separated, washed with brine, dried over MgSO\(_4\) and concentrated. The product was distilled under reduced pressure (0.5 mbar) and three fractions were collected. The first fraction (45 °C) contained mostly diallylated product (these products were very hard to separate by chromatography). The desired product 29 was thus obtained (3.49 g, 13.9 mmol, 61%) as a colourless liquid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.69 (s, 1H), 5.47 (s, 1H), 3.82 (t, \(J = 7.5\) Hz, 1H), 3.75 (s, 6H), 3.02 (d, \(J = 7.5\) Hz, 2H). Data in agreement with literature values [28].

**Dimethyl 2-(2-bromoallyl)malonate (29).** A modified literature protocol for acrolein conjugate addition was applied [29]. To a mixture of acrolein (120 µL, 1.78 mmol, 1.0 eq.) and bromoallyl malonate 29 (448 mg, 1.78 mmol, 1.0 eq.) in MeOH (5.2 mL) at room temperature was slowly added NaOMe (25% wt solution in MeOH, 82 µL, 0.36 mmol, 0.2 eq.). The resulting mixture was stirred for 4 h, then the solvent was evaporated under reduced pressure. The residue was dissolved in EtO and washed with water, brine, dried over MgSO\(_4\) filtered and concentrated under reduced pressure. The residue was purified via flash column chromatography (pentane/EtOAc 7:3) to give 30 (259 mg, 0.84 mmol, 47%) as a viscous liquid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.73 (t, \(J = 1.3\) Hz, 1H), 5.67 (dt, \(J = 1.8, 0.9\) Hz, 1H), 5.60 (d, \(J = 1.8\) Hz, 1H), 3.74 (s, 6H), 3.18 (d, \(J = 0.9\) Hz, 2H), 2.52–2.46 (m, 2H), 2.37–2.27 (m, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 200.3, 170.5, 126.6, 122.3, 121.7, 77.2, 75.4, 51.8, 51.7, 47.2, 43.8, 29.8, 27.3, 21.7.

**Diethyl 2-(bromoallyl)-2-(3-oxopropyl)malonate (30).** Prepared according to a literature procedure [26]. To a stirred suspension of N-tosylbenzylamine (1.50 g, 5.74 mmol, 1.0 eq.) and powdered Cs\(_2\)CO\(_3\) (2.81 g, 8.61 mmol, 1.5 eq.) in DMF (4.3 mL), at 50 °C was added trichloroethylene (0.57 mL, 6.31 mmol, 1.1 eq.) dropwise over 10 min. The resulting mixture was stirred at 50 °C until the reaction reached completion as judged by TLC (~1–2 h). The mixture was cooled to room temperature, then partitioned between EtOAc and H\(_2\)O. The organic layer was separated and further washed with water, brine, dried over MgSO\(_4\) filtered and concentrated. Recrystallisation from EtOAc (10–20 mL) afforded 32 (1.50 g, 4.20 mmol, 73%) as white crystals. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.86 (d, \(J = 8.3\) Hz, 2H), 7.36 (d, \(J = 8.3\) Hz, 2H), 7.34–7.27 (m, 5H), 6.27 (s, 1H), 5.08–3.69 (very br s, 2H) 2.47 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 144.7, 135.2, 133.4, 129.8, 129.4, 128.5, 128.5, 128.4, 121.7, 77.2, 51.8, 21.7. Data in agreement with literature values [26].

**(F)-N-Benzyl-N-(1,2-dichlorovinyl)-4-methylbenzenesulfonamide (32).** Prepared according to a literature procedure [26]. To a stirred suspension of N-tosyldibenzyamine (1.50 g, 5.74 mmol, 1.0 eq.) and powdered Cs\(_2\)CO\(_3\) (2.81 g, 8.61 mmol, 1.5 eq.) in DMF (4.3 mL), at 50 °C was added trichloroethylene (0.57 mL, 6.31 mmol, 1.1 eq.) dropwise over 10 min. The resulting mixture was stirred at 50 °C until the reaction reached completion as judged by TLC (~1–2 h). The mixture was cooled to room temperature, then partitioned between EtOAc and H\(_2\)O. The organic layer was separated and further washed with water (2×) and brine. The organic layer was then dried (MgSO\(_4\)), filtered and concentrated. Recrystallisation from EtOAc (10–20 mL) afforded 32 (1.50 g, 4.20 mmol, 73%) as white crystals. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.86 (d, \(J = 8.3\) Hz, 2H), 7.36 (d, \(J = 8.3\) Hz, 2H), 7.34–7.27 (m, 5H), 6.27 (s, 1H), 5.08–3.69 (very br s, 2H) 2.47 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 144.7, 135.2, 133.4, 129.8, 129.4, 128.5, 128.5, 128.4, 121.7, 77.2, 51.8, 21.7. Data in agreement with literature values [26].

**Dimethyl 2-(5-((N-benzyl-4-methylphenyl)sulfonamido)-3-((tert-butyldimethylsi- lyloxy)-pent-4-yn-1-yl)-2-(bromoallyl)malonate (34).** Synthesized according to the protocol for ynamide synthesis developed by Anderson et al. [26]. To an oven dried, argon flushed flask was added 1,2-dichloroanemide 32 (116 mg, 0.33 mmol, 2.5 eq.) and anhydrous THF (1.1 mL), and the mixture was cooled to −78 °C whilst stirring. A solution of phenyllithium (1.9 M solution in dibutyl ether, 0.34 mL, 5.0 eq.) was then added dropwise, and the mixture was left to stir at −78 °C for 15 min. After complete conversion to the lithiated ynamide (as confirmed by TLC consumption of the dichloroanemide), a solution of the aldehyde 30 (40 mg, 0.13 mmol, 1.0 eq.) in anhydrous THF (0.6 mL) was added at −78 °C and the mixture was stirred for 1 h. The reaction was quenched with NH\(_4\)Cl (at −78 °C, sat., aq.), then warmed to room temperature and extracted with EtO. The organic
extract was washed with brine, dried (MgSO\textsubscript{4}) and concentrated. The crude product was used directly in the next step.

To a stirred solution of the crude alcohol in DMF (1 mL) at room temperature was added imidazole (14 mg, 0.19 mmol, 1.5 eq.) and TBSCI (20 mg, 0.13 mmol, 1.0 eq.), and the mixture was stirred for 1 h until complete (as monitored by TLC). Water and Et\textsubscript{2}O were added, then the organic layer was separated and washed with brine, dried (MgSO\textsubscript{4}) and concentrated. Since the ynamide impurity (resulting from protonation of excess lithiated ynamide from previous step) has a similar R\textsuperscript{t} value to the product, it was removed by washing the crude product with pentane several times (until the yellow colour faded). A solid, white impurity that is not soluble in pentane remains as a precipitate. The pentane washes were concentrated, and the residue was purified via flash chromatography (pentane/EtOAc 85:15) to afford 34 (28 mg, 0.04 mmol, 30% over two steps) as an oil. \textsuperscript{1}H NMR (400 MHz, d\textsubscript{6}-acetone) \(\delta\) 7.84 (d, \(J = 8.3\) Hz, 2H), 7.49 (d, \(J = 8.3\) Hz, 2H), 7.40–7.24 (m, 5H), 5.81–5.69 (m, 1H), 5.56 (d, \(J = 1.1\) Hz, 1H), 4.54 (s, 1H), 4.52 (s, 1H), 4.50–4.46 (m, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 2.82 (s, 2H), 2.44 (s, 3H), 2.07–2.02 (m, 1H), 1.82–1.71 (m, 1H), 1.68–1.58 (m, 1H), 0.79 (s, 9H), 0.00 (s, 3H), 0.02 (s, 3H). \textsuperscript{13}C NMR (101 MHz, d\textsubscript{6}-acetone) \(\delta\) 170.4, 144.9, 135.1, 134.9, 130.0, 128.7, 128.5, 128.2, 128.1, 127.7, 126.9, 122.1, 78.2, 72.0, 62.5, 56.4, 55.4, 52.1, 52.1, 42.9, 33.3, 27.2, 25.3, 20.7, 17.8, 105.3, 59.04 (s, 3H). HRMS (ESI) calc. for C\textsubscript{3}H\textsubscript{14}BrNO\textsubscript{5}Si [M+Na]\textsuperscript{+} 728.1683, found 728.1679.

To a vial loaded with bromoynamide (11 mg, 0.016 mmol, 1.0 eq.) and potassium vinyltrifluoroborate (20 (3.1 mg, 0.023 mmol, 1.5 eq.) was added dry and degassed THF (0.40 mL), degassed K\textsubscript{2}CO\textsubscript{3} solution in water (6.4 mg in 40 \(\mu\)L water, 0.047 mmol, 3.0 eq.) and Pd(PPh\textsubscript{3})\textsubscript{4} (1.8 mg, 0.002 mmol, 10 mol%). The mixture was further degassed by bubbling N\textsubscript{2} then sealed and heated overnight at 80 °C. After cooling to rt, water and EtOAc were added, the organic layer was separated and washed with brine, dried over MgSO\textsubscript{4} and concentrated. Purification via flash chromatography (pentane/EtOAc 7:3) afforded undesired products 37 (2.8 mg, 0.005 mmol, 28%) and 38 (3.1 mg, 0.005 mmol, 30%). 37: \textsuperscript{1}H NMR (400 MHz, Acetone) \(\delta\) 7.76 (d, \(J = 8.4\) Hz, 2H), 7.52–7.38 (m, 2H), 7.40–7.24 (m, 5H), 5.14 (d, \(J = 16.8\) Hz, 1H), 5.00 (s, 1H), 4.79 (d, \(J = 16.8\) Hz, 1H), 4.28 (br s, 1H), 3.68 (s, 3H), 3.62 (s, 3H), 3.23–3.18 (m, 2H), 2.44 (s, 3H), 2.24–2.40 (m, 1H), 2.08–2.02 (m, 1H), 1.82–1.71 (m, 1H), 1.68–1.58 (m, 1H), 0.79 (s, 9H), –0.00 (s, 3H), –0.02 (s, 3H). 38: \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.74 (d, \(J = 8.3\) Hz, 2H), 7.34–7.27 (m, 5H), 6.25 (dd, \(J = 17.5, 10.9\) Hz, 1H), 5.20 (d, \(J = 17.5\) Hz, 1H), 5.14 (s, 1H), 5.00 (d, \(J = 10.9\) Hz, 1H), 4.94 (s, 1H), 4.51 (d, \(J = 14.0\) Hz, 1H), 4.43 (d, \(J = 14.0\) Hz, 1H), 4.33 (t, \(J = 6.1\) Hz, 1H), 3.68 (s, 3H), 3.67 (s, 3H), 2.82 (s, 2H), 2.44 (s, 3H), 2.07–1.85 (m, 2H), 1.54–1.39 (m, 2H), 0.81 (s, 9H), –0.04 (s, 3H), –0.08 (s, 3H). Further structural assignment is provided in the Supporting information.

N-Benzyl-N-((3S,3aR,6aR)-3a-(2-bromoallyl)-2,2-dimethyl-5-oxohexahydrofuro[3,2-b]furan-3-yl)-3-hydroxybut-1-yn-1-yl)-4-methylbenzenesulfonamide (39). To an oven dried, argon flushed flask was added 1,2-dichloroanemide 32 (18 mg, 0.051 mmol, 3.0 eq.) and anhydrous THF (0.5 mL), and the mixture was cooled to –78 °C. A solution of phenyllithium (1.9 M solution in dibutyl ether, 25 \(\mu\)L, 2.8 eq.) was then added dropwise, and the mixture was left to stir at –78 °C for 15 min. After almost complete conversion to the lithiated ynamide (the 1,2-dichloroanemide is in excess, so a small amount remains), the aldehyde 6 (5.4 mg, 0.017 mmol) in anhydrous THF (0.5 mL) was added at –78 °C and stirred for 1 h. The reaction was quenched by the addition of NH\textsubscript{4}Cl (at –78 °C, sat., aq.), then warmed to room temperature and extracted with Et\textsubscript{2}O. The organic extract was washed with brine, dried (MgSO\textsubscript{4}) and concentrated. The product was purified via flash chromatography to afford 39 (5.1 mg, 0.008 mmol, 50%) as a 2:1 mixture of diastereomeric...
alcohols. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.78–7.74 (m, 2H), 7.39–7.25 (m, 2H+5H), 5.77–5.63 (m, 2H), 4.83–4.79 (m, 1H), 4.58–4.54 (m, 1H), 4.51–4.43 (m, 2H), 3.37–3.25 (m, 1H), 2.93–2.82 (m, 1H), 2.71–2.59 (m, 1H), 2.59–2.52 (m, 1H), 2.46 (s, 3H), 2.29 (dd, $j$ = 9.6, 3.9 Hz, 1H), 1.94 (d, $j$ = 5.6 Hz, 1H), 1.74–1.67 (m, 1H), 1.46–1.38 (m, 1H), 1.13 (s, 3H), 1.02 (s, 3H). HRMS (ESI) calc. for C$_{35}$H$_{35}$BrNO$_5$ [M+H]$^+$ 602.1207, found 602.1207. Due to insufficient material, the product structure was assigned using $^1$H NMR, $^1$H–$^1$H COSY and $^{13}$C edited-HSQC (see the Supplementary Materials).

4. Conclusions

In conclusion, a tandem carbopalladation, Suzuki coupling and 6π- or 8π-electrocyclisation reaction of bromo-ynamenamides in which the ynamide nitrogen is exocyclic to the forming ring was explored in the context of synthesis of terpenes from the Schisandraceae family. It was shown that this tactic can be applied to the synthesis of 5,6- and 5,8-fused bicyclic ring systems in high yields. A route to a versatile dienylboronic ester building block was also developed. The reactivity of the resulting enamides was explored, and it was found that reactivity patterns differ to those observed with ynamides. Synthesis of 7,5- and 7,8 ring systems using the developed cascade was tested; however, the greater difficulty of 7-membered ring closure and propensity to form 7,4-fused ring by-products hindered the application of this cascade. Nevertheless, for smaller ring tethers, the tandem carbopalladation, Suzuki coupling and 6/8π electrocyclisation was shown to be a highly efficient tactic, allowing a rapid increase in molecular complexity, and with a novel positioning of the ynamide nitrogen group. This process may therefore enable future applications in the synthesis of other classes of polycyclic natural products.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules28114468/s1. Copies of $^1$H, $^{13}$C and 2D NMR spectra.

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References


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