Rietveld method (GSAS)[10] on both X-ray and neutron diffraction data ($Rp = 0.058$, $Rwp = 0.084$). $La_2Ca_2MnO_7$ crystallizes in the space group $R\bar{3}$ (no. 148), $Z = 3$, with the lattice constants $a = 5.62176(4)$, $c = 17.3161(2)$, $V = 473.968(7)$. The refined atomic coordinates are Mn1: (3a) 0, 0, 0; La1: (6c) 0, 0, 0.37757(3); Ca1: (6c) 0, 0, 0.82745(7); O1: (18f) 0.0148(4), 0.502(3), 0.6024(1); O2: (18f) 0, 0.128(1), 0.5. The refined x and z values of the O2 position were $x = -0.026(15)$ and $z = 0.499(3)$, which are very close to 0 and ½, they were therefore fixed to improve the displacement parameters. The occupation factor of O2 was refined and fixed to ⅙ in the final refinement. The refinement also indicates mutual replacement of La and Ca atoms at the La1 and Ca1 positions, and the ratio was refined and fixed to La1: La/Ca = 0.933/0.077 and Ca1: Ca/La = 0.933/0.077 in the final refinement.

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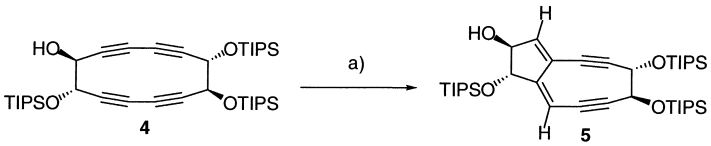
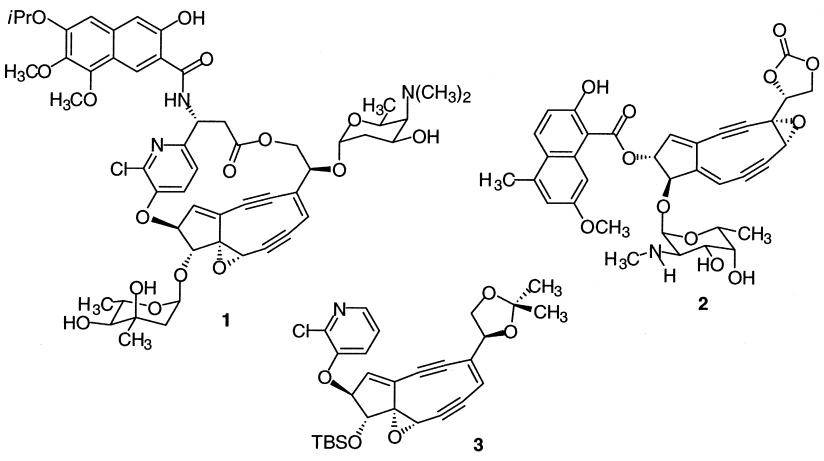
Synthesis of the Kedarcidin Core Structure by a Transannular Cyclization Pathway**

Andrew G. Myers* and Steven D. Goldberg

Kedarcidin is a chromoprotein enediyne antibiotic that is marked by the structural complexity and extraordinary reactivity of its chromophore component (**1**).[1] Like the related chromoprotein natural product neocarzinostatin,[1, 2] kedarcidin exhibits potent antitumor activity. The kedarcidin chromophore (**1**) and neocarzinostatin chromophore (**2**) share a common bicyclic carbon skeleton, but the site of epoxidation in the two structures is different (Scheme 1). As a result of this difference **1**, which contains a conjugated (*Z*)-enediyne group, is capable of cycloaromatization upon mild thermal activation alone (facile at 37 °C), whereas **2** requires nucleophilic activation for biradical formation.[2, 3] The reactivity of compound **1** and also its many unusual structural features—a highly unsaturated and strained core, bridging macrolactone, 2-chloro-3-pyridyl ether, and β-amino ester functionalities, as well as uncommon carbohydrate residues—make it an exceedingly challenging synthetic problem. Outstanding progress toward this goal has been achieved in Hirama's laboratory, including the preparation of a functional core model.[4] Recently, we described a new strategic approach to the synthesis of the common bicyclic carbon skeleton of **1** and **2** that featured the reductive transannular cyclization of a tetrayne precursor promoted by hydride addition (**4** → **5**, Scheme 2).[5] Unresolved issues regarding the adaptation of this approach to the synthesis of the kedarcidin core structure were the compatibility of the hydride reagent with a more highly functionalized substrate that would be suitable for the synthesis of **1**, the problem of regio- and stereoselective epoxidation of the diene product, and the introduction of the central olefin of the (*Z*)-enediyne group. These problems have been addressed, as described herein, within the context of an enantioselective synthesis of the kedarcidin core structure **3** (Scheme 1).



Scheme 2. Reductive transannular cyclization of the tetrayne **4**. a) KHMDS, $NaAlH(OCH_2CH_2N(CH_3)_2)_3$, THF, −78 °C, 50–54 %.[5]



Scheme 1. The structures of kedarcidin chromophore (**1**), neocarzinostatin chromophore (**2**), and the synthetic kedarcidin core structure **3**.

The prior reductive cyclization (**4** → **5**) was problematic with regard to a synthesis of **1** from two standpoints: (1) the requirement for a free propargylic hydroxyl group to direct the hydride addition meant that introduction of the pyridyl ether of **1** must occur after formation of the reactive core, and (2), as discussed, functional group compatibility was limited by the strongly reducing hydride reagent. To address these problems we considered an alternative strategy for the generation of the vinyl–metal intermediate believed to mediate the transannular ring closure, one involving low-temperature lithium–halogen exchange within a vinyl halide precursor such as the bromide **6**. To test this hypothesis, precursor **6** was synthesized, using as starting materials the dibromoolefin **7** and the diyne **8**,[6] two optically pure components of similar size and complexity (Scheme 3).

The enantioselective synthesis of the dibromoolefin **7**, a molecule with a latent C_2-symmetry axis, evolved from the exploration of several different synthetic routes, and ulti-

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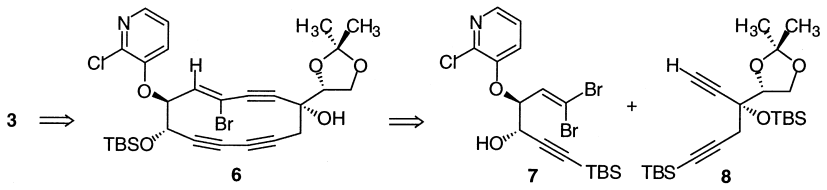
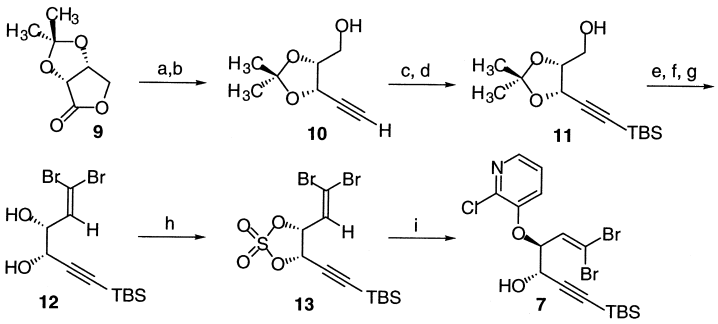


Scheme 3. Retrosynthetic analysis of **3**.

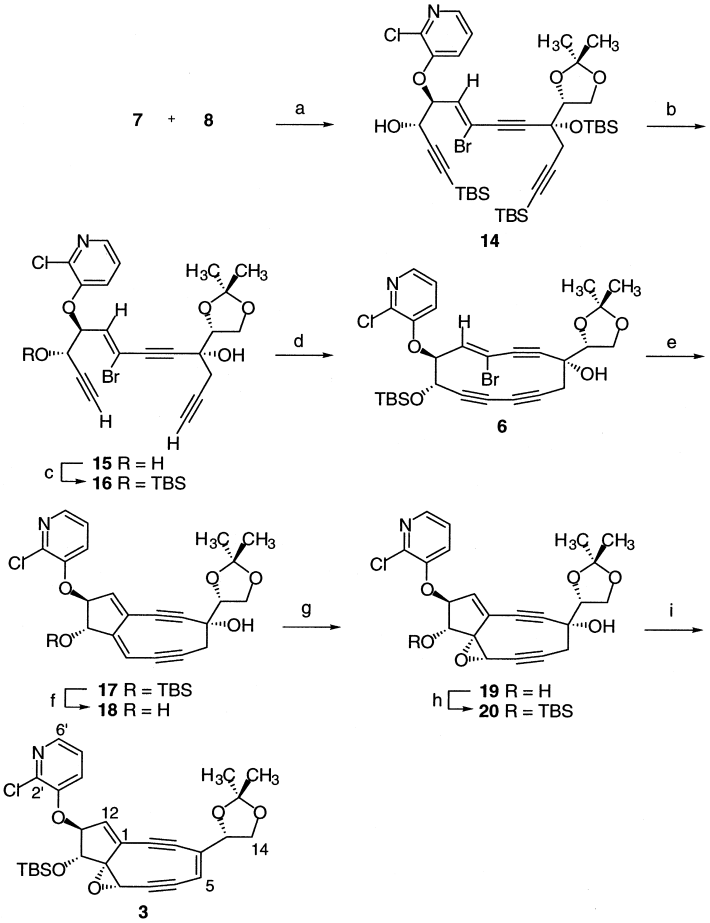
mately relied upon a subtle difference in the reactivity of the allylic and propargylic C–O bonds of the cyclic sulfate **13**, which was prepared using 2,3-*O*-isopropylidene-D-erythronolactone (**9**) as starting material (Scheme 4). A useful new



Scheme 4. Synthesis of the dibromide **7**. a) DIBAL (1.15 equiv), toluene, −78 °C, 96 %; b) LDA (2.4 equiv), $TMSCHN_2$ (1.2 equiv) THF, −78 →23 °C, 81 %; c) [LHMDS (1.25 equiv); TBSOTf (1.25 equiv)] × 2, THF, −78 °C; d) $Et_3N \cdot 3HF$ (2.5 equiv), THF, 23 °C, 82 % (from **10**); e) $(COCl)_2$ (2.0 equiv), DMSO (4.0 equiv), Et_3N (4.0 equiv), CH_2Cl_2, −78 →0 °C; f) PPh_3 (4.0 equiv), CBr_4 (2.0 equiv), Et_3N (4.0 equiv), CH_2Cl_2, 0 °C, 86 % (for 2 steps); g) TsOH (0.5 equiv), EtOH, reflux, 95 %; h) SO_2Cl_2 (1.8 equiv), Et_3N (4.0 equiv), DMAP (0.4 equiv), CH_2Cl_2, −78 °C, 50–70 %; i) NaH (2.0 equiv), 2-chloro-3-pyridinol (2.5 equiv), CH_3CN, −40 °C, 82 %. TMS = trimethylsilyl, LHMDS = lithium hexamethyldisilazanide, TBS = *tert*-butyldimethylsilyl, tf = triflate = trifluoromethanesulfonyl, Ts = toluene-4-sulfonyl.

homologative alkynylation sequence[7] was developed to transform the lactone **9** into the acetylene **10**. Reduction of **9** with diisobutylaluminum hydride (DIBAL, 1.15 equiv)[8] in toluene (−78 °C), followed by addition of a solution of the resultant lactols in tetrahydrofuran (THF) to a mixture of lithium diisopropylamide (LDA, 1.2 equiv) and (trimethylsilyl)diazomethyllithium[9] (1.2 equiv, formed from LDA and $TMSCHN_2$) in THF (−78 → 23 °C), provided **10** in 77 % yield. Iterative silylation of the hydroxyl and alkynyl groups of **10**, respectively, followed by selective cleavage of the Si–O bond with $Et_3N \cdot 3HF$ afforded the C-protected product **11** (82 % overall). Oxidation of **11** under Swern conditions, dibromoolefination[10] of the resultant aldehyde, and acidic hydrolysis of the acetonide protective group within the olefinic product furnished the diol **12** in 82 % yield for the three-step sequence. Activation of **12**, in the form of the corresponding cyclic sulfate **13** (50–70 % yield), was then accomplished by the slow addition of a solution of freshly distilled sulfuryl chloride (1.8 equiv, 79 mM, approximately 0.3 mL min^{-1}) in dichloromethane to a cold (−78 °C) solution of **12** (44 mM) in dichloromethane containing triethylamine (4.0 equiv) and 4-(dimethylamino)pyridine (DMAP, 0.4 equiv).[11] Addition of a solution of **13** in acetonitrile to a suspension of 2-chloro-3-pyridinol (2.5 equiv) and sodium hydride (2.0 equiv) in acetonitrile at −40 °C, followed by a brief acidic work-up to hydrolyze the intermediate sulfate ester,[11] afforded the pyridyl ether **7**, in which the allylic sulfate had been displaced selectively, in 82 % yield. The selectivity observed in this reaction (approximately 11:1 favoring allylic displacement) is noteworthy. Although allylic halides undergo solvolysis more readily than propargylic halides,[12] prediction of the outcome of the present transformation, with its greater S_N2 character and substituent effects (1,1-dibromoolefin, silylacetylene), was not obvious.

Palladium-mediated coupling of the dibromoolefin **7** and the diyne **8**[6] in diethyl ether in the presence of cuprous iodide (0.3 equiv) and triethylamine (2.0 equiv) proceeded optimally using tetrakis(triphenylphosphine) palladium(0) (0.1 equiv)



Scheme 5. Synthesis of the kedarcidin core structure **3**. a) $Pd(PPh_3)_4$ (0.1 equiv), Et_3N (2.0 equiv), CuI (0.3 equiv), Et_2O, 23 °C, 61 %; b) TBAF (4.0 equiv), 2-nitrophenol (4.5 equiv), THF, 0 →23 °C, 87 %; c) TBSOTf (1.2 equiv), 2,6-lutidine (2.4 equiv), CH_2Cl_2, 0 °C, 95 %; d) $Cu(OAc)_2$ (30 equiv), pyridine, THF, then CuI (5 equiv), 60 °C, then **16**, 74–86 %; e) 3 Å molecular sieves, 23 °C; LHMDS (1.05 equiv), THF, −96 °C; *t*BuLi (1.05 equiv), −96 °C; HOAc (12 equiv), 44–60 %; f) $Et_3N \cdot 3HF$ (20 equiv), THF, 23 °C; g) $VO(acac)_2$ (1.0 equiv), TBHP (2.0 equiv), EtOAc, 23 °C; h) TBSOTf (17 equiv), 2,6-lutidine (30 equiv), EtOAc, 23 °C, 53 % (from **17**); i) MsCl (4 equiv), Et_3N (8 equiv), CH_2Cl_2, 0 °C; DBU (12 equiv), 23 °C, 78 %.[4]

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as catalyst and afforded the (*Z*)-vinyl bromide **14** exclusively, in 61% yield (Scheme 5). The selectivity of this coupling reaction is presumably steric in origin[13] and involves oxidative addition of Pd^0 into the less-hindered carbon–bromine bond. There is precedence for (*E*)-selective coupling (replacement of the more hindered (*Z*)-halide within a 1,1-dibromoolefin) in a related system, a result which was attributed, in that case, to internal delivery of Pd^0 by prior coordination to a tethered terminal acetylene.[14] The presence of the bulky *tert*-butyldimethylsilyl group in the present case may preclude such a directing effect.

Attempted cleavage of the silyl protective groups within **14** using tetrabutylammonium fluoride (TBAF) was complicated by the concurrent elimination of hydrogen bromide (to afford the corresponding tetrayne). This undesired pathway was found to be minimized in the presence of phenolic additives, but only those that fell within a narrow range of acidity.[15] Under optimum conditions, involving the addition of TBAF (4.0 equiv) to a solution of **14** and 2-nitrophenol (4.5 equiv, $pK_a = 7.22$)[16] in THF at 0 °C, followed by warming of the resultant solution to 23 °C over 17 h, the desilylated product **15** was formed cleanly, in 87% yield. The incorporation of less acidic additives, such as phenol ($pK_a = 10.0$) or 2-bromophenol ($pK_a = 8.42$),[16] led to greater amounts of the elimination product and correspondingly lower yields of the desired product, whereas more acidic additives, such as 2,6-dichlorophenol ($pK_a = 6.79$) or pentachlorophenol ($pK_a = 4.4$),[16] retarded the rate of desilylation to such an extent as to be impractical.

With the development of an efficient procedure for the cleavage of both silicon–carbon bonds (as well as the tertiary silyl ether) within **14**, the secondary hydroxyl group of the product (**15**) was protected, selectively, using TBSOTf (1.2 equiv) and 2,6-lutidine (2.4 equiv, 95%),[17] primarily to lend stability to the macrocyclic intermediate that is formed in the next step. Many experiments were necessary before efficient, reproducible, and scalable reaction conditions were found to achieve the oxidative coupling (Glaser reaction)[18] necessary for this transformation (**16** → **6**). The optimized procedure, a modification of Eglinton conditions,[19] involved the addition of a dilute solution of **16** in pyridine:THF (2:1, 4.0 mM, approximately 1 mL min^{-1}) to a mixture of copper(II) acetate ($Cu(OAc)_2$, 30 equiv) and copper(I) iodide (CuI, 5.0 equiv) in pyridine:THF (2:1, $[Cu]_{total} = 0.15$ M) at 60 °C under an argon atmosphere. For successful coupling it was essential to prepare the mixture of copper salts by an exacting protocol. Specifically, it was necessary to age the copper(II) acetate in pyridine:THF at 23 °C (5 min), forming a (sparingly soluble) royal-blue precipitate,[20] prior to the addition of the (more soluble) copper(I) iodide, heating to 60 °C (20 min), and addition of substrate **16**. Co-mixing of the solid reagents, by contrast, gave lower yields of product.[21] After an aqueous work-up and isolation by flash column chromatography the macrocycle **6** was obtained in 74–86% yield. This procedure deviates from the standard Eglinton conditions by the incorporation of a Cu^I salt and by the use of an inert atmosphere (as opposed to oxygen). Breslow and co-workers have already described such a modification, but used a mixture of CuCl and $CuCl_2$,[22] a reagent combination which did not lead to successful coupling within **16**. As anticipated, the product **6** exhibited greater stability than the cyclic tetraynes (such as structure **4**) that were prepared in our earlier route but did decompose if held in neat form.

In preparation for the key step of the synthetic sequence, a dried solution (3 Å molecular sieves, THF, 23 °C, 20 min) of the macrocyclic bromo alcohol **6** was cooled to −96 °C, then was treated with a solution of lithium hexamethyldisilazanide (LHMDS) in THF (0.5 M, 1.05 equiv) to deprotonate the tertiary hydroxyl group. Subsequent addition of a solution of *tert*-butyllithium (1.47 M in pentane, 1.05 equiv) at −96 °C and immediate quenching with acetic acid (12 equiv) then afforded the bicyclic product **17** in 44–60% yield after aqueous work-up and chromatographic isolation. A small amount (approximately 20%) of the product of protonation of the putative vinyllithium intermediate was also isolated. This side-product, undiminished by delaying the acid quench, is believed to arise by proton transfer with hexamethyldisilazane, formed stoichiometrically in the reaction. The proposed transannular cyclization is evidently quite rapid to compete with such a process.[23]

Completion of the core synthesis was achieved by hydroxyl-directed epoxidation and elimination of the tertiary hydroxyl group within the substrate **18**, which was prepared by desilylation of **17** with triethylamine trihydrofluoride ($Et_3N \cdot 3HF$, 20 equiv) in THF at 23 °C. Treatment of **18** with vanadyl acetoacetonate ($VO(acac)_2$, 1.0 equiv) and *tert*-butyl hydroperoxide (TBHP, 2.0 equiv) at 23 °C in ethyl acetate provided the desired epoxide **19** as a single regio- and stereoisomer in good yield (determined at a later stage, see below). In contrast to this, attempts to epoxidize **18** using 4-chloroperoxybenzoic acid (*m*CPBA) or dimethyldioxirane were not successful. These findings are in excellent agreement with proposed transition-state models for hydroxyl-directed epoxidations.[24, 25] The optimum dihedral angle formed by the hydroxyl group and the olefinic plane (∢ O-C-C=C) in the directed epoxidation of allylic alcohols is proposed to be 50° for the vanadium catalyst,[24] approximately 120° for *m*CPBA,[24] and about 130° for dimethyldioxirane;[25] we estimate this dihedral angle to be approximately 60° in the lowest energy conformer of **18**. Selective protection of the secondary hydroxyl group of **19** (TBSOTf (17 equiv), 2,6-lutidine (30 equiv), ethyl acetate, 23 °C) then afforded the product **20** in 53% yield (from **17**, three steps). Finally, the central olefin (C4-C5) of **3** was introduced by elimination of the tertiary hydroxyl group of **20** under conditions developed by Hirama and co-workers in their kedarcidin core synthesis (methanesulfonyl chloride (MsCl, 4 equiv), triethylamine (8 equiv), CH_2Cl_2, 0 °C; 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 12 equiv), 23 °C),[4] providing the kedarcidin core structure (**3**) in 78% yield. This product proved to be sufficiently stable for chromatographic isolation and full characterization (^1H NMR, ^{13}C NMR, and IR spectroscopy and high resolution mass spectrometry),[26] but it did undergo cycloaromatization upon standing at ambient temperature (18 h, 1,4-cyclohexadiene) to form the tricyclic epoxide **21** (21% yield from **20**, Scheme 6). The latter product (**21**) was also unstable, particularly toward silica gel, presumably due to

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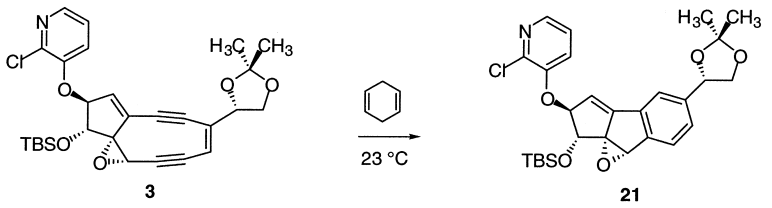

Scheme 6. Cycloaromatization of **3**.

facile solvolytic cleavage of the benzylic C–O bond of the epoxide ring.

The synthetic route described provides the fully functionalized core of kedarcidin chromophore (**3**) in 18 linear steps with an average yield of 81% per step (overall yield 2.3%) and demonstrates the feasibility of the transannular cyclization approach in this context. In addition, we have established a viable protocol for epoxidation of the product and have shown that all intermediates in the synthetic sequence are sufficiently stable to be isolated. On the basis of these findings, a parallel approach to the synthesis of **1** itself, in which transannular cyclization is conducted within a substrate containing the macrolactone ring, now appears feasible. Findings of potentially general value in synthesis include the development of a two-step sequence for the homologative alkynylation of lactones, new and mild conditions for the cleavage of acetylenic Si–C bonds, and a new procedure for oxidative acetylenic coupling.

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[26] Physical Data for compound **3** (see Scheme 5, Scheme 6 for proton numbering): ^{1}H NMR (500 MHz, [D$_6$]benzene, 25 °C): $\delta = 7.78$ (dd, $^3J_{H,H} = 1.5$, 1H, 4.9 Hz; 6′-H), 6.39 (dd, $^3J_{H,H} = 4.9$, 8.3 Hz, 1H; 5′-H), 6.13 (dd, $^3J_{H,H} = 1.0$, 8.3 Hz, 1H; 4′-H), 5.79 (br. s, 1H; 5-H), 5.62 (d, $^3J_{H,H} = 2.0$ Hz, 1H; 12-H), 4.68 (dd, $^3J_{H,H} = 1.5$, 4.9 Hz, 1H; 11-H), 4.30 (d, $^3J_{H,H} = 4.9$ Hz, 1H; 10-H), 4.26 (dd, $^3J_{H,H} = 6.3$, 6.8 Hz, 1H; 13-H), 3.79 (dd, $^3J_{H,H} = 6.3$, 8.3 Hz, 1H; 14-H), 3.74 (dd, $^3J_{H,H} = 6.8$, 8.3 Hz, 1H; 14-H), 3.67 (d, $^3J_{H,H} = 1.5$ Hz, 1H; 8-H), 1.50 (s, 3H; CH_3), 1.28 (s, 3H; CH_3), 0.86 (s, 9H; $SiC(CH_3)_3$), −0.03 (s, 3H; $SiCH_3$), −0.05 (s, 3H; $SiCH_3$); ^{13}C NMR (100 MHz, [D$_6$]benzene, 25 °C): $\delta = 149.7$, 143.4, 141.5, 141.3, 137.3, 125.9, 123.0, 121.6, 120.1, 110.6, 105.5, 102.2, 100.6, 89.4, 84.2, 76.5, 75.9, 69.5, 69.0, 47.8, 26.9, 26.0, 25.9, 18.3, −4.2, −4.9; FTIR (neat): $\tilde{\nu} = 2930$ (m), 2858 (m), 2280 (w, C≡C), 2186 (w, C≡C), 1566 (m), 1420 (s), 1287 (s), 1253 (m), 1207 (m), 1157 (m), 1085 (m), 840 (s), 781 (m) cm^{-1}; HR-MS (FAB): m/z calcd for $C_{28}H_{32}O_5ClNSiNa$ [M+Na$^+$]: 548.1636; found: 548.1630.

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