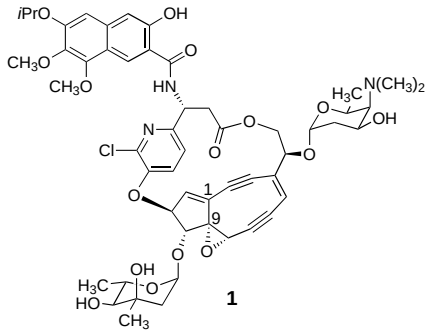
Enantioselective Synthesis of Kedarcidin Chromophore Aglycon in Differentially Protected Form**

Andrew G. Myers,* Philip C. Hogan, Alexander R. Hurd, and Steven D. Goldberg

Kedarcidin is a highly reactive and complex chromoprotein enediyne natural product with potent antiproliferative and antibiotic activities.[1] It is a member of the subset of enediyne antibiotics that includes neocarzinostatin,[2] C-1027,[3] macromomycin,[4] actinoxanthin,[5] and maduropeptin.[6] Each of these agents is composed of protein and small-molecule (chromophore) components, which form a 1:1 complex. The chromoprotein agents are thus distinguished from the nonproteinaceous (10-membered) cyclic enediyne agents (calicheamicin γ_1, esperamicin, and dynemicin A),[7] and further by the fact that their chromophoric components, when separated from the binding protein, are exceedingly unstable. Kedarcidin chromophore (**1**) has extremely limited



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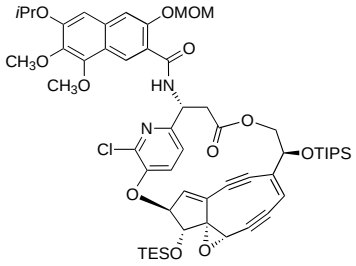
stability in solution and has been shown to undergo spontaneous cycloaromatization in the presence of sodium borohydride.[1d] These issues of reactivity, coupled with structural features such as the chloropyridine-containing ansa-bridge, the highly unusual epoxy bicyclo[7.3.0]dodecadienediyne core, and the appended naphthoic acid amide, kedarose, and mycarose substituents, contribute to make the synthesis of **1** a formidable challenge. In addition to our own efforts to develop a synthesis of **1**, the Hirama group has reported the synthesis of core models,[8a] an ansa-bridged macrolactone model,[8b] and subsequent glycosylation studies of this macrolactone model structure.[8c]

In a new strategy for the synthesis of the reactive core structures of the chromoprotein enediyne agents, we recently described the synthesis of a model compound that comprises the epoxy bicyclo[7.3.0]dodecadienediyne core functionality of **1**. This route targeted the C1–C9 fusion bond for disconnection and featured the transannular addition of a vinyllithium intermediate to an internal diacetylene group.[9] In theory, this approach was well suited for the synthesis of **1** itself, for it would allow for the assembly of the ansa-bridged macrocycle prior to the reactive core functionality, although the feasibility of the proposed anionic transannular addition reaction, within the context of a functionally more complex macrolactone structure, was uncertain. Here, we demonstrate that the transannular cyclization strategy is effective within an ansa-bridged macrolactone substrate and implement it successfully in the first enantioselective synthesis of kedarcidin chromophore aglycon, in differentially protected form (structure **2**; MOM = methoxymethyl, TIPS = triisopropylsilyl, TES = triethylsilyl).



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Our retrosynthetic analysis is outlined in Scheme 1. Final-stage operations for the synthesis of **2** were envisioned to involve C10 hydroxy group directed epoxidation of the C8–C9 olefin of the ansa-bridged bicyclo[7.3.0]dodecadienediyne **3**, selective protection of the C10 hydroxy group, and dehydration to form the C4–C5 olefin[9, 10] steps successfully executed within our earlier, albeit simpler model system. The substrate for these operations, compound **3**, was imagined to arise by cyclization of the bromide **4**, induced by lithium–halogen exchange. Although potentially complicated by deprotonation reactions (see below), as well as competing carbonyl addition reactions, we felt that the proposed lithium–halogen exchange/transannular addition held sufficient merit to pursue the development of a synthetic route to **4**. Further, three σ bonds within the precursor **4** were targeted for disconnection: the internal diacetylene linkage (C7–C8), the lactone C–O bond, and the bromoenyne linkage (C1–C2). These could reasonably be formed in any order (six different sequences); two were investigated here. Both sequences converged upon the intermediate **5** in a proposed Glaser reaction[11] to form the last of the three σ bonds targeted and thus to yield the macrobicycle **4**. The paths then diverged in the ordering of the remaining two σ bond forming steps, one involving macrocyclization by lactonization, and the other by Pd-catalyzed C–C bond formation to generate the macrolactone. Both sequences were initiated by the same three starting materials (**6**–**8**) and incorporated an acetonide protective group within the diacetylene intermediate **7** to position the hydroxymethyl and terminal alkyne substituents in an orientation favorable for macrocyclization. Disconnection of the pyridyl ether bond within the intermediate **6**

[*] Prof. A. G. Myers, P. C. Hogan, A. R. Hurd, S. D. Goldberg
Department of Chemistry and Chemical Biology
Harvard University
Cambridge, Massachusetts 02138 (USA)
Fax: (+1) 617-495-4976
E-mail: myers@chemistry.harvard.edu

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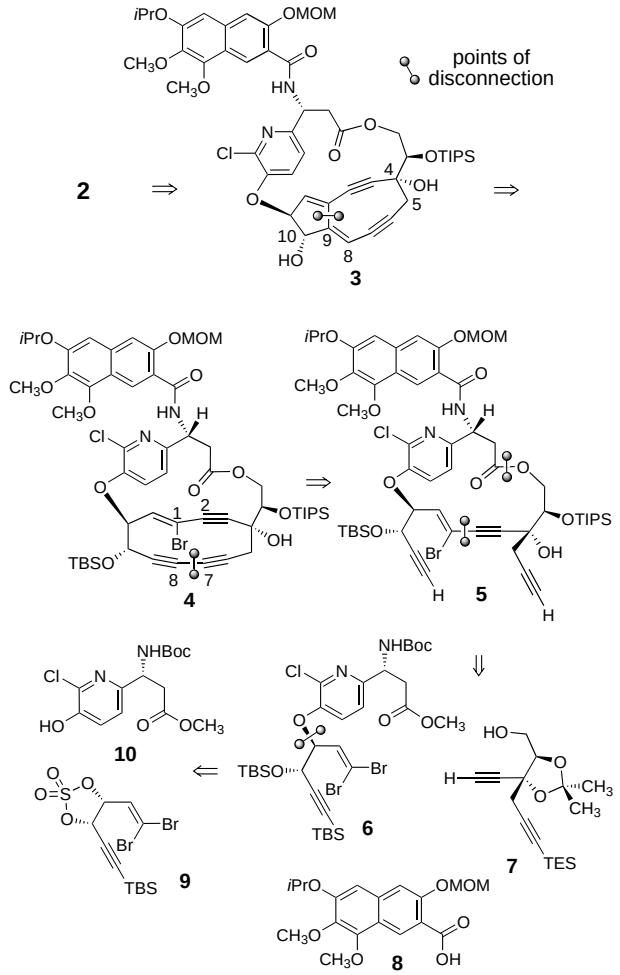
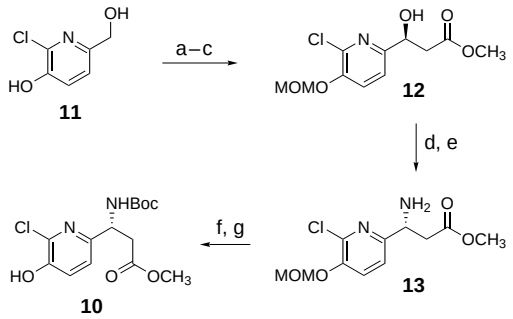


Scheme 1. Retrosynthetic analysis of **2**. TBS = *tert*-butyldimethylsilyl, Boc = *tert*-butoxycarbonyl.

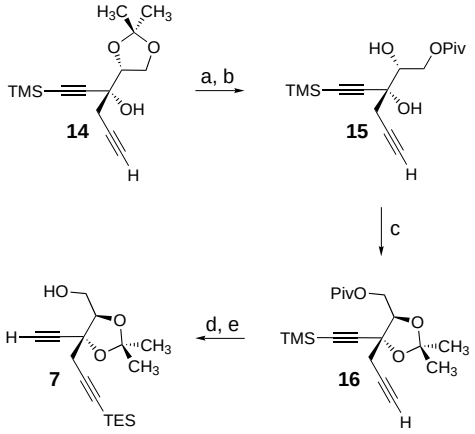
produced the two key fragments **9** and **10**. This was considered to be an advantageous feature of the approach, for it established the rather difficult pyridyl ether bond early in the sequence, rather than later, where stability issues would severely limit the options available for that transformation. Each of the four components (**7**–**10**) defined by this sequence of disconnections was prepared in multi-gram quantities. The naphthoic acid **8** was synthesized by protection of an intermediate from a prior route.[12] The cyclic sulfate **9** was also prepared by a prior route with D-erythronolactone as starting material.[9] The remaining components, **7** and **10**, were prepared in optically pure form, as follows.

The crystalline β-azatyrosine residue **10** was synthesized on a large scale by the highly practical and convenient Carreira–Singer aldol methodology[13] (>30 g in one reaction, **11**[14] →**12**, Scheme 2), adapted here for the synthesis of a β-amino acid by a subsequent Mitsunobu azidation reaction,[15] followed by Staudinger reduction (**12** →**13**).[16] The enantioselectivity of the asymmetric acetate aldol reaction was reproducibly high (92–94% *ee*); one recrystallization of the solid product provided optically pure material, in 90% yield. Hydrolysis of the methoxymethyl ether **13** and Boc protection of the amino group then afforded the desired β-azatyrosine fragment **10** for subsequent coupling.



Scheme 2. Synthesis of β-azatyrosine residue **10**. a) MOMCl (1.15 equiv), iPr$_2$NEt (3.0 equiv), CH_2Cl_2, 23 °C, 81%; b) oxalyl chloride (2.0 equiv), DMSO (4.0 equiv); Et_3N (9.0 equiv), CH_2Cl_2, −78 →0 °C, 92%; c) (*S*)-(−)-Carreira ligand (1.1 mol%), Ti(OiPr)$_4$ (0.5 mol%), 3,5-di-*tert*-butylsalicylic acid (1 mol%), methyl trimethylsilyl ketene acetal (2.0 equiv), 90%, 94% *ee*; d) PPh_3 (1.2 equiv), diethyl azodicarboxylate (1.2 equiv), hydrazoic acid in toluene (1.0 N, 1.2 equiv); e) PPh_3 (1.2 equiv), H_2O (10 equiv), 23 °C, 77%; f) 12 N HCl, methanol, 23 °C; g) di-*tert*-butyl dicarbonate (1.5 equiv), Et_3N (2.2 equiv), methanol, 23 °C, 88% (two steps).

The fragment **7** was prepared from the known intermediate **14**[17] by a five-step sequence, as shown in Scheme 3. Cleavage of the acetonide protective group and selective protection of



Scheme 3. Synthesis of alcohol **7**. a) 3 N HCl, MeOH, 23 °C 88%; b) pivaloyl chloride (1.13 equiv), pyridine, 23 °C, 87%; c) *p*-TsOH (0.2 equiv), 2,2-dimethoxypropane (10 equiv), DMF, 70 °C, 93%; d) LiHMDS (1.5 equiv), THF, −78 °C; TESCl (1.5 equiv), −78 →23 °C 92%; e) K_2CO_3 (2 equiv), MeOH, −10 °C, 18 h, 84%. TMS = trimethylsilyl, HMDS = bis(trimethylsilyl)amide.

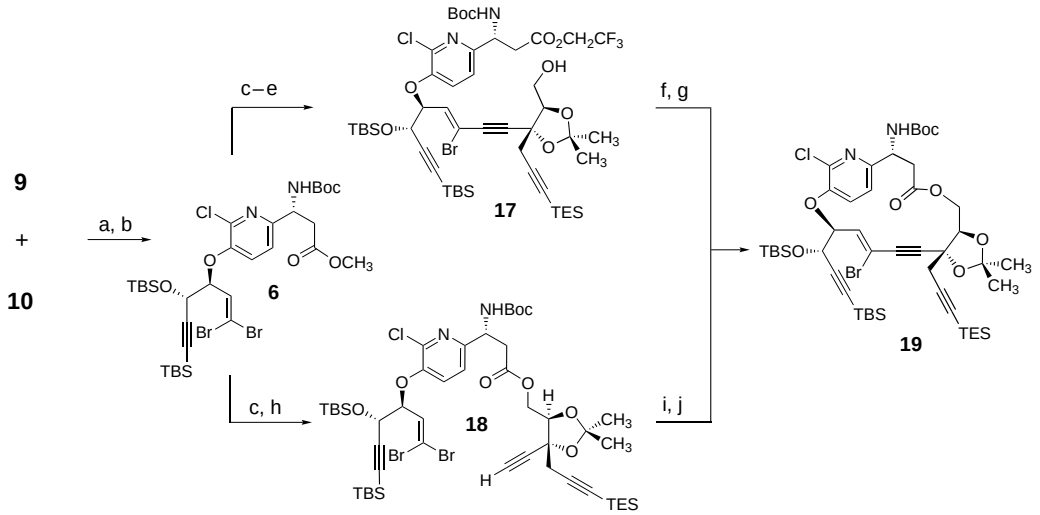
the primary hydroxy group of the resulting triol by pivaloylation provided the diol **15**. Reintroduction of an acetonide protective group, now to mask the secondary and tertiary hydroxy groups, was accomplished by using 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid in DMF at 70 °C to afford **16**. C-Deprotonation of **16** with lithium bis(trimethylsilyl)amide and trapping of the resultant acetylide anion with chlorotriethylsilane gave the corresponding differentially silylated dialkyne. Selective cleavage of the pivaloate and trimethylsilylalkyne groups then occurred upon exposure to potassium carbonate in methanol at −10 °C to produce **7** in 55% yield (over 5 steps). This sequence served to transfer the acetonide group of **14** to the contrathermodynamic position it occupies in **7**, as well as to transfer the location of the

acetylenic (silyl) protective group, necessary to allow the desired sequence of C–C bond-forming reactions.

In the first fragment-assembly step the β-azatyrosine residue **10** was coupled with the cyclic sulfate **9** to form, after sulfate hydrolysis and hydroxy protection, the pyridyl ether **6** (Scheme 4).[9] Thus, addition of **9** to the potassium phenolate derived from **10** led to smooth and selective cleavage of the allylic sulfate ester bond (regioselectivity 9:1). Sulfate ester hydrolysis[18] and subsequent protection of the resultant secondary alcohol with *tert*-butyldimethylsilyl chloride[19] then afforded **6**. An apparent kinetic effect operated in the silylation reaction which served to further enrich the mixture in the desired allylic pyridyl ether regioisomer (**6**, selectivity $\sim$20:1). The overall coupling sequence was quite efficient (73% from **9**) and routinely provided **6** in amounts of 5–15 g.

The pyridyl ether **6** served as a common point of departure for two different sequences to the macrolactone **19** (Scheme 4). The first employed a more traditional macrolactonization reaction. For this sequence, it proved necessary to transform the methyl ester **6** into the corresponding trifluoroethyl ester prior to Pd-mediated coupling (see upper pathway). Sonogashira coupling of the resultant trifluoroethyl ester with the terminal alkyne of **7** then proceeded with selective replacement of the *trans*-bromide to furnish the bromoolefin **17** in 50–60% yield.[20] Bis-coupling in this reaction was a problem that, despite many efforts, was never completely suppressed. Saponification of the trifluoroethyl ester **17** (the corresponding methyl ester underwent competitive dehydrobromination) with lithium hydroperoxide cleanly afforded the corresponding hydroxy acid, which was readily cyclized by using modified Yamaguchi conditions[21] at high dilution (ca. 0.5 mM) to form **19** in 70% yield (efforts to cyclize **17** directly were not successful).

In an alternative and preferred sequence, ester bond formation between **6** and **7** was accomplished first, and macrocyclization was achieved in a subsequent Pd-mediated process, after a particularly useful and efficient in situ *C*-stannylation reaction (lower pathway, Scheme 4). Hydrolysis of the methyl ester **6** and activation of the resultant carboxylic acid allowed for smooth coupling with the primary hydroxy group of **7** to afford ester **18** in 87% yield (2 steps). Initially, we sought to close the macrocyclic ring by direct Pd-mediated C–C bond formation within **18** (Castro–Stephens–Sonogashira coupling). Although the desired macrolactone (**19**) could be obtained in this way, yields were low ($<$40%) and difficult to reproduce. Considering it likely that metalation of the hindered terminal alkyne of **18** was problematic in the coupling reaction, we investigated ways to activate this group prior to cyclization. Stannylation with the reagent diethylaminotrimethylstannane (caution! toxic), introduced by Lappert et al.[22] and used by Stille[23] in his initial coupling studies, proved extraordinarily successful within the multifunctional substrate **18**. Significantly, we found that the reaction could be modified by the use of toluene as solvent (as opposed to the use of neat diethylaminotrimethylstannane), and was rapid at ambient temperature with a moderate excess of reagent (3.0 equiv, $\approx$0.1 M). Concentration of the reaction solution removed volatile by-products as well as excess reagent. Neither the alkynyl C–H nor the amido proton resonance was detected in ^{1}H NMR analysis of the residue. Sequential addition of ethyl ether, $[Pd_2(dba)_3]$, and tri-2-furylphosphane[23c] to the concentrated stannylation product then led to smooth formation of the macrolactone **19** within 12 h at 23 °C (68% yield from **18**). A noteworthy feature of this cyclization reaction was the fact that high dilution conditions were not necessary to obtain good yields of **19**, making this the method of choice for the production of **19**. We have found that the procedure described for the in situ stannylation of **18** is also effective by using other, structurally diverse terminal alkynes as substrates, and that it is tolerant of a range of functional groups (ester, amide, halide, and epoxide functional groups, among others). We recommend it as a convenient alternative to lithiation/stannyl halide trapping procedures. The products of both coupling–macrocyclization sequences (**19**, Scheme 4) were shown to be indistinguishable by ^{1}H NMR analysis.[24] Parenthetically, we note that the acetonide protective group



Scheme 4. Synthesis of macrolactone **19**. a) **10** (1.2 equiv), KHMDS (1.1 equiv), CH_3CN, -40 °C; **9** (1.0 equiv), CH_3CN, -40 °C, 88%; b) TBSCl (1.5 equiv), Im (6.0 equiv), DMF, 23 °C, 83%; c) LiOH (2.0 equiv), 30% aqueous H_2O_2/THF (1:3), 23 °C, 20 h; Na_2SO_3; d) trifluoroethanol (5.0 equiv), EDC·HCl (1.5 equiv), DMAP (0.1 equiv), CH_2Cl_2, 23 °C, 86% (2 steps); e) **8**, (1.22 equiv), $[Pd(PPh_3)_4]$ (0.1 equiv), CuI (0.32 equiv), Et_3N (2.2 equiv), *tert*-butyl methyl ether, 23 °C, 61%; f) LiOH (2.0 equiv), 30% aqueous H_2O_2/THF (1:3), 23 °C, 30 min; g) 2,4,6-Trichlorobenzoyl chloride (20 equiv), DMAP (10 equiv), Et_3N (20 equiv), toluene, 50 °C, 70% (two steps); h) **7** (1.05 equiv), EDC·HCl (2.4 equiv), DMAP (0.1 equiv), CH_2Cl_2, 23 °C, 87% (2 steps); i) $Et_2NSn(CH_3)_3$ (3.0 equiv), toluene, 23 °C; j) $[Pd_2(dba)_3]$ (0.1 equiv), tri-2-furylphosphane (0.8 equiv), Et_2O, 23 °C, 68% (2 steps). Im = imidazole, dba = dibenzylideneacetone, EDC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide, DMAP = 4-dimethylaminopyridine.

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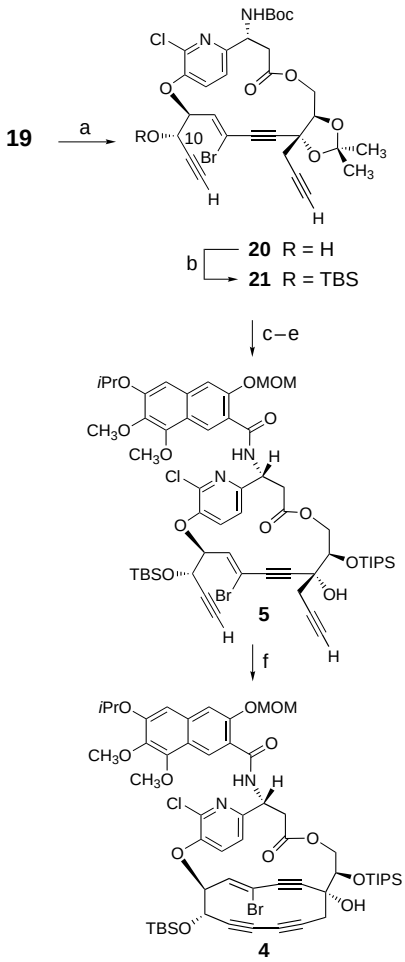
within **17** and **18** was critical to the success of both macrocyclization reactions; presumably it serves as a preorganizing element that favors ring closure. Substrates with alternative noncyclic protective groups cyclized more slowly, and in lower yield.

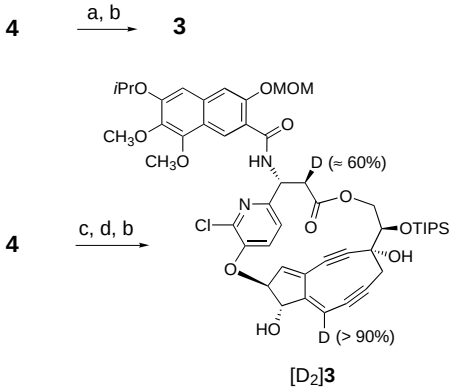
With ready access to gram-quantities of the macrolactone intermediate **19**, efforts turned toward the introduction of the naphthoamide residue, and protective group manipulations necessary to allow for Glaser cyclization to form the transannular cyclization precursor **4** (Scheme 5). Toward this end,



Scheme 5. Glaser cyclization to prepare the transannular cyclization precursor **4**. a) TBAF (4.5 equiv), *o*-nitrophenol (5.0 equiv), THF, 23 °C, 98 %; b) TBSCl (2.0 equiv), Im (6.0 equiv), DMF, 23 °C, 97 %; c) 33 % TFA/CH_2Cl_2, H_2O (2.0 equiv), 23 °C; d) **7** (1.3 equiv), EDC·HCl (3.0 equiv), HOBT (1.0 equiv), Et_3N, CH_2Cl_2, 23 °C, 12 h, 81 % (2 steps); e) TIPSOTf (5.0 equiv), Et_3N (15.0 equiv), CH_2Cl_2, −65 °C, 81 %; f) $Cu(OAc)_2$ (60.0 equiv), CuI (15.0 equiv), pyridine, THF, 45 °C, 65 %. TBAF = tetrabutylammonium fluoride, HOBT = 1-hydroxybenzotriazole.

the macrolactone **19** was globally desilylated by using *o*-nitrophenol-buffered tetrabutylammonium fluoride in THF (98 % yield)[9] to provide the crystalline derivative **20**, whose structure was secured by single crystal X-ray analysis.[24] After reintroduction of the TBS ether that had been cleaved in the prior step (→**21**),[19, 24] the *tert*-butyl carbamate and acetonide groups were removed selectively by exposure of **21** to a solution of 33 % trifluoroacetic acid in dichloromethane. Concentration afforded the trifluoroacetate salt, which was treated with a solution of the naphthoic acid **8**, previously activated for coupling (EDC·HCl, HOBT), to form the corresponding naphthoic acid amide derivative in 81 % yield for the two-step sequence. Selective silyl protection of the C13 secondary hydroxy group then served to fully differentiate each hydroxy group in the molecule (→**5**, 81 %).[24]

At this point a second macrocyclization reaction was achieved by employing carefully optimized, modified Eglinton conditions[26] to afford the macrobicyclic product **4** (Scheme 5).[24] Thus, slow addition of a solution of the macrolactone **5** in pyridine/THF (2:1) to a prewarmed (45 °C) suspension of copper(II) acetate and copper(I) iodide in pyridine/THF (2:1) produced the transannular cyclization substrate **4** in 63 % yield.[24] This product proved to be exceedingly unstable when concentrated and, in this regard, was the most unstable intermediate in the entire synthetic sequence.[27] Although **4** could be stored as a dilute solution in toluene (−20 °C), typically, this was not done; rather, **4** was subjected to direct metalation–transannular cyclization (Scheme 6).



Scheme 6. Transannular cyclization and deuterium labeling. a) LiHMDS (3.5 equiv), THF, toluene, −96 °C, *t*BuLi (1.7 M, 5.0 equiv); HOAc/THF (1:10), 45–60 %; b) $Et_3N \cdot 3HF$ (75 equiv), CH_3CN, 23 °C, 75 %; c) CD_3OD, 23 °C; d) LiHMDS (3.5 equiv), THF, toluene, −96 °C, *t*BuLi (1.7 M, 5.0 equiv); [D_4]acetic acid/THF (1:3).

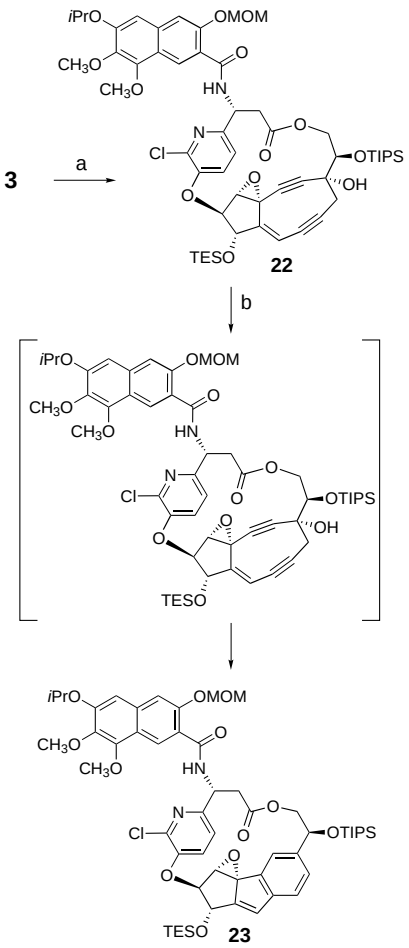
Lithium–halogen exchange within the intermediate **4** was potentially complicated by at least three competing proton-transfer events (from the secondary amide, the tertiary hydroxy group, and the α-position of the lactone). In the optimized procedure for transannular cyclization (Scheme 6), these competing processes were mitigated by prior treatment of **4** with a solution of LiHMDS in THF. After 5 min, a solution of *tert*-butyllithium in pentane was added, followed immediately (<3 s) by a quenching solution of acetic acid in THF. After cleavage of the secondary TBS ether with triethylamine trihydrofluoride and purification by flash column chromatography, the transannular cyclization product **3** was obtained, reproducibly, in 38–45 % yield.[28] Some insight into the mechanistic details of this process was gained by conducting a deuterium labeling experiment (Scheme 6). Treatment of **4** with [D_4]methanol followed by concentration from toluene (to remove methanol), dilution with THF, and sequential addition at −96 °C of solutions of LiHMDS

(3.5 equiv in THF), *tert*-butyllithium (5.0 equiv in pentanes), and [D_4]acetic acid/THF (1:3) gave rise to the isotopically labeled transannular cyclization product [D_2]-**3**, after cleavage of the TBS ether, as before. ^{1}H NMR analysis showed that deuterium incorporation at C8 was virtually quantitative. Interestingly, stereoselective incorporation of deuterium at the α-position of the lactone had also occurred, albeit to a lesser degree ($\approx$60%, stereochemistry assigned tentatively as shown on the basis of ^{1}H,^{1}H NMR coupling constants). From this result, it is reasonable to conclude that transannular cyclization of **4** had proceeded through a polyanionic intermediate, perhaps even a tetraanion.

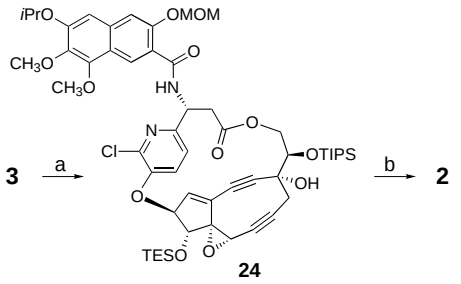
All that remained to complete the synthesis of **2** was the sequence of final stage operations initially outlined (see above; Scheme 2). However, at this point we encountered a serious problem when V-catalyzed hydroxy group directed epoxidation of **3** was found to provide the C1–C12 epoxide **22**[24] (after selective triethylsilylation of the C10 hydroxy group), and not the desired C8–C9 epoxide (Scheme 7). This stood in contrast to our earlier findings in a model system lacking the ansa bridge, and was felt to reflect a less optimal dihedral angle for the V-catalyzed process (dihedral angles of allylic alcohol estimated to be 75° in **3** and 60° in the model structure). It proved to be nontrivial to distinguish **22** from the desired epoxide **24** spectroscopically; definitive assignment of **22** was achieved in two ways. First, dehydration of the C4 tertiary hydroxy group (Martin sulfurane,[29] benzene-1,4-cyclohexadiene (1:1)) provided the cycloaromatized elimination product **23**;[28] its enediyne precursor was not observable. ^{1}H NMR analysis of **23** was consistent only with the assigned structure, and not the cycloaromatized product that would have arisen from **2**. A more definitive structural assignment was made by epoxidation/triethylsilylation of [8-D]-**3**. ^{1}H NMR analysis of the resultant epoxide ([8-D]-**22**) showed no vinyl proton resonance which conclusively established that epoxidation had occurred at C1–C12 of **3**. A wide range of alternative epoxidizing reagents was screened; however, most of these led to decomposition of the substrate. Notably, Jacobsen's [Mn^{III}(*R*,*R*)-(salen)] catalyst,[30] Yamamoto's asymmetric vanadium catalyst,[31] and dibutyltin oxide-*tert*-butylhydroperoxide[32] each formed the undesired epoxide **22** as the only isolable product.

Further investigation revealed that the desired epoxide **24**[24] was formed in preference to **22** when more hindered hydroperoxides were used in the V-catalyzed process. Both triphenylmethyl hydroperoxide[33] and 1,1-diphenylethyl hydroperoxide[34] gave the desired epoxide (**24**), with only a trace of **22** (Scheme 8). The use of 1,1-diphenylethyl hydroperoxide led to an increased rate of reaction, and an improved yield (32% vs. 20%, after in situ silylation), and was therefore preferred.[35] With the desired epoxide **24** in hand, completion of the synthesis of **2** was achieved by dehydration in the presence of the Martin sulfurane. Synthetic **2** provided spectral data in complete accord with the assigned structure.[24] In addition, cycloaromatization of **2**[25] in the presence 1,4-cyclohexadiene produced the expected aromatic product[28] which further confirms the assignment of **2**.

In conclusion, we have developed a convergent, enantioselective synthetic route to kedarcidin chromophore aglycon in differentially protected form (**2**). The route is 25 steps in the longest linear sequence, with an average yield of 82% per step (overall yield 1%).



Scheme 7. Epoxidation of **3** to form the undesired epoxide **22**; dehydration and cycloaromatization. a) [VO(acac)$_2$] (0.2 equiv), *t*BuOOH (20 equiv), benzene, 23 °C; TESCl (50 equiv), Im (100 equiv), CH_2Cl_2, 23 °C; b) Martin sulfurane (10 equiv), benzene-1,4-cyclohexadiene (1:1), 23 °C, 10% (four steps). acac = acetyl acetonate.



Scheme 8. Epoxidation of **3** to afford the desired epoxide **24** and subsequent dehydration to form **2**. a) [VO(acac)$_2$] (0.2 equiv), CH_3CPh_2OOH (1.3 equiv), benzene, 23 °C; TESCl (50 equiv), Im (100 equiv), CH_2Cl_2, 23 °C, 32%; b) Martin sulfurane (10 equiv), benzene, 23 °C, 83%.

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