Construction of the Complete Aromatic Core of Diazonamide A by a Novel Hetero Pinacol Macrocyclization Cascade Reaction**

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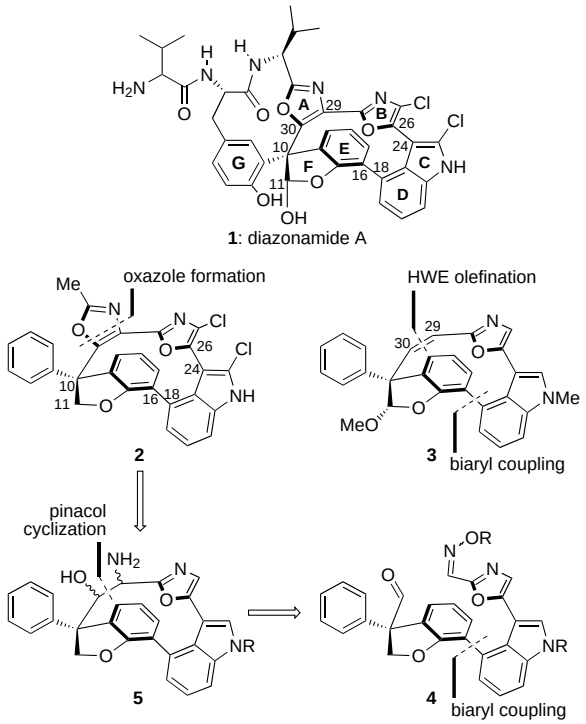
In 1991, Fenical and Clardy disclosed the structure of diazonamide A (**1**, Scheme 1), a secondary metabolite isolated from the colonial ascidian *Diazona chinensis*, whose unprecedented molecular architecture includes a cyclic polypeptide backbone, a strained halogenated heteroaromatic core trapped as a single atropisomer, and a lone quaternary center at the epicenter of the two major macrocyclic subunits.[1] Significant synthetic efforts have been directed towards diazonamide A by a number of laboratories around the world because of the unique challenges posed by this structural framework, its impressive in vitro cytotoxicity, and the inability to harvest additional material from the original source.[2] However, despite much progress, a route to this fascinating compound still remains elusive.



Scheme 1. Structure of diazonamide A (**1**) and retrosynthetic analysis of model system **2**.

To date, the majority of synthetic approaches derive from two distinct retrosynthetic analyses of the diazonamide problem, namely initial synthesis of the peptide framework (the AG macrocycle) with late-stage closure of the C_{16}–C_{18} bond, or alternatively, early introduction of the C_{16}–C_{18} biaryl axis followed by a macrocyclization event to form the crucial C_{29}–C_{30} linkage with subsequent A-ring oxazole synthesis. Although advanced synthetic intermediates have proven recalcitrant in the face of intensive efforts to forge the C_{16}–C_{18} bond in the former approach,[2c] the overall viability of the latter retrosynthetic blueprint has been verified based on studies in which we developed a highly convergent route to **3** (Scheme 1) by calling upon the power of the Suzuki and Horner–Wadsworth–Emmons (HWE) reactions to generate the C_{16}–C_{18} biaryl linkage and the C_{29}–C_{30} alkene, respectively.[3] In addition, an approach in which C_{29}–C_{30} bond formation was accomplished by Dieckmann condensation also realizes this goal.[2b] Herein, we report the elaboration of the previously synthesized **3** to the complete ABCDEF macrocycle as well as the development of a novel and concise hetero pinacol macrocyclization cascade sequence induced by SmI_2/HMPA which enables access to the parent 12-membered diazonamide model system **2** (Scheme 1) in only sixteen linear steps.

Shortly after our disclosure of **3**,[3] we established that the final A-ring oxazole of the diazonamide skeleton could be fashioned from the C_{29}–C_{30} olefinic residue by following a four step sequence as delineated in Scheme 2. First, exposure of **3** to $KMnO_4$ in acetic anhydride[4] led to the formation of a diketone, which was then transformed to **6** by selective conversion of the more activated and less sterically hindered carbonyl group to its corresponding methoxime derivative. Significantly, although dihydroxylation of the alkene in **3** could readily be achieved using stoichiometric amounts of OsO_4 activated by quinuclidine,[5] the resulting diol proved highly unstable as it decomposed rapidly both in solution and during isolation, which led to the near exclusive formation of benzofuran side products by the cyclofragmentation pathway we have observed frequently in this type of system.[6] With **6** in hand, the oxime function was reductively cleaved through hydrogenolysis in acidified methanol.[7] Subsequent in situ acetylation of the resultant amine using AcCl furnished acetamide **7**. Finally, formation of the desired oxazole ring in **8** was achieved from **7** by Gabriel–Robinson cyclodehydration initiated by *p*TsOH in refluxing benzene (50% yield);[8] significantly, no other condition screened proved equally effective for this oxazole formation.[9]

Overall, although the above route proved successful for completion of the aromatic core of diazonamide A, the

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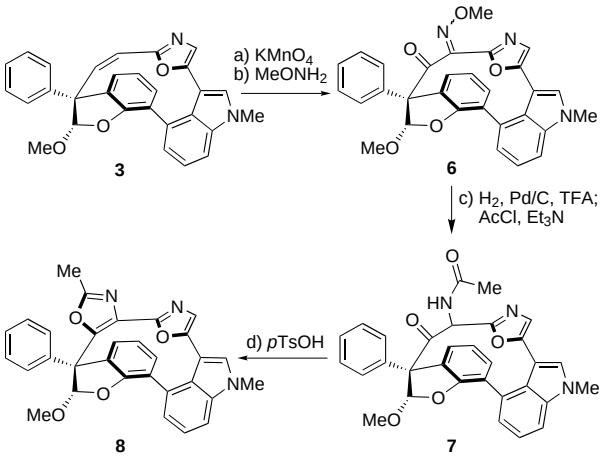
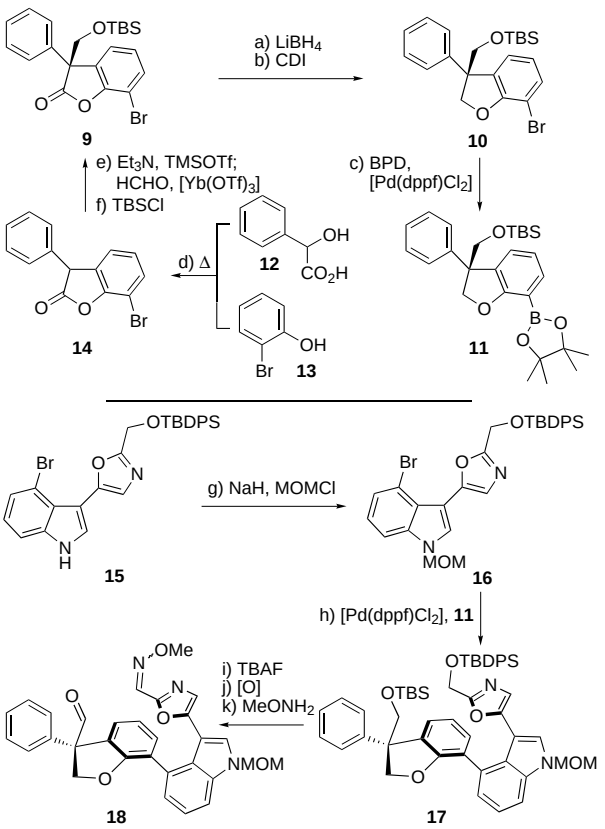


Scheme 2. Initial model studies which led to the complete heteroaromatic skeleton (**8**) of diazonamide A: a) $KMnO_4$ (6.0 equiv), Ac_2O, 0 °C, 2 h, 35 %; b) $MeONH_2 \cdot HCl$ (20 equiv), EtOH, 25 °C, 12 h, 95 %; c) Pd/C (10 %, 2.0 equiv), H_2 (3.0 atm), TFA/MeOH (1:20), 25 °C, 12 h; then AcCl (3.0 equiv), Et_3N (3.0 equiv), CH_2Cl_2, 25 °C, 30 min, 80 %; d) *p*TsOH, benzene, 80 °C, 20 h, 50 %. TFA = trifluoroacetic acid, *p*TsOH = *p*-toluenesulfonic acid.

relatively modest yields observed for initial HWE closure to generate **3** as well as for diketone formation suggested that it would be potentially challenging to process sufficient material by using the developed sequence to complete the total synthesis of diazonamide A in the context of a fully elaborated G ring. As such, we sought a second-generation strategy to prepare model system **2** (Scheme 1). Mindful of our previous use of the McMurry reaction to form the challenging eight-membered ring in our total synthesis of Taxol,[10] we hypothesized that we could enlist a hetero pinacol coupling reaction to fashion a fully functionalized C_{29}–C_{30} bond directly suitable for A-ring oxazole formation (**5**, Scheme 1) from a percursor aldehyde – oxime (**4**). Since the pioneering efforts from the groups of Corey, Hart, and Bartlett,[11] which established oximes as highly competent radical acceptors in reductive cyclizations, numerous examples of hetero pinacol coupling reactions of alkyl, vinyl, and ketyl radicals with oxime ethers have been reported in both inter-[12] and intramolecular[13] contexts. To the best of our knowledge, however, this variant of the pinacol reaction has not yet been successfully applied in a macrocyclization reaction to generate a ring size greater than seven, despite precedent for medium-size ring formation in related systems in which dialdehydes were employed.[14] As such, the diazonamide problem offered a unique and challenging test for the power of this synthetic methodology.

To pursue this idea, the requisite synthetic fragments were prepared as shown in Scheme 3, commencing from the previously reported lactone **9** (prepared in nine steps from known starting materials).[3] Complete reduction of the lactone with $LiBH_4$ was followed by the smooth formation of dihydrobenzofuran **10** in 95 % yield upon heating the resultant diol with 1,1′-carbonyldiimidazole in THF at reflux, a result which has been previously reported in related systems except under far more forcing conditions.[15] Subsequent conversion of **10** to boronate **11** was then achieved in 70 % yield by using the conditions developed by Ishiyama et al.[16] For the



Scheme 3. Synthesis of key intermediate **18**: a) $LiBH_4$ (8.0 equiv), THF, 25 °C, 4 h, 95 %; b) CDI (2.0 equiv), THF, reflux, 2 h, 95 %; c) BPD (1.2 equiv), $[Pd(dppf)Cl_2] \cdot CH_2Cl_2$ (0.2 equiv), KOAc (3.0 equiv), DMSO, 90 °C, 6 h, 70 %; d) **12** (1.0 equiv), **13** (1.0 equiv), H_2SO_4 (70 % aq.), 45 min, 42% (95% based on recovered **13**); e) Et_3N (3.0 equiv), TMSOTf (1.2 equiv), CH_2Cl_2, 0 °C, 1 h; then HCHO (37 % in H_2O, 5.0 equiv), $[Yb(OTf)_3]$ (0.1 equiv), THF, 25 °C, 24 h, 78 %; f) TBSCl (3.0 equiv), imidazole (6.0 equiv), DMF, 25 °C, 6 h, 95 %; g) NaH (2.0 equiv), THF, 0 °C, 5 min; then MOMCl (2.0 equiv), THF, 0 °C, 10 min, 94 %; h) **11** (1.0 equiv), $[Pd(dppf)Cl_2] \cdot CH_2Cl_2$ (0.2 equiv), K_2CO_3 (5.0 equiv), DME, 110 °C, 8 h, 66 %; i) TBAF (3.0 equiv), THF, 25 °C, 10 min, 93 %; j) Dess – Martin periodinane (3.0 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 25 °C, 1 h, 88 %; k) $MeONH_2 \cdot HCl$ (10 equiv), DMSO, 25 °C, 10 min, 91 %. CDI = 1,1′-carbonyldiimidazole, BPD = bis(pinacolato)diboron, dppf = (diphenylphosphanyl)ferrocene, LiHMDS = lithium salt of 1,1,1,3,3,3-hexamethyldisilazane, TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl, MOM = methoxymethyl, TBAF = tetrabutylammonium fluoride.

purposes of this model study, lactone **9** was also accessed through initial reaction of mandelic acid (**12**) with 2-bromophenol (**13**) using Padwa's method,[17] followed by facile elaboration of **14** to **9**,[18] which enabled the synthesis of boronate **11** in just six linear synthetic operations.

Next, the previously reported indole – oxazole **15**[3] (available in six steps from 4-bromoindole) was protected as its MOM ether (**16**) in 94 % yield by a standard protocol. In a final series of steps, **11** and **16** were smoothly coupled by using $[Pd(dppf)Cl_2]$ and K_2CO_3 in DME at 105 °C[16] to afford **17** in 66 % yield. Finally, a tandem deprotection – oxidation sequence cleanly provided an intermediate dialdehyde, with the more activated benzylic aldehyde selectively engaged as a methyloxime ether upon exposure to excess methoxylamine hydrochloride in DMSO (75 % overall for three steps). With **18** in hand, the stage was set to attempt the critical hetero pinacol macrocyclization.

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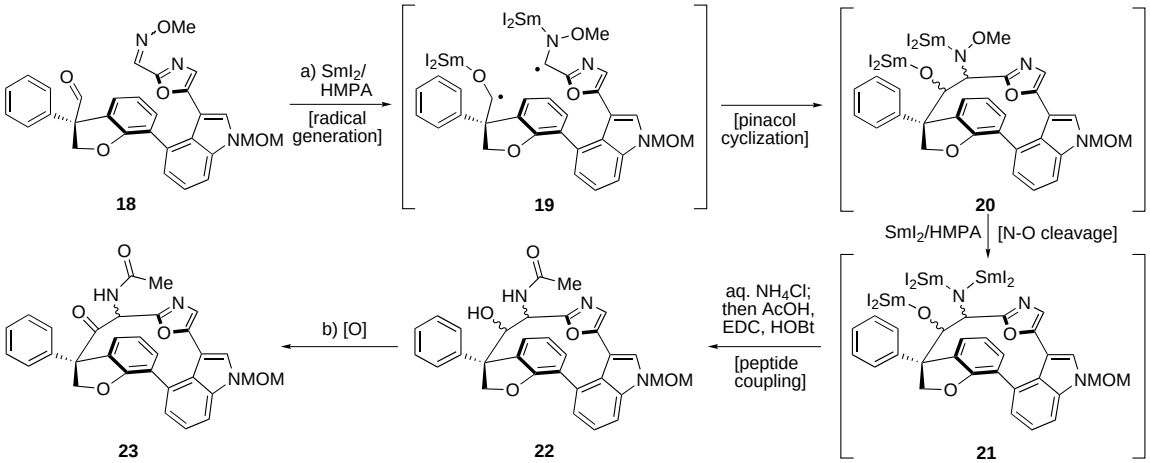
In assessing reaction conditions to initially screen, the power of SmI_2[19] seemed uniquely suited for our purposes, and the recent reports of SmI_2-induced scission of the N–O bond of oximes[20] suggested that it might be possible to effect a cascade sequence involving macrocyclization followed by in situ N–O cleavage to generate an amino alcohol such as **5** (Scheme 1) directly. However, despite extensive literature searches, we could find only one isolated example of reductive cyclization with subsequent oxime cleavage in the presence of SmI_2,[21] in which the use of a large excess of SmI_2 (6.0 equiv) followed by prolonged treatment with deoxygenated H_2O[22] led to an amino alcohol product. In light of the fact that there are no other reports of amino alcohol products arising from SmI_2-induced reductive cyclization, in which typically only three to four equivalents of SmI_2 are employed, we hypothesized that only through the use of a gross excess of SmI_2 in conjunction with a donor ligand additive such as HMPA would the desired cascade sequence proceed.

Most gratifyingly, after treatment of aldehyde–oxime **18** with a premixed complex of 9.0 equiv of SmI_2 and 36.0 equiv of HMPA in THF at ambient temperature for 1 h, followed by quenching with aqueous NH_4Cl, extraction, solvent removal, and subsequent peptide coupling with a DMF solution of AcOH, EDC, and HOBt, we observed the formation of compound **22** as a mixture of stereoisomers in 25% overall yield (Scheme 4). In the event, we believe that initial exposure of **18** to SmI_2/HMPA led to the generation of diradical intermediate **19**, which then cyclized to provide **20**. The presence of excess SmI_2 complexed with HMPA then effected N–O cleavage, which first led to intermediate **21**, and then provided the desired amino alcohol upon workup which was trapped as its acetamide (**22**). As such, each step in the cascade proceeded in an average yield of 63%. Although one could also envision solely the generation of a ketyl radical which then engaged the oxime directly to provide **20**, the isolation of noncyclized material with both the aldehyde and oxime reduced suggests that diradical **19** cannot be excluded. In accordance with earlier reports exploring aldehyde–oximes,[13a,e] the macrocyclization did not proceed at all in the absence of HMPA. Significantly, when the ratio of HMPA/SmI_2 was reduced from 4:1 to 2:1 (still with 9.0 equiv of SmI_2), **22** was observed along with significant amounts of cyclized product with the N–O linkage firmly intact, indicating that the presence of a suitable donor ligand in conjunction with excess SmI_2 is the critical combination required for reliable oxime cleavage after reductive cyclization. Moreover, these results suggest that in cases where one wishes to effect only N–O cleavage, the addition of HMPA might greatly facilitate the transformation in cases which prove difficult or low-yielding with SmI_2 alone.[20a,c] This proposition, along with an exploration of the generality of this cascade sequence, is the subject of current investigations. Finally, one should note that the final peptide coupling is a highly general reaction and L-valine amino acids bearing Fmoc, Boc, and Cbz protecting groups were readily coupled in yields comparable to those obtained with AcOH. This procedure represents a step forward in terms of overall synthetic utility, since previous reports have only indicated that products from SmI_2 reactions could be trapped directly with simple acylating reagents.

After the desired cascade sequence, oxidation of **22** to ketoamide **23** was smoothly effected with Dess–Martin periodinane in 94% yield. As shown in Scheme 5, formation of the A-ring oxazole was then accomplished by heating **23** in neat $POCl_3$ at 70 °C for 2 h, providing **24** and **25** in a ratio of 2.4:1 and in an overall yield of 65%.[23] The formation of **25** was significant in that it indicated that MOM cleavage was far more facile with the heterocyclic skeleton completed, since numerous synthetic precursors such as **16** were recovered unscathed under these reaction conditions.[24] Simply treating **25** with aqueous NaOH in THF[25] then readily effected the expulsion of formaldehyde which led to the fully deprotected diazonamide skeleton **26**. Additionally, the A-ring oxazole could also be fashioned from **23** with *p*TsOH in refluxing benzene, albeit in lower yield with prolonged reaction times, whereas the use of the Burgess reagent in refluxing THF[26] afforded **24** exclusively in comparable yield to that obtained with $POCl_3$.



Scheme 4. Novel pinacol coupling cascade sequence to efficiently prepare ketoamide **23**. a) SmI_2 (0.1M in THF, 9.0 equiv), HMPA (36 equiv), THF, 25 °C, 1 h; then saturated aq. NH_4Cl, 25 °C, 1 h; solvent removal; then AcOH (3.0 equiv), EDC (3.0 equiv), HOBt (3.0 equiv), DMF, 25 °C, 4 h, 25% overall, 63% per synthetic operation in the cascade sequence; b) Dess–Martin periodinane (15 equiv), $NaHCO_3$ (50 equiv), CH_2Cl_2, 25 °C, 1.5 h, 94%. HMPA = hexamethylphosphoramide, EDC = 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide, HOBt = 1-hydroxy-1*H*-benzotriazole.

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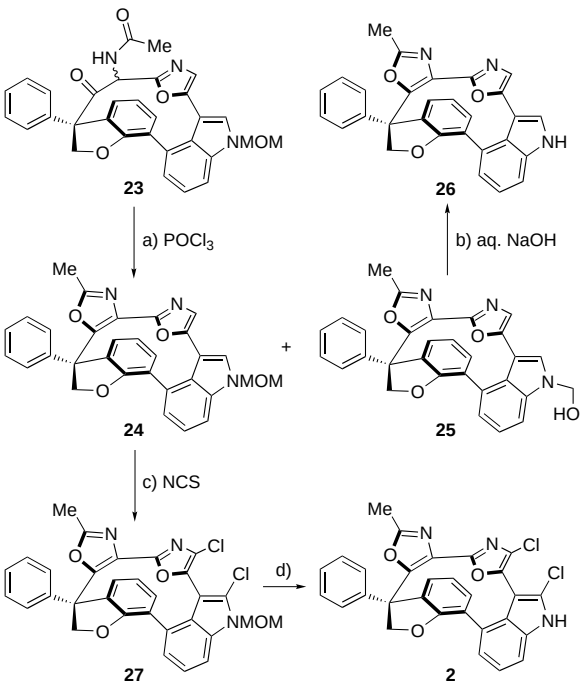

Scheme 5. Completion of the synthesis of the fully elaborated heterocyclic skeleton **2** of diazonamide A (**1**). a) $POCl_3$, 70 °C, 2 h, **24**/**25** (2.4:1), 65 %; b) aq. NaOH (15 %, excess), THF, 25 °C, 10 min, 74 %; c) NCS (3.0 equiv), THF/CCl_4 (1:1), 55 °C, 8 h, 73 %; d) BBr_3 (1.0 M in CH_2Cl_2, 2.0 equiv), CH_2Cl_2, −78 °C, 20 min; then aq. NaOH (15 %, excess), THF, 25 °C, 10 min, 61 %.

In a final study, exposure of **24** to 3.0 equiv of NCS in THF/CCl_4 (1:1) at 55 °C for 10 h cleanly provided dichloro compound **27** as a single atropisomer along the C_{24}–C_{26} biaryl axis. Formation of the ABCDEF macrocycle prior to chlorination was critical for the selectivity of this reaction, as chlorination of earlier synthetic intermediates such as **17** proceeded with equal facility, but provided a 1:1 mixture of atropisomers which could not be interconverted in CD_3CN at 340 K over 30 min. Subsequent use of BBr_3 in CH_2Cl_2 at −78 °C for 20 min led to the exclusive cleavage of the methyl ether linkage of the MOM protecting group in **27**, which upon immediate treatment with aqueous NaOH completed the synthesis of **2** in just sixteen linear steps from known or commercially available starting materials.[27]

In summary, the entire highly strained ABCDEF aromatic core of diazonamide A has been constructed and a novel samarium(II)-based macrocyclization cascade reaction has been developed. Applications of the gathered knowledge and developed technology to the total synthesis of diazonamide A and analogues thereof for chemical biology studies are anticipated.

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Studies in the Total Synthesis of Heliquinomycinone: Proof of Concept and Assembly of a Fully Mature Spirocyclization Precursor**

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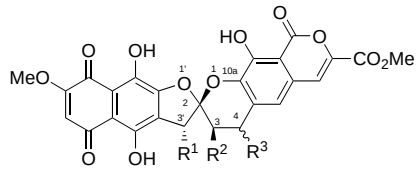
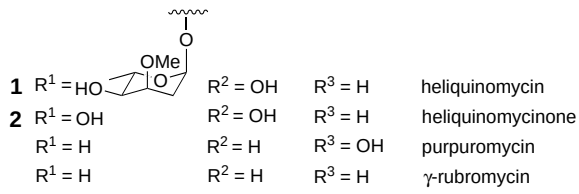
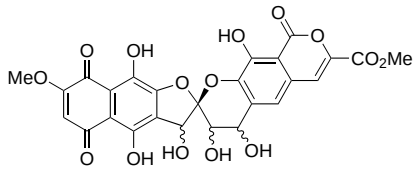
Heliquinomycin (**1**) was isolated by Chino et al. from *Streptomyces sp.* MJ 929-SF2.[1] The structure of its aglycone moiety **2**, which we term heliquinomycinone, is related to structures encountered in the purpuromycin,[2] γ-rubromycin,[3] and griseorhodin antibiotics.[4] Although spiroketal







griseorhodin C

linkages in natural products are well known,[5] it is less common that such a moiety is derived from two phenolic hydroxy groups (C2). An arrangement in which the spiroketal core of the hexacyclic structure is linked to a glycoside, in this case to a 2,6-dideoxyhexose (cymarose) sugar, seems to be unique to **1**.

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