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1 # A Convergent Total Synthesis of the Kedarcidin Chromophore: 20-Years in the Making

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4 Hirama*[b,c,d]

6 *Dedicated to Professor Samuel J. Danishefsky for his outstanding contributions to the total synthesis*
7 *of highly complex and biologically important natural products*

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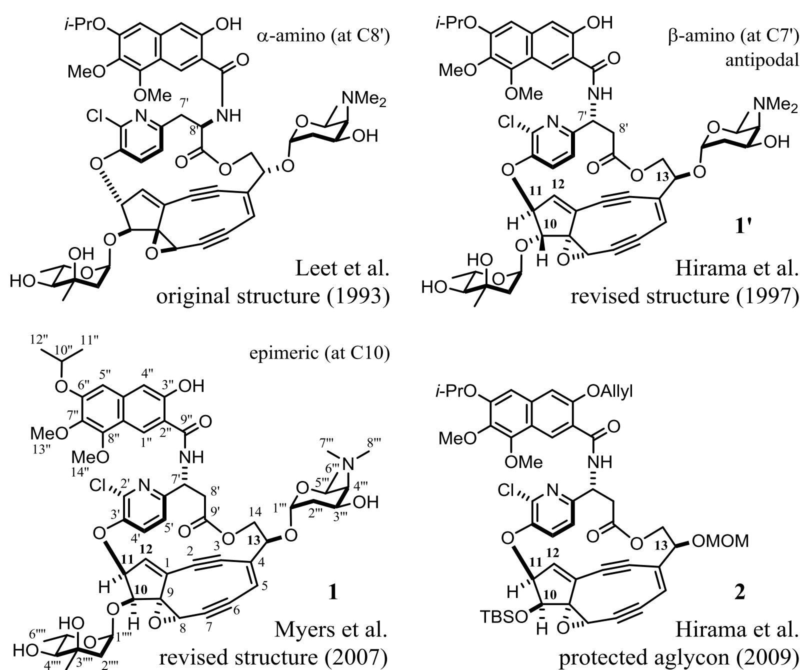
18 **Abstract:** The kedarcidin chromophore is a formidible target for total synthesis. Herein, we
19 describe a viable synthesis of this highly unstable natural product. This entailed the early
20 introduction and gram-scale synthesis of 2-deoxysugar conjugates of both L-mycarose and L-
21 kedarosamine. Key advances include: (**1**) stereoselective allenylzinc keto-addition to form an
22 epoxyalkyne; (**2**) α-selective glycosylations with 2-deoxy thioglycosides ($AgPF_6$/DTBMP)
23 and Schmidt donors ($TiCl_4$); (**3**) Mitsunobu aryl etherification to install a hindered 1,2-*cis*-
24 configuration; (**4**) atropselective and convergent Sonogashira-Shiina cyclization sequence;
25 (**5**) Ohfune-based amidation protocol for naphthoic acid; (**6**) Ce(III)-mediated nine-
26 membered enediyne cyclization and ester/mesylate derivatisation; (**7**) SmI_2-based reductive
27 olefination and global HF-deprotection end-game. The longest linear sequence from gram-
28 scale intermediates is 17-steps, and HRMS data of the synthetic natural product was obtained
29 for the first time.

31 ## Introduction

33 Total synthesis is a challenging field. Even more so if the natural product is complex in
34 structure and non-obvious in construction. The ensuing challenge reach unprecedented levels
35 when the natural product is highly unstable. Even more so, if late-stage synthetic precursors
36 are equally unstable. Very few natural products have been tackled under such criteria.
37 Outstanding cases in the anitumor antibiotic field include the ten- and nine-membered cyclic
38 enediynes.[1–6] Complexity aside, the latter enediynes are arguably more challenging to make
39 because of increased ring-strain[7–13] A case in point is the kedarcidin chromophore (**1**, Figure
40 1). This nine-membered cyclic enediyne exists kinetically stabilized in Nature as part of its
41 chromoprotein complex, kedarcidin.[14,15] The enediyne **1**, for example, decomposes within 1-2
42 h at room temperature once separated from its non-covalently bound apoprotein, even in
43 aprotic solvents. Notably, nine-membered bicyclic enediynes like **1** readily undergo both
44 spontaneous and nucleophile-induced cycloaromatizations via highly reactive *p*-benzyne
45 diradical species to give aromatized benzenoid products,[16–18] some of which are more readily
46 isolated and synthesized in stable cyclized forms on the bench.[19–23]

48 Kedarcidin itself was first discovered in 1990 by Bristol-Myers Squibb. It was identified as a
49 cytotoxic product from the supernatant of an unkown microbe cultured from a soil sample
50 collected in the Maharasta State of India. In 1991, the company disclosed the product
51 (kedarcidin) to be a new potent, chromoprotein antitumor antibiotic.[24,25] The producing
52 organism was eventually designated to be an actinomycete strain L585-6 of uncertain

taxonomy. Today, the genus is likely to be *Streptoalloteichus* sp. ATCC 53650 (not *Saccharothrix*). This particular species has recently been shown to produce kedarcidin. Gene sequencing has also shown ATCC 53650 to contain all of the biosynthetic machinery necessary to construct the kedarcidin chromophore (**1**).[26]



^{1}H HMR	natural **1**	synthetic **1'**	aglycon **2**
H10	**(d, 5.4 Hz)**	**(s)**	**(d, 5.6 Hz)**
H11	(dd, 5.4, 3.3 Hz)	(d, 3.0 Hz)	(dd, 5.6, 2.8 Hz)
H12	(d, 3.3 Hz)	(d, 3.0 Hz)	(d, 2.8 Hz)

Figure 1. Structural revisions and numbering system of the kedarcidin chromophore (**1**).

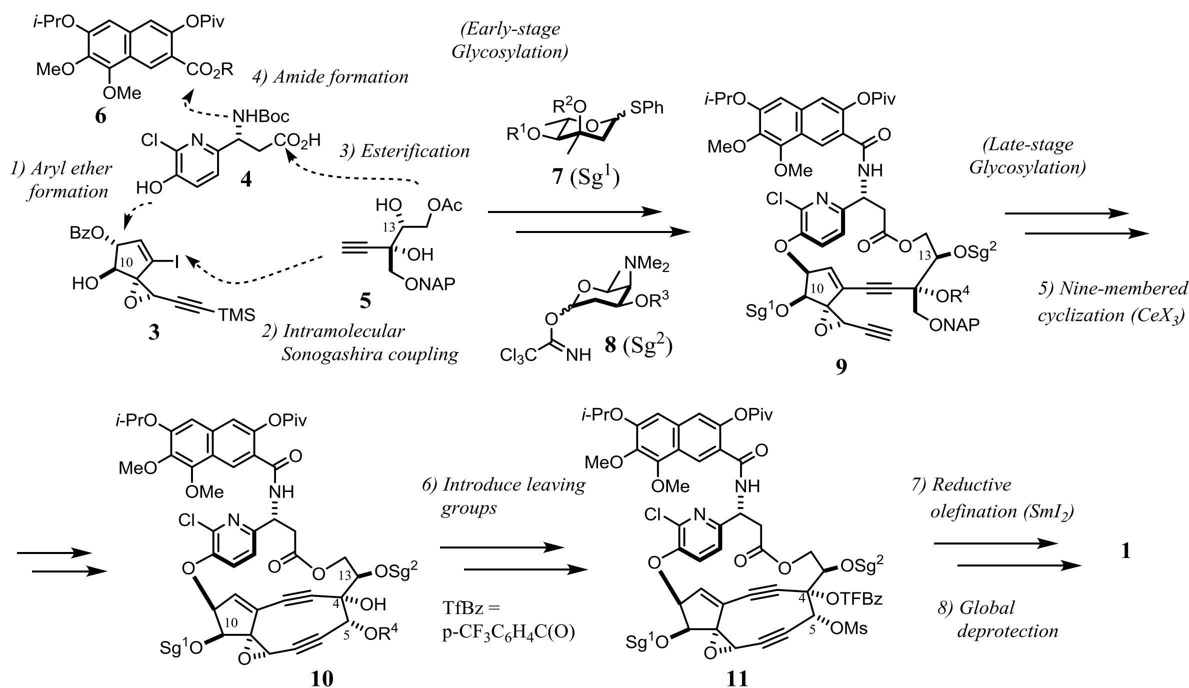
During 1992-1994, the bioactivities and structures of the isolated chromophore (**1**) and apoprotein of kedarcidin were further elucidated by Leet and colleagues within Bristol-Myers Squibb.[27–29] Like other chromoprotein antitumor antibiotics, kedarcidin elicits an extraordinary ability to drive an astonishing sequence of histone/DNA recognition and peptide/nucleotide cleavage events.[1–12] The acidic apoprotein of kedarcidin is proposed to first associate and enzymatically cleave the basic histone-coiled proteins.[30] Subsequent exposure of chromosomal DNA, release of the enediyne core (**1**), naphthyl-based DNA intercalation, 5'-TCCT*N*-3' sequence recognition, and Masamune-Bergman cycloaromatization of **1**, thereby generates a p-benzyne diradical that is transiently and non-covalently bound to DNA. This latter species then initiates DNA-strand breaking and crosslinking events via hydrogen abstraction of the deoxyribose backbone. These oxidative events consequently trigger cell death via the generation of carbon-centered radicals and radical oxygen species (ROS). Despite this non-trivial sequence of events, kedarcidin still elicits potent, yet selective in vivo antitumor activity against P388 leukemia and B16 melanoma cells.

Equally eventful and non-trivial has been the structural elucidation of the kedarcidin chromophore (**1**). To date, extensive NMR, MS/MS, chemical degradation, derivatization, reductive, radical-trapping, biosynthetic and total synthesis studies have provided convincing evidence for the enediyne structure **1**. In 1993, Leet et al. described in full their seminal

characterization studies of the chromophore structure.[28] They first proposed an azatyrosyl α-amino motif about the *ansa*-macrolide bridge (Figure 1). In 1997, we updated the whole structure to be antipodal and demonstrated the chromophore to be a β-amino acid derived *ansa*-macrolide (**1'**).[31] It is noteworthy that the amino-mutase to achieve such a β-amino motif has only recently been characterized.[32] In 2007, Myers and coworkers completed an impressive total synthesis of this 1997-structure **1'**.[33] Comparison of natural and synthetic ^{1}H NMR data, nevertheless, indicated the C10-α-epimeric stereoconfiguration of **1'** should be inverted to **1**.

In 2009, we provided strong NMR spectroscopic evidence for Myers' C10-β-epimer **1** through the synthesis of the complete aglycon **2** of the kedarcidin chromophore in protected form.[34] The currently accepted target for synthesis is thus Myers' structure **1**. Herein, we report a detailed account of our early-stage incorporation of both kedarcidin sugars (as elaborate *O*-protecting groups) and the convergent construction of the multicyclic, fully functionalized cyclic epoxyenediyne core. Collectively, our efforts have led to the development of a viable total synthesis of **1** as characterised by HRMS. Product instabilities have, however, prevented clean NMR characterization of the cyclic enediyne material in unprotected form.

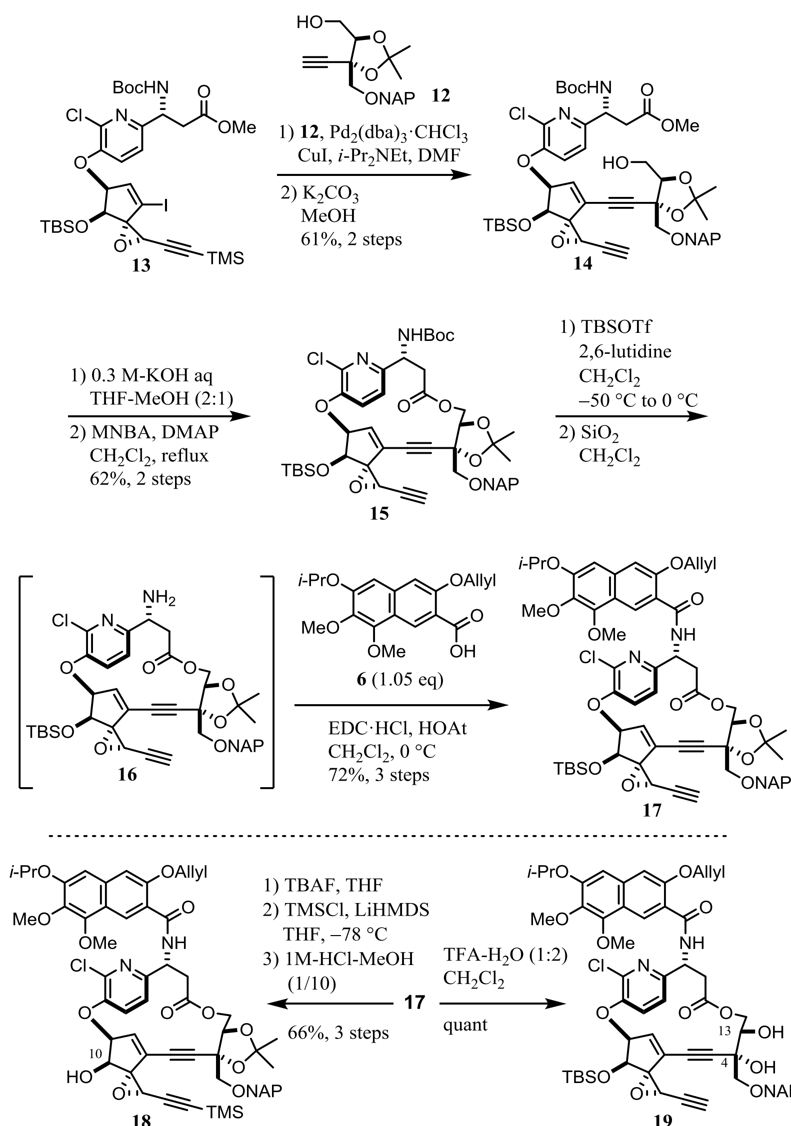
Results and Discussion



Scheme 1. General total synthesis plan for the kedarcidin chromophore (**1**).

In previous studies to the kedarcidin aglycon **2**, we secured several enantioselective routes to gram quantities of all key fragments: epoxy-iodocyclopentene **3**, aza-β-tyrosine **4**, alkyne-polyol **5**, and naphthoic acid **6** (Scheme 1).[31,34–38] We also determined practical methods to synthesize the 2-deoxy sugars, L-mycarose **7** and L-kedarosamine **8**.[39] Not only this, but we developed and achieved the direct α-selective glycosylation of several advanced C10-α-epimeric aglycon precursors to **1'**.[33,40,41] The key question now was when to incorporate the kedarcidin sugars into our general synthesis plan (Scheme 1). The C4/C5-dioxy, epoxybicyclo[7.3.0]-dodecenediyne frameworks like **10** and **11** are known to be exceedingly

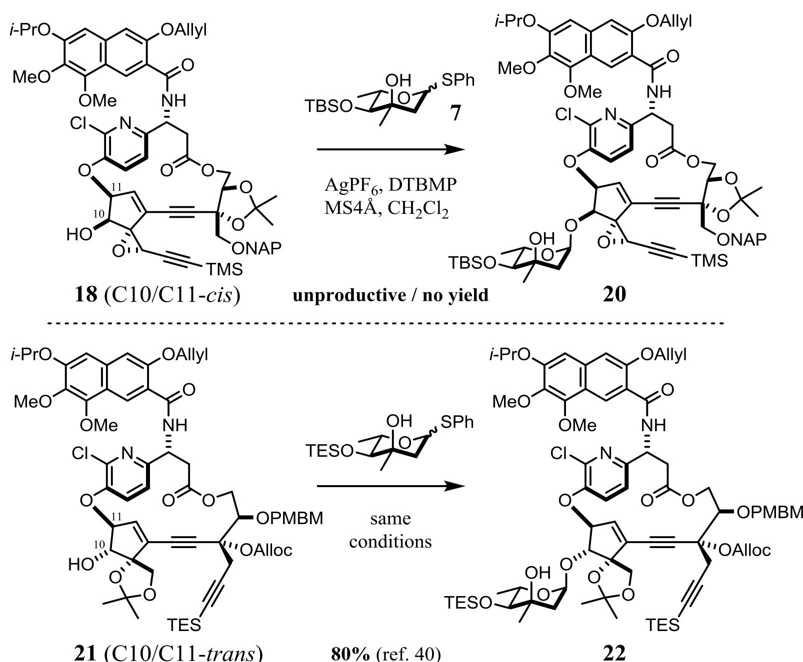
unstable.[34] Among other decomposition possibilities, such frameworks are prone to undergo facile oxy-Cope ring openings to afford bis-allenyl species.[37] The question thus came down to incorporating the sugars at an early or late stage *en route* to making **9**. Importantly, these glyosylation events should be executed before cyclization into a highly labile, nine-membered ring system like **10**. In either case, the efficiency and α-stereoselectivity of our current glycosylation protocols[40,41] needed to be tested on newly functionalized substrates of unknown reactivity (cf. **3**, **5**, and **9**).



Scheme 2. Synthesis of late-stage, C10-α-epimeric aglycon acceptors **18** (for L-mycarose) and **19** (for L-kedarosamine).

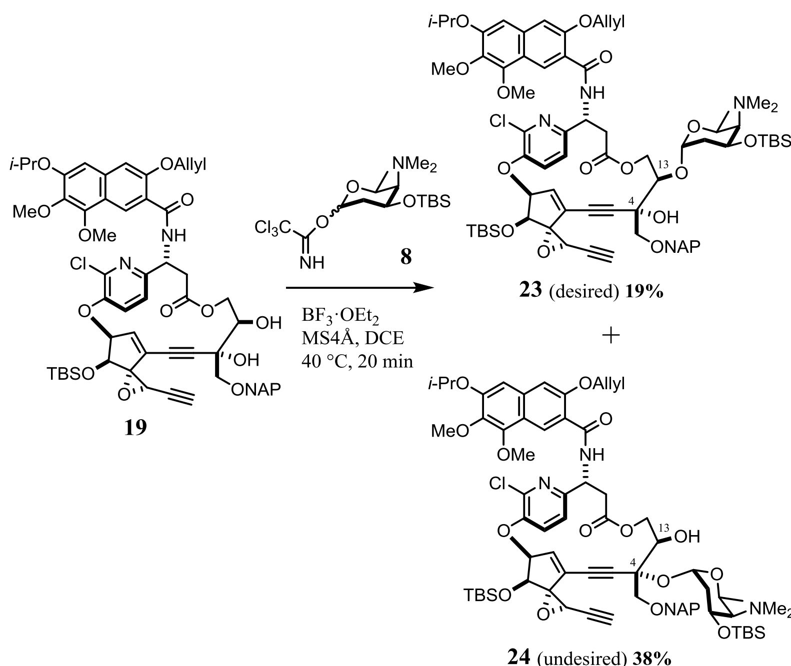
At first, a late-stage glycosylation strategy was investigated. The *ansa*-macrolides **18** and **19** (akin to **9**) were thus targeted as suitable L-mycarose and L-kedarosamine acceptors, respectively (Scheme 2). Treatment of **5** with 2,2-dimethoxypropane and acetyl deprotection afforded the acetonido-alkyne **12** in 76% yield, 2 steps. Sonogashira coupling of **12** with the known iodo-cyclopentene **13**[34] in degassed DMF under $Pd_2(dba)_3·CHCl_3$ / CuI catalysis, followed by selective protio-desilylation of the TMS-*C*-acetylene, gave the *ansa*-macrolide precursor **14** in 61% yield, 2 steps. Saponification of **14** afforded the corresponding carboxylic acid. This acid was immediately subjected to Shiina macrolactonization conditions

133 with 2-methyl-6-nitrobenzoic anhydride (MNBA).[42,43] These conditions gave the macrolide
134 **15** as a single atropisomer in 62% yield, 2 steps. Mild and selective *N*-Boc deprotection of **15**
135 (via an *O*-TBS carbamate)[44] and HOAt-mediated[45] condensation of the free amine **16** with
136 the known naphthoic acid **6** (R= H)[31] gave the amide **17**. Final treatment of **17** with TBAF,
137 dual *C*- and *O*-trimethylsilylation, and chemoselective C10-*O*-desilylation, gave the L-
138 mycarose C10-*O*-acceptor **18** with its terminal acetylene suitably *C*-protected (thereby
139 minimizing known complications via Ag(I)-complexation).[40] The alternative treatment of
140 amide **17** with TFA/H_2O (1:2) gave the L-kedarosamine C13-*O*-acceptor **19** with the C4-OH
141 free (thereby improving known reactivity issues).[41]
142
143 Having the desired macrocyclic glycosyl acceptors in hand, we first examined the reactivity
144 of **18** with L-mycarose (Scheme 3). The C10/C11-*cis* acceptor **18** under established α-
145 selective conditions ($AgPF_6$/DTBMP) with the thioglycoside **7** failed to yield any 2-
146 deoxypyranoside (**20**). This result could not be overturned and was in contrast to the
147 reactivity of the known C10/C11-*trans* acceptor **21** to give **22**[40], as well as the success of the
148 $AgPF_6$/DTBMP glycosylation method during the advanced stages of the total synthesis of the
149 C10-epimer **1'** by the group of Myers.[33] Clearly, the *cis*-facial proximity of the chloropyridyl
150 unit sterically prevented the glycosylation event.
151



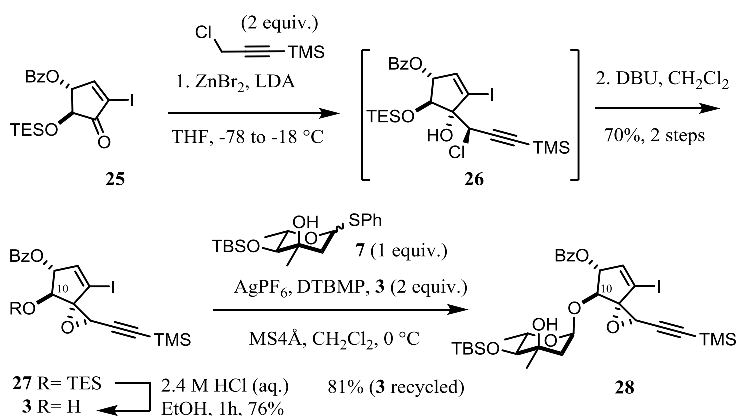
152
153 **Scheme 3**. Glycosylation of C10-α-epimeric alcohol **18** with L-mycarose (**7**).
154
155 Next, the glycosylation of the L-kedarosamine Schmidt donor **8** with the C4/C13-diol
156 acceptor **19** was examined (Scheme 4). Initially, our reported α-selective conditions were
157 found unsuccessful, for example, by using BF_3 or $TiCl_4$ at low or ambient temperatures in
158 chlorinated solvents.[41] Eventually, we succeeded with $BF_3 \cdot Et_2O$ in dichloroethane (DCE) at
159 an elevated temperature (40 °C). This gave the desired 2°-α-pyranoside **23** as the minor
160 product (19% isolated yield) in a 1:2 ratio with the 3°-glycoside **24**. As found previously, no
161 glycosylation occurred when the C4-OH group was protected. Such results do not fair well
162 for a total synthesis.
163
164 According to these findings, both glycosylations would be better performed at an early-stage
165 of the synthesis (cf. Scheme 1). Such timings would allow for steric hindrances to be

minimized (cf. **3** and **18**; **5** and **19**). In effect, the 2-deoxy-α-pyranoside sugar functionalities may be viewed as elaborate THP protecting groups (Sg^1, Sg^2) *en route* to constructing a bis-glycosylated enediyne cyclisation precursor (cf. **9**). Although more risky, this strategy offers a more convergent total synthesis of **1**. The acid lability, free hydroxyl and amino functionality, and extra steric potentials of the 2-deoxypyranosides, were thus considered to present additional synthetic challenges (*vide infra*).



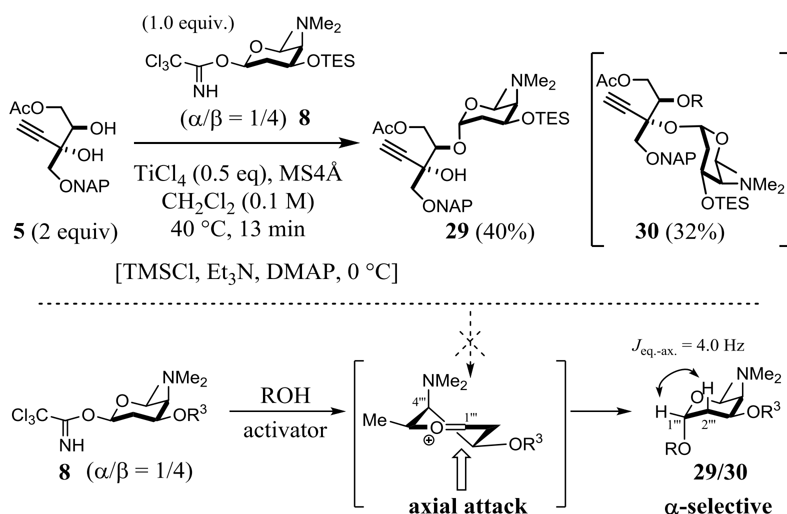
Scheme 4. Glycosylation of C4/C13-diol acceptor **19** with L-kedarosamine (**8**).

Undeterred by such challenges, we elected to prepare gram quantities of the C10 and C13 *O*-glycosylated versions of **3** and **5**, respectively (cf. Scheme 1). These fragments would be used later for azatyrosine (**4**) incorporation and Sonogashira coupling studies (*vide infra*). We first targeted the propargyl oxirane moiety **3** as a suitable C10/C11-*trans* glycosyl acceptor (Scheme 5). After a few modifications to established procedures, the iodo-cyclopentenone **25** was prepared as its C10-OTES silyl ether (not as its TBS ether).[36] Similar to the protocols of Chemla and Caddick,[46,47] the allenyl zinc species of 3-chloro-1-trimethylsilylpropyne (prepared at –78 °C) was reacted with the ketone **25** at –18 °C overnight. The crude chlorohydrin **26** was then treated with DBU in dichloromethane to afford the epoxyalkyne **27** stereoselectively in 70% yield, 2 steps. This latter step avoided the use of potassium carbonate,[34] so that the TMS-*C*-protected alkyne **27** could be formed directly. Unlike its C10-OTBS counterpart,[34] the TES ether of **27** could also be removed chemoselectively under Brønsted acid conditions to give the desired C10-OH acceptor **3**. Gratifyingly, the thioglycoside **7** reacted smoothly with 2 equivalents of the 2°-alcohol **3** in the presence of $AgPF_6$/DTBMP.[40] This furnished the C10/C11-*trans* α-pyranoside **28** exclusively in 81% yield. The excess alcohol **3** was then recovered and recycled. Gram quantities of pure **28** were produced in this manner.



Scheme 5. Synthesis of C10-OH acceptor **3** and α-glycosylation with L-mycarose (**7**).

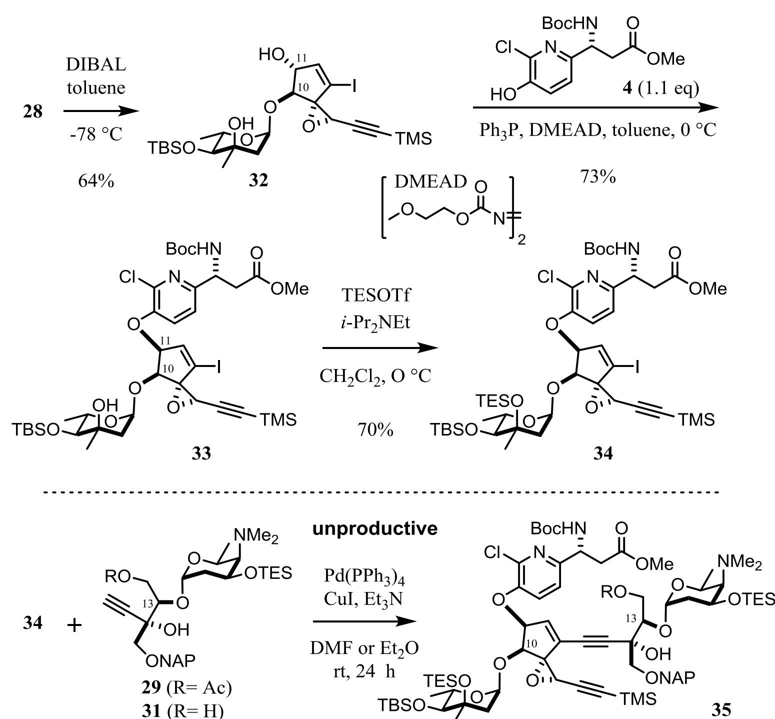
Next, the gram-scale, α-selective glycosylation of the C13/C4-diol acceptor **5** was pursued with various L-kedarosamine donors **8** (Scheme 6). Due to no silyl acetylene protection, $AgPF_6$/DTBMP conditions were incompatible with **5**.[41] We thus chose NIS/TfOH to activate the thioglycoside of **8**.[48] This afforded the 2°-α-pyranoside **29** in a maximum yield of 26 %. Coupling with the alternative glycosyl fluoride of **8** under $Cp_2HfCl_2/AgClO_4$ conditions did not improve yields (15 % at best).[49,50] Eventually, we found $TiCl_4$ to be superior to $BF_3{\cdot}Et_2O$ in coupling the Schmidt donor **8** and diol **5** under our reported conditions.[41] For scale-up purposes, two-equivalents of diol **5** were used relative to **8**, whereby 0.5 equivalents of $TiCl_4$ were added under the gentle reflux of CH_2Cl_2. This rapidly gave the desired 2°-α-pyranoside **29** in a 40% isolated yield. Excess **5** was also recovered (ca. one-equivalent) and all cases produced minor amounts of the 3°-α-pyranoside **30** (R= H) as an inseparable mixture with **29**. Gratifyingly, all pyranosides **29**/**30** were found to be α-anomeric (J = 4.0 Hz coupling constants). This is consistent with high kinetic control, presumably by virtue of the axial NMe_2 group within an oxocarbenium conformation (**8**→**29**).



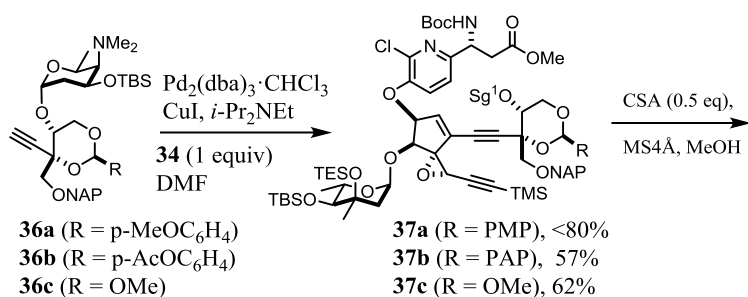
Scheme 6. Glycosylation of diol **5** with L-kedarosamine (**8**) and origin of α-selectivity.

Having gram quantities of the L-mycarose and L-kedarosamine fragments **28** and **29** in hand, azatyrosine incorporation of **4** and the search for suitable Sonogashira coupling substrates were explored (Scheme 7). Low temperature, reductive deprotection of the benzoate **28**, by using DIBAL in toluene, thus provided **32**. The *cis*-relative C10/C11-stereochemistry was

next achieved by phenolic Mitsunobu inversion[51] of the allylic C11-β-alcohol **32** by the β-amido-2-chloroazatyrosine **4**. For scale-up purposes, the use of DMEAD was found preferable to DEAD.[52] Triethylsilyl (TES) protection of the tertiary alcohol on L-mycarose then gave the L-mycarose fragment **34**. Initial attempts at Sonogashira coupling between the iodoalkene **34** and the alkyne **29** or its diol **31** were, however, unproductive. These attempts were in contrast to previous studies with a C13-OMOM equivalent of the L-kedarosamine fragment **29**.[34] We therefore decided to explore alternative substrates to achieve this key Sonogashira coupling step.

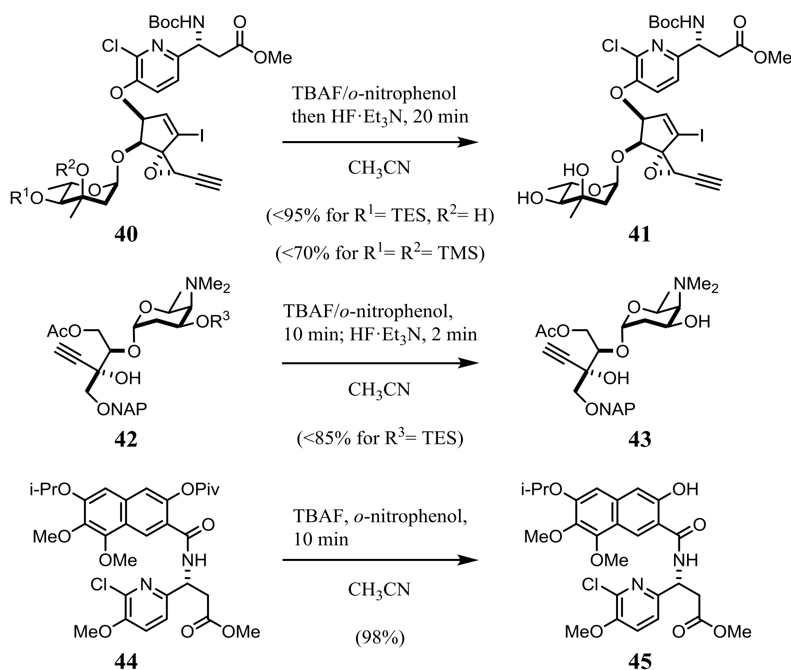


Scheme 7. Mitsunobu installation of azatyrosine **4** to afford C10/C11-*trans* fragment **33** and attempted Sonagashira coupling between the sugar bearing fragments **34** and **29.**



Scheme 8. Sonogashira coupling and saponification-macrolactonization study.

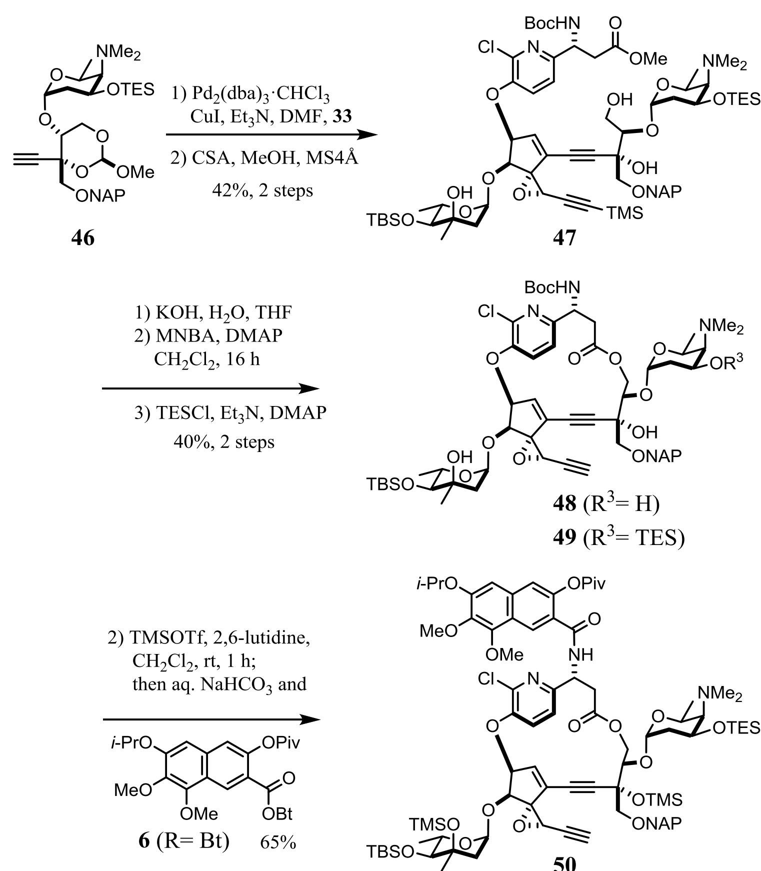
Additional steric and conformational effects by the kedarosamine moiety were considered the primary causes for the unproductive iodoalkene-alkyne coupling between **29** and **34**. We thus prepared various cylic diol-protected versions of **29**. These modified substrates **36a–c** proved to be successful under established Pd(0)/Cu(I) Sonogashira conditions (Scheme 8).[35–38] The orthoester **36c** was selected as the optimal substrate for subsequent hydrolytic, *ansa*-macrolactonization studies. This minimized the loss of acid labile 2-deoxypyranoside moieties during the methanolysis of **37c** to its free diol **38** (82%). The alternative cyclic acetals **37a/b** could not be deprotected cleanly and gave the diol **38** in yields below 55%.[53,54] Final saponification of **38** and Shiina macrolactonization[55] generated the atropisomeric *ansa*-macrolide **39** exclusively in 52%, two steps. ROESY NMR analysis between the protons of the pyridyl C4' and epoxy C8 of **39** confirmed its structure. We thus secured a viable route to bis-glycosylated cyclization precursors like **9** (cf. Scheme 1).



Scheme 9. Protecting group selection under Myers' global deprotection conditions.[33]

Before progressing forward with **39** and attaching the naphthamide moiety **6**, we became concerned at our protecting group strategy to **1** (cf. Scheme 1). Thus far, relatively strong *O*-TBS protected 2-deoxysugar fragments **34** and **36** were selected. Although useful in establishing the chemistry to advanced *ansa*-macrolides, a final global deprotection sequence to **1** needs to be both rapid and mild due to enediyne instabilities (cf. **10** and **11**). We thus directed our attention to adjusting the protecting groups on the L-mycarose (**7**), L-kedarosamine (**8**) and naphthamide (**6**) moieties. Model substrates **40**, **42**, and **44**[14] were thus prepared and subjected to excess TBAF/*o*-nitrophenol and $HF\cdot Et_3N$ according to Myers' established deprotection sequence to **1'** (Scheme 9).[33] This study demonstrated the clear need for TES protection of the sugar moieties **40** (for R^1) and **42** (for R^3) during the end-game of a total synthesis, as well as the need for pivaloyl (Piv) phenolic protection for the naphthamide (**44**). In all these cases, deprotection could be achieved cleanly within 10-30 minutes. In contrast, the TBS ethers of **40** (for R^1) and of **42** (for R^3) remained intact even after 3 hours. Bis-TMS protection (R^1, R^2) of the mycarose **40** was also found acceptable, but other silyl combinations were not.

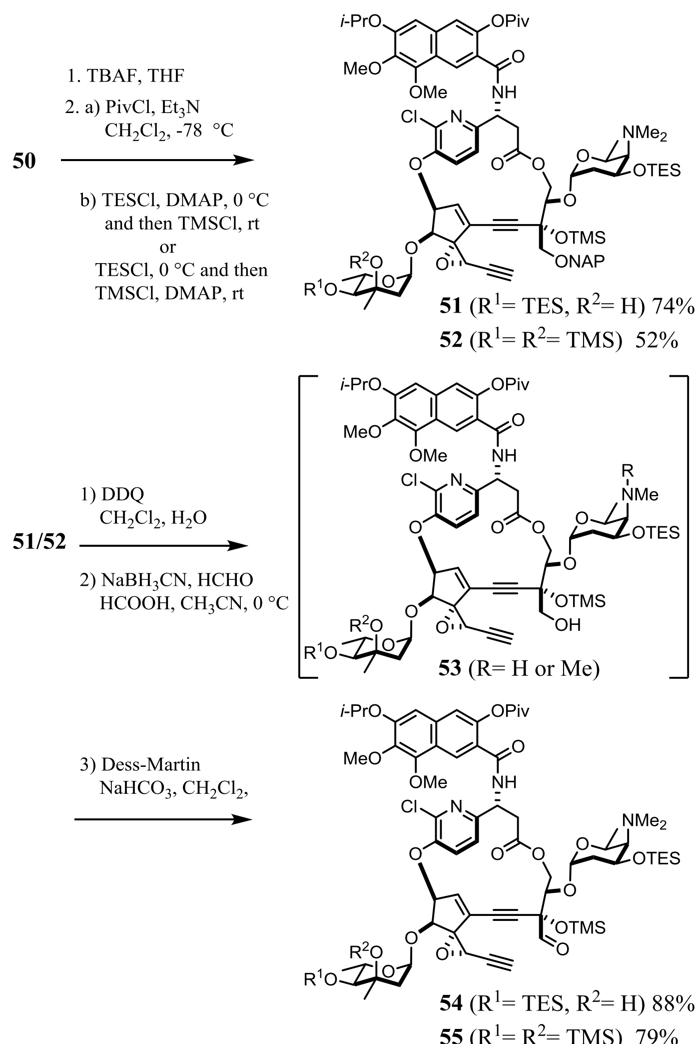
Armed with this information and the experience gained in preparing **39**, we turned our attention to assembling a suitably protected version of the advanced intermediate **9** for subsequent enediyne cyclisation studies. After several trials, we settled on making the bis-glycosylated *ansa*-macrolide **50** according to Scheme 10. In this particuar case, we began with the TES-protected kedarosamine fragment **46** (freshly prepared) and the TBS-protected mycarose fragment **33** (3°-OH free). After Sonogashira coupling and orthoester methanolysis to diol **47**, the TES ether proximal to NMe_2 was found to cleave during the Shiina macrolactonization step. This generated the *ansa*-macrolide **48**. After TES ether re-protection of the L-kedarosamine moiety of **48**, a chemoselective one-pot amidation procedure was developed. This entailed the sequential addition of TMSOTf/2,6-lutidine, akin to Ohfune's NH-Boc deprotection conditions,[44] followed by saturated aqueous sodium bicarbonate solution and the one-pot addition of a preformed CH_2Cl_2 solution of the HOBt-activated naphthoate ester **6**. This afforded the fully protected *ansa*-macrolide **50** in 63% yield from **48**.



Scheme 10. Reliable assembly of a fully protected, storable *ansa*-macrolide (**50**).

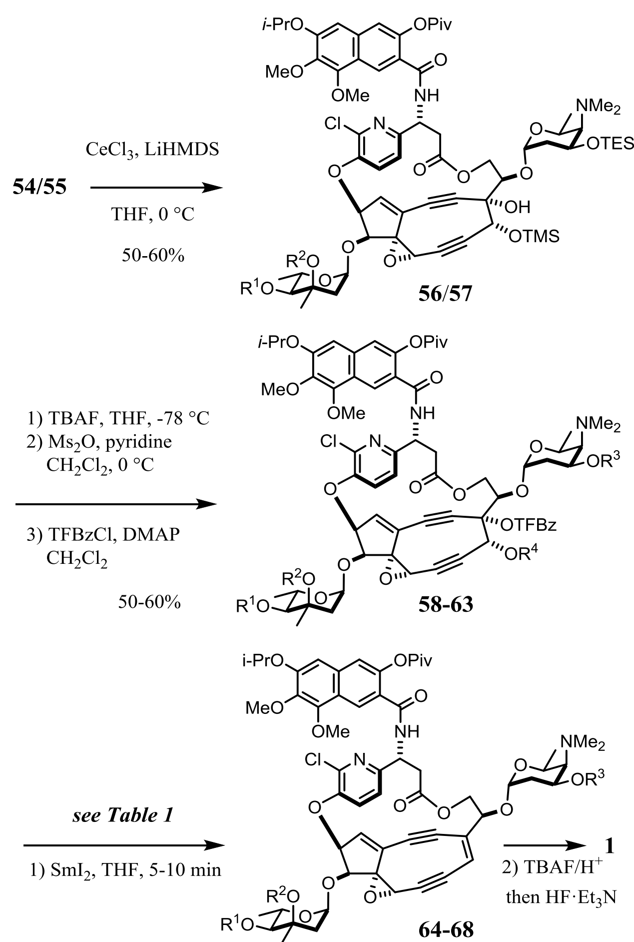
Under this scheme, we could reliably prepare 30–90 mg quantities of **50**. Here, samples could be safely stored as dilute CH_2Cl_2 solutions at –20 °C over a couple of months. When required, a suitably protected aldehyde substrate would thus be prepared for immediate enediyne cyclization studies. Preparations of the mono-TES (**54**) and bis-TMS (**55**) protected aldehydes are given in Scheme 11. After complete TBAF deprotection of **50** to its unstable pentaol, care was needed to achieve the differential Piv, TES, and TMS *O*-protection pattern as achieved in **51** and **52**. In one-pot operations, mono-pivalation of the naphtholic group was first effected at –78 °C with PivCl. Next, mono-triethylsilylation of the kedarsoamine moiety was effected at 0 °C. This was followed by either mono-TES or bis-TMS silyation of the

mycarose moiety in the presence of cat. DMAP. Ultimately, in the same pot, the C4-OH was protected as its TMS ether. Subsequent treatment of **51**/**52** with DDQ resulted in the *N*-demethylated alcohol **53**. Although the oxidative *N*-methyl cleavage process could not be circumvented, crude **53** was readily *N*-methylated under reductive amination conditions using formalin and $NaBH_3CN$. Dess-Martin periodinane (DMPI) oxidation of the primary alcohol then delivered the aldehydes **54** and **55** in good overall yields (75–90 % over 3 steps).



Scheme 11. Preparation of aldehyde enediyne cyclisation precursors (**54**/**55**).

The formidable challenges to transform multicyclic alkyne-aldehydes like **54**/**55** into fully fledged, epoxybicyclo[7.3.0]-dodecadienediyne cores should not be underestimated by any means. Whilst the aldehydes themselves are considered unstable in traditional senses, once the nine-membered enediyne cores are forged closed, all subsequent synthetic operations and characterization studies should be ideally performed within 16 hours, especially for kedarcidin-based chromophores. All reagents, methods and work-up operations need to be mild, streamlined and rapid in both chemical and practical senses. After considerable experimentation and refinement of reaction timings and bench skills, a 6-step sequence to **1** was eventually shown to be viable over a total time period of 12-hours (Scheme 12). This entailed the cyclisation of the enediyne-aldehydes **54**/**55** via the highly unstable *cis*-diol derivatives **58–63** and SmI_2-based reductive transformation into the equally unstable epoxy-dienediynes **64–69** (Table 1).



Scheme 12. Nine-membered enediyne cyclisation and end-game sequence to **1**.

Table 1. End-game olefination-deprotection sequence to kedarcidin chromophore (**1**).

Entry[a]	R^1, R^2, R^3, R^4	ΔHRMS[b]	t (TBAF / HF)[c]	**1**[d]
58→64	TES, H, TES, Ms	0.0015	10 / 2 min	nd
59→65	TBS, H, TES, Ms	nd	10 / 5 min	nd
60→66	TMS, H, TES, Ms	nd	10 / 2 min	nd
61→67	TBS, TES, TBS, Ms	0.0004[e]	10 / 5 min	nd
62→68	TMS, TMS, TES, Ms	0.0002	10 / 25 min	2%[f]
63→68	TMS, TMS, TES, TFBz	0.0001	10 / 20 min	3%[f]

[a] All entries were repeated twice; see Scheme 12 and Supporting Information for conditions of preparation. [b] Difference between calculated and found HRMS data for **64–69** after treatment of **58–66** with SmI_2 in THF at –20°C for 5–10 min. [c] Respective times of treatments with TBAF/o-nitrophenol and then HF-pyridine. [d] nd = not detected. [e] Cycloaromatized product from **67** had an HRMS difference of 0.005 after treatment with cyclohexa-1,4-diene in THF over 22 h. [f] Relative percentage of **1** to the major (100%) species observed by HRMS: 1030.3734 calculated for $[M+H]^+$ = $[C_{53}H_{61}ClN_3O_{16}]^+$, found 1030.3732 (from **62** *via* **68**) and 1030.3733 (from **63** *via* **68**).

334 Specifically, nine-membered epoxy-enediyne cyclizations of **54/55** using $CeCl_3$/LiHMDS to
335 give the C4→C5 *O*-migrated TMS products **56/57** necessitated careful quenching with
336 phosphate buffer (pH 7) at –78 °C. The resulting products **56/57** were treated with TBAF
337 carefully at –78 °C to remove the C5-*O*-TMS group. For the *cis*-C4,C5-diol mesylate
338 derivatives (**58–62**), desilylation was immediately followed by mesylate formation and then
339 esterification with *p*-trifluoromethybenzoyl (TfBz) chloride. The bis-OTMS, bis-OTfBz
340 substrate (**63**) was also prepared by omitting the mesylation step. This proved to be more time
341 economical, but **63** was found to be more unstable than its C5-OMs counterpart (**62**). It
342 should be noted that electron withdrawing C4,C5-diol substituents marginally reduce the
343 propensity of nine-membered cores from undergoing oxy-Cope like sigmatropic
344 rearrangments.[35,37] Nevertheless, all enediyne cores **58–62** remained highly unstable to all
345 silica gel chromotography techniques and all work-up operations. As a result, we were only
346 able to obtain high resolution mass spectroscopic (HRMS) data for all compounds in Scheme
347 12 (cf. Table 1).
348
349 Further discussion is necessary for these final olefination-deprotection studies. Thus, all
350 cyclized C4,C5-diol mesylate derivatives **58–63** were first subjected to reductive olefination
351 by SmI_2 at –20 °C to afford the fully-fledged epoxydienediynes **64–69** (Table 1).[38,56,57] After
352 HRMS data collection, these were immediately subjected to the established global
353 deptrotection conditions, namely, by brief exposure with TBAF/o-nitrophenol and then
354 exposure to HF-Et_3N over differing time scales (cf. Scheme 9). Whilst the TBS-protected
355 mesylate derivatives **59**/**60** conferred the greatest stabilities, these could not be transformed to
356 **1**. The protected and cycloaromatized forms of **1** were, however, detected by HRMS analysis
357 of **67** before and after treatment with cyclohexa-1,4-diene in THF (cf. Table 1). Interestingly,
358 the more successful derivatives **61**–**63** all featured bis-silyl ether protection on the mycarose
359 moiety. These derivatives all gave accurate HRMS data correlations after SmI_2 olefination to
360 **67–69**. We thus suspected complexation/activation issues from samarium(II/III)-salts, but
361 additives like pyridine and 2,6-lutidine during work-up procedures (prior to filtration through
362 Celite) did not improve the results. Ultimately, after exhaustive use of the advanced precursor
363 **50**, the bis-TMS ethers **62** or **63** gave an accurate match of the HRMS data patterns for **1**,
364 albeit in relatively low percentages. A viable total synthesis route to the kedarcidin
365 chromophore was thus identified for the first time in our laboratories.
366
367 **Conclusion**
368
369 Herein, we have disclosed our concerted efforts towards securing a total synthesis of the
370 latest revised structure of the kedarcidin chromophore **1** (cf. Scheme 1).[33,34] Initial
371 glycosylation studies demonstrated the poor reactivity of late-stage aglycon acceptors like **18**
372 and **19** (cf. Schemes 2 to 4). Consequently, pre-α-glycosylated fragments of the epoxy-
373 iodoalkene **33** and alkyne-orthester **44** were prepared on gram scales by reworking previously
374 developed chemistry (cf. Schemes 5 to 8).[34–38] These fragments were then assembled after
375 optimization of Sonogashira coupling,[58] Shiina macrolactonization,[55] and mixed-anhydride
376 amidation protocols.[45] These efforts eventually furnished the *ansa*-macrolide **50** as a storable
377 substrate that is fully-adorned with all the components of the kedarcidin chromophore (cf.
378 Scheme 10).
379
380 During latter enediyne cyclisation studies, our protecting group strategy was assessed for its
381 potential to succeed at the last step of the synthesis. This highlighted the need for either
382 mono-TES or bis-TMS ether protection of the 2-deoxysugar moieties (cf. Scheme 9). The
383 alkyne-aldehyde cyclization precursors **54**/**55** were thus prepared in appropriately protected

384 forms (cf. Scheme 11). The subsequent development of a streamlined cyclisation-
385 derivatisation-deprotection sequence to the fully-fledged, nine-membered enediyne proved to
386 be extraordinarily challenging on the bench (cf. Scheme 12). After exhaustive trials and
387 tribulations, the bis-OTMS ether **55** (freshly prepared from **50**) was first cyclized to **56**/**57**
388 under Ce(III)-amide mediation, then derivatized as its C4-*O*-trifluorobenzoate (TfBz) ester **62**
389 or **63**, deoxygenated by SmI_2 to its olefin **68**, and finally deprotected under buffered fluoride
390 conditions to afford the kedarcidin chromophore (**1**), as inferred by HRMS analysis (cf. Table
391 1).
392
393 To close this paper, we note that the early introduction of 2-deoxy-α-pyranosides as elaborate
394 THP protecting groups offered a convergent route to **1**. Accordingly, a viable total synthesis
395 strategy was founded in only 17-steps via the equally convergent synthesis of suitably
396 protected L-α-mycaroside (**33**) and L-α-kedarosaminide (**44**) fragments. This result is
397 meaningful for a target of this complexity and fragility, and was achieved in spite of the
398 additional challenges imposed by free hydroxyl/amino-groups and extra bulky/labile-
399 functionality. At the root of our tactical and evolutionary pursuit of this formidable natural
400 product were the development of several powerful, yet chemoselective methods. Over 20-
401 years since kedarcidin was isolated and first characterized,[24–30] several new synthetic organic
402 methods may now be highlighted, namely: Myers' anionic transannular cyclization,[33]
403 stereoselective epoxyalkyne formation,[34] atropselective Pd/Cu-Sonogashira coupling,[36–38] 2-
404 deoxy-α-glycosylation,[40,41] CeX_3-mediated enediyne cyclisation,[14] and SmI_2-based reductive
405 olefination.[56,57] Further application of some of these key methods to the synthesis of the
406 putative biomimetic enediyne-precursors of the fijiolides will be reported in due course.[21]
407
408 **Experimental Section**: see SI
409
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418
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