Bioinspired Synthesis

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Biomimetic Total Synthesis of Cyanosporaside Aglycons from a Single Enediyne Precursor through Site-Selective *p*-Benzyne Hydrochlorination**

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In memory of Satoru Masamune

Abstract: *The cyanosporasides A–F are a collection of monochlorinated benzenoid derivatives isolated from the marine actinomycetes Salinispora and Streptomyces sp. All derivatives feature one of two types of cyanocyclopenta[a]indene frameworks, which are regioisomeric in the position of a single chlorine atom. It is proposed that these chloro-substituted benzenoids are formed biosynthetically through the cycloaromatization of a bicyclic nine-membered enediyne precursor. Herein, we report the synthesis of such a bicyclic precursor, its spontaneous transannulation into a p-benzyne, and its differential 1,4 hydrochlorination reactivity under either organochlorine or chloride-salt conditions. Our bioinspired approach culminated in the first regiodivergent total synthesis of the aglycons A/F and B/C, as well as cyanosporasides D and E. In addition, empirical insights into the site selectivity of a natural-like p-benzyne, calculated to be a ground-state triplet diradical, to hydrogen, chlorine, and chloride sources are revealed.*

Deciphering and mimicking how natural products are formed and how they act biologically have long inspired chemists.[1] For instance, the enediyne classes of antitumor antibiotics continue to fascinate because of their innate modes of action, biosynthetic origins, and informative, albeit delicate, structures.[2] These natural enediynes act principally through reductive, nucleophilic, or spontaneous cycloaromatization events to give highly reactive benzenoid species, which oxidatively cleave DNA.[3] One of the first known benzenoids, a *p*-benzyne intermediate, was found by the Masamune group in 1971 during their attempted synthesis of a strained bicyclic [10]annulene.[4] Bergman and Jones formally and independently characterized these reactive species to be 1,4-didehydrobenzenes.[5] Both groups thus demonstrated that enediynes can cyclize reversibly and react thermally in a diradical fashion with hydrogen sources. The Bergman group extensively studied this behavior in the 1980s and also showed halogen sources, such as CCl_4, to react.[6] Typically, the cycloaromatized intermediates are doubly quenched with the same atom or functionality. However, in 2004 we demonstrated the possibility of the site-selective monofunctionalization of unsymmetrical *p*-benzyne diradicals through ^{13}C isotope labeling, radical spin trapping, and electron spin resonance studies.[7] More recently, Perrin et al. raised the possibility of not only radical but also ionic reaction modes operating in the chloroprotonation (or protochlorination) of symmetrical *p*-benzynes.[8] These possibilities are particularly pertinent to understanding the biosynthetic and regiochemical origins of the monochlorinated cyanosporasides,[9] sporolides,[10] and fijiolides,[11] which were discovered from deep-sea Actinomycetales and proposed by Fenical and colleagues. Central to these origins is a putative enediyne precursor.[2d]

In this context, we decided to extend our *p*-benzyne diradical trapping studies[7a] and pursue the biomimetic monochlorination of the putative enediyne precursor (**1**) of the cyanosporasides under either organochlorine or chloride-salt conditions (Figure 1). This would not only corroborate possible biosynthetic and regiochemical origins as delineated by Fenical and Moore,[9b] but also pave the way to a regiodivergent strategy to the cyanosporaside family of natural products. We thus reasoned that the cyclized *p*-benzyne diradical **2** is monochlorinated under either radical[7] or ionic[8] conditions to give cyanosporaside aglycons of type A/F (**3**) or of type B–E (**4**).[9] Here, the regiochemistry would depend on the initial, irreversible coupling with a hydrogen, chlorine, or chloride source. As a close nine-membered enediyne mimic of putative **1**, we first studied the Masamune–Bergman cyclization[4,5] of the strained, bicyclic trienediyne **5** via its *p*-benzyne diradical **6**. Next, we explored monochlorination conditions to afford the chloro-substituted cyclopenta[*a*]indenes **7** and **8** directly from the enediyne mimic **5** of

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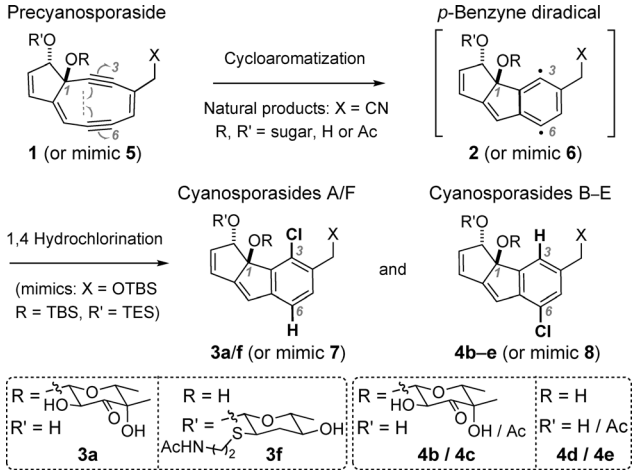
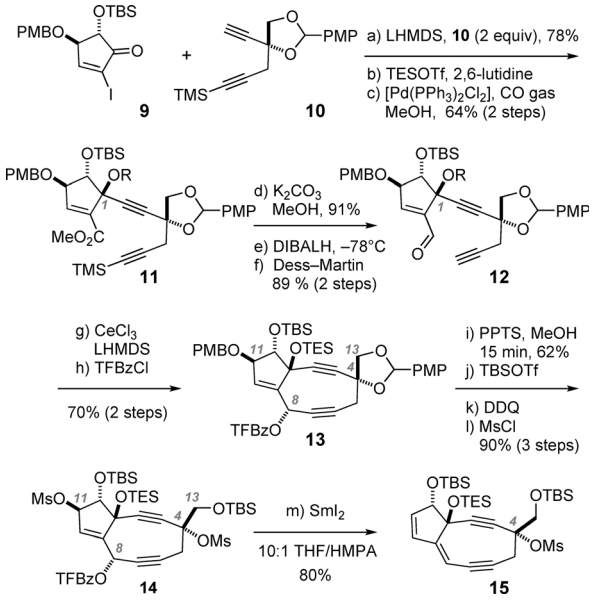


Figure 1. Bioinspired, regiodivergent strategy to the cyanosporasides. TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

precyanosporaside (**1**). Our findings and total syntheses of the cyanosporaside aglycons **3** and **4** are described herein.

Reliable routes to bicyclic nine-membered enediynes necessitate careful planning and execution on the bench because of the extraordinary instabilities of the strained products and intermediates.[12] We first targeted the electron-deficient mesylate **15** as a possibly more stable predecessor to the fully fledged, nine-membered trienediyne **5** (Scheme 1). The iodocyclopentenone **9**[13] and diyne **10**[14] fragments were thus prepared (see the Supporting Information)[15] and subsequent addition of the acetylide to the carbonyl group proceeded in 78% yield with high stereoselectively. Following



Scheme 1. Reliable route to the precyanosporaside mimic **5** via mesylate **15**. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIBALH = diisobutylaluminium hydride, HMPA = hexamethylphosphoramide, LHMDS = lithium hexamethyldisilazanide, Ms = methanesulfonyl, PMB = *p*-methoxybenzyl, PMP = *p*-methoxyphenyl, PPTS = pyridinium *p*-toluenesulfonate, Tf = trifluoromethanesulfonyl, TFBz = 4-trifluoromethylbenzoyl, TMS = trimethylsilyl.

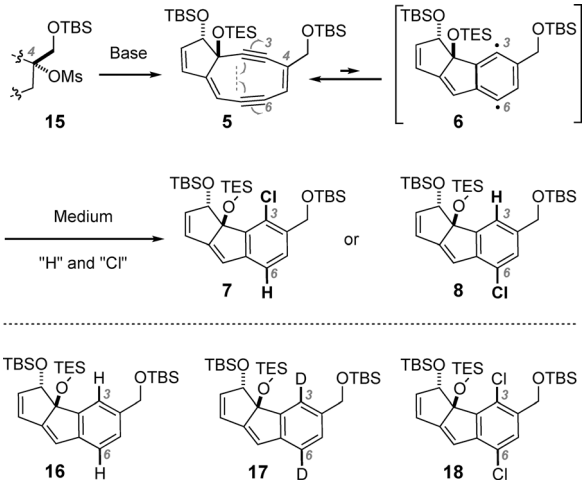
etherification at C1 and Pd-catalyzed methoxycarbonylation, the silyl ether **11** (R = TES) was isolated in 64% yield over two steps. Selective removal of the acetylenic TMS group, reduction of the ester to the primary alcohol with DIBAL, and oxidation with Dess–Martin periodinane (DMP) afforded the aldehyde **12** (R = TES) in good yield over three steps. Next, the key reaction, that is, the closure of the nine-membered ring of **12**, was investigated. This necessitated optimization because the strained enediyne products were too unstable to isolate. Immediate esterification with an electron-deficient functionality solved this issue. After an improved[16] Ce^{III}-mediated cyclization between the acetylide and aldehyde moieties of **12** (R = TES), the TFBz[17] ester at C8 of **13** was thus formed and could be isolated as a single diastereoisomer (70% yield, two steps). Notably, the methoxymethyl ether **12** (R = MOM) failed to cyclize, presumably because of unfavorable Ce^{III} chelation modes enforced between the neighboring MOM and aldehyde groups.

After careful deacetalization of **13** to a C4/C13 diol, O-silylation at C13, and O-mesylation at C11, the bismesylated TFBz ester **14** was subjected to an unprecedented Grob-like, reductive olefination step. In the event, **14** was treated with SmI_2[17] at 0 °C for 2 min. This caused a rapid 1,4 elimination of the mesylate at C11 by reductive C–O bond cleavage of the OTFBz group at C8. Although only stable in a dilute CH_2Cl_2 solution for 1–2 days at −20 °C, the strained bicyclo[7.3.0]-dodecadienediyne monomesylate **15** could be prepared from the stable bismesylated **14** in a reliable yield of 80%. In contrast, the more electron-rich C4-OTES analogue of the mesylate **15** readily decomposed, presumably through an oxy-Cope ring opening of the strained nine-membered carbocycle.[12a,16] The scene was now set to generate the trienediyne **5** from **15** and study its Masamune–Bergman cyclization into the transient *p*-benzyne **6** (Table 1).

Elimination of the mesylate at C4 by treatment of **15** with DBU in THF afforded the 3,6-dihydrocyclopenta[*a*]indene **16** in 72% yield (Table 1, entry 1). The intermediacy of the trienediyne **5** during the elimination of **15** was clearly supported by high-resolution ESI mass spectroscopy and 800 MHz ^{1}H NMR spectroscopy (found: *m*/*z* 579.3121; calcd: 579.3122 for **5**, $C_{31}H_{52}NaO_3Si_3^+$; see the Supporting Information). The bisdeuterated **17** was produced from **15** in [D_8]THF using DBU (entry 2) or NaH (entry 3). Notably, NaH generated the [D_2]-indene **17** in 64% yield with the deuteration of positions C3 and C6 being greater than 95% (entry 3). The percentage of C3 and C6 deuteration in **17** dropped to 59% and 38%, respectively, with the use of DBU (entry 2) and dropped even lower by using 2:1 and 1:1 mixtures of [D_8]THF and THF with NaH (entry 3, footnote d). Besides indicating that DBU is a better hydrogen donor than THF, these experiments show that the C6 position of **5** not only selects hydrogen over deuterium but also reacts more readily than the C3 position.

To study chlorine abstraction, we next explored the possibility of a competitive atom transfer[7] to the apparently more reactive C6 position of diradical **6** (Table 1, entries 4–6). In other words, we speculated that monochlorination to a cyanosporaside of type A/F (**7**) or type B–E (**8**) system would depend on the initial hydrogen or chlorine abstraction

Table 1: Generation, cycloaromatization, and site-selective hydrochlorination of precyanosporaside mimic **5** via *p*-benzyne **6** to aglycons of type A/F (**7**) or B–E (**8**).[a]



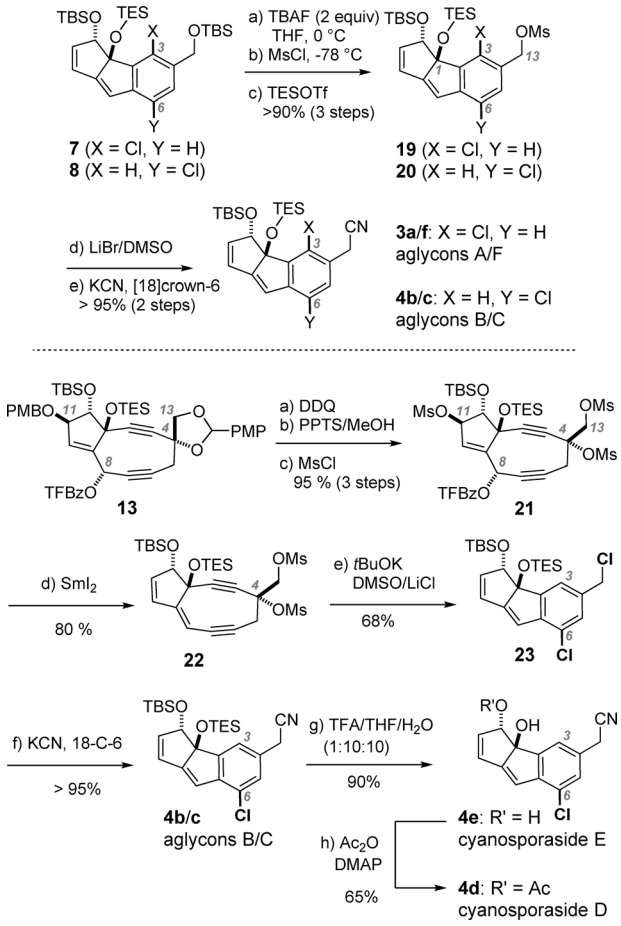
Entry	Base [equiv]	Medium (time)	Yield [%]				
			7	**8**	**16**	**17**	**18**
1	DBU [85]	THF (3 h)	–	–	72	–	–
2	DBU [100]	$[D_8]$THF (3 h)[b]	–	–	–	65	–
3	NaH [85]	$[D_8]$THF (5 h)[c,d]	–	–	–	64	–
4	*t*BuOK [85]	CCl_4 (5 h)	–	–	–	–	70
5	DBU [85]	CCl_4 (5 h)	32	–	3	–	15
6	*t*BuOK [85]	1:1 Et_2O/CCl_4 (15 h)	43	–	–	–	22
7	DBU [85]	0.7 M LiCl/DMSO (12 h)[e]	–	50	10	–	–
8	DBU [170]	0.7 M LiCl/DMSO (2.5 h)	–	32	30	–	–
9	*t*BuOK [85]	0.7 M LiCl/DMSO (12 h)[f]	–	65	–	–	–

[a] All reactions were conducted at room temperature with 5–10 μmol of **15** in 1.5 mL of the medium, equivalents relate to **15**, and yields of isolated products are given. [b] C3: 59% D and C6: 38% D. [c] C3 and C6 ≥95% D. [d] $[D_8]$THF/THF (2:1) gave C3: 57% D and C6: 34% D; $[D_8]$THF/THF (1:1) gave C3: 28% D and C6: 6% D. [e] Addition of AcOH (20 equiv) gave comparable results. [f] $[D_6]$DMSO gave $[D_1]$-**8** (C3: 85% D) in 60% yield. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMSO = dimethyl sulfoxide.

by the *p*-benzyne **6**. The enediyne **5** was thus tested for its diradical behavior to chlorine abstraction by treating **15** with *t*BuOK in CCl_4 (entry 4). Because of a lack of suitable hydrogen sources, the anticipated 3,6-dichloroindene **18** was the only product observed (70% yield). With DBU as both the base and hydrogen source, and CCl_4 as the chlorine source, the 3-chloro-6-hydroindene **7** formed selectively (entry 5). The indene **7** was isolated in 32% yield together with the 3,6-dichloroindene **18** (15%) and 3,6-dihydroindene **16** (3%). With *t*BuOK acting only as a base, an increase in the formation of **7** from **15** was achieved with a 1:1 mixture of Et_2O/CCl_4 as competitive hydrogen/chlorine atom sources (entry 6). This reaction gave the 3-chloro-6-hydroindene **7** in 43% yield and the 3,6-dichloroindene **18** in 22% yield. In the reactions summarized in entries 4–6, the formation of a 6-chloro-3-hydroindene **8** was not detected, thus indicating that the C6 position preferentially abstracts hydrogen over chlorine atoms.

With the prospect of ionic reaction modes[8] being open to an electrophilic *p*-benzyne diradical **6**, our above results indicated that the sterically more accessible C6 position of trienediyne **5** would react preferentially with a chloride anion to give a cyanosporaside of type B–E (**8**, Table 1, entries 7–9). The mesylate **15** was thus treated with DBU (85 equiv) in the presence of excess LiCl (425 equiv) in DMSO for 12 h (entry 7). The reaction proceeded smoothly and gave rise to the 6-chloroindene **8** in 50% yield together with 10% of the 3,6-dihydroindene **16**, irrespective of the presence of AcOH.[8a] When more DBU was added as a hydrogen atom source, the yield of **8** decreased and that of **16** increased (entry 8). Therefore, *t*BuOK with its poor hydrogen-donating ability was used as the base in DMSO, and the yield of **8** increased to 65% (entry 9). Use of $[D_6]$DMSO afforded the 6-chloroindene $[D_1]$-**8** in a similar manner, but with 85% deuteration at the C3 position, thus indicating DMSO as the primary proton source.

Having both 1,4-hydrochlorinated indene regioisomers **7** and **8** in hand, we pursued the divergent total synthesis of the aglycons A/F and B/C as well as cyanosporasides D and E (Scheme 2). Stoichiometric bisdesilyation of **7**/**8** at 0 °C with TBAF and sequential monomesylation of the OH group at C13, followed by resilylation of the OH group at C1, gave the mesylates **19**/**20**. Subsequent bromide formation and cyanide displacement thus completed the synthesis of aglycons A/F (**3**) and B/C (**4**). Although the mesylate could not be displaced



Scheme 2. Total syntheses of aglycons A/F, B/C, and cyanosporasides D/E. DMAP = 4-dimethylaminopyridine, TBAF = tetra-*n*-butylammonium fluoride, TFA = trifluoroacetic acid.

directly with cyanide, we found that the use of the C13-chloride counterparts of **19**/**20** also afforded **3** or **4** efficiently. This led to the testing of a more concise and robust strategy to the aglycons B/C. Thus, the trismesylate **21** was targeted from **13** and treated briefly with SmI_2 in THF. The C8/C11-deoxygenated diene–diyne **22** was then treated with *t*BuOK in DMSO/LiCl (compare with Table 1, entry 9). As anticipated, this reaction afforded the cycloaromatized bischloride **23** in one step and allowed the synthesis of aglycons B/C (**4b**/**c**) and cyanosporasides D/E (**4d**/**e**).

Several mechanistic insights can be inferred from Table 1 (Figure 2). Collectively, the results in entries 1–4 provide strong evidence for the existence of the *p*-benzyne diradical (**6**). This is further supported by NMR spectroscopic observations of trienediyne **5** cycloaromatizing to [D_2]-indene **17**

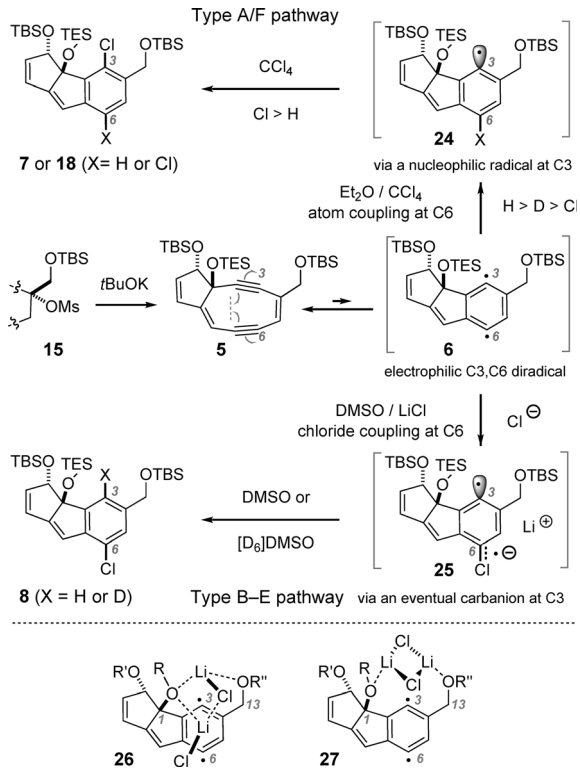


Figure 2. Regiodivergent hydrochlorination of the *p*-benzyne mimic (**6**) to generate the cyanosporaside aglycons A/F (**7**) and B–E (**8**).

and isolation of the C3/C6 bisfunctionalized indene products **16**–**18**. Furthermore, the results summarized in entries 1–6 demonstrate that the C6 radical center of diradical **6** can abstract atoms (H, D, or Cl) faster than the sterically more shielded C3 position. This is in agreement with our previous studies.[7a,b] Specifically, the C6 position experiences a greater H/D isotope effect and reacts selectively as an electrophilic 1,4 diradical[18] in the order of H > D > Cl. For example, entries 4–6 show there is a 2:1 chemical selectivity for C6-hydrogen abstraction from Et_2O over C6-chlorine abstraction from CCl_4. In comparison, the resultant C3-phenyl monoradical (**24**) is more nucleophilic[19] and, if a donor source is available, the order of atom abstraction was found to be Cl > H. These arguments agree well with fundamental polar effects on atom abstraction by electrophilic and nucleophilic radicals.[20] In addition, a phenyl radical can be viewed to possess a singly occupied molecular orbital (SOMO) energy level higher than that of a *p*-benzyne diradical.[21]

It is also noteworthy that all radical conditions (Table 1, entries 4–6) only gave the cyanosporasides of type A/F (**7**). In contrast, all anionic conditions (entries 7–9) only gave the cyanosporasides of type B–E (**8**). These latter cases demonstrate that DMSO acts as a latent proton source, which subsequently neutralizes a plausible C3-carbanionic indene[8] formed via the diradical π-anion **25** by initial chloride-ion bonding with the C6 position of the diradical **6** (Figure 2). In spite of these ionic conditions, radical modes of reactivity for the *p*-benzyne **6** were also observed to operate, as evidenced by isolation of the 3,6-dihydroindene **16** (entries 7 and 8). It is conceivable that in seawater environments, where these natural products are produced, both regioselective modes of *p*-benzyne reactivity could occur.

In order to gain more fundamental insights into the chemical and site selectivity of the unsymmetrical *p*-benzyne **6** to H and Cl atom or ion sources, we studied the ab initio calculated transition states and free-energy profiles of **5** (and a trimethoxy-substituted analogue of **5**) reacting with Et_2O (in Et_2O), CCl_4 (in Et_2O), and LiCl (in DMSO) by using density functional theory (DFT) at the UwB97XD/6-31G(d,p) level (see the Supporting Information for details). Several general conclusions can be drawn at this juncture. First, the precyanosporaside mimic **5** does not react directly with LiCl or CCl_4 in a nucleophilic fashion before cycloaromatization. Second, the cyclization of enediyne **5** likely proceeds via a singlet transition state that settles into a triplet ground state for the 3,6-dehydrobenzene **6**, for example, by intersystem crossing or vibrational relaxation.[22] Here, the triplet energy of **6** is 13–14 kcal mol^{-1} lower than its singlet state. This means that singlet resonance forms of the reactive benzenoid species **6** do not operate, for example, as C3/C6 zwitterions, biscarbenes or singlet diradicals,[23] and that through-space spin pairings[18a] of the σ-electrons at C3/C6 do not occur. In short, the precyanosporaside-like benzenoid **6** is calculated to react as a triplet *p*-benzyne diradical.

Third, the activation energy (E_a) for hydrogen atom abstraction from Et_2O is significantly more favorable (4–5 kcal mol^{-1}) than chlorine atom abstraction from CCl_4, although the E_a differences favoring C6 versus C3 atom abstraction are small for **6** (0.4–0.7 kcal mol^{-1}). This currently does not fully corroborate the proposed C6-regiochemical selectivity for hydrogen atom abstraction under radical conditions, but we still favor steric arguments for the observed C6-site selectivity by the triplet *p*-benzyne diradical **6** via the phenyl radical **24** (Table 1, entry 6). Fourth, our DFT experiments with DMSO as the solvent show that LiCl coordinates strongly with both the oxygen atoms at C1 and C13, and multiply so, forming clusters such as **26** and **27** (compare with Figure 2). These LiCl clusters tend to prevent bond formation at the C3 position of **6** with chloride anions, but **26** does permit a transition-state pathway to C6 bond formation giving the diradical/anion **25**, a π–Li complex (see the Supporting

Information). Although the extent to which these clusters occur in DMSO is uncertain, such a coordinative blocking effect helps explain the exclusive chlorination at C6 of the *p*-benzyne mimic **6** when using a large excess of LiCl.

Collectively, the observed differential reactivity of a *p*-benzyne species (**6**) from the enediyne mimic **5** provides convincing evidence for the regiodivergent biosynthesis of the cyanosporasides A/F (**3**) and B–E (**4**) through the site-selective hydrochlorination of a transient benzenoid species (**2**) that forms spontaneously from a single, although elusive, natural enediyne precursor coined precyanosporaside (**1**).[2d,9] More fundamentally, our biomimetic enediyne model **5** suggest that the benzenoid **2** reacts as an electrophilic *p*-benzyne C3/C6 diradical in a triplet ground state. This proposal is in contrast to the typical singlet states that have been calculated on simpler model systems with unnatural *p*-benzyne substitution patterns.[18,22] We further propose that the C3/C6 diradical of **2** first reacts with a hydrogen atom donor or a chloride anion source preferentially at its sterically exposed C6 position, after which the ensuing phenyl-like radical at C3 or carbanion at C3 reacts with an organochlorine or proton source, respectively (Figure 2). These sequential coupling events on the common *p*-benzyne diradical **2** thereby lead to cyanosporasides of type A/F (**3**) or B–E (**4**), respectively. Currently, we are applying our findings to provide insights into analogous enediyne cycloaromatization events in the prospect of guiding our total synthesis efforts to the sporolides A and B[10] and the fijiolides A and B.[11]

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