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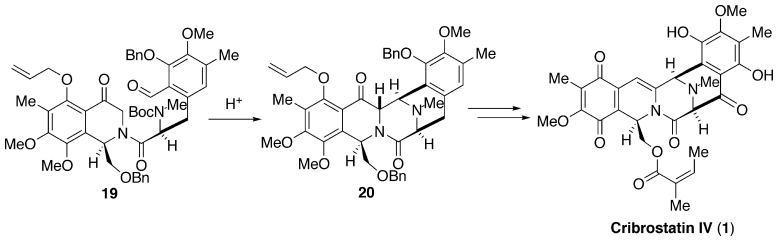

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Total Synthesis of Cribrostatin IV: Fine-Tuning the Character of an Amide Bond by Remote Control

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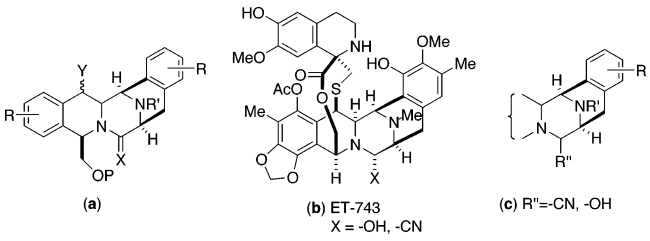
The piperizinohydroisoquinoline motif (**a**) appears in a diverse series of alkaloids, including naphthyridinomycin, the quinocarcinoids, the saframycins, the reneiramycins, and the ecteinascidins.[1] Exemplary of the ecteinascidins is ET-743,[2] (**b**), one of the most potent cytotoxins known. This drug, whose availability is to a great extent due to the dominant total synthesis of E. J. Corey and associates,[3] is currently being evaluated at various clinical levels for the treatment of a range of cancers.

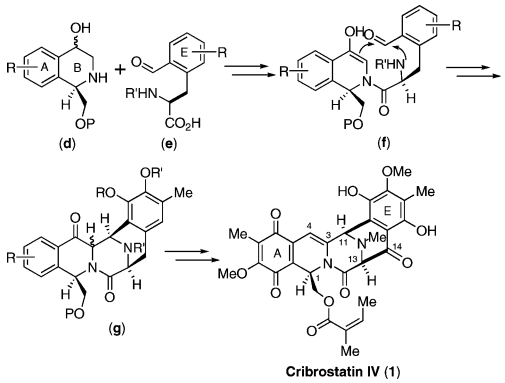


In 2000, Pettit reported the isolation and structural deduction of a neoplastic agent, cribrostatin IV (**1**), from a blue marine sponge, *Cribrochalina*, in reef passages in the Republic of Maldives.[4] Shortly thereafter, Kubo and colleagues reported a reassignment of the structure of the semisynthetically derived reneiramycin H,[5a] thereby showing it to be the same as **1**.[5b]

Several considerations converged to direct our attentions to a possible total synthesis of cribrostatin IV (**1**). While lacking the propeller-like character of ET-743, **1** is arguably the most functionalized of the traditional pentacyclic-type core alkaloids. *Thus, every skeletal carbon atom in **1** appears in oxidized form, with its A-ring in the quinonoidal oxidation level and its E-ring as an ET−saframycin "hybrid"*[6] *in its core domain.* The presence of the C_3-C_4 double bond, in the context of the A-ring quinone, serves as a central connecting element in a formal vinylogous imidic network.[7] Also worthy of note is the hydroquinone E-ring, which owes its otherwise surprising stability to the presence of the keto group at C_{14}.[8]

Not the least intriguing feature of cribrostatin IV (**1**) is that it is a potent (low micromolar) cytotoxic agent. While in the context of saframycins and particularly ET-743, much higher cytotoxicities are expected and encountered, **1** lacks the characteristic N_2-C_{21} cyanomethinyl or the N_2-C_{21} hydroxymethinyl (i.e., hemiaminal) motifs [see (**c**)].[1] Pre-C_{21} iminium ion functionalities had been presumed to be essential to both in vitro and in vivo activity.[9] Because **1** is isolatable in only trace amounts, total synthesis could well surpass isolation as a means to access quantities of material suitable for evaluation of biological activity. Thus, a viable synthetic route to **1** could set into motion a focused discovery program seeking to optimize between potency, maximum tolerable dose, and therapeutic index of potential congeners.

Scheme 1. Synthetic Strategy for Cribrostatin IV (**1**)



Obviously, conciseness and efficiency would be pivotal for a total synthesis to service such broader ends. Our plan involved joining an AB-ring moiety to a putative DEF precursor via fashioning of an amide bond [see (**f**)]. In the defining **f** → **g** transformation, C_{11}, ultimately in the form of an aldehyde, interpolates itself between C_3 and N_{12}. This line of reasoning led us back to genus-type structures [(**d**) and (**e**)].

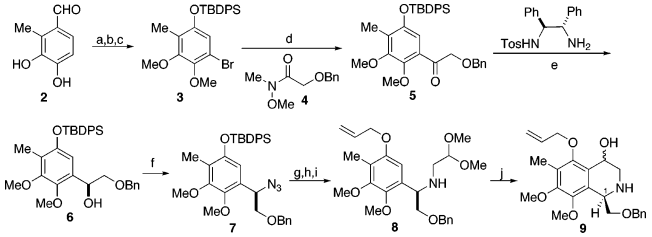
Needless to say, for such a scheme to be implementable in an organized way, the components to be merged [(**d**) and (**e**)] must be presented as suitably functionalized subunits, whose absolute configurations correspond, at pertinent stereogenic centers, to cribrostatin IV (**1**). Specifically, we elected to couple components **9** and **17**. We first describe the syntheses of these configurationally "matched" compounds using reagent-controlled enantiotopic induction in catalytic settings. From there, we go on to describe the first total synthesis of cribrostatin IV (**1**).

Commercially available 3-methyl-1,2-dimethoxybenzene was converted to **2** (Scheme 2).[10] Regiospecific bromination *ortho* to the phenolic group, followed sequentially by methylation and Baeyer−Villiger-like cleavage of the aldehyde function, provided a new phenol, in which the hydroxyl group was subsequently protected as its −TBDPS derivative (see compound **3**). Lithiation of the bromo function was followed by C-acylation with compound **4**, which corresponds to the Weinreb amide of −OBn glycolic acid.[11]

Entrance to the "chiral pool" was accomplished through reduction of the benzyl ketone (cf. **5** → **6**), following protocols first described by Noyori and associates.[12] Displacement of the hydroxyl group through the agency of diphenylphosphoryl azide provided **7**.[13] Reduction of **7**, and two-carbon homologation, followed by regiospecific exposure of the A-ring phenol group, was followed by its temporary protection in the form of allyl ether **8**. Finally, Bobbitt modified Pomeranz−Fritsch cyclization of **8** gave rise to **9**.[14] The configurational inhomogeneity of the future C_4 at the stage

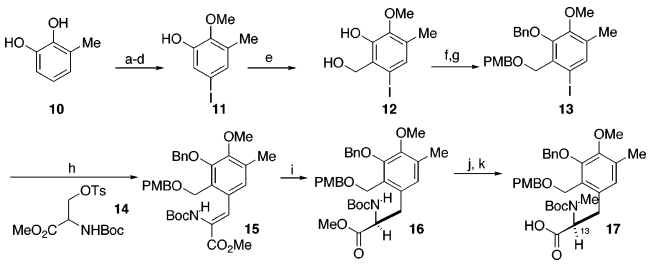
10.1021/ja050203t CCC: $30.25

Scheme 2. Synthesis of Coupling Partner **9**[a]



[a] Key: (a) i. Br_2, NaOAc, AcOH; ii. Me_2SO_4, Bu_4NBr, NaOH, CH_2Cl_2, 76% over two steps; (b) i. mCPBA, $CHCl_3$; ii. HCl, MeOH, 78% over two steps; (c) TBDPSCl, TEA, DMAP, DMF, 89%; (d) i. *n*-BuLi, toluene:THF (9:1), −78 °C; ii. **4**, 80% over two steps; (e) $(RuCl_2)_2$(*p*-cymene)$_2$, DMF/HCO_2H/TEA, 40 °C, 94%, 95% ee; (f) DPPA, DBU, toluene:DMF (9:1), 50 °C, 82%, 95% ee; (g) 5% Pd/C, 1 atm H_2, EtOAc, 80%; (h) i. $(MeO)_2CHCHO$, AcOH, $NaCNBH_3$, $MgSO_4$, MeOH; ii. TBAF, THF, 99% over two steps; (i) allyl bromide, NaH, DMF, 87%; (j) 8.0 M HCl/dioxane, 97%.

Scheme 3. Synthesis of Coupling Partner **17**[a]



[a] Key: (a) TsCl, Et_3N, CH_2Cl_2, 84%; (b) ICl, AcOH, 96%; (c) MeI, K_2CO_3, acetone, 95%; (d) NaOH, EtOH, 90%; (e) $(CH_2O)_n$, Et_2AlCl, CH_2Cl_2, 86%; (f) BnBr, K_2CO_3, acetone, 85%; (g) PMBCl, NaH, THF:DMF, 99%; (h) TEA, **14**,[18] Bu_4NBr, (*o*-tolyl)$_3$P, $Pd(OAc)_2$, CH_3CN, 87% (Z isomer only); (i) Rh[(COD)-(*S*,*S*)-Et-DuPhos]$^+TfO^-$, 100 psi H_2, CH_2Cl_2/MeOH, 93%, 99% ee; (j) LiOH, MeOH/THF/H_2O, 93%; (k) MeI, NaH, THF, 82%.

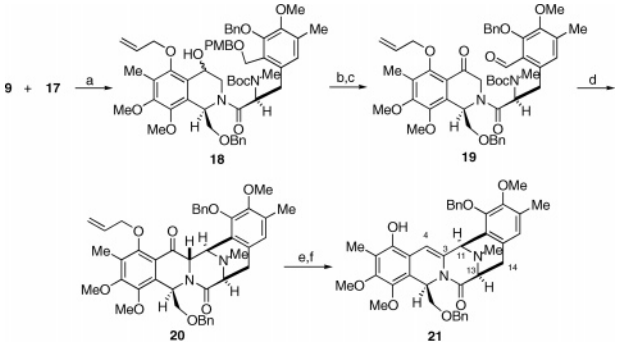
of **9** constitutes an esthetic awkwardness rather than a substantive complication to the overall synthesis (vide infra).

To reach the configurationally matched coupling partner **17**, we started with the commercially available 3-methylcatechol (**10**) (Scheme 3). Temporary protection of the less hindered phenol as its tosylate derivative was followed by regiospecific iodination. The iodo compound was converted, as shown, to **11**, which following *ortho*-hydroxymethylation, afforded **12**.[15]

To enable orderly progress, it would be helpful to differentiate the protecting patterns on the phenolic hydroxyl versus the benzylic alcohol, corresponding to the future C_{11} aldehyde. Fortunately, it proved possible to define conditions leading to clean benzylation of the phenolic group. This reaction was, in turn, followed by *para*-methoxybenzylation of the benzylic alcohol, giving rise to compound **13**. The latter served admirably as a substrate in a Jeffery−Heck coupling reaction, thus affording compound **15** as the only isomer.[16] Reduction of the double bond with enantiotopic control, in the manner indicated, afforded **16** in good yield.[17] Simple hydrolysis of the methyl ester and N-methylation gave rise to coupling partner **17**.

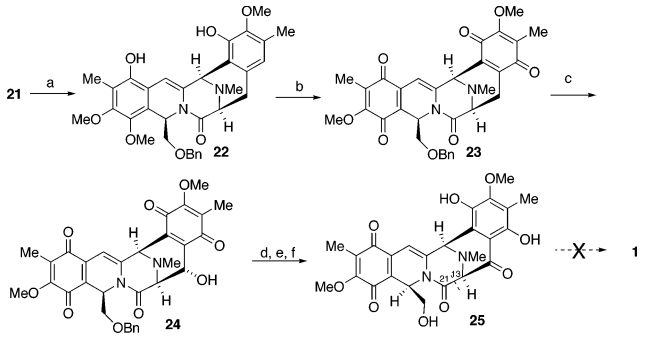
Amidation of the carboxylic acid of **17** with secondary amine **9** gave rise to **18** (Scheme 4).[19] Oxidative deprotection of the PMB group, followed by simultaneous oxidation of the primary and secondary alcohols, afforded the key *seco*-substrate **19**.[20] The stage was set for the critical intramolecular lynchpin-like Mannich reaction. In the event, cleavage of the Boc function of **19** set into motion a predictable sequence culminating in the desired product, **20**, in good yield.[21] From this intermediate, we were able to gain access to **21** in short order.

Scheme 4. Cyclization Leading to Pentacyclic Core **21**[a]



[a] Key: (a) BOPCl, TEA, CH_2Cl_2, 89%; (b) DDQ, CH_2Cl_2/buffer (pH 7), 90%; (c) DMP, 2,6-lutidine, CH_2Cl_2, 84%; (d) HCO_2H, 100 °C, 59%; (e) i. $NaBH_4$, THF/H_2O; ii. AcOH, Bu_3SnH, $(Ph_3P)_2PdCl_2$, CH_2Cl_2,[3] 98% over two steps; (f) CSA, benzene, 80 °C, 80%.

Scheme 5. Unsuccessful Route to **1**[a]

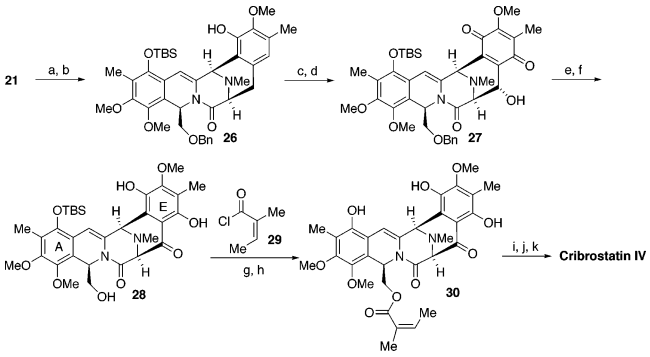


[a] Key: (a) 5% Pd/C, H_2 (1 atm) EtOAc; (b) Fremy salt, KH_2PO_4, CH_3CN/H_2O; (c) SeO_2, dioxane, 100 °C; (d) DMP, CH_2Cl_2; (e) 10% Pd/C, H_2 (1 atm), MeOH; (f) air, MeOH.

Compound **22**, arising from selective deprotection of the aromatic benzyl group of **21**, was oxidized with Fremy salt to afford bisquinone **23** (Scheme 5).[22] Oxidation of **23** with selenium dioxide occurred regio- and stereospecifically at C_{14} to give rise to **24**.[23] The latter, following exposure to Dess−Martin periodinane (DMP), gave rise to a relatively stable keto bisquinone. Reduction of the two quinone rings as well as deprotection of the primary alcohol at C_{22} was followed by selective air oxidation of the A-ring hydroquinone. Clearly, the selectivity in this oxidation arises from the high-energy character of the E-ring quinone due to the C_{14} ketone.[24] Compound **25**, requiring only "angelation" of the primary alcohol (see C_1 hydroxymethyl group), was now in hand.

However, despite extensive efforts, all attempts to accomplish the requisite esterification failed. Substrate **25** exhibited instability to a range of mildly basic conditions of the type needed to mediate the acylation reaction. We attributed the vulnerability of the substrate to various bases as reflecting its susceptibility to nucleophilic attack at C_{21}. This was then followed by cleavage of the $C_{21}-C_{13}$ (β-dicarbonyl) bond.[25] It was noted that the character of the C_{21} carbonyl function in compound **25** was that of a vinylogous imide. Indeed in such a context, the β-dicarbonyl connectivity of C_{14} and C_{21} could well exhibit high base lability. Our remaining possibility was to attempt the esterification at an earlier stage, while the A-ring was in the hydroquinone, rather than in the quinone, oxidation level. We hoped that this change in oxidation level, though somewhat remote from the reactive C_{21} center, could profoundly alter its character in electronic terms, perhaps allowing for angelation at C_{22}. Of course, in such a setting, we would be obliged to conduct significant chemistry with the potentially labile angelate already in place.

Scheme 6. Completion of Synthesis of Cribrostatin IV (**1**)[a]



[a] Key: (a) TBSOTf, TEA, CH_2Cl_2, 90%; (b) 5% Pd/C, H_2 (1 atm), EtOAc, 90%; (c) Fremy salt, KH_2PO_4, CH_3CN/H_2O, 84%; (d) SeO_2, dioxane, 100 °C, 87%; (e) DMP, CH_2Cl_2; (f) 10% Pd/C, H_2 (1 atm), MeOH, 89% over two steps; (g) **29**, CH_2Cl_2; (h) AcOH, TBAF, THF, 75% over two steps; (i) PIFA, CH_3CN/H_2O; (j) Zn, AcOH; (k) air, DMF, 24 h, 65% over three steps.

In the event, compound **26**, prepared from compound **21**, was oxidized to **27**, and the latter converted to **28** according to the procedures described above (Scheme 6). Upon treatment of **28** with acyl chloride **29**,[26] angelation occurred uneventfully. Compound **30** was obtained following TBS deprotection. The angelated intermediate, **30**, was converted to cribrostatin IV (**1**) through a series of straightforward manipulations of rings A and E.[8] The selective air oxidation of the ring A hydroquinone in the last step follows, as above (see **24** → **25**), from the high-energy character of an E-ring quinone flanked by a ketone.[24] The spectroscopic properties of synthetic **1** were in complete accord with those of natural cribrostatin IV (**1**).[4]

In summary, an enantioselective synthesis of cribrostatin IV (**1**) has been accomplished through a convergent coupling of two extremely functionalized, matched enantiopure compounds, a "lynchpin Mannich" cyclization to establish the pentacyclic core, a selective angelation strategy, and the use of the C_{14} keto function to distinguish between two hydroquinone−quinone oxidation resting states in rings A and E. A key feature of the synthesis described above was the ability to modulate the character of N_2 and, accordingly, C_{21} by varying the oxidation state of ring A. It is well within reason that this concept[27] could find further application in fine-tuning SAR profiles of prospective drug candidates in this series. Studies of the SAR profiles of analogues of cribrostatin IV (**1**) by synthesis or by diverted total synthesis[28] are underway.

Acknowledgment. This paper is dedicated to the memory of Professor Louis Fieser, who explicated the notion of high-energy quinones to one of the authors in 1959 (see ref 24). The authors wish to thank Professor G. Pettit for a sample of natural cribrostatin IV, which was used for comparison to the synthesized material. This work was supported by the National Institutes of Health (Grant HL 25848) and by Pharmamar Corporation of Madrid, Spain. R.H. is grateful for financial support from Merck.

Supporting Information Available: Experimental procedures, ^1H and ^{13}C spectra, optical rotations, HRMS, and additional information on key intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a review of these compounds, see: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669.
(2) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Stroh, J. G.; Keifer, P. A.; Sun, F.; Li, L. H.; Martin, D. G. *J. Org. Chem.* **1990**, *55*, 4512.
(3) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202.
(4) Pettit, G. R.; Knight, J. C.; Collins, J. C.; Herald, D. L.; Pettit, R. K.; Boyd, M. R.; Young, V. G. *J. Nat. Prod.* **2000**, *63*, 793.
(5) (a) Parameswaran, P. S.; Naik, C. G.; Kamat, S. Y. *Indian J. Chem.* **1998**, *37B*, 1258. (b) Saito, N.; Sakai, H.; Suwanborirux, K.; Pummangura, S.; Kubo, A. *Heterocycles* **2001**, *55*, 21.
(6) Martinez, E. J.; Corey, E. J. *Org. Lett.* **1999**, *1*, 75.
(7) For an elegant solution to reaching the C3−C4 olefin series bearing the C21 lactam, see: Jin, W.; Metobo, S.; Williams, R. M. *Org. Lett.* **2003**, *5*, 2095. For a particularly concise route to saframycin, see: Myers, A. G.; Kung, D. W. *J. Am. Chem. Soc.* **1999**, *121*, 10828.
(8) Saito, N.; Harada, S.; Nishida, M.; Inouye, I.; Kubo, A. *Chem. Pharm. Bull.* **1995**, *43*, 777.
(9) Jin, S.; Gorfajn, B.; Faircloth, G.; Scotto, K. W. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 6775.
(10) Sinhababu, A. K.; Ghosh, A. K.; Borchardt, R. T. *J. Med. Chem.* **1985**, *28*, 1273.
(11) Williams, R. M.; Ehrlich, P. P.; Zhai, W.; Hendrix, J. *J. Org. Chem.* **1987**, *52*, 2615.
(12) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521.
(13) Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886.
(14) (a) Bobbitt, J. M.; Sih, J. C. *J. Org. Chem.* **1968**, *33*, 856. (b) Bobbitt, J. M.; Moore, T. E. *J. Org. Chem.* **1968**, *33*, 2958.
(15) Bigi, F.; Casiraghi, G.; Casnati, G.; Sartori, G.; Fava, G. G.; Belicchi, M. F. *J. Org. Chem.* **1985**, *50*, 5018.
(16) (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, *19*, 1287. (b) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synthesis* **1994**, *1*, 31.
(17) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.
(18) Attempts to perform the Jeffery−Heck reaction directly with dehydroalanine gave lower yields due to polymerization. Accordingly, precursor **14** was used, and the requisite dehydroalanine was formed in situ.
(19) For previous examples of connecting the subunits by amide bond formation to a secondary amine, see: (a) Martinez, E. J.; Corey, E. J. *Org. Lett.* **2000**, *2*, 993. (b) Zhou, B.; Guo, J.; Danishefsky, S. J. *Tetrahedron Lett.* **2000**, *41*, 2043.
(20) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 902.
(21) In our previous demonstration of this type of reaction (see ref 19b), a *syn* relationship was established between C_3 and C_{11}. In the case of **19** → **20**, the relationship is *anti*. We note that, to the best of our knowledge, compound **20** is the first example of a C_3-C_{11} *anti* structure in the saframycin-like backbone series. It is now recognized that the C_3-C_{11} *anti* vs *syn* relationship is governed by the relative configurations at C_1 and C_{13}. In the matched series, as shown in **19**, we obtain *anti* product. With C_1 as shown, and C_{13} in the D-amino acid configuration, the C_3-C_{11} relationship emerges *syn*. A full account of this remote control element will be provided shortly.
(22) Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229.
(23) (a) Saito, N.; Ohira, Y.; Wada, N.; Kubo, A. *Tetrahedron* **1990**, *46*, 7711. (b) Saito, N.; Ohira, Y.; Kubo, A. *Chem. Pharm. Bull.* **1990**, *38*, 821. (c) Saito, N.; Nishida, M.; Kubo, A. *Chem. Pharm. Bull.* **1991**, *39*, 1343.
(24) Conant, J. B.; Fieser, L. F. *J. Am. Chem. Soc.* **1924**, *46*, 1858.
(25) The range of products arising from the unraveling of the amidic *β*-dicarbonyl system has not been fully sorted out. However, we have support for $C_{13}-C_{21}$ bond cleavage in some products.
(26) Beeby, P. J. *Tetrahedron Lett.* **1977**, *18*, 3379.
(27) The notion of the reductive unveiling of drug-like activity from bioactivatable pro-drugs was globally summarized in 1977: Moore, H. W. *Science* **1977**, *197*, 527. For a summary of its pertinence to the mitomycins, see: Danishefsky, S. J.; Schkeryantz, J. M. *Synlett* **1995**, 475.
(28) Njardarson, J. T.; Gaul, C.; Shan, D.; Huang, X.-Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 1038.

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