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Kedarcidin Chromophore: Synthesis of Its Proposed Structure and Evidence for a Stereochemical Revision

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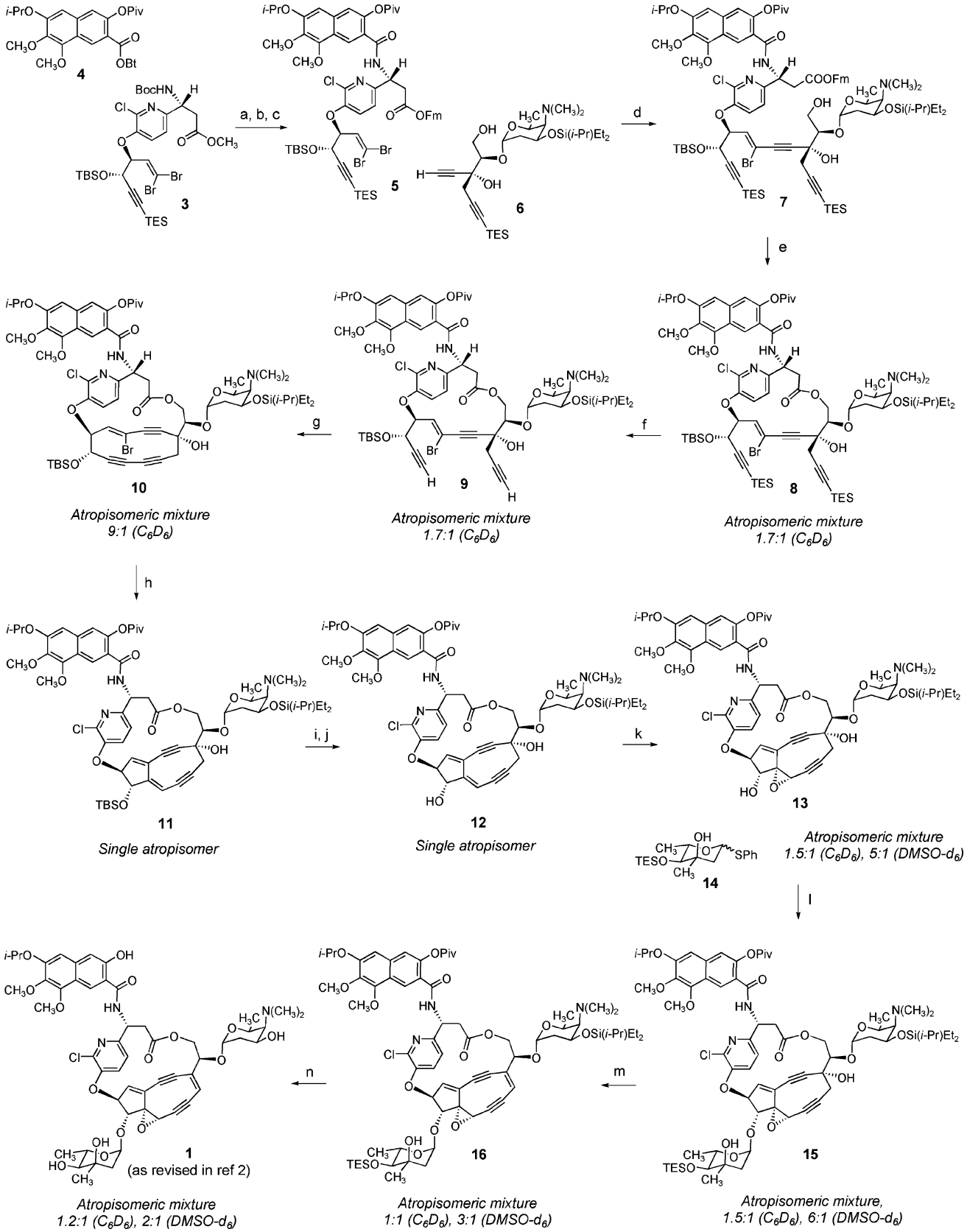
The structure of the chromophore component of the cytotoxic protein−chromophore complex kedarcidin was determined by researchers at BMS in 1992 on the basis of an extensive spectroscopic analysis of the isolated chromophore and its degradation products, an undertaking that was greatly complicated by the reactivity of the chromophore and its low natural abundance.[1] The original structural proposal was modified (as **1**, Scheme 1 and Figure 1) by Hirama and co-workers in 1997, thereby transforming the originally proposed α-azatyrosyl residue of the ansa-bridge to the corresponding *β*-amino acid derivative and reversing the handedness of the molecule.[2] Here, we describe an unambiguous, enantioselective synthesis of structure **1**. Our spectroscopic data show that the structure of kedarcidin chromophore must be further revised, we suggest by epimerization of the mycarose-bearing carbon, C10 (structure **2**, Figure 1, see below).

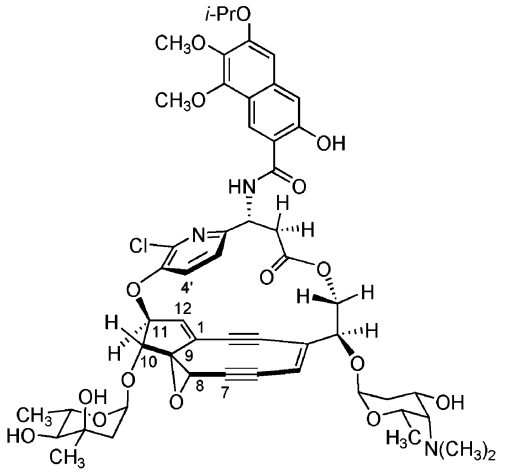
We synthesized structure **1** using a highly convergent route (Scheme 1). The sequence was initiated with the azatyrosyl dibromide **3** as starting material (>95% ee), prepared by extension of our published route to the corresponding *tert*-butyldimethylsilyl (TBS)-alkynyl derivative[3] using a different, auxiliary-based route to the *β*-amino acid component[4] (see Supporting Information; use of the triethylsilyl (TES)-alkynyl group within **3** is a refinement that allows for a simultaneous deprotection reaction later, **8**→**9**, vide infra). The methyl ester group of **3** was transformed into the corresponding 9-fluorenylmethyl (Fm) ester[5] by saponification with lithium hydroperoxide and esterification of the resulting carboxylic acid with 9-fluorenemethanol using 2-methyl-6-nitrobenzoic anhydride as an activating agent (93%, two steps).[6] Cleavage of the *N*-*tert*-butoxycarbonyl (BOC) protective group with trimethylsilyl triflate-2,6-lutidine[7] and, in the same flask, addition of saturated aqueous sodium bicarbonate solution and a solution of the pivaloyl-protected, hydroxybenzotriazole-activated 2-naphthoic acid derivative **4**[8] in dichloromethane afforded the coupled product **5** in 97% yield (22-g scale). Selection of the pivaloyl group to protect the naphthol group in the latter step allowed for a mild, fluoride-based deprotection reaction in the final step of the sequence (vide infra). Sonogashira coupling of the dibromoolefin **5** with the α-kedarosylated dialkyne component **6**[9] formed the *cis*-bromoolefin **7** in 50−60% yield.[10] Although the stereoisomeric *trans*-coupling product was never observed, the (chromatographically separable) bis-coupling product was detected as a side product, one whose formation was never completely suppressed. Selective cleavage of the Fm ester in the presence of the pivaloate ester within **7** (Et_3N, THF) cleanly afforded the corresponding carboxylic acid, which was cyclized using the Shiina macrolactonization protocol[11] to provide the macrolactone **8** (atropisomeric mixture; see Scheme 1 for details concerning the conformations of this and subsequent macrocyclic intermediates). The macrolactonization reaction could be performed on the gram-scale without diminishing its yield (66%). Both TES-alkynyl protective groups of **8** were selectively cleaved in the presence of the two silyl ethers by the Hirama procedure ($AgNO_3$, H_2O, THF),[12] providing the substrate for intramolecular oxidative acetylenic coupling (**9**, 73% yield). At this point, a second macrocyclization reaction was performed employing modified Eglinton conditions ($Cu(OAc)_2$, CuI, THF, pyridine),[3,13] producing the macrobicyclic intermediate **10**. The latter product was found to be extremely unstable and, for this reason, was directly subjected to transannular cyclization (**10**→**11**).[14] Thus, sequential treatment of a solution of the macrobicyclic vinyl bromide **10** in THF/toluene (1:1, prestirred at 23 °C with 4 Å MS for 15 min prior to cooling to −78 °C) with LHMDS (1.0 M in THF, 6.0 equiv) then, after 2 min, with a solution of *t*-BuLi in pentane (1.7 M, 8.0 equiv) and immediately thereafter (<5 s) with a quenching solution of acetic acid in THF (1:3, 50 equiv), all at −78 °C, afforded the tricyclic kedarcidin core structure **11** in 50% yield.[3] The TBS ether group of **11** was selectively removed in the presence of the diethyl-*iso*-propylsilyl ether of the kedarose sugar using *o*-nitrophenol-buffered tetra-*N*-butylammonium fluoride (TBAF);[3a] this simultaneously cleaved the pivaloate ester, which was re-introduced (75%, two steps **11**→**12**). Vanadium-directed epoxidation[15] of the resulting allylic alcohol **12** was successful only with the hindered oxygen atom source 1,1-diphenylethyl hydroperoxide,[16] and afforded the epoxy alcohol **13** (28% yield) as well as recovered starting material (**12**, 30%). The position- and stereoselectivity of the epoxidation reaction as well as the conformation of the ansa-bridge were unambiguously established by several reinforcing NOE measurements within **13**, as well as by chemical shift and coupling constant based arguments (see Supporting Information). An α-glycosidic linkage was readily formed between **13** and the thioglycoside donor **14** (a mixture of anomers) using $AgPF_6$ (2.5 equiv) as activator in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 3.5 equiv),[17] methodology previously developed by the Hirama group in their studies directed toward a synthesis of **1**.[18]

The α-mycarosylated product **15** was formed in 59% yield; approximately 15% of the starting material (**13**) was also recovered. Completion of the synthesis of **1** was achieved by dehydration of **15** using the Martin sulfurane in benzene (65% yield), followed by global deprotection of the dehydration product **16** (TBAF, *o*-nitrophenol, CH_3CN;[3a] then $Et_3N{\cdot}3HF$, 50% yield). Synthetic **1** provided spectroscopic data in complete accord with the proposed structure, as did its cycloaromatization product (formed in the presence of 1,4-cyclohexadiene at 23 °C, 12 h, ∼50% yield), but our ^1H NMR measurements differed substantially from those reported for the natural product.[1] After rigorous reevaluation of our synthetic process, in which we reconfirmed all stereochemistry and each reaction outcome, as reported herein,[19] we were led to carefully reconsider the original spectroscopic data for kedarcidin chromophore, leading us to identify inconsistencies between these data and both the original and the revised (**1**) structural assignments.[1,2] In particular, the observation of a nonzero coupling between protons bound to C10 and C11 (3.1 Hz in DMSO-d_6), the lack of an NOE between the pyridyl C4′ proton and H10, and the

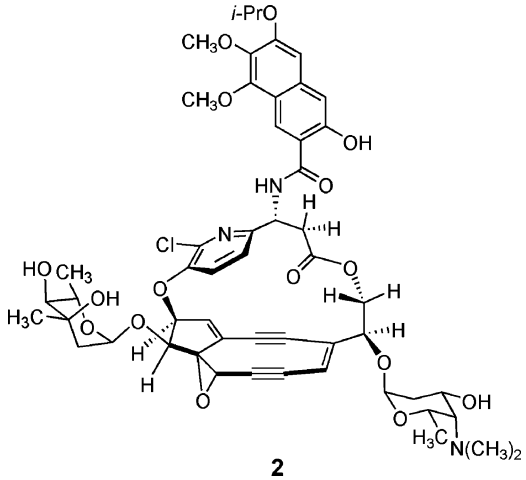
Scheme 1 [a]



[a] Conditions: (a) **3**, LiOH, H_2O_2, THF, H_2O, 23 °C; (b) 9-fluorenemethanol (FmOH), 2-methyl-6-nitrobenzoic anhydride (MNBA), DMAP, CH_2Cl_2, 23 °C, 93% (two steps); (c) TMSOTf, 2,6-lutidine, CH_2Cl_2, 23 °C; then $NaHCO_3$, **4**, 97%; (d) **6**, $Pd(PPh_3)_4$, CuI, Et_3N, Et_2O, 23 °C, 61%; (e) Et_3N, THF; MNBA, DMAP, benzene, 23 °C, 66%; (f) $AgNO_3$, THF, H_2O, 23 °C; 2,6-lutidine, 73%; (g) $Cu(OAc)_2$, CuI, pyridine, THF, 60 °C, 59%; (h) LHMDS, THF, toluene, −78 °C; *t*-BuLi; HOAc, 52%; (i) TBAF, *o*-nitrophenol, THF, 23 °C; (j) PivCl, Et_3N, CH_2Cl_2, 23 °C, 76%; (k) $CH_3C(Ph)_2OOH$, $VO(acac)_2$, benzene, 23 °C, 28%; (l) $AgPF_6$, DTBMP, **14**, CH_2Cl_2, 0 °C; pyridine, 59%; (m) Martin sulfurane, benzene, 23 °C, 65%; (n) TBAF, *o*-nitrophenol, CH_3CN, 23 °C; then $Et_3N{\cdot}3HF$, 50%.



1



2

Figure 1. Previous (**1**, ref 2) and current (**2**) structural revisions of kedarcidin chromophore.

observation of an NOE between H10 and H12b in the product of borohydride-induced cycloaromatization of kedarcidin chromophore[1] (derived from hydride addition to C12) suggested that the stereochemistry of C10 may have been misassigned (in synthetic **1**, H10 appears as a sharp singlet in C_6D_6 and as a slightly broadened singlet in DMSO-d_6). On enquiry (Dr. John Leet, BMS), we have learned that the observed coupling between protons bound to C10 and C11 of authentic kedarcidin chromophore in $CDCl_3$ (not previously reported) is 5.4 Hz, which aligns perfectly with reported values for several (cis-oriented) like compounds in the literature.[20] The revised structure we propose (**2**, Figure 1) is consistent with all reported NOE, chemical shift, and coupling constant values. Further, it explains the observations that natural kedarcidin chromophore is a single atropisomer, whereas the trans-oriented molecule we synthesized (**1**) is a mixture of atropisomers, in two different NMR solvents (see Scheme 1). Presumably, kedarcidin chromophore (**2**, as proposed herein) cannot exist in the atropisomeric form that positions the chlorine atom toward the C10-mycarosyl substituent.

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Supporting Information Available: Detailed experimental procedures and tabulated spectroscopic data (^{1}H and ^{13}C NMR, FT-IR, and MS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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