A Remarkable Glycosylation Reaction: The Total Synthesis of Calicheamicin γ_1^I

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Abstract: An account of the reasoning and reduction to practice of a highly convergent total stereospecific synthesis of calicheamicin γ_1^I (**1**) is provided. The key finding was the use of a very mild promoter system (silver triflate and 4 Å molecular sieves in methylene chloride) to allow for coupling of trichloroacetimidate **21** with advanced calicheamicinone-like acceptors (see **17** and **18**). Glycosidation with **17** affords a 3:1 ratio of equatorial to axial glycosides. The use of **18** seems to afford only the equatorial β-glycoside. Remarkably, use of the enantiomer of **17** as the acceptor gave an 18:1 ratio of axial to equatorial product.

Introduction

In the preceding paper[1] we have outlined the strategies which culminated in the total synthesis of the oligosaccharide domain of calicheamicin γ_1^I (**1**).[2] Using lessons garnered from earlier investigations in the esperamicin series, and profiting from studies conducted while reaching the methyl glycoside of that domain, the nature of the required protection states of the nitrogen function of the hydroxylamino group (TEOC) and the various hydroxyl groups in the domain was identified. In the remarkable total synthesis of **1** by Nicolaou and colleagues,[2] this eventual hydroxylamine connector was contained, at the point of glycosylation, in oxidized form as an oxime−ether linkage. Thus, reduction of the oxime ether was necessary after glycosylation. In this critical sense, the two syntheses were quite different. However, the Nicolaou effort did provide for us a valuable insight as to the means for protecting (FMOC) the nitrogen of the *N*-ethyl group. In this way, the aryltetrasaccharide domain, in the required oxidation state, girded with necessary and realistic blocking groups, and containing a free reducing end, was prepared. Earlier, we had described[3,4] the first synthesis of (±)-calicheamicinone (**4**), the fully functionalized aglycon segment of calicheamicin. In this paper we describe and document the intertwining of these efforts, in the process of achieving a highly convergent total synthesis of **1**.[5]

Synthetic Strategy

The complex and highly functionalized structure of calicheamicin would benefit from a convergent strategy in which the suitably protected fragments of the molecule could be assembled and unmasked effectively under conditions consistent with survival of the multifaceted and labile functionality which is present in the coupling product. Broadly speaking, two general views of the coupling problem could be entertained. In one paradigm, coupling is conducted where either the aglycon or the carbohydrate domain is not yet fully functional. While the use of less elaborated coupling partners would favor the success of the coupling step per se, the disadvantage would lie in the need for buildup of the missing functionality in a highly complex setting. More preferable from our perspective was the strategy of coupling the most advanced possible components. While this policy places maximum demands on the coupling reaction, it would benefit from minimal manipulation subsequent to convergence.

Since the prospects for fashioning the enediyne linkages or the bridgehead enone or tertiary alcohol functionalities post-glycosylation were intimidating, these moieties surely had to be in place in a realistic glycosyl acceptor. The issue which awaited experimental clarification centered around the nature of the allylic functionality at the C_1 bridge (see R in structure **2**). To approach ultimate convergence, the provocative allylic trisulfide linkage should be in place in the aglycon acceptor. The Nicolaou total synthesis[2] had, of course, demonstrated that this allylic trisulfide could be fashioned postglycosylation in a multistep program starting with a protected allylic alcohol (in **2**, R = benzoate). A central element of our strategy in fashioning a glycosyl donor (cf. **3**), which corresponds in oxidation level to that sector in the target, was the hope that coupling and deprotection could, perhaps, be conducted with *the trisulfide already in place*. These thoughts gave rise to a

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(1) Preceding paper in this issue: Halcomb, R. L.; Boyer, S. H.; Wittman, M. D.; Olson, S. H.; Denhart, D. J.; Liu, K. K. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, XXX.

(2) For the first total synthesis of calicheamicin, see: (a) Nicolaou, K. C.; Hummel, C. W.; Pitsinos, E. N.; Nakada, M.; Smith, A. L.; Shibayama, K.; Saimoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 10082. (b) Groneberg, R. D.; Miyazaki, T.; Stylianides, N. A.; Schulze, T. J.; Stahl, W.; Schreiner, E. P.; Suzuki, T.; Iwabuchi, Y.; Smith, A. L.; Nicolaou, K. C. *Ibid.* **1993**, *115*, 7593. (c) Smith, A. L.; Pitsinos, E. N.; Hwang, C.-K.; Mizuno, Y.; Saimoto, H.; Scarlato, G. R.; Suzuki, T.; Nicolaou, K. C. *Ibid.* **1993**, *115*, 7612. (d) Nicolaou, K. C.; Hummel, C. W.; Nakada, M.; Shibayama, K.; Pitsinos, E. N.; Saimoto, H.; Mizuno, Y.; Baldenius, K.-U.; Smith, A. L. *Ibid.* **1993**, *115*, 7625.

(3) (a) Cabal, M. P.; Coleman, R. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 3253. (b) Haseltine, J. N.; Cabal, M. P.; Mantlo, N. B.; Iwasawa, N.; Yamashita, D. S.; Coleman, R. S.; Danishefsky, S. J.; Schulte, G. K. *Ibid.* **1991**, *113*, 3850.

(4) For the first total synthesis of (−)-calicheamicinone, see: Smith, A. L.; Hwang, C.-K.; Pitsinos, E. N.; Scarlato, G. R.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1992**, *114*, 3134.

(5) For a preliminary communication see: Hitchcock, S. A.; Boyer, S. H.; Chu-Moyer, M. Y.; Olson, S. H.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 858.

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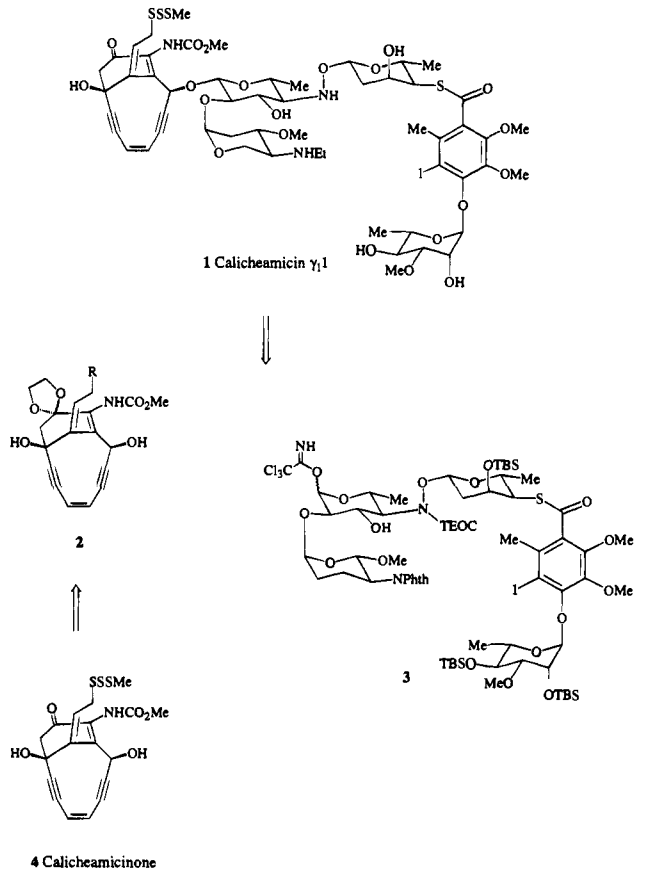
Scheme 1

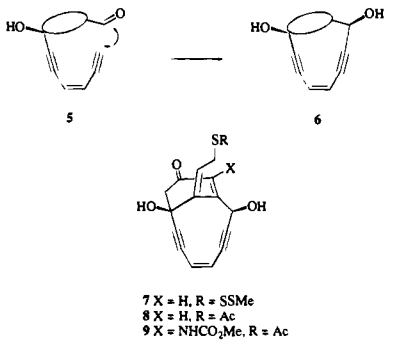


retrosynthetic analysis which called for employment of a suitably protected glycosyl donor, **3** (the elaboration of which is discussed in the preceding paper), and a masked form of the enantiopure aglycon **2** as the requisite intermediates (Scheme 1). Experiments would reveal which version of **2** (R = protected hydroxyl; R = protected thiyl; R = SSSMe) could possibly be sustained in the synthesis.

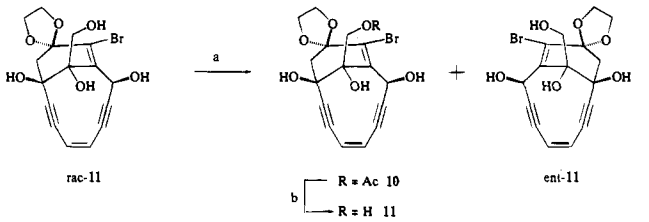
Discussion of Results

Aglycon Synthesis. The first synthesis of racemic calicheamicinone (**4**) was reported by our laboratory in 1990.[3] Pivotal to this synthesis, and the syntheses of less elaborate constructs reported by us[6] and others,[7] was the closure of the bicyclic enediyne-containing framework via cyclization of an acetylide anion to the corresponding secondary alcohol in a stereoselective fashion (Scheme 2, **5** → **6**). This reaction in various modified forms has found broad application in syntheses of complex enediynes. In the evolutionary stages of this program, the synthesis of a series of functionalized aglycon derivatives including (±)-descarbamoylcalicheamicinone (**7**)[8] was thus realized, culminating in calicheamicinone (**4**) itself along with the *S*-acetate analogs **8** and **9**. Subsequently, we

Scheme 2

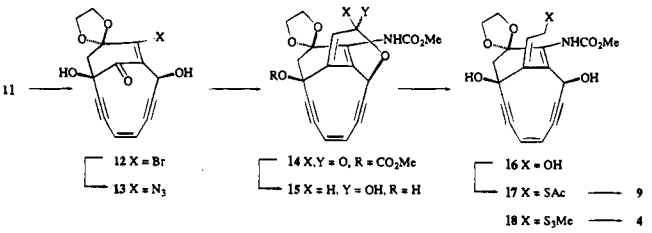


Scheme 3



[a] Conditions: (a) vinyl acetate, lipase PS-30, DME; (b) 7 N NH_3, MeOH.

Scheme 4



reported[9] an enzymatically mediated resolution protocol which afforded key intermediates **11** and *ent*-**11** en route to calicheamicinone, in enantiomerically homogeneous form (Scheme 3). Following the protocols documented for the synthesis of racemic calicheamicinone,[3] the natural and unnatural enantiomers of **4**, as well as the *S*-acetate congeners **9** and *ent*-**9** (Scheme 4),[10] were prepared.

Biological evaluation of these and other aglycon derivatives, lacking the carbohydrate domain, as potential DNA cleaving agents led to a series of striking findings. Firstly,[11,12] the double-stranded DNA cleaving capacity of these aglycon derivatives although reduced in magnitude, and without any of the sequence selectivity exhibited by the intact drug, was still formidable relative to conventional organic DNA cleaving agents. Secondly,[11] it became apparent that the *S*-acetate analogs **8** and **9** could be more conveniently activated for Bergman cyclization simply by pH adjustment, obviating the need for the exogenous reducing agents required for triggering the corresponding trisulfide analogs. Thirdly,[10] and perhaps most intriguingly, the fully deprotected aglycon *S*-acetate *ent*-**9** possessing the unnatural absolute configuration exhibited a significantly higher propensity for cleaving double-stranded DNA than did com-

(6) Danishefsky, S. J.; Mantlo, N. B.; Yamashita, D. S.; Schulte, G. *J. Am. Chem. Soc.* **1988**, *110*, 6890.

(7) Calicheamicin: (a) Kende, A. S.; Smith, C. A. *Tetrahedron Lett.* **1988**, *29*, 4217. (b) Crévisy, C.; Beau, J.-M. *Tetrahedron Lett.* **1991**, *32*, 3171. (c) Semmelhack, M. F.; Gallager, J. J.; Minami, T.; Date, T. *J. Am. Chem. Soc.* **1993**, *115*, 11618. Dynemicin: (d) Nicolaou, K. C.; Hwang, C.-K.; Smith, A. L.; Wendeborn, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 7416. (e) Nishikawa, T.; Isobe, M.; Goto, T. *Synlett* **1991**, 393. (f) Wender, P. A.; Zercher, C. K. *J. Am. Chem. Soc.* **1991**, *113*, 2311. (g) Wender, P. A.; Zercher, C. K.; Beckham, S.; Haubold, E.-M. *J. Org. Chem.* **1993**, *58*, 5867. Neocarzinostatin chromophore: (h) Myers, A. G.; Harrington, P. M.; Kuo, E. Y. *J. Am. Chem. Soc.* **1991**, *113*, 694.

(8) (a) Haseltine, J. N.; Danishefsky, S. J.; Schulte, G. *J. Am. Chem. Soc.* **1989**, *111*, 7638. (b) Haseltine, J. N.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2576.

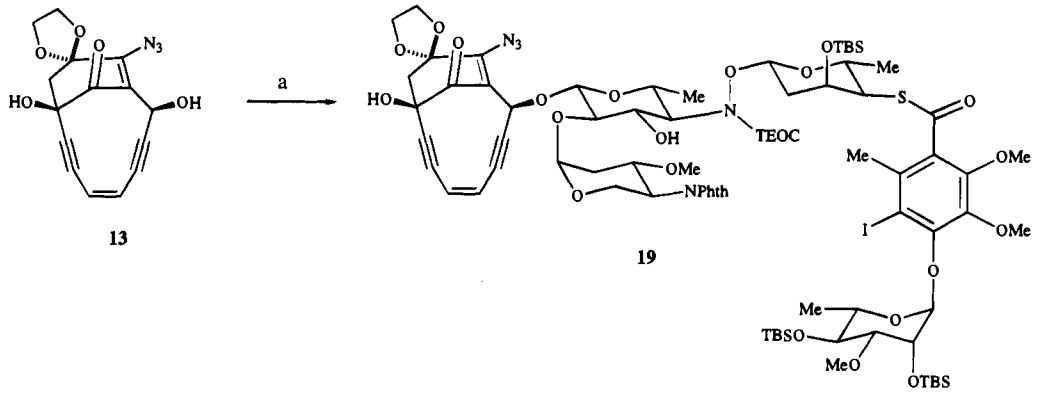
(9) Rocco, V. P.; Danishefsky, S. J.; Schulte, G. K. *Tetrahedron Lett.* **1991**, *32*, 6671.

(10) Aiyar, J.; Hitchcock, S. A.; Denhart, D. J.; Liu, K. K.-C.; Danishefsky, S. J.; Crothers, D. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 855.

(11) Drak, J.; Iwasawa, N.; Danishefsky, S. J.; Crothers, D. M. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 7464.

(12) Aiyar, J.; Danishefsky, S. J.; Crothers, D. M. *J. Am. Chem. Soc.* **1992**, *114*, 7552.

Scheme 5



[a] Conditions: (a) **3**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C (28%).

pound **9** which is of the natural absolute configuration. Furthermore, the inherent difference between the two enantiomers could not be overridden by the presence of the carbohydrate domain in the absence of a covalent link between the recognition and cleaving elements.[10] Preincubation of the DNA with the oligosaccharide portion of **1** in the form of its methyl glycoside, followed by exposure to the racemic *S*-acetates, led to the appearance of enhanced cleavage sites at positions flanking the carbohydrate binding region.[12] Although the observed effect was in the same direction when repeated individually with each enantiomer, the greater potency of the unnatural enantiomer as a DNA cleaving effector prevailed.[10] Thus, it became apparent that the carbohydrate component of calicheamicin was responsible for the bulk of the DNA sequence selectivity of the drug, but when not covalently bound to the aglycon was unable to influence the inherently greater efficacy of the unnatural enantiomer as a DNA cleaving agent. These revelations stimulated the pursuit of drug congeners bearing the unnatural aglycon in addition to the ultimate goal system, calicheamicin itself.

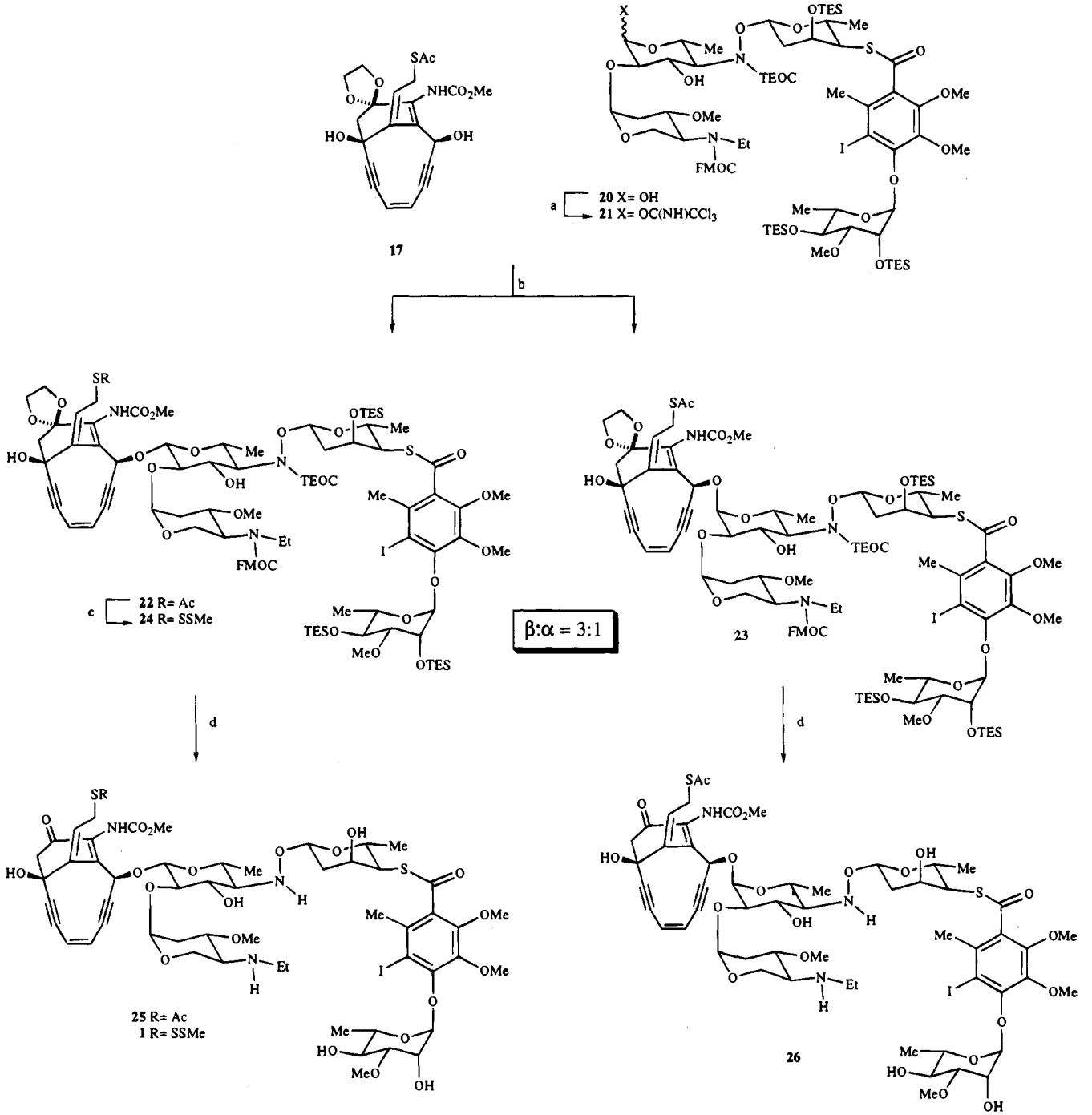
Coupling Strategies. The first demonstration of the possibility of coupling a complete calicheamicin aryltetrasaccharide to a functionalized enantiopure aglycon precursor was disclosed in 1992.[13] Activation of the glycosyl donor as the corresponding trichloroacetimidate according to the method of Schmidt[14] was selected in recognition of the relatively mild conditions employed, and the impressive range of glycosylations achieved by this method. In practice, treatment of the imidate **3**, bearing *N*-phthalyl protection, as a mixture of anomers (ca. 3:1 α:β) with the aglycon azide **13** in CH_2Cl_2 in the presence of $BF_3{\cdot}OEt_2$ at low temperature afforded the desired glycoside **19** in modest yield as a mixture of anomers (1:3 α:β) (Scheme 5). Although the viability of the approach was suggested, it became evident that the underdeveloped state of the components which went into fashioning **19** rendered the total synthesis venture nonfeasible. While all of the deprotections proved to be possible in the course of preparing the aryltetrasaccharide domain, attempts to extend this chemistry to achieve deprotection of **19** were confounded.

As described in the previous paper,[1] we refashioned our protecting groups on the donor to those shown in **20**. We first evaluated the possibility of using a trisulfide-bearing aglycon (see **18**) as the acceptor with trichloracetimidate **21** as the donor. We were, however, disappointed to witness decomposition of **18** upon exposure to standard coupling conditions employing $BF_3{\cdot}OEt_2$ as catalyst at −78 to −48 °C. Similar failures resulted from other activation catalysts including $ZnCl_2$ and *p*-toluenesulfonic acid. The times seemed to call for a tactical retreat. We thus turned our efforts to *S*-acetate **17** as a possible glycosyl acceptor. We were finally rewarded with success. Encouraged by recent reports describing silver triflate as a mild activating agent in the Schmidt glycosidation reaction,[15] we opted to apply this catalyst to a coupling between **17** and the trichloroacetimidate **21** prepared by treatment of lactol **20** with cesium carbonate[16] and trichloroacetonitrile in CH_2Cl_2 (Scheme 6). After exposure of **21** (ca. 3:1 α:β) and (−)-*S*-acetate **17** to silver triflate and 4 Å molecular sieves in CH_2Cl_2 for 12 h a separable 3:1 mixture of the desired β-coupled compound **22** along with the α-anomer **23** was obtained in a combined 58% yield. The conversion of *S*-acetate **22** to the corresponding trisulfide **24** was then successfully addressed following similar conditions described in our calicheamicinone synthesis.[3,17] Thus, the *S*-acetate **22** was treated with excess DIBAL in CH_2Cl_2 at −78 °C to expose the corresponding labile thiol which, after usual workup, was treated immediately with excess *N*-(methyldithio)-phthalimide to afford **24** in an overall 53% yield.

Having assembled all of the diverse functionalities of **24** to correspond to the goal system **1**, the remaining task of removing the protecting groups could now be addressed. As the first phase of deprotection, we elected to remove the ketal from the aglycon by treatment of **24** with CSA in aqueous THF. After 96 h, TLC analysis revealed several components presumably due to partial loss of the silyl protecting groups from the carbohydrate which accompanied the deketalization. Unperturbed by this, the crude mixture was carefully treated with TBAF at 0 °C (for ca. 15 min) to remove any persisting silyl groups along with exposure of the hydroxylamino and ethylamino NH groups from the TEOC and FMOC functions, respectively. *In this way calicheamicin* γ_1^I, identical with an authentic sample by physical and spectroscopic comparisons (TLC, $[\alpha]^{25}_D$, ^{1}H NMR, MS, and IR) was obtained. In a similar fashion, deprotection of **22** in a two-step sequence delivered **25**, the congener of **1** bearing an *S*-acetate in place of the trisulfide. As an additional source of corroboration for this structure, the high-field ^{1}H NMR spectrum of our synthetically prepared compound was identical with a spectrum kindly provided by Professor K. C. Nicolaou.[18] The corresponding α-anomer **23** was treated in an analogous manner to reveal **26**, which differs from **25** only at the configuration of the anomeric center linking the aglycon to the carbohydrate sector.

(13) Halcomb, R. L.; Boyer, S. H.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 338.
(14) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 213.
(15) Douglas, S. P.; Whitfield, D. M.; Krepinsky, J. J. *J. Carbohydr. Chem.* **1993**, *12*, 131.
(16) Urban, F. J.; Moore, B. S.; Breitenbach, R. *Tetrahedron Lett.* **1990**, *31*, 4421.
(17) For the first synthesis of a related trisulfide, see: Magnus, P.; Lewis, R. T.; Bennett, F. *J. Chem. Soc., Chem. Commun.* **1989**, 916.
(18) We thank Professor K. C. Nicolaou for apprising us of the existence of this compound and of its potent biological activity prior to publication.

Scheme 6



[a] Conditions: (a) Cs_2CO_3, Cl_3CCN, CH_2Cl_2, 25 °C (91%); (b) AgOTf, 4 Å molecular sieves, CH_2Cl_2, 25 °C, (58%); (c) DIBAL, CH_2Cl_2, −78 °C, then *N*-(methyldithio)phthalimide, CH_2Cl_2, 25 °C (54%); (d) camphorsulfonic acid, THF, H_2O, 25 °C, then TBAF, THF, 0 °C, R = Ac (40% overall), R = SSMe (37% overall).

In attempting to realize our goal of securing a product wherein the *ent*-aglycon is covalently linked to the carbohydrate segment of calicheamicin (*vide infra*), we witnessed a surprising result (Scheme 7). Coupling of *ent*-**17**, the aglycon derivative bearing the unnatural absolute configuration, with glycosyl donor **21** gave a 38% yield of a separable mixture of two anomers (in a ratio of 1:18). Remarkably, the *minor* product corresponded to the desired β-glycoside **27**, the major product being the α-glycoside **28**. This compound was deprotected in the usual two-step sequence, giving rise to **29**, the α-glycoside version of **25** bearing the *ent*-effector domain.

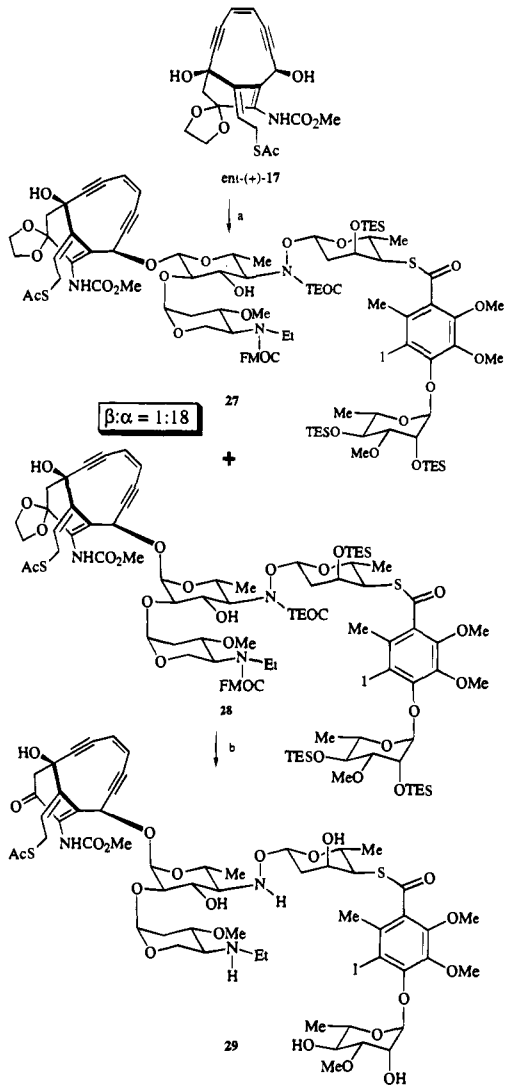
The marked difference in stereochemical outcome in the coupling reactions of two enantiomers of a glycosyl acceptor is not without precedent.[19] This effect can be attributed to double stereodifferentiation in which the donor forms matched and mismatched pairs with each enantiomer in the glycoside transition state. In general, we have noticed a pronounced predominance for α-glycoside formation in other examples in which glycosyl donor **21** has been employed in coupling reactions with a variety of nonrelated glycosyl acceptors.[20] A rationale for the fact that aglycon acceptor **17** affords predominantly β-coupled material rests on the reasoning that the transition state leading to the α-glycoside constitutes a mis-

(19) Spijker, N. M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 180.

(20) Boyer, S. H. Ph.D. Thesis, Yale University, New Haven, CT, 1994. Olson, S. H.; Hitchcock S. A.; Danishefsky, S. J. Unpublished results.

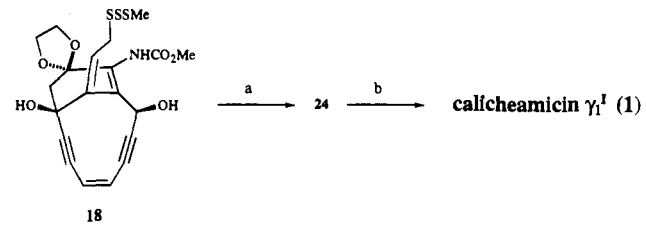
(21) None of the corresponding α-anomer has been detected as of this writing.

Scheme 7



[a] Conditions: (a) **21**, AgOTF, 4 Å molecular sieves, CH_2Cl_2, 25 °C (38%); (b) camphorsulfonic acid, THF, H_2O, 25 °C, then TBAF, THF, 0 °C (40% overall).

Scheme 8



[a] Conditions: (a) **21**, AgOTF, 4 Å molecular sieves, CH_2Cl_2, 25 °C, 34%; (b) camphorsulfonic acid, THF, H_2O, 25 °C, then TBAF, THF, 0 °C (32%).

matched pair. This is suggested by inspection of structure **27** wherein the relative chiralities of the two sectors render their accommodation in a single covalent structure quite difficult. By contrast, the axial glycoside linkage in **28** allows for much greater autonomy of the two sectors.

Finally, having demonstrated the effectiveness of our glycosidation procedure with the *S*-acetate-bearing aglycon derivatives **17** and *ent*-**17**, we were emboldened to reattempt coupling at the originally desired stage, i.e., that of trisulfide **18** (Scheme 8) using silver triflate–molecular sieves as the glycosidation promoter. Remarkably, a 34% yield of **24** was obtained. (Interestingly, none of the α-glycosidation product was observed.) Two-step deprotection of **24** had already been shown (*vide supra*) to provide calicheamicin γ^1_I. The feasibility of this coupling with the allylic trisulfide in place is eloquent testimony to the mildness of the conditions which have been devised. We note that this route now embodies ultimate convergence for the synthesis of calicheamicin since the aglycon portion is unveiled in a single (deketalization) step and the entire carbohydrate domain is delivered in a form where it is also retrieved in a single step (TBAF).

Summary. A highly convergent total synthesis of calicheamicin γ_1^I has been achieved. A donor trichloracetimidate (see structure **21**) was fashioned to fully correspond to the aryltetrasaccharide section of calicheamicin. The ultimate glycosyl acceptor was the enantiopure ketal **18**, which is the ketal of calicheamcinone (**4**). Full deprotection of product **24** is achieved in two steps: (i) acid-induced ketal cleavage and (ii) fluoride-induced cleavage of all silyl-based protecting groups and the FMOC function. Extensions of the use of glycosyl donor **21** with other acceptors to create various hybrid agents for biological evaluation are well underway.[20]

Experimental Section

Lipase Resolution of Racemic Tetrol (11) to Each Enantiomer. The corresponding acetate *rac*-**10** (2.99 g, 7 mmol) in anhydrous methanol (40 mL) was treated with 7 N NH_3 in methanol (70 mL) at room temperature. After the reaction was stirred for 2 h, the solvent was removed *in vacuo* and the residue was dissolved in DME (70 mL). Vinyl acetate (215 mL) and lipase PS-30 (18 g, 6 wt equiv) were added, and the reaction was stirred at room temperature (rt) for 6 days. The reaction mixture, after removal of lipase by filtration, was concentrated and subjected to SiO_2 column chromatography (ethyl acetate:hexane = 1:1 to 4:1) to give the enantiomerically enriched acetate **10** (72% yield) and nearly enantiomerically pure (+)-tetrol *ent*-**11** (98% ee (enantiomeric excess), 22% yield, $[\alpha]^{23}_D = +247.5°$ (*c* 1.05, MeOH), mp 84–85 °C). ^{1}H-NMR measurements of the derived Mosher esters were taken to determine the ee. The recovered enantiomerically enriched acetate was treated with 7 N NH_3 in MeOH to recycle back to the (−)-enriched tetrol **11**. The (−)-enriched tetrol **11** was subjected to lipase resolution as before at rt for 24 h. The usual workup followed by chromatography afforded enantiomerically pure (−)-acetate **10** (98% ee, 26% yield, $[\alpha]^{23}_D = -227.8°$ (*c* 0.6, MeOH)) and nearly racemic tetrol (70% yield). The enantiomerically pure (−)-acetate **10** was treated with 7 N NH_3 in MeOH to give (−)-tetrol **11** (98% yield, $[\alpha]^{23}_D = -248°$ (*c* 0.5, MeOH), mp 85–86 °C). After a total of three cycles of lipase double resolution we obtained a 42% yield of enantiomerically pure (−)-tetrol **11** and 40% of the enantiomerically pure (+)-antipode *ent*-**11**: IR (KBr) ν_{max} 3500–3320 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (d, J = 9.2 Hz, 1H), 5.85 (d, J = 9.2 Hz, 1H), 4.26–3.99 (m, 9H), 2.66 (d, J = 14.3 Hz, 1H), 2.56 (d, J = 14.3 Hz, 1H) ppm; HRMS (EI) for $C_{16}H_{15}BrO_6$, calcd 383.0130, found 383.0067.

***S*-Acetates 22 and 23.** Anhydrous cesium carbonate (18.6 mg, 57.1 μmol) was added in one portion to a stirred solution of lactol **20** (91.0 mg, 54.5 μmol) in dichloromethane (400 μL) and trichloroacetonitrile (82 μL, 820 μmol) and the mixture stirred at ambient temperature for 4 h. The mixture was then rapidly filtered through a short pad of silica, washing with 30% ethyl acetate in hexane. Concentration *in vacuo* afforded the crude trichloroacetimidate **21** (90.0 mg, 91%) as a yellow solid (ca. 3:1 α:β) which was immediatly combined with the aglycon *S*-acetate **17** (17.4 mg, 40.4 μmol), and the mixture was azeotroped from benzene (3 × 2 mL). Powdered, activated 4 Å molecular sieves (ca. 0.5 g) and dichloromethane (750 μL) were added, and the resulting mixture was stirred at ambient temperature for 15 min. Anhydrous silver(I) trifluoromethanesulfonate (12.7 mg, 49.5 μmol) was then added in one portion followed by stirring for a further 12 h in the dark. The mixture was then filtered through Celite, washing with ethyl acetate, and the filtrate concentrated *in vacuo*. Purification by column chromatography on silica, eluting with 50% ethyl acetate in hexane, afforded a mixture of α- and β-coupled compounds **22** and **23** (48.1 mg, 58%) which was further purified by column chromatography on silica, eluting with 20% ethyl acetate in benzene, to afford firstly the α-anomer **23** (11.0 mg, 13%) followed by the β-anomer **22** (31.2 mg,

37%) both as white foams. Data for **23**: $R_f = 0.33$ (silica, 20% ethyl acetate in benzene); $[\alpha]^{25}_D = -48°$ (*c* 0.83, CH_2Cl_2); IR (film) ν_{max} 2955, 2935, 2877, 1733, 1694, 1684, 1664, 1456, 1417, 1277, 1251, 1139, 1085, 1017, 963, 909, 838, 741, 667 cm^{-1}; ^1H NMR (490 MHz, DMSO-d_6, 100 °C) δ 7.84 (d, $J = 7.1$ Hz, 2H, ArH), 7.63−7.60 (m, 3H, NH, 2 × ArH), 7.40 (app t, $J = 7.1$ Hz, 2H, ArH), 7.32 (app t, $J = 7.1$ Hz, 2H, ArH), 5.98 (dd, $J = 10.6$, 6.5 Hz, 1H, C=C*H*CH_2), 5.94 (d, $J = 9.4$ Hz, 1H, CH=CH), 5.84 (d, $J = 9.4$ Hz, 1H, CH=CH), 5.74 (br s, 1H, C≡CCH), 5.39 (d, $J = 2.1$ Hz, 1H, D-1), 5.16−5.19 (m, 2H, B-1, E-1), 5.05 (d, $J = 4.2$ Hz, 1H, A-1), 4.42−4.35 (m, 6H, E-4, D-2, A-3, CH_2 (FMOC), B-3), 4.26 (app t, $J = 6.0$ Hz, 1H, CH (FMOC)), 4.23−4.12 (m, 3H, A-5, CH_2 (TEOC)), 4.08−3.82 (m, 8H, D-5, B-5, CH_2S, OCH_2CH_2O), 3.81 (s, 3H, ArOMe), 3.78 (s, 3H, ArOMe), 3.74−3.64 (m, 5H, E-3, A-4, D-4, B-4, $E\text{-}5_{ax}$), 3.59 (s, 3H, $NHCO_2CH_3$), 3.58 (m, 2H, D-3, A-2), 3.40 (s, 3H, OMe), 3.28 (s, 3H, OMe), 3.28−3.22 (m, 1H, $E\text{-}5_{eq}$), 2.98 (br s, H_2O (solvent), CH_2N), 2.35 (s, 3H, CH_3CO), 2.31 (s, 3H, ArMe), 2.28 (m, 1H, $E\text{-}2_{eq}$) 2.22 (ABq, $J = 13.5$ Hz, $\Delta\nu = 230$ Hz, 2H, CH_2), 2.05 (br d, $J = 13.0$ Hz, 1H, $B\text{-}2_{eq}$), 1.81 (m, 1H, $B\text{-}2_{ax}$), 1.38 (m, 1H, $E\text{-}2_{ax}$), 1.34 (d, $J = 6.2$ Hz, 3H, B-6), 1.32, (d, $J = 6.2$ Hz, 3H, A-6), 1.17 (d, $J = 6.2$ Hz, 3H, D-6), 1.10−0.82 (m, 29H, 3 × $Si(CH_2CH_3)_3$, CH_2Si (TEOC)), 0.68−0.45 (m, 21H, 3×$Si(CH_2CH_3)_3$, NCH_2CH_3), 0.03 (s, 9H, $SiMe_3$); HRMS (FAB) for $C_{97}H_{142}IN_3O_{27}S_2Si_4Na$ (M + Na), calcd 2106.7293, found 2106.7285. Data for **22**: $R_f = 0.25$ (silica, 20% ethyl acetate in benzene); $[\alpha]^{25}_D$ −122° (*c* 0.55, CH_2Cl_2); IR (film) ν_{max} 2955, 2925, 2877, 1730, 1690, 1664, 1502, 1457, 1420, 1249, 1213, 1141, 1102, 1031, 888, 835, 741, 6941 cm^{-1}; ^1H NMR (490 MHz, DMSO-d_6, 100 °C) δ 7.84 (d, $J = 7.1$ Hz, 2H, ArH), 7.667 (m, 2H, ArH), 7.52 (br s, 1H, NH) 7.40 (app t, $J = 7.1$ Hz, 2H, ArH), 7.33 (app t, $J = 7.1$ Hz, 2H, ArH), 6.07−5.89 (m, 3H, C=C*H*-CH_2, *CH*=*CH*), 5.85 (bs, 1H, C≡CCH), 5.64 (br s, 1H, OH), 5.47 (br s, 1H, OH), 5.41 (d, $J = 2.1$ Hz, 1H, D-1), 5.17 (m, 1H, E-1), 4.92 (br d, $J = 8.0$ Hz, 1H, B-1), 4.56 (d, $J = 7.2$ Hz, 1H, A-1), 4.52-4.33 (m, 5H, D-2, A-3, CH_2 (FMOC), B-3), 4.27 (app t, $J = 6.2$ Hz, 1H, CH (FMOC)), 4.25−4.14 (m, 3H, E-4, CH_2 (TEOC)), 4.12−3.85 (m, 10H, D-5, B-5, A-5, $E\text{-}5_{ax}$, CH_2S, OCH_2CH_2O), 3.84 (s, 3H, ArOMe), 3.79 (s, 3H, ArOMe), 3.76−3.62 (m, 4H, E-3, A-4, D-4, B-4), 3.59 (s, 3H, $NHCO_2CH_3$), 3.58 (app br d, $J = 9.0$ Hz, 1H, D-3), 3.48 (app t, $J = 8.2$ Hz, 1H, A-2) 3.41 (s, 3H, OMe), 3.21 (m, 1H, $E\text{-}5_{eq}$), 3.16 (s, 3H, OMe), 3.02 (br s, H_2O (solvent), CH_2N), 2.35 (2 s, 6H, CH_3CO, ArMe), 2.32 (m, 1H, $E\text{-}2_{eq}$) 2.16 (ABq, $J = 13.5$ Hz, $\Delta\nu = 218$ Hz, 2H, CH_2), 2.08 (br d, $J = 13.0$ Hz, 1H, $B\text{-}2_{eq}$), 1.86 (m, 1H, $B\text{-}2_{ax}$), 1.42−1.38 (m, 1H, $E\text{-}2_{ax}$), 1.35 (d, $J = 6.2$ Hz, 3H, B-6), 1.21, (d, $J = 6.2$ Hz, 3H, A-6), 1.18 (d, $J = 6.2$ Hz, 3H, D-6), 1.10−0.78 (m, 29H, 3 × $Si(CH_2CH_3)_3$, CH_2Si (TEOC)), 0.75−0.54 (m, 21H, 3 × $Si(CH_2CH_3)_3$, NCH_2CH_3), 0.04 (s, 9H, $SiMe_3$); HRMS (FAB) for $C_{97}H_{142}IN_3O_{27}S_2Si_4Na$ (M + Na), calcd 2106.7293, found 2106.7156.

Trisulfide 24. Method A: From *S*-Acetate 22. A solution of DIBAL (50 μL) in dichloromethane (1M, 50 μmol) was added dropwise to a solution of the *S*-acetate **22** (11.6 mg, 5.5 μmol) in dichloromethane (1 mL) at −78 °C and the mixture stirred for 25 min. The mixture was quenched with methanol (200 μL) and the cooling bath removed. Ethyl acetate (1 mL) and saturated aqueous Rochelle's salt (1 mL) were added and the two phases vigorously stirred for 10 min. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* and the crude thiol immediatly dissolved in dichloromethane (1 mL). *N*-(Methyldithio)-phthalimide (15.0 mg, 60 μmol) was then added and the mixture stirred for 25 min at ambient temperature. Purification by preparative thin layer chromatography on silica, eluting with 45% ethyl acetate in hexane, afforded the trisulfide **24** (6.2 mg, 53%) as a white foam.

Method B: Coupling of Trisulfide (18). Anhydrous cesium carbonate (9.5 mg, 20 μmol) was added in one portion to a solution of lactol **20** (48 mg, 29 μmol) in dichloromethane (300 μL) and trichloroacetonitrile (44 μL, 430 μmol) and the mixture stirred at ambient temperature for 4 h. The mixture was then rapidly filtered through a short pad of silica, washing with 30% ethyl acetate in hexane. Concentration *in vacuo* afforded the crude trichloroacetimidate **21** (45 mg, 87%) as a yellow solid (ca. 3:1 α:β) which was immediately combined with the aglycon trisulfide **18** (4.0 mg, 8.6 μmol), and the mixture was azeotroped from benzene (3 × 2 mL). Powdered, activated 4 Å molecular sieves (ca. 0.2 g) and dichloromethane (250 μL) were then added, and the resulting mixture was stirred at ambient temperature for 15 min. Anhydrous silver(I) trifluoromethanesulfonate (11.0 mg, 43 μmol) was then added in one portion followed by stirring for a further 12 h in the dark. The mixture was then filtered through Celite, washing with ethyl acetate, and the filtrate concentrated *in vacuo*. Purification by column chromatography on silica, eluting with 40% ethyl acetate in hexane, afforded coupled trisulfide **24** (6.3 mg, 34%): $R_f = 0.36$ (silica, 40% ethyl acetate in hexane); $[\alpha]^{25}_D = -109°$ (*c* 0.83, CH_2Cl_2); IR (film) ν_{max} 2951, 2922, 1730, 1686, 1456, 1417, 1324, 1274, 1246, 1142, 1084, 1019, 964, 907, 801, 736 cm^{-1}; ^1H NMR (250 MHz, C_6D_6, 80 °C) δ 7.84−7.65 (m, 4H, ArH), 7.25−7.05 (m, 4H, ArH), 6.42 (br s, 1H, C=C*H*CH_2), 6.26 (br s, 1H, C≡CCH), 5.91 (br s, 1H, D-1), 5.87 (m, 1H, E-1), 5.62 (d, $J = 9.5$ Hz, 1H, CH=CH), 5.52 (m, 1H, B-1), 5.46 (d, $J = 9.5$ Hz, 1H, CH=CH), 4.95−4.05 (series of m, 22H, OCH_2's, OCH's, CH_2S, CH (FMOC), B-4), 3.88 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.58−3.48 (m, 5H), 3.56 (s, 3H, OMe), 3.52 (s, 3H, OMe), 3.43 (s, 3H, OMe), 3.22 (m, 2H, CH_2N), 2.88 (s, 3H, ArMe), 2.85 (ABq, $J = 13.5$ Hz, $\Delta\nu = 45$ Hz, 2H, CH_2), 2.58 (s, 3H, SSSMe), 2.45 (m, 1H, $E\text{-}2_{eq}$), 1.90−1.65 (obs, 3H, $B\text{-}2_{eq}$, $B\text{-}2_{ax}$, $E\text{-}2_{ax}$), 1.80 (d, $J = 6.5$ Hz, 3H, B-6), 1.72 (d, $J = 6.5$ Hz, 3H, A-6), 1.55 (d, $J = 6.5$ Hz, 3H, D-6), 1.50−0.75 (m, 50H, 3 × $Si(CH_2CH_3)_3$, NCH_3CH_3, CH_2Si (TEOC)), 0.11 (s, 9H, $SiMe_3$); HRMS (FAB) for $C_{96}H_{142}IN_3O_{26}S_4Si_4Na$ (M + Na), calcd 2142.6785, found 2142.6663.

Calicheamicin γ_1I (1). The ketal **24** (6.2 mg, 2.9 μmol) was dissolved in a solution of (±)-camphorsulfonic acid (2.0 mg, 8.6 μmol) in THF (1.0 mL) and water (1 drop) and the resulting mixture stirred at ambient temperature for 96 h. The mixture was then filtered through a short pad of silica, washing with ethyl acetate, and the filtrate concentrated *in vacuo*. The crude residue was dissolved in THF (500 μL), cooled to 0 °C, and treated with a solution of TBAF (25 μL) in THF (1 M, 25 μmol) for 15 min. Purification by preparative thin layer chromatography, eluting with 10% methanol in ethyl acetate, afforded calicheamicin γ_1^I (1) (1.4 mg, 32% for two steps) as a white amorphous solid: $R_f = 0.43$ (silica, 10% methanol in ethyl acetate); $[\alpha]^{25}_D = -97°$ (*c* 0.18, EtOH); IR (film) ν_{max} 3390, 2928, 1729, 1681, 1456, 1412, 1386, 1323, 1240, 1073, 963, 914, 753 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.42 (app t, $J = 7.4$ Hz, 1H, C=C*H*CH_2), 6.23 (d, $J = 1.4$ Hz, 1H, C≡CCH), 5.90 (d, $J = 9.5$ Hz, 1H, CH=CH), 5.82 (dd, $J = 9.4$, 1.5 Hz, 1H, CH=CH), 5.73 (d, $J = 1.4$ Hz, 1H, D-1), 5.68 (m, 1H, E-1), 5.04 (br d, $J = 10.1$ Hz, 1H, B-1), 4.68 (d, $J = 7.7$ Hz, 1H, A-1), 4.48 (m, 1H, D-2), 4.32 (m, 1H, B-3), 4.20 (dq, $J = 9.5$, 6.2 Hz, 1H, D-5), 4.08 (dq, $J = 11.0$, 6.2 Hz, 1H, B-5), 4.02 (app t, $J = 9.7$ Hz, 1H, A-3), 3.88−3.78 (m, 5H, A-2, D-3, A-5, CH_2S), 3.89 (s, 3H, ArOMe), 3.82 (s, 3H, ArOMe), 3.76 (obs, 1H, B-4), 3.71 (s, 3H, $NHCO_2CH_3$), 3.63 (app t, $J = 9.5$ Hz, 1H, D-4), 3.58 (s, 3H, OMe), 3.62−3.56 (obs, 2H, $E\text{-}5_{ax}$, $E\text{-}5_{eq}$), 3.43 (s, 3H, OMe), 3.41 (m, 1H, E-3), 3.01 (ABq, $J = 16.7$ Hz, $\Delta\nu = 89$ Hz, 2H, CH_2), 2.76−2.65 (m, 2H, CH_2N, E-4), 2.52 (s, 3H, SSSMe), 2.51 (obs, 1H, CH_2N), 2.39 (app t, $J = 9.7$ Hz, 1H, A-4), 2.38 (s, 3H, ArMe), 2.37 (obs, 1H, $E\text{-}2_{eq}$), 2.05 (m, 1H, $B\text{-}2_{eq}$), 1.78 (m, 1H, $B\text{-}2_{ax}$), 1.52 (m, 1H,$E\text{-}2_{ax}$), 1.42 (d, $J = 6.4$ Hz, 3H, B-6), 1.37 (d, $J = 6.2$ Hz, 3H, A-6), 1.31 (d, $J = 6.2$ Hz, 3H, D-6), 1.19 (t, $J = 7.1$ Hz, 3H, NCH_2CH_3); MS (FAB) for $C_{56}H_{74}IN_3O_{21}S_4Na$ (M + Na), calcd 1368 found, 1368.

***S*-Acetate Enone 25.** The ketal **22** (5.1 mg, 2.5 μmol) was dissolved in a solution of (±)-camphorsulfonic acid (2.0 mg, 8.6 μmol) in THF (1.0 mL) and water (1 drop) and the resulting mixture stirred at ambient temperature for 96 h. The mixture was then filtered through a short pad of silica, washing with ethyl acetate, and the filtrate concentrated *in vacuo*. The crude residue was dissolved in THF (500 μl), cooled to 0 °C, and treated with a solution of TBAF (25 μL) in THF (1 M, 25 μmol) for 15 min. Purification by preparative thin layer chromatography, eluting with 10% methanol in ethyl acetate, afforded the enone **25** (1.4 mg, 42% for two steps) as a white amorphous solid: $R_f = 0.45$ (silica, 10% methanol in ethyl acetate); $[\alpha]^{25}_D = -135°$ (*c* 0.20, CH_2Cl_2); IR (film) ν_{max} 3420, 2926, 1729, 1681, 1456, 1323, 1239, 1072, 913 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.22 (d, $J = 1.5$ Hz, 1H, C≡CCH), 6.20 (dd, $J = 8.6$, 6.5 Hz, 1H, C=C*H*CH_2), 5.88 (d, $J = 9.4$ Hz, 1H, CH=CH), 5.82 (dd, $J = 9.4$, 1.5 Hz, 1H, CH=CH), 5.75 (d, $J = 1.4$ Hz, 1H, D-1), 5.73 (m, 1H, E-1), 5.06 (dd, $J = 10.2$, 1.5 Hz, 1H, B-1), 4.72 (d, $J = 7.2$ Hz, 1H, A-1), 4.50 (br d, $J = 3.2$ Hz, 1H, D-2), 4.32 (m, 1H, B-3), 4.22 (dq, $J = 9.7$, 6.2 Hz, 1H, D-5), 4.18−4.02 (m, 2H, B-5, A-3), 3.90 (s, 3H, ArOMe), 3.85 (s, 3H, ArOMe), 3.84−3.60 (m, 10H, D-3, A-2, A-5, B-4, $E\text{-}5_{ax}$, $E\text{-}5_{eq}$, D-4, CH_2SAc), 3.79 (s, 3H, $NHCO_2CH_3$), 3.58 (s, 3H, OMe), 3.42 (s, 3H, OMe), 3.38 (m, 1H, E-3), 2.86 (ABq, $J = 16.5$ Hz, $\Delta\nu = 131$ Hz, 2H,

CH_2), 2.78−2.50 (m, 3H, CH_2N, E-4), 2.38 (m, 1H, E-2_{eq}), 2.36 (s, 3H, ArMe), 2.32 (s, 3H, CH_3CO), 2.30 (m, 1H, A-4), 2.05 (m, 1H, B-2_{eq}), 1.82 (m, 1H, B-2_{ax}), 1.55 (obs, 1H, E-2_{ax}), 1.42 (d, J = 6.4 Hz, 3H, B-6), 1.39 (d, J = 6.2 Hz, 3H, A-6), 1.32 (d, J = 6.2 Hz, 3H, D-6), 1.18 (t, J = 7.2 Hz, 3H, NCH_2CH_3); MS (FAB) for $C_{56}H_{75}IN_3O_{22}S_2$ (M + H), calcd 1332, found 1332.

***S*-Acetate Enone 26.** The ketal **23** (4.4 mg, 2.1 μmol) was dissolved in a solution of (±)-camphorsulfonic acid (2.0 mg, 8.6 μmol) in THF (1.0 mL) and water (1 drop) and the resulting mixture stirred at ambient temperature for 96 h. The mixture was then filtered through a short pad of silica, washing with ethyl acetate, and the filtrate concentrated *in vacuo*. The crude residue was dissolved in THF (500 μL), cooled to 0 °C, and treated with a solution of TBAF (25 μL) in THF (1 M, 25 μmol) for 15 min. Purification by preparative thin layer chromatography, eluting with 10% methanol in ethyl acetate, afforded the enone **26** (1.2 mg, 43% for two steps) as a white amorphous solid: R_f = 0.48 (silica, 10% methanol in ethyl acetate); $[\alpha]^{25}_D$ = −71° (*c* 0.17, CH_2Cl_2); IR (film) ν_{max} 3380, 2929, 1731, 1682, 1456, 1324, 1239, 1072, 913 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.68 (br s, 1H, NH), 6.26 (dd, J = 11.6, 3.4 Hz, 1H, C=C*H*CH_2), 5.96 (d, J = 9.6 Hz, 1H, CH=CH), 5.94 (d, J = 1.5 Hz, 1H, C≡CCH), 5.86 (dd, J = 9.6, 1.5 Hz, 1H, CH=CH), 5.73 (d, J = 1.4 Hz, 1H, D-1), 5.49 (d, J = 2.9 Hz, 1H, E-1), 5.07 (d, J = 3.8 Hz, 1H, A-1), 5.04 (dd, J = 10.2, 1.8 Hz, 1H, B-1), 4.49 (m, 1H, D-2), 4.31 (m, 1H, B-3), 4.22 (dq, J = 9.5, 6.2 Hz, 1H, D-5), 4.12 (m, 1H, B-5), 3.95 (br d, J = 9.2 Hz, 1H, A-3), 3.89 (s, 3H, ArOMe), 3.83 (s, 3H, OMe), 3.88−3.65 (m, 7H, D-3, A-2, A-5, B-4, D-4, CH_2SAc), 3.85 (s, 3H, $NHCO_2CH_3$), 3.58 (s, 3H, OMe), 3.61−3.41(m, 3H, E-5_{ax}, E-5_{eq}, E-3), 3.40 (s, 3H, OMe), 2.93 (ABq, J = 17.5 Hz, Δν = 123 Hz, 2H, CH_2), 2.77 (m, 1H, CH_2N), 2.56 (m, 1H, CH_2N), 2.48 (m, 2H, E-2_{eq}, E-4), 2.38 (s, 3H, ArMe), 2.33 (s, 3H, CH_3CO), 2.26 (m, 1H, A-4), 2.12 (m, 1H, B-2_{eq}), 1.85 (m, 1H, B-2_{ax}), 1.56 (obs, 1H, E-2_{ax}), 1.46 (d, J = 6.4 Hz, 3H, B-6), 1.42 (d, J = 6.2 Hz, 3H, A-6), 1.28 (d, J = 6.2 Hz, 3H, D-6), 1.17 (t, J = 7.2 Hz, 3H, NCH_2CH_3); MS (FAB) for $C_{56}H_{75}IN_3O_{22}S_2$ (M + H), calcd 1332, found 1332.

***S*-Acetates 27 and 28.** Anhydrous cesium carbonate (22.0 mg, 68 μmol) was added in one portion to a solution of lactol **20** (110 mg, 65 μmol) in dichloromethane (400 μL) and trichloroacetonitrile (100 μL, 997 μmol) and the mixture stirred at ambient temperature for 4 h. The mixture was then rapidly filtered through a short pad of silica, washing with 30% ethyl acetate in hexane. Concentration *in vacuo* afforded the crude trichloroacetimidate **21** (106 mg, 89%) as a yellow solid (ca. 3:1 α:β) which was immediatly combined with the aglycon *S*-acetate *ent*-**17** (16.0 mg, 36 μmol), and the mixture was azeotroped from benzene (3 × 2 mL). Powdered, activated 4 Å molecular sieves (ca. 0.5 g) and dichloromethane (750 μL) were then added, and the resulting mixture was stirred at ambient temperature for 15 min. Anhydrous silver(I) trifluoromethanesulfonate (15.6 mg, 61 μmol) was added in one portion followed by stirring for a further 12 h in the dark. The mixture was then filtered through Celite, washing with ethyl acetate, and the filtrate concentrated *in vacuo*. Purification by column chromatography on silica, eluting with 45% ethyl acetate in hexane, afforded firstly the α-coupled compound **28** (28.0 mg, 36%) followed by the β-coupled compound **27** (1.6 mg, 2%) as white foams. Data for **28**: R_f = 0.50 (silica, 50% ethyl acetate in hexane); $[\alpha]^{25}_D$ = +46° (*c* 2.05, CH_2Cl_2); IR (film) ν_{max} 3300, 2953, 2877, 1733, 1683, 1456, 1417, 1329, 1278, 1250, 1098, 1017, 963, 910, 834, 741 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6, 90 °C) δ 7.84 (d, J = 7.2 Hz, 2H, ArH), 7.64 (d, J = 7.2 Hz, 2H, ArH), 7.62 (br s, 1H, NH), 7.40 (app t, J = 7.4 Hz, 2H, ArH), 7.31 (app t, J = 7.4 Hz, 2H, ArH), 6.02 (dd, J = 10.9, 8.6 Hz, 1H, C=C*H*CH_2), 6.00 (d, J = 9.4 Hz, 1H, CH=CH), 5.91 (d, J = 9.4 Hz, 1H, CH=CH), 5.61 (br s, 1H, C≡CCH), 5.40 (d, J = 1.7 Hz, 1H, D-1), 5.12−5.29 (m, 2H, B-1, E-1), 5.00 (d, J = 4.0 Hz, 1H, A-1), 4.48−4.38 (m, 6H, E-4, D-2, A-3, CH_2 (FMOC), B-3), 4.36−3.82 (m, 12H, CH (FMOC), A-5, CH_2 (TEOC), D-5, B-5, CH_2SAc, OCH_2CH_2O), 3.84 (s, 3H, ArOMe), 3.80 (s, 3H, ArOMe), 3.80−3.63 (m, 5H, E-3, A-4, D-4, B-4, E-5_{ax}), 3.63−3.53 (m, 2H, D-3, A-2), 3.55 (s, 3H, $NHCO_2CH_3$), 3.43 (s, 3H, OMe), 3.35 (m, 1H, E-5_{eq}), 3.18 (s, 3H, OMe) 3.00 (br s, H_2O (solvent), CH_2N), 2.36 (s, 3H, CH_3CO), 2.35 (s, 3H, ArMe), 2.28 (m, 1H, E-2_{eq}), 2.25 (ABq, J = 17.1 Hz, Δν = 104 Hz, 2H, CH_2), 2.12 (m, 1H, B-2_{eq}), 1.92 (m, 1H, B-2_{ax}), 1.42 (m, 1H, E-2_{ax}), 1.38 (d, J = 6.2 Hz, 3H, B-6), 1.23, (d, J = 6.2 Hz, 3H, A-6), 1.18 (d, J = 6.2 Hz, 3H, D-6), 1.10−0.83 (m, 29 H, 3 × $Si(CH_2CH_3)_3$, CH_2Si (TEOC)), 0.75−0.57 (m, 21H, 3 × $Si(CH_2CH_3)_3$, NCH_2CH_3), 0.03 (s, 9H, $SiMe_3$); HRMS (FAB) for $C_{97}H_{142}IN_3O_{27}S_2Si_4Na$ (M + Na), calcd 2106.7293, found 2106.7235. Data for **27**: R_f = 0.32 (silica, 50% ethyl acetate in hexane); $[\alpha]^{25}_D$ +68° (*c* 0.22, CH_2Cl_2); IR (film) ν_{max} 3420, 2952, 2879, 1735, 1683, 1456, 1417, 1330, 1279, 1098, 1015, 909, 740 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6, 85 °C) δ 7.84 (d, J = 7.2 Hz, 2H, ArH), 7.63 (d, J = 7.2 Hz, 2H, ArH), 7.54 (br s, 1H, NH), 7.40 (app t, J = 7.2 Hz, 2H, ArH), 7.31 (app t, J = 7.2 Hz, 2H, ArH), 6.09 (t, J = 7.3 Hz, 1H, C=C*H*CH_2), 5.99 (d, J = 9.0 Hz, 1H, CH=CH), 5.96 (d, J = 9.0 Hz, 1H, CH=CH), 5.59 (br s, 1H, C≡CCH), 5.43 (m, 1H, E-1), 5.40 (d, J = 1.4 Hz, 1H, D-1), 5.16 (dd, J = 9.8, 1.3 Hz, 1H, B-1), 4.75 (d, J = 7.3 Hz, 1H, A-1), 4.58−4.33 (m, 6H, E-4, D-2, A-3, CH_2 (FMOC), B-3), 4.32−3.98 (m, 12H, CH (FMOC), A-5, CH_2 (TEOC), D-5, B-5, CH_2SAc, OCH_2CH_2O), 3.82 (s, 3H, ArOMe), 3.79 (s, 3H, ArOMe), 3.74−3.56 (m, 7H, E-3, A-4, D-4, B-4, E-5_{ax}, D-3, A-2), 3.59 (s, 3H, $NHCO_2CH_3$), 3.40 (s, 3H, OMe), 3.35 (m, 1H, E-5_{eq}), 3.18 (s, 3H, OMe) 3.05 (br s, H_2O (solvent), CH_2N), 2.42 (ABq, J = 16.9 Hz, Δν = 79 Hz, 2H, CH_2), 2.31 (s, 3H, CH_3CO), 2.28 (s, 3H, ArMe), 2.23 (m, 1H, E-2_{eq}) 2.08 (m, 1H, B-2_{eq}), 1.87 (m, 1H, B-2_{ax}), 1.40 (m, 1H, E-2_{ax}), 1.34 (d, J = 6.2 Hz, 3H, B-6), 1.17, (d, J = 6.2 Hz, 3H, A-6), 1.10 (d, J = 6.2 Hz, 3H, D-6), 1.05−0.82 (m, 29H, 3 × $Si(CH_2CH_3)_3$, CH_2Si (TEOC)), 0.75−0.55 (m, 21H, 3 × $Si(CH_2CH_3)_3$, NCH_2CH_3), 0.06 (s, 9H, $SiMe_3$); HRMS (FAB) for $C_{97}H_{142}IN_3O_{27}S_2Si_4Na$ (M + Na), calcd 2106.7293, found 2106.7197.

***S*-Acetate Enone 29.** The ketal **28** (11.8 mg, 5.6 μmol) was dissolved in a solution of (±)-camphorsulfonic acid (2.0 mg, 8.6 μmol) in THF (1.0 mL) and water (1 drop) and the resulting mixture stirred at ambient temperature for 96 h. The mixture was then filtered through a short pad of silica, washing with ethyl acetate, and the filtrate concentrated *in vacuo*. The crude residue was dissolved in THF (500 μL), cooled to 0 °C, and treated with a solution of TBAF (50 μL) in THF (1 M, 50 μmol) for 15 min. Purification by preparative thin layer chromatography, eluting with 10% methanol in ethyl acetate, afforded the enone **29** (3.7 mg, 49% for two steps) as a white amorphous solid: R_f = 0.32 (silica, 10% methanol in ethyl acetate); $[\alpha]^{25}_D$ = +106° (*c* 0.31, CH_2Cl_2); IR (film) ν_{max} 3420, 2929, 1731, 1682, 1455, 1389, 1320, 1239, 1072, 963, 915, 731 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.17 (dd, J = 10.0, 4.1 Hz, 1H, C=C*H*CH_2), 5.97 (s, 1H, C≡CCH), 5.90 (S, 2H, CH=CH), 5.75 (d, J = 1.4 Hz, 1H, D-1), 5.20 (m, 1H, E-1), 5.16 (d, J = 3.3 Hz, 1H, A-1), 5.03 (m, 1H, B-1), 4.60−4.43 (m, 2H, D-2, B-3), 4.33-4.04 (m, 2H, D-5, B-5), 3.96 (dd, J = 7.4, 2.5 Hz, 1H, A-3), 3.91 (s, 3H, ArOMe), 3.86 (s, 3H, OMe), 3.88−3.61 (m, 7H, D-3, A-2, A-5, B-4, D-4, CH_2SAc), 3.70 (s, 3H, $NHCO_2CH_3$), 3.58 (s, 3H, OMe), 3.52−3.38 (m, 3H, E-5_{ax}, E-5_{eq}, E-3) 3.40 (s, 3H, OMe), 2.92 (ABq, J = 17.5 Hz, Δν = 126 Hz, 2H, CH_2), 3.00 (m, 1H, CH_2N), 2.78 (m, 2H, CH_2N, E-4), 2.41 (s, 3H, ArMe), 2.38 (s, 3H, CH_3CO), 2.25 (m, 2H, E-2_{eq}, A-4), 2.00 (m, 1H, B-2_{eq}), 1.75 (m, 1H, B-2_{ax}), 1.58 (m, 1H, E-2_{ax}), 1.53 (d, J = 6.4 Hz, 3H, B-6), 1.32 (d, J = 6.2 Hz, 3H, A-6), 1.28 (d, J = 6.2 Hz, 3H, D-6), 1.02 (t, J = 7.2 Hz, 3H, NCH_2CH_3); MS (FAB) for $C_{56}H_{75}IN_3O_{22}S_2$ (M + H), calcd 1332, found 1332.

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