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An Alkyne Metathesis Based Approach to the Synthesis of the Anti-malarial Macrodiolide Samroiyotmycin A

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Abstract: We report the first total synthesis of samroiyotmycin A (1), a C₇-symmetric 20-membered anti-malarial macrodiolide isolated from Streptomyces sp. The convergent synthetic strategy orchestrates bisalkyne fragment-assembly using an unprecedented Schöllkopf-type condensation on a substituted β-lactone and an ambitious late-stage one-pot alkyn e cross metathesis – ring-closing metathesis (ACM-RCAM) reaction. The demanding alkyn e metathesis sequence is achieved using the latest generation of molybdenum alkylidyne endowed with a tripodal silanolate ligand framework. Subsequent conversion to the required E-alkenes uses contemporary hydrometallation chemistry catalysed by tetrameric cluster [(Cp*RuCl)₄]₂.

In 2013, Pittayakhajonwut and co-workers reported that the crude extracts of Streptomyces sp. BCC30756, exhibited potent activity against a multi-drug resistant (MDR) malarial strain.[3] A C₇-symmetric macrodiolide from this extract, samroiyotmycin A (1), was shown to be active against both the MDR malarial strain P. falciparum K1 (IC₅₀: 3.65 μg mL⁻¹) and lung carcinoma cell line NCI-H187 (IC₅₀: 24.14 μg mL⁻¹).[5] We envisaged rapid access to this promising scaffold using a one-pot alkyn e cross metathesis / ring closing alkyn e metathesis (ACM-RCAM) approach. Our previous work on the macrodiolide disorazole C₁₀[5], suggested this would allow rapid construction of the macrodiolide core with control over both the orientation of subunits and ring size.

A priori, the initial disconnection for this ACM-RCAM approach can be implemented across either the E-configured C(5)–C(6)/C(21)–C(22) d-substituted alkenes, or the C(3)–C(4)/C(19)–C(20) E-enoates (black and grey routes respectively, Scheme 1 (i)). Comparing end-games: in the former strategy, conversion of bis(ene) 2 to the E-configured alkenes in the absence of protic groups proximal to the acetylene, is likely to be challenging.[3–5] whilst in the second strategy, conversion of bis(ynoate) precursor 5 to samroiyotmycin A via ynoate-ene isomerisation,[8–13] bisiodination[14] and double Stille/Negishi coupling,[15,16] has better precedent. Examining the ACM-RCAM step, although both ACM and RCAM reactions of ynoates have been explored in isolation previously, the number of successful examples is small[17–23] likely because electron-deficient triple bonds in general are poorly reactive and ynoates in particular were beyond reach of the classical catalysts.[24,25] To our

Scheme 1. Conventional one-pot ACM-RCAM approaches to samroiyotmycin A. (i) Ring deconstruction via routes based on C(5)/C(6)/C(21)/C(22) or C(3)/C(4)/C(19)/C(20) disconnections to key intermediate 6, (ii) Installation of C(9)/C(10) and C(25)/C(26) stereochemistry via cyclocondensation onto α-chiral aldehyde 9.
knowledge there are no examples of a one-pot ynolate ACM-RCAM, as required for the assembly of the 20-membered core of samroiyotmycin A (1). With this in mind, we devised a unified strategy for construction of the bisalkyne building blocks, which would allow us to explore both routes. This strategy centered on desulfonification of 5-substituted 4-tosylazoles 7 and esterification of the resultant secondary alcohols 6 to give bisalkyne fragments 4 and 5. Influenced by prior work,[26] we hypothesised that formation of linchpin fragments 7 (Scheme 1(ii)) could be achieved through a Schöllkopf-type condensation of 4-substituted β-lactones 8 with anionic TosMIC,[27,29] if successful, this ambitious strategy would allow simultaneous installation of the 1,3-oxazoline unit and stereochemistry at C(10). Furthermore, we envisaged that construction of the diastereomerically pure β-lactones 8 would be possible via an asymmetric ketene cycloaddition to an α-methyl aldehydes 9.[30] Our synthetic approach to exploring these two proposed one-pot ACM-RCAM strategies is outlined below.

To explore our novel synthetic approach to setting the C(9)-C(10) stereochemistry required generation of α-chiral aldehydes 9a.b. Our initial approach focused on the diastereoselective alkylation of N-acylated oxazolidinones (Scheme 2(ii)). Due to competing elimination reactions observed when alkylating the propanoate derivative, diastereoselective methylation of the oxazolidinone derivatives 10a.b (see SI for preparation) was the preferred route. This reaction delivered the N-acyl derivatives 11a/b on a multi-gram scale in good to excellent yield (77-98%) and with high selectivity (dr > 20:1).[31] Hydrolytic cleavage of the chiral auxiliary in the presence of H2O gave the corresponding acids 12a.b in almost quantitative yield (95%). Conversion to the configurationally stable Weinreb amides 13a/b was accompanied by a very slight erosion of enantiomeric purity, as observed by chiral HPLC. DIBAL-H reduction (Scheme 3(i)) provided the sensitive α-methyl aldehydes 9a.b, primed for chain elongation by an acetate aldol equivalent.[32] The asymmetric ketene-aldehyde cycloaddition catalysed by the Lewis base O-TMS quinoline 14 was chosen for this purpose due to high levels of stereochemical control exerted by this chenonic alkylidene catalyst in intramolecular nucleophile-catalyzed aldol lakttonisation (NCAL) reactions of α- or β-substituted aldehyde acids,[33] and in intermolecular NCAL reactions featuring aldehydes with remote substitution.[34] This reaction converted crude aldehyde 9a into the thermally unstable β-lactone 8a with excellent diastereoccontrol over the newly-formed stereocentre at C(10) (>99:1 dr). To the best of our knowledge, this is the first example of an intermolecular NCAL reaction with double diastereof differentiation, where the catalyst control dominates over the influence of an α-chiral centre on the aldehyde. Immediate low-temperature Schöllkopf-type condensation of 8a with anionic TosMIC, furnished chiral alcohol 7a in excellent overall yield (35% from oxazolidinone 11a, following a five-step telescoped sequence) and with high diastereoselectivity (96:4 dr). When repeated with the longer chain oxazolidinone 11b, the same five-step sequence yielded alcohol 7b in 43% overall yield (> 99:1 dr). In both cases, the configuration at C(10)OH was confirmed by conversion to Mosher esters 15 and 16 (see SI for details).

For the total synthesis of samroiyotmycin A, we streamlined our route by switching to the use of Myers’ acylated pseudopseudephedrine auxiliary 17, since the amide formed upon alkylation can be directly converted to the enantioenriched α-methyl aldehyde (Scheme 2(ii)). Diastereoselective alkylation of the lithio enolate of 17 using 5-iodopent-2-ynyl afforded multigram quantities of amide 18a in very good yield (79%, 75:1 dr). Reductive cleavage of the auxiliary using LiAIH4 generated in-situ at low temperature gave aldehyde 9a,[35,36] which was used directly in the cyclocondensation catalysed by O-TMS quinine 14 to afford β-lactone 8a (> 99:1 dr). Immediate condensation of crude 8a with anionic TosMIC provided chiral alcohol 7a in excellent yield (52%, over a three-step telescoped sequence) and with high diastereoselectivity (97:3 dr) on multi-gram scale. 4-Tosylazole 7b was also obtained by adaptation of this synthetic route; asymmetric alkylation of the acylated auxiliary with 7-iodo-2-ynye to give 18b, reduction to aldehyde 9b and elaboration to diastereomerically pure β-lactone 8b. Careful optimisation of the cycloaddition reaction conditions showed that use of an equilibrium mixture of Et2O and CH2Cl2 as solvent gave the highest conversion and diastereoselectivity for this substrate. Subsequent condensation of the crude lactone 8b with TosMIC, delivered fragment 7b in good yield (24% over a three-step telescoped sequence) and similarly high diastereoselectivity (> 99:1 dr).
A number of methods were initially evaluated for the reductive desulfonylation of advanced intermediates 7a and 7b.\textsuperscript{[37-39]} To our surprise, sonication of fragment 7a in THF/EtOH with Na(Hg) amalgam, delivered the fragile chiral alcohol 6a, which was found to be prone to degradation even on silica.\textsuperscript{[38]} Gratifyingly, EDC-mediated esterification with acid 19 (see SI for preparation) furnished the stable bisalkyne 4, which seems to be independent of the initial isomer were discernible by LC-MS [47] (Scheme 4) (Table 1, entry 1). Unfortunately, sonication of both fragment 7b, or its TBS ether 21b, in THF/EtOH with Na (Hg) amalgam (2.0 - 10.0 equiv., 10 mol% Na) either failed completely, or led to instantaneous decomposition. Even the use of SmI\textsubscript{2} with DMPU, reported to be a particularly mild alternative,\textsuperscript{[39]} only led to the recovery of starting material. This unforeseen subtlety rendered the ynoate-yne one-pot ACM-RCAM strategy non-viable and enforced an adjustment to our final synthetic plan.

For our one-pot ACM-RCAM investigation, we employed the two latest generation molybdenum alkylidyne complexes 22a and 22b (Scheme 4) endowed with the privileged tripod silanolate ligand framework.\textsuperscript{[37,38]} Based on prior work from our group, we treated a solution of bisalkyne 4 in toluene (50 mM) with molybdenum alkylidyn complex 22a (10 mol%) at ambient temperature, in the presence of molecular sieves (5 Å) to scavenge the released 2-butyne.\textsuperscript{[22]} Following the reaction by reverse-phase LC-MS (λ=254 nm) indicated no conversion even after four hours at room temperature. However, full conversion to cyclobis(enyne) 2 was attained within two hours, by raising the temperature to 60 °C (Table 1, entry 1). Routine chromatography gave the cross-dimer 2 in analytically pure form in 53 % yield. Although no linear dimers, higher-order oligomers, nor the corresponding homodimeric isomer were discernible by LC-MS, we nonetheless suspected competing concentration-induced polymerisation. This undesired pathway, which seems to be independent of the initial catalyst loading (Table 1, entry 2), can be effectively suppressed by performing the reaction at a higher dilution. Indeed, treatment of a more dilute solution of monomer 4 (30 mM) with complex 22a (20 mol%) gave a significantly improved yield (Table 1, entry 3). Higher catalyst loading (Table 1, entry 4) and further dilution (Table 1, entry 5) gave no additional improvements with complex 22b, full conversion to the desired one-pot ACM-RCAM product 2 was only achieved after overnight heating at 80 °C (Table 1, entry 6) and isolation of the product was hindered by fragmentation of the catalyst ligand. These results highlight the remarkable functional group tolerance and robustness of catalyst 22a,\textsuperscript{[40]} which activates even the most demanding triple bonds under mild conditions in the presence of basic heterocycles. We suggest that the rigidified backbone and greater steric encumbrance of the coordination sphere of the podand complex 22b, is responsible for its reduced reactivity, particularly for electron-deficient substrates such as 1,3-enynes, which are known to be less reactive.\textsuperscript{[41]}

With the desired 20-membered macrocyclic framework in hand, our two end game steps could be tackled. Inspired by the recent formal synthesis of the lichen-derived macrolide (+)-aspicilin,\textsuperscript{[18]} we envisioned that trans-reduction of the newly formed alkenes to the required E-configured alkenes would be achieved via a bis(trans-hydrostannation-proto destannation) sequence. However, these key steps bore substantial risk, since electron-rich arenes and 1,3-enynes often act as catalyst poisons.

### Table 1. Optimisation of the one-pot ACM-RCAM of bisalkyne 4.

| Entry | Catalyst Loading (mol %) | Temp (°C) | Molarity (mM) | Time (h) | Isolated yield of 2 (%) |
|-------|--------------------------|-----------|---------------|----------|------------------------|
| 1\textsuperscript{a} | 10 | 60 | 50 | 2 | 53 |
| 2\textsuperscript{a} | 20 | 60 | 50 | 2 | 55 |
| 3\textsuperscript{a} | 30 | 60 | 30 | 1 | 74 |
| 4\textsuperscript{a} | 30 | 60 | 30 | 1 | 71 |
| 5\textsuperscript{a} | 30 | 60 | 15 | 3 | 71 |

[a] Reaction conditions: catalyst: complex 22a, solvent: toluene, additive: 5 Å MS. [b] Reaction conditions: catalyst: complex 22b, solvent: toluene, additive: 5 Å MS.

Scheme 4. Synthesis of bisalkyne building blocks and bisalkyne cyclic dimers. Reagents and Conditions: (a) TBSOTf, 2,6-lutidine, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C → RT, 18 h, 73 % (7b); (b) Na/Hg (10 mol % Na), Na\textsubscript{2}HPO\textsubscript{4}, THF/EtOH (1:1), 4 h; (c) EDC-HCl, acid 19, DMAP (10 mol%), CH\textsubscript{2}Cl\textsubscript{2}, 0 °C → RT, 18 h, 70 % over two steps (4); (d) see Table 1.

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in the trans-hydrostannation reaction.\cite{42} This stems from the ability of these substrates to bind to the [Cp*Ru] fragment through kinetically stable nπ* or nπ complexation, halting trans-hydrometallation of the alkyne triple bond (A and B, Scheme 4(i)).\cite{43} Furthermore, neighbouring group coordination often facilitates both the productive binding of the [Cp*Ru] and the selective proximal delivery of SnBu3 to the triple bond (C and D, Scheme 4(ii)).\cite{43} In the absence of directing groups, we anticipated that a double hydrostannation reaction would lead to a statistical mixture of proximal and distal stannylated products (E, F and G, Scheme 4(iii)). All of which derive from a double trans-hydrometallation process and can effectively deliver the desired E-configured alkenes upon protodestannation. In practice, hydrostannation of bis(enyne) 2 with the aid of tetrameric ruthenium catalyst 23 proceeded smoothly at ambient temperature to deliver an ill-defined mixture of stannylated products, which was not separable by flash chromatography on silica or reverse-phase HPLC. Therefore, the overall trans-selectivity of the double hydrostannation reaction was only determined after protodestannation had taken place.

Despite the ease of forging and subsequent elaboration of the macrocyclic core, protodestannation of the alkenylstannanes was particularly taxing. Treatment of the mixture of stannanes with TFA, silica, TBAF or even in situ generated HF, in both coordinating and non-coordinating media led either to no conversion or to decomposition. Confronted by this impasse, we resorted in a different approach. Given that most synthetic methodologies available for the downstream functionalisation of alkenylstannanes rely on the reversible transmetalation of tin to copper in polar solvents, we considered protodestannation via the formation of an organocopper species in the presence of a tin scavenger and an exogeneous proton source. After extensive experimentation we found that employing a mixture of DMF-MeOH (10:1) in the presence of copper(I) salt 24 at ambient temperature led to successful protodestannation (Scheme 4(iv)), furnishing the desired (5E,21E) isomer 1 as the major stereoisomer (crude HPLC ratio 78:22, (1):E:Z isomers). To our satisfaction, the analytical and spectroscopic data of the synthetic sample of 1, matched those of the natural product.

In summary, we have completed the first total synthesis of the anti-malarial macrodiolide samroiyotmycin A (1) (9 steps longest linear sequence, with an overall yield of 6 %). This convergent and scalable route, showcases an initial asymmetric alkylation of commercial 17, followed by a three-step telescoped sequence to set the C(10)OH stereochemistry and install the 1,3-oxazole unit, utilising an unprecedented Schöllkopf-type condensation on enantioenriched beta-lactones. Forging the rigid macrocyclic core was achieved by an efficient one-pot ACM-RCAM reaction using the latest generation of alkyne metathesis catalysts. While the final elaboration to the desired C2-symmetric macrodiolide was possible via a delicate trans-hydrostannation–protodestannation sequence. These results demonstrate that, when combined with contemporary hydrometallation chemistry, the one-pot ACM-RCAM can be a powerful manifold for the assembly of complex molecular architectures. We anticipate that this synthetic route will provide a solid base for future exploration of other members of this family, and the design of analogues with improved application profiles.

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Keywords: alkynes • hydrostannation • metathesis • natural products • total synthesis

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Forging of the 20-membered macrocyclic core of samroiyotmycin A can be readily achieved by combining a Mo-catalysed one-pot alkyne cross-metathesis ring-closing metathesis of bisalkyne building blocks and Ru-catalysed hydrometallation chemistry. These key transformations have enabled the first total synthesis of this antimalarial C$_2$-symmetric macrodiolide.

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