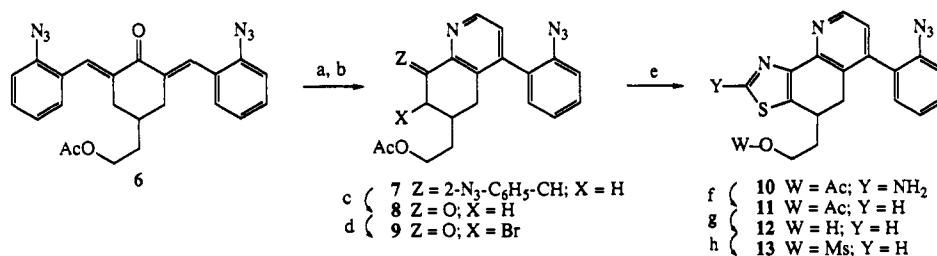
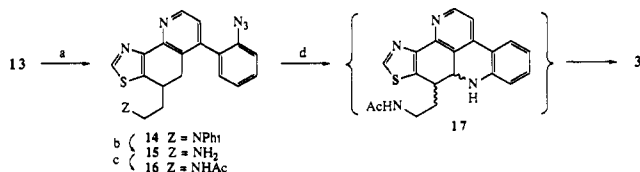
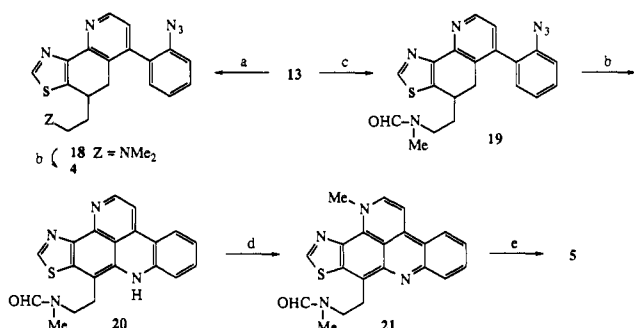


Scheme II^a

^a (a) Ethyl vinyl ether, Yb(fod)₃, (CH₂Cl)₂, reflux, 99%; (b) HONH₃⁺Cl⁻, MeCN, reflux, 61%; (c) O₃, CH₂Cl₂/MeOH, -78 °C, then Me₂S, -78 °C to room temperature, 78%; (d) pyridinium tribromide, AcOH, 50 °C, 70%; (e) thiourea, EtOH, 35 °C, 15 min, 95%; (f) *i*-AmONO, DMF, 80 °C, 82%; (g) K₂CO₃, MeOH, 94%; (h) MsCl, Et₃N, CH₂Cl₂, 0 °C, 99%.

Scheme III^a

^a (a) *K*-phthalimide, DMF, 50 °C, 84%; (b) N₂H₄·H₂O, MeOH, room temperature, 30 min, 94%; (c) Ac₂O, pyridine, room temperature, 86%; (d) *hν*, 9:1 chlorobenzene/acetophenone, 110 °C, 62% chromatographed.

Scheme IV^a

^a (a) 40% aqueous Me₂NH, DMF, 86%; (b) *hν*, 9:1 chlorobenzene/acetophenone, 110 °C, 61% (chromatographed) for 4, 63% (chromatographed) for 20; (c) MeNHCHO, NaH, 0 °C, 77%; (d) MeI, K₂C₂O₃, PhH, 70 °C, 99%; (e) POCl₃, then NaBH₄, DME, 87%.

Fully synthetic nordercitin¹⁵ was obtained from 13 by mesylate displacement with dimethylamine and photolysis (61% chromatographed yield) of the intermediate 18.¹⁷ The synthesis of dercitin itself required selective N-methylation of the pyridine ring. It was surmised that such selectivity might be achieved within the domain of compound 19, where the highly nucleophilic side chain dimethylamino group, which would interfere with the methylation step, is present in latent form. It was further assumed that the feeble nucleophilicity of the dihydroacridine segment of the molecule should permit full expression of the well-established 20-fold greater reactivity of the pyridine nitrogen vs its thiazole counterpart toward methyl iodide.¹⁸ These expectations were realized. Thus, reaction of 13 with *N*-sodio-*N*-methylformamide¹⁹ generated amide 19,¹⁵ which was converted into the aromatized pentacyclic compound 20¹⁵ in 63% chromatographed yield by the now familiar photolytic step. Treatment of 20 with MeI provided derivative 21¹⁵ in quantitative yield. The formamide was best reduced to a dimethylamine by the method of Kuehne,²⁰ a transformation that secured fully synthetic dercitin¹⁵ in 87% yield.¹⁷ The overall yields of 4 and 5 from 6 were 12.5% and 10.0% over

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(20) Kuehne, M. E.; Shannon, P. J. *J. Org. Chem.* 1977, 42, 2082.

10 steps and over 12 steps, respectively.

These practical syntheses dramatically increase the availability of the new natural products. In addition, they confirm the structure of 5 and define a general entry to the thiazolopyridoacridine alkaloids. The synthetic plan should permit introduction of diverse structural variations into side chain and ring system analogues of 1-5, facilitating eventual medicinal chemistry work. From a chemical standpoint, this work reaffirms the value of our pyridine-forming reaction and of photochemical transformations of azides in the construction of complex polycyclic heteroaromatic molecules. Further ramifications of these principles will be described in due course.

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Supplementary Material Available: Listings of spectral data for selected compounds (4 pages). Ordering information is given on any current masthead page.

Total Synthesis of Calicheamicin γ_1^1

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As one of Nature's most extraordinary molecular constructions, with phenomenal biological activity and a fascinating mode of action, calicheamicin γ_1^1 (1, Figure 1)^{1,2} has captured the imagination of synthetic organic chemists around the world.³⁻⁶

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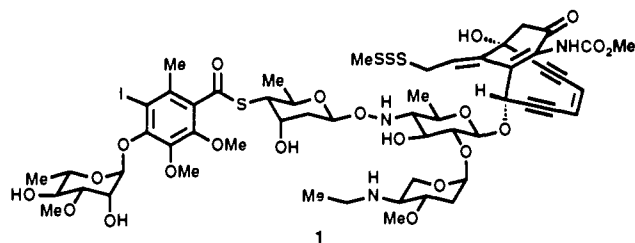


Figure 1. Molecular structure of calicheamicin γ_1^1 (1).

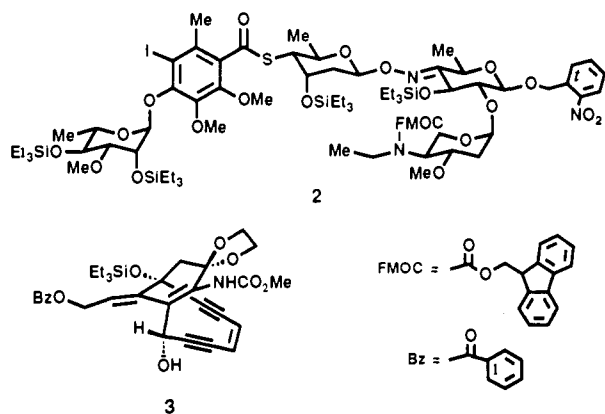


Figure 2. Advanced key intermediates 2 and 3 for the construction of calicheamicin γ_1^1 (1).

Herein we report the first total synthesis of this molecule in its naturally occurring enantiomeric form.

The convergent synthesis of calicheamicin γ_1^1 (1) required as advanced intermediates the oligosaccharide fragment 2 and the aglycon precursor 3 (Figure 2). These intermediates were synthesized in enantiomerically pure forms by modifications and extensions of procedures previously reported from these laboratories.^{4,5} Crucial to the success of this total synthesis were (a) the ready access to fragments 2 and 3 in gram quantities; (b) a stereospecific and efficient coupling of the two key segments; and (c) the specific sequence of high-yielding reactions described below.

Photodeprotection of *o*-nitrobenzyl glycoside 2⁷ (Hanovia mercury lamp, THF-H₂O) generated the corresponding lactol (82% yield, ca. 1:1 anomeric mixture by ¹H NMR, plus 16% starting material, chromatographically separated), which was converted to the trichloroacetimidate 4 (Figure 3), according to Schmidt's procedure (NaH catalyst, Cl₃CCN),⁸ in high yield.

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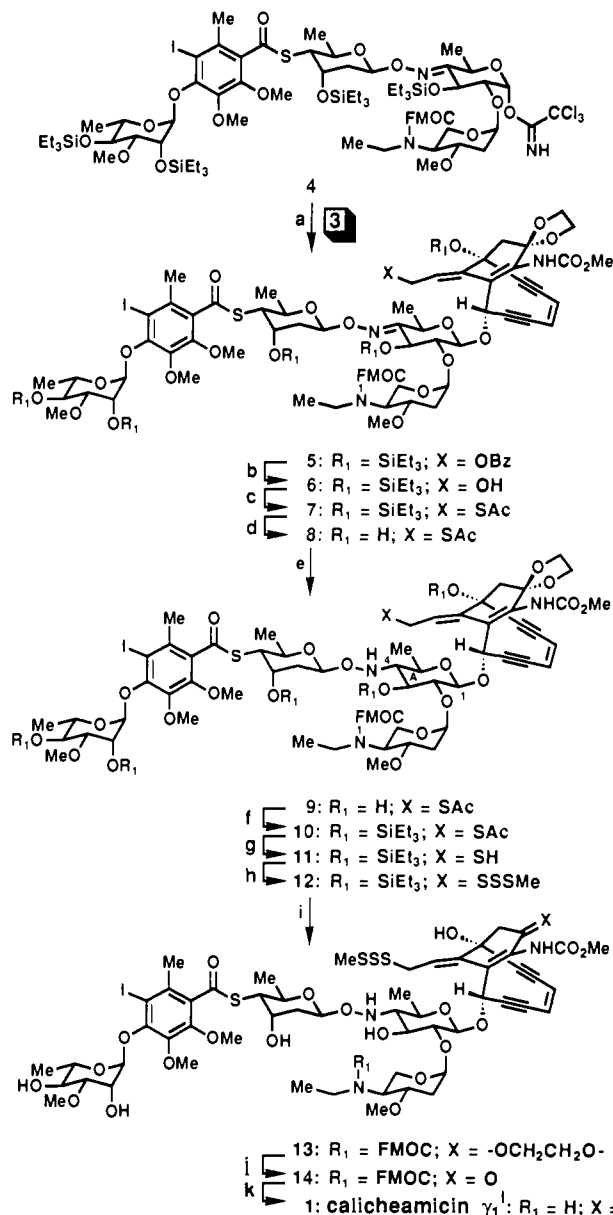


Figure 3. Total synthesis of calicheamicin γ_1^1 (1). Reagents and conditions: (a) 1.0 equiv of 4, 1.4 equiv of 3, 3.0 equiv of BF₃·OEt₂, CH₂Cl₂, -40 °C, 1.75 h, 76% (45% 5, plus 31% monodesilylated product; this product was quantitatively converted to 5 with 5.0 equiv of Et₃SiOTf, 10.0 equiv of ⁱPr₂NEt, CH₂Cl₂, 0 °C, 1 h); (b) 4.0 equiv of DIBAL, CH₂Cl₂, -78 °C, 1 h, 88%; (c) 15.0 equiv of PPh₃, 12.0 equiv of DEAD, 13.0 equiv of AcSH, THF, 0 °C, 0.5 h, 96%; (d) excess HF-pyr, THF-CH₂Cl₂ (6:1), 0 °C, 3 h, 94%; (e) 10.0 equiv of NaCNBH₃, 2.0 equiv of BF₃·OEt₂, THF, -40 °C, 3.5 h, 80% (2:1 mixture of isomers, 75% conversion); (f) 20.0 equiv of Et₃SiOTf, 40.0 equiv of ⁱPr₂NEt, CH₂Cl₂, 0 °C, 2 h; then excess AcOH, EtOAc-H₂O (100:1), 25 °C, 24 h, 75%; (g) 3.0 equiv of DIBAL, CH₂Cl₂, -90 °C, 0.5 h; (h) 7.0 equiv of *N*-(methylthio)phthalimide, CH₂Cl₂, 0 → 25 °C, 15 h, 75% (over two steps); (i) excess HF-pyr, THF-CH₂Cl₂ (5:1), 0 → 25 °C, 18 h, 90%; (j) 1.0 equiv of TsOH·H₂O, THF-H₂O (20:1), 25 °C, 18 h, 70%; (k) Et₂NH-THF-H₂O (5:25:1), 25 °C, 1.5 h, 90%.

Crude trichloroacetimidate 4 was then coupled with the aglycon derivative 3⁷ (1.4 equiv) in CH₂Cl₂ under the influence of BF₃·Et₂O at -40 °C⁹ to afford the desired product 5 (Figure 3) in 76% yield.¹⁰ The correct stereochemical outcome of this

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glycosidation reaction (β -glycoside bond as shown in **5**) was anticipated from precedent in trichloroacetimidate chemistry¹¹ and was confirmed by a value of 7.4 Hz for coupling constant $J_{1,2}$ (anomeric proton, ring A) of compound **9** (Figure 3) obtained after reduction of the oxime bond (C=N). At this juncture the first sulfur atom of the trisulfide moiety was introduced as a thioacetate by a two-step procedure involving DIBAL-induced removal of the benzoate group to generate selectively the allylic alcohol **6** (88% yield) followed by Mitsunobu reaction using AcSH as the nucleophile^{5,6a,b} to give compound **7** in 96% yield. Attempts to reduce the C=N bond in ring A revealed the need for desilylation prior to this crucial operation. All five silyl groups were, therefore, removed using excess HF-pyr, leading to pentaol **8** (94% yield) in preparation for the next step.

Reduction of the C=N bond in **8** with excess NaCNBH₃ in the presence of BF₃·Et₂O in THF proceeded smoothly^{9a,b} to afford a mixture of **9** (4 α -epimer, major) and its 4 β -epimer (**9-epi**, minor) in 80% total yield (ca. 2:1 ratio of isomers, ca. 75% conversion). Rapid flash chromatography separated the desired isomer **9** from its 4 β -epimer (**9-epi**), but not from starting material **8**, suggesting further purification at a subsequent step. At this point it was also recognized that reprotection of the free hydroxyl groups was desirable for the pending steps leading to the establishment of the trisulfide moiety. Thus, the mixture of **9** + **8** (ca. 2:1 ratio) was fully silylated by exposure to Et₃SiOTf-Pr₂NEt followed by treatment of the crude product mixture with excess AcOH-H₂O in EtOAc furnishing pentasilyl ether **10** together with the oxime derivative **7** in 75% total yield. Reaction of this mixture (**10** + **7**, ca. 2:1) with 3.0 equiv of DIBAL in CH₂Cl₂ at -90 °C gave selectively the corresponding mixture of thiols (**11**, plus oxime thiol). Exposure of this mixture to excess *N*-(methylthio)-phthalimide^{12,13} followed by flash chromatography afforded trisulfide **12** in 75% yield (two steps, based on the content of **9** in the starting mixture **9** + **8**).

Finally, deprotection of **12** by sequential exposure to (i) HF-pyr (**12** → **13**, 90% yield); (ii) TsOH·H₂O (**13** → **14**, 70% yield); and (iii) Et₂NH (**14** → **1**, 90% yield) furnished calicheamicin γ_1^1 (**1**). Synthetic calicheamicin γ_1^1 (**1**) exhibited identical physical and spectroscopic data (TLC, HPLC, $[\alpha]_D^{25}$, ¹H and ¹³C NMR, mass, IR and UV spectra) with those of an authentic sample.¹⁴

The reported total synthesis is remarkably efficient considering the complexity of the target molecule, and in addition to opening a synthetic route to calicheamicin γ_1^1 (**1**), it provides an entry into a new family of designed variations of the natural substance.¹⁵

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Supplementary Material Available: A listing of selected physical data for compounds **5-9**, **9-epi**, **12**, **13**, and **1** (12 pages). Ordering information is given on any current masthead page.

(10) Partial loss of one of the SiEt₃ groups (unassigned) occurred under these conditions; the desilylated coupling product was quantitatively converted to **5** by exposure to excess Et₃SiOTf-Pr₂NEt leading to a combined yield of 76% for this reaction.

(11) Trichloroacetimidate **4** (predominantly the α -anomer, thermodynamic product) is apparently undergoing stereoselective glycosidation to afford the β -anomer **5** (see ref 8).

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(15) All new compounds exhibited satisfactory spectral and exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.

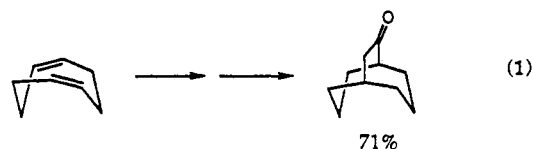
Novel Free Radical Ring-Forming Reaction of Dichlorocyclobutanones and Sequential Ring Expansion

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We have discovered an unusual reaction sequence that interconverts the elements of ketene into a 1,5-diene and forms a new seven-membered-ring ketone, as illustrated for 1,5-cyclooctadiene (eq 1). Since we are unaware of any comparable sequence in the literature, our findings are reported here.



The new reaction makes use of the regio- and chemoselective cycloaddition of dichloroketene to an olefin to form the dichlorocyclobutanone adduct (Scheme I).^{1,2} In the key step, tri-*n*-butyltin hydride reduction of the adduct leads to free radical addition to the second double bond of the diene,^{3,4} followed by reduction of the second chloride.⁵ When the cyclobutanone product is treated with trimethylsilyl iodide,⁶ ring opening occurs to yield the seven-membered keto iodide. The iodide can then either be reduced with tin hydride to yield the saturated ketone or the iodide can be eliminated with DBU to give the enone. This sequence is illustrated in Scheme I, where readily available *endo*-6-vinylbicyclo[2.2.1]hept-2-ene is transformed to the interesting and unusual tricyclo[6.2.1.0^{6,10}]undec-2-en-4-one. The yields in each step are quite reasonable. Further examples of the new reaction are shown in Table I.

Alkyl chlorides are not ordinarily good substrates for radical addition and are generally avoided on that account.⁷ The dichlorocyclobutanone cycloaddition in the examples above is successful because the chlorides involved are α to the carbonyl and to a second chloro substituent, and they are more reactive than normal alkyl chlorides.⁸⁻¹⁰ Like the 5-hexenyl radical,¹¹

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