Synthetic studies on calicheamicin γ_1^I—synthesis of (−)-calicheamicinone and models representing the four sugars and the aromatic system

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The synthesis of (−)-calicheamicinone (2), the carbohydrates 88, 101, 111, 119 and 120, and the hexasubstituted benzene 139, is described; these compounds formally represent the subunits of the antitumor antibiotic calicheamicin γ_1^I (1).

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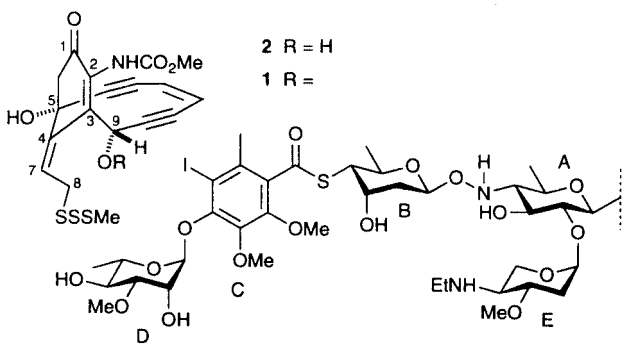
The antitumor antibiotic calicheamicin γ_1^I (**1**)[1] has attracted much attention as a synthetic target.[2] Two syntheses have been reported,[3] but the structure is so complicated that further synthetic work will surely provide many opportunities for new discoveries.



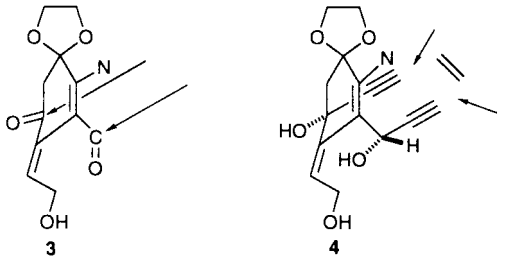
Synthesis of calicheamicin γ_1^I is a major undertaking—both chemical and financial—and a suitably cautious approach would be guided by the dominant structural characteristic that the compound is composed of several subunits—the aglycone (**2**), four carbohydrates, and a hexasubstituted benzene ring. Accordingly, synthetic work would first involve construction of each subunit, and the information thus gained might then be used in the more complex task of modifying the routes so that they can be integrated harmoniously into a composite synthesis of the whole structure. We describe here our own work[4–6] on the simpler of these tasks—synthesis of the subunits.[7,8]

Synthesis of (−)-calicheamicinone

The aglycone, (−)-calicheamicinone (**2**), presented the most difficult synthetic problem among the subunits of calicheamicin γ_1^I, because the substance is a rare structural type which had not been made before when we began our studies; in contrast, the carbohydrate segments and the aromatic unit—unusual though they are—did at least possess much in common with well-known compound classes.

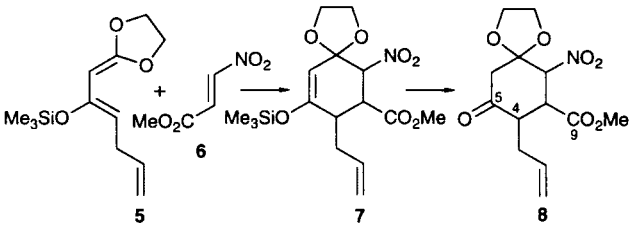
Synthetic plan

Exploratory work by the Magnus group[9] had indicated that the allylic trisulfide of **2** should be accessible from the corresponding alcohol. Further analysis of the synthetic problem showed that two very suggestive features of calicheamicinone are the tertiary and secondary acetylenic alcohols. Their presence suggested that they might be assembled by acetylide addition to a suitably protected form of the hypothetical dicarbonyl subunit **3** (see arrows). It was then obvious that the enediyne might be



added in several ways: as an intact six-carbon enediyne unit, as an acetylene and an enyne, or as two acetylenes, followed by addition of a two-carbon unit and, in the event, this last process (see **4**, arrows), was the one we eventually used.

Although the above analysis is straightforward, the proper choice of dicarbonyl compound (*cf.* **3**) required a great deal of experimental effort before a promising structure was identified. This was based on the Diels–Alder reaction summarized (without stereochemical implications) in Scheme 1.



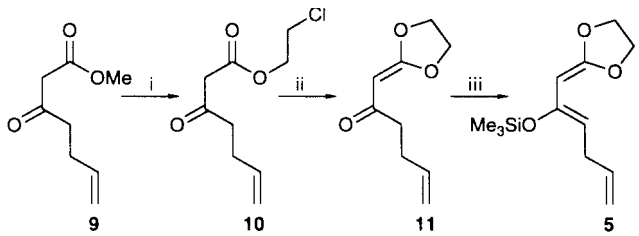
Scheme 1

Mild hydrolysis of the initial adduct **7** would be expected to afford **8**, which has many of the features of the schematic structure **3**: the carbonyl groups at C(5) and C(9) could serve as points of attachment for the acetylene units, the nitro group could eventually provide part of the carbamate, and the chain at C(4) would serve as the precursor to the allylic trisulfide. The choice of a cyclic ketal (see **8**) was based on the expectation that this form of protection would be more stable than the corresponding dimethyl ketal.

A number of ketene acetals (*cf.* **5**) had been reported[10] and an analogy for the proposed cycloaddition (*cf.* **5** + **6** → **7**) was also available.[11] On the basis of this encouraging background, we then proceeded with work along the lines of Scheme 1.

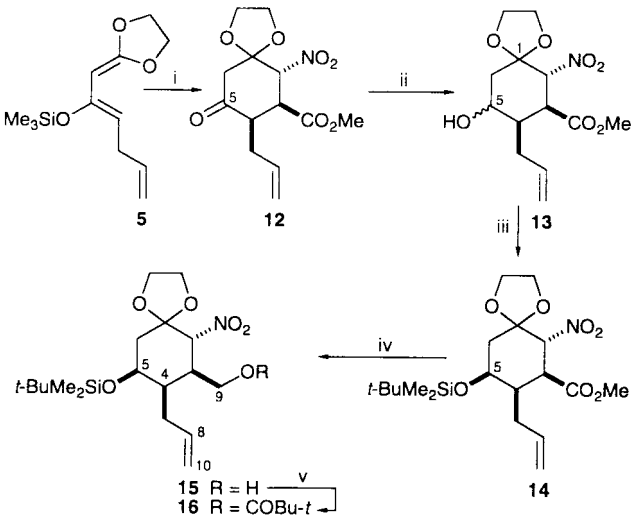
Formation of the central ring by Diels–Alder reaction

The readily available β-keto ester **9**[12] was subjected to ester exchange with 2-chloroethanol (**9** → **10**), and the resulting (2-chloroethyl) ester was converted into the required acyl ketene acetal **11** by the action of anhydrous potassium carbonate in DMF (Scheme 2).[10b] Attempts to effect the cyclization with sodium hydride were unsuccessful.



Scheme 2 *Reagents and conditions*: i, 2-chloroethanol, Ti(OPr-*i*)$_4$, 55 °C, 16 h, 75 °C, 24 h, 63%; ii, K_2CO_3, DMF, 80%; iii, $(Me_2PhSi)_2NLi$, Me_3SiCl, THF, −78 °C.

The next task was to convert the acyl ketene acetal into the *Z* silyl enol ether **5**, the *Z* geometry being preferred to facilitate the intended Diels–Alder reaction. For generating the silyl enol ether, LDA, lithium hexamethyldisilazide, and the very hindered base $(Me_2PhSi)_2NLi$ were evaluated, but only the latter produced the required geometry, which it did exclusively, and silylation *in situ* then gave **5**. This compound is not very stable but, fortunately, it can be used without purification, as even in the presence of $(Me_2PhSi)_2NH$ it reacts (Scheme 3) with the



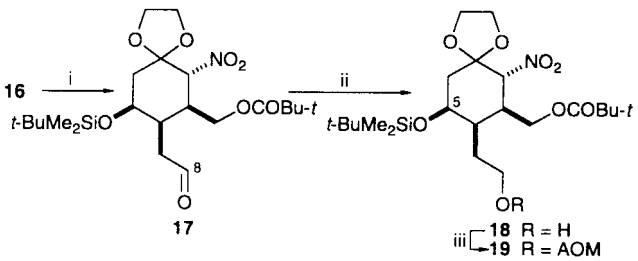
Scheme 3 *Reagents and conditions*: i, methyl (*E*)-2-nitropropenoate (**6**), THF, 0 °C, 1.5 h; aqueous NH_4Cl, 2 h, room temperature, 56% from **11**; ii, $NaBH_4$, MeOH, 0 °C, 99%; iii, *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 65% 5β epimer, 33% 5α epimer from **12**; iv, DIBAL-H, CH_2Cl_2, 99% for 5β, 99% for 5α; v, *t*-BuCOCl, DMAP, PhMe, 99% for 5β, 99% for 5α.

nitro ester **6**, and mild acidic workup affords crystalline ketone **12** in 56% yield overall from the acyl ketene acetal **11**.

Keto ester **12** is a key intermediate, and its structure was confirmed by X-ray analysis. From **12**, the first task was to protect the C(5) carbonyl. This was best done by simple reduction to give, in the event, a 2 : 1 mixture of alcohols, which were then silylated and separated (**12** → **13** → **14**). Although efficient *and* stereoselective ketone reduction was not possible, both of the C(5) epimers could be used; they were each subjected to the same reactions and, after several steps, both epimeric series converge to a single compound. These circumstances make the whole process quite efficient.

Next, the ester group in **14** (and in its 5α epimer) was reduced and the resulting alcohol protected by pivaloylation (**14** → **15** → **16**). At that point, with the C(5) and C(9) oxygen functions protected, it was appropriate to remove C(10) and introduce an oxygen at C(8), as these operations would adjust the side chain to the correct length and appropriate functionality.

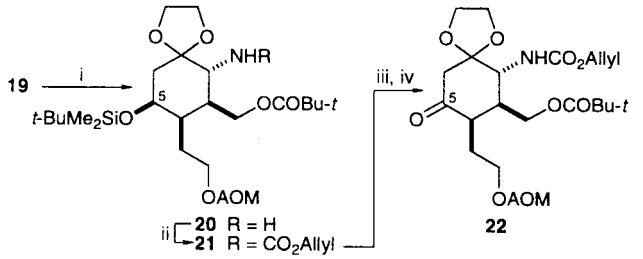
Cleavage of the C(8)-C(10) double bond under classical conditions (Scheme 4), with osmium tetraoxide and sodium periodate, and reduction of the resulting aldehyde **17** gave the



Scheme 4 AOM = $CH_2OC_6H_4OMe$-*p*. *Reagents and conditions*: i, OsO_4, $NaIO_4$, CCl_4, H_2O, *t*-BuOH, 73% for 5β, 77% for 5α; ii, $NaBH_4$, MeOH, 96% for 5β, 92% for 5α; iii, *p*-$MeOC_6H_4OCH_2Cl$, *i*-Pr_2NEt, DMAP, PhMe, 91% for 5β, 89% for 5α.

expected alcohol; this was protected with *p*-anisyloxymethyl chloride (**16** → **17** → **18** → **19**). Each of these steps was efficient in both the 5β series shown in Scheme 4, and in the corresponding 5α series.

With **19** and its 5α epimer in hand, the time had come to reduce the nitro group. Reduction of aliphatic nitro compounds is not as easy as in the aromatic series, but we found that the reagent generated by sonication of nickel(II) chloride hexahydrate and sodium borohydride[13] works very well (Scheme 5,



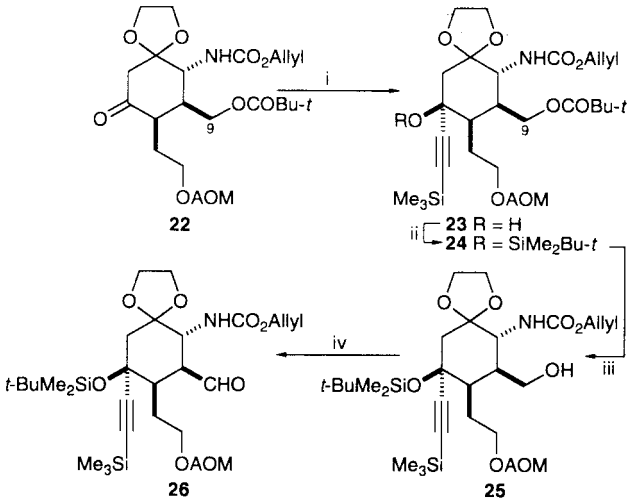
Scheme 5 AOM = $CH_2OC_6H_4OMe$-*p*. *Reagents and conditions*: i, $NaBH_4$, $NiCl_2.6H_2O$, MeOH, sonication, 95% for 5β, 95% for 5α; ii, allyl chloroformate, pyridine, THF, 82% for 5β, 82% for 5α; iii, Bu_4NF, THF, 95% for 5β, 96% for 5α; iv, CrO_3, pyridine, CH_2Cl_2, 95% for 5β, 90% for 5α.

19 → **20**) for both C(5) epimers. In each case, the resulting amine was protected as its allyl carbamate and, finally, the C(5) oxygen function was deprotected and oxidized by the Collins procedure (**21** → **22**).

At the stage of the resulting ketone (**22**) both of the C(5) epimers converge to the same product, and in both series identical reactions have been used, with almost identical results.

Attachment of two acetylene units

Ketone **22** gave a complex mixture with lithium trimethylsilylacetylide—a result that was very worrying—but we quickly found that it reacts cleanly (91%) with the corresponding cerium salt[14] to afford alcohol **23** (Scheme 6), in which the

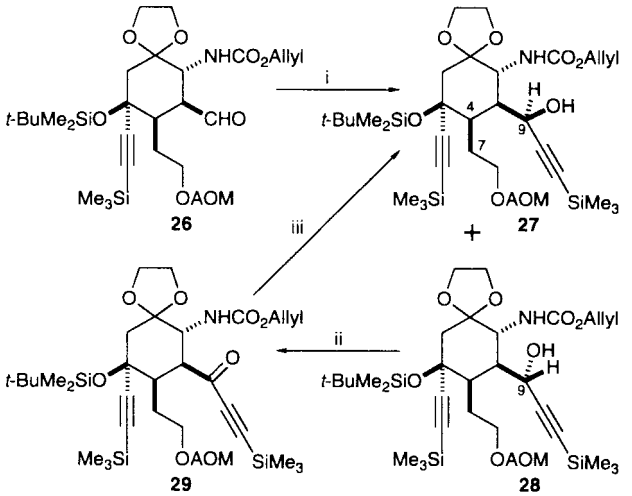


Scheme 6 AOM = $CH_2OC_6H_4OMe$-*p*. *Reagents and conditions*: i, $Me_3SiC{\equiv}CLi$, $CeCl_3$, THF, −78 °C, 91%; ii, *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 97%; iii, DIBAL-H, CH_2Cl_2, 95%; iv, CrO_3, pyridine, CH_2Cl_2, 90%.

acetylide has added from the same face as the nitrogen substituent. The hydroxy group was then protected by silylation (**23** → **24**), and preparations could now be made to introduce the second acetylene.

To that end, the pivaloyl group at C(9) was removed by the action of DIBAL-H, and the resulting alcohol was oxidized by the Collins procedure (**24** → **25** → **26**), with all the steps proceeding in high yield.

Treatment of aldehyde **26** with the cerium salt of trimethylsilylacetylene at −90 °C gave a 7:2 separable mixture of the required alcohol **27** and its C(9) epimer **28** (Scheme 7).

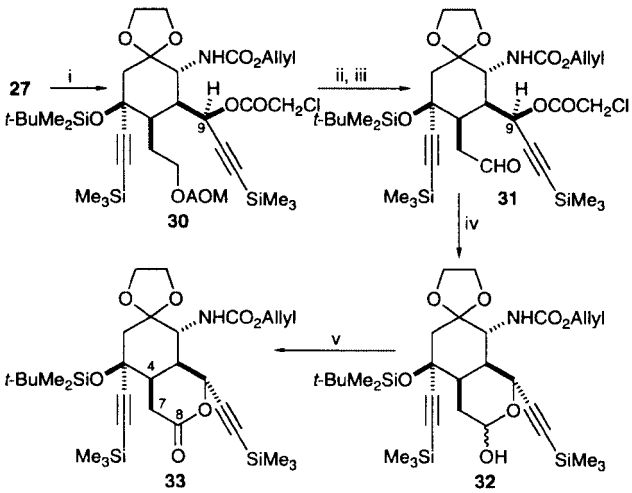


Scheme 7 AOM = $CH_2OC_6H_4OMe$-*p*. *Reagents and conditions*: i, $Me_3SiC{\equiv}CLi$, $CeCl_3$, THF, −90 °C, 79% for **27**, 16% for **28**; ii, PCC, 4 Å molecular sieves, CH_2Cl_2, 93%; iii, $NaBH_4$, MeOH, 0 °C, 88%

Attempts to improve the stereoselectivity by running the reaction at an even lower temperature, or by use of the ytterbium salt[15] of the acetylene were not successful. Fortunately, oxidation of the undesired isomer **28** gave a ketone that was reduced stereoselectively (11.6:1) to **27**, by sodium borohydride; thus, the overall transformation of **26** into **27** is quite efficient (92%), but required several experiments.

Introduction of the C(4)–C(7) double bond

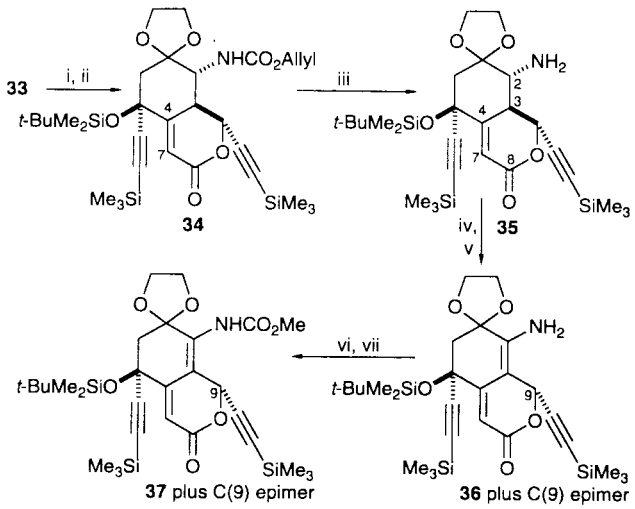
With both acetylenic units in place, the next task was to incorporate the two-carbon chain at C(4) into a ring, so as to be able to generate the C(4)-C(7) double bond with the correct geometry (see **2**). Ring formation was accomplished by the straightforward operations summarized in Scheme 8.



Scheme 8 AOM = $CH_2OC_6H_4OMe$-*p*. *Reagents and conditions*: i, $(ClCH_2CO)_2O$, pyridine, 99%; ii, $(NH_4)_2Ce(NO_3)_6$, pyridine, MeOH, H_2O, 89%; iii, CrO_3, pyridine, CH_2Cl_2, 91%; iv, NH_3(aq), MeOH, 0 °C; v, CrO_3, pyridine, CH_2Cl_2, 92% from **31**.

Protection of the C(9) hydroxy as a chloroacetate (**27** → **30**), followed by removal of the *p*-anisyloxymethyl group by exposure of the chloroacetate to ceric ammonium nitrate, gave an alcohol that was oxidized with the Collins reagent. Treatment of the resulting aldehyde **31** with dilute aqueous ammonium hydroxide released the C(9) hydroxy group, and this closed spontaneously onto the aldehyde group, so as to afford a mixture of lactols **32**. Another Collins oxidation then gave lactone **33**.

At this point the C(4)–C(8) chain is restrained within a ring so that the C(4)–C(7) double bond could be introduced (see Scheme 9) with the required *E* geometry. Phenylselenenylation



Scheme 9 *Reagents and conditions*: i, LDA, THF, PhSeBr, −78 °C; ii, dimethyldioxirane, −42 °C, 67% from **33**; iii, $(Ph_3P)_4Pd$, dimedone, THF, 80%; iv, *t*-BuOCl, Et_2O–THF; v, DABCO, PhMe; vi, $Cl_3COCO_2CCl_3$, pyridine, CH_2Cl_2; vii, MeOH, 78% (as an 8:1 isomer mixture) from **35**.

at C(7) and oxidation with dimethyldioxirane—an excellent reagent for use in selenoxide elimination—gave the desaturated lactone **34**. The intermediate phenyl selenide is not very stable and was not characterized, but the fact that it undergoes the selenoxide fragmentation indicates that the phenylseleno group must be on the same face as the C(4) hydrogen. We next removed the nitrogen protecting group by the action of tetrakis(triphenylphosphine)palladium(0) in the presence of dimedone,[16] the latter nucleophile being the best of several we tried. The resulting amine (**35**) was crystalline, and X-ray analysis confirmed the structure.

Introduction of the C(2)–C(3) double bond

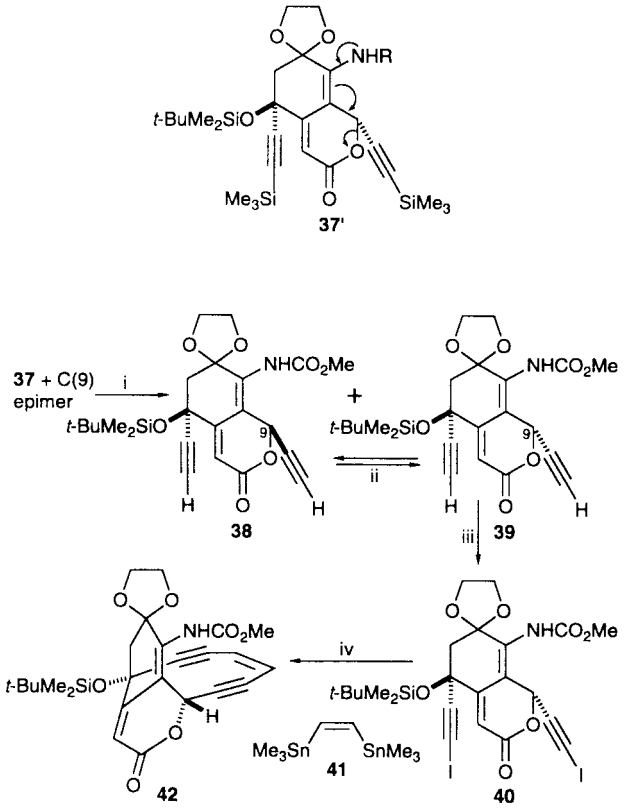
Introduction of the C(2)–C(3) double bond required a great deal of exploratory work before we identified the structural features that would allow efficient desaturation. This exploratory work guided many details of the synthetic plan discussed so far and directed us to the route leading ultimately to **35**, which has the two features we identified as important: the presence of a C(4)–C(7) double bond and incorporation of C(7) and C(8) into a ring.

Freshly prepared *t*-butyl hypochlorite converted **35** into its *N*-chloro derivative, and treatment with an excess of DABCO generated the corresponding imine, which underwent tautomerization to afford the fully conjugated enamide **36** and its C(9) epimer in an 8:1 ratio. The mixture of enamides is not very stable, and it was necessary to convert them promptly into the corresponding isocyanates, by treatment with triphosgene; the isocyanates, in turn, were immediately quenched with methanol. These operations gave carbamate **37** as an 8:1 mixture of C(9) epimers, the predominant one being that shown in Scheme 9. Neither of the epimer mixtures—enamide or carbamate—could be separated, but separation and isomerization of the *anti* isomer into the desired *syn* compound was easily achieved after the next step.

We assume that isomerization occurs by ring opening (see arrows in **37′**), followed by reclosure.

Formation of the enediyne ring

Our plan for closing the enediyne ring called for use of a double Stille reaction, and so we had first to remove the acetylenic silicon groups from **37**. Treatment with tetrabutylammonium fluoride did indeed give the corresponding terminal acetylene (Scheme 10), but under the reaction conditions further epimerization occurred at C(9). Fortunately, the epimeric acetylenes **38** and **39** were very easily separated, and the *anti* bisacetylene



Scheme 10 *Reagents and conditions*: i, Bu_4NF, THF, 39% for **38**, 46% for **39**; ii, Bu_4NOAc, 100% of a 4:6 mixture of **38** and **39**; iii, NIS, $AgNO_3$, acetone, 89%; iv, **41**, $(Ph_3P)_4Pd$, DMF, 60 °C, 72%.

could be converted in 100% yield into a 4:6 mixture in favor of **39**. After one recycling the yield of **39** was 69% from the mixture of **37** and its C(9) epimer. X-Ray analysis of the desired *syn* bisacetylene showed that the distance between the terminal acetylenic carbons is 4.154 ± 0.005 Å.

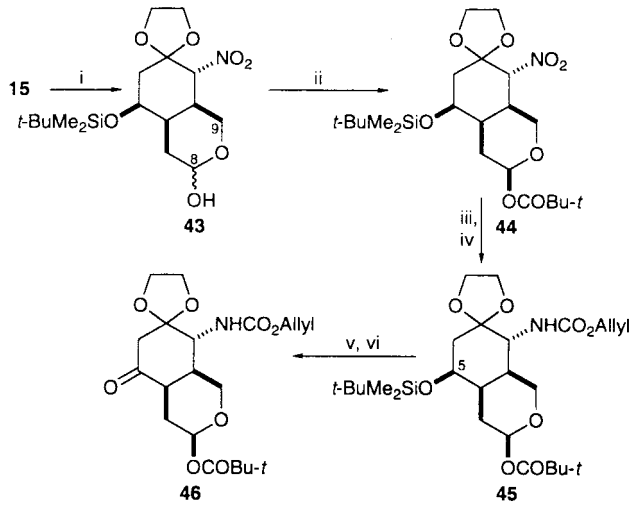
The acetylenic hydrogens were next replaced by iodine (**39** → **40**), using *N*-iodosuccinimide in the presence of silver nitrate.[17] Finally, a double Stille coupling of the diiodide with (*Z*)-1,2-bis(trimethylstannyl)ethene (**41**) gave the cyclic enediyne **42** in 72% yield, bringing the synthesis to a point where we needed to build up the allylic trisulfide and remove any remaining protecting groups.

Second route to the *syn* bisacetylene 39

During our development of the above route to **39** we encountered so many unexpected difficulties that we took the precaution of seeking another route to the same compound; in the event, this additional work had unusual and beneficial consequences.

The second route begins with the same Diels–Alder adduct used earlier and, as before, this was converted into alcohol **15** (see Scheme 3) and its C(5) epimer. In the first route the C(9) hydroxy group was protected before cleavage of the pendant double bond, but in the present case (Scheme 11), the double bond was cleaved without hydroxyl group protection and, as expected, the lactols **43** were formed. These were then protected by treatment with pivaloyl chloride. During the reaction epimerization of **43** occurs at C(8), so as to give only the product **44**, with the pivaloyl group equatorial. The nitro group was then reduced in high yield, again using the sodium borohydride–nickel chloride combination, and the resulting amine was protected as its allyl carbamate (**44** → **45**).

Finally, the C(5) oxygen was desilylated and oxidized, just as before (**45** → **46**). An identical set of reactions was done in the 5α series, and, at the stage of ketone **46**, both series converge to the same product, just as in the earlier route. Although both C(5) epimers were processed individually, the same reaction condi-

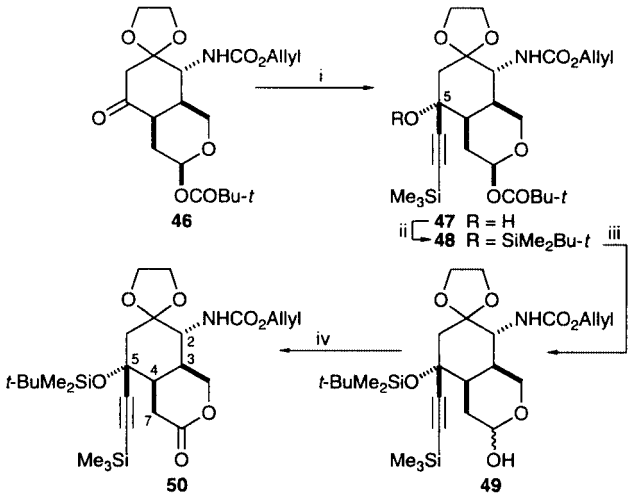


Scheme 11 *Reagents and conditions*: i, OsO_4, $NaIO_4$, CCl_4, H_2O, *t*-BuOH, 98% for 5α, 98% for 5β; ii, *t*-BuCOCl, pyridine, CH_2Cl_2, 96% for 5α, 96% for 5β; iii, $NaBH_4$, $NiCl_2{\cdot}6H_2O$, MeOH, sonication, 95% for 5β, 91% for 5α; iv, allyl chloroformate, pyridine, THF, 94% for 5β, 93% for 5α; v, Bu_4NF, THF, 97% for 5β, 95% for 5α; vi, PCC, 4 Å molecular sieves, CH_2Cl_2, 91% for 5β, 92% for 5α.

tions were used for both, and in each step the corresponding yields were almost identical.

Second route—introduction of the first acetylene

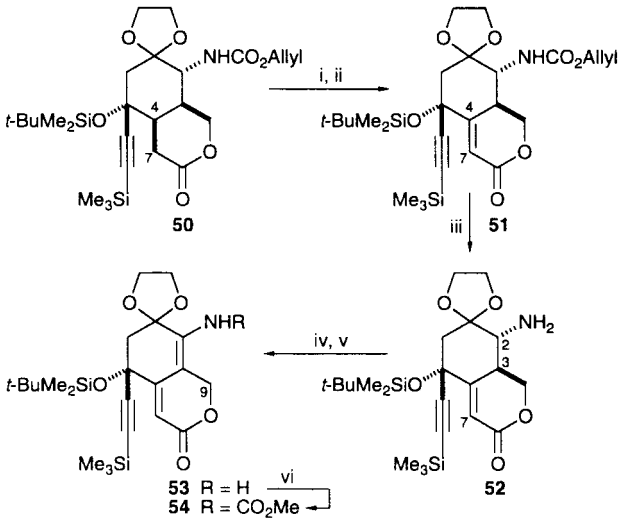
For introducing the first acetylene unit we again used the cerium salt of trimethylsilylacetylene and obtained, in high yield, alcohol **47** (Scheme 12), in which the acetylide had entered *anti*



Scheme 12 *Reagents and conditions*: i, $Me_3SiC{\equiv}CLi$, $CeCl_3$, THF, −78 °C, 91%; ii, *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 93%; iii, DIBAL-H, CH_2Cl_2, 96%; iv, CrO_3, pyridine, CH_2Cl_2, 97%.

to the nitrogen, in contrast to the result in the first route (*cf.* **22** → **23**, Scheme 6). The stereochemical assignment in the present case was made by X-ray analysis. The alcohol was protected by silylation (**47** → **48**), and the pivaloyl group was then removed by treatment with DIBAL-H. Oxidation of the resulting lactols took the route to a point (**50**) where we had again to introduce double bonds at C(4)–C(7) and at C(2)–C(3). Both of these operations were done by the methods that had worked well in the first route.

The C(4)–C(7) double bond was introduced by phenylselenenylation and dimethyldioxirane oxidation of the intermediate selenide (Scheme 13, **50** → **51**), for which we again assume on mechanistic grounds that the phenylseleno group is *syn* to the C(4) hydrogen. Removal of the allyloxycarbonyl group (**51** → **52**) by the action of a palladium catalyst in the

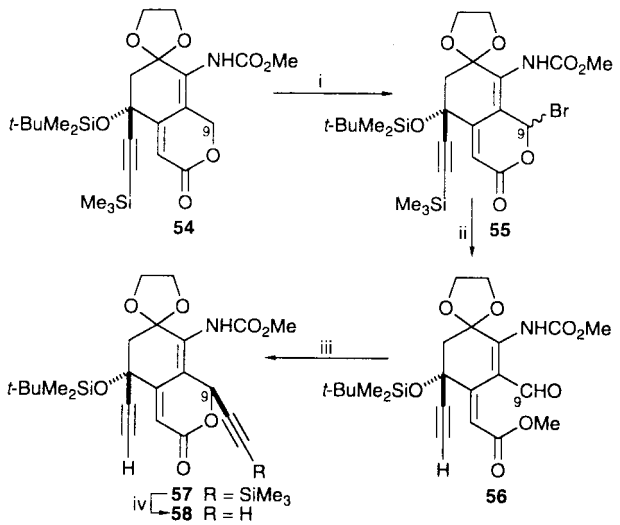


Scheme 13 *Reagents and conditions*: i, LDA, THF, PhSeBr, −78 °C; ii, dimethyldioxirane, 85%; iii, $(Ph_3P)_4Pd$, dimedone, THF, 93%; iv, *t*-BuOCl, Et_2O–THF; v, DBU, PhMe, 81% from **52**; vi, $Cl_3COCO_2CCl_3$, pyridine, CH_2Cl_2, then MeOH, 91%.

presence of dimedone liberated the free amine and, once again, that was chlorinated with *tert*-butyl hypochlorite. Exposure to a hindered base—in this case DBU—gave an imine, which immediately isomerized to the fully conjugated enamide **53**. This was converted into its isocyanate, which was quenched with methanol, thereby generating the required methyl carbamate **54**.

Second route—introduction of the second acetylene

Introduction of the second acetylene—that at C(9) in lactone **54**—required, of course, that the C(9) carbon be oxidized. In the event, we were very pleased to find that our first attempt at oxidation was successful (Scheme 14). We took advantage of



Scheme 14 *Reagents and conditions*: i, NBS, $(PhCO)_2O_2$, light, CCl_4; ii, $AgNO_3$, THF, H_2O, pyridine; then CH_2N_2, 77% from **54**; iii, $Me_3SiC{\equiv}CLi$, $CeCl_3$, THF, −78 °C, 91%; iv, Bu_4NF, THF, 46% for **58**, 42% of the C(9) epimer of **58**.

the fact that the C(9) hydrogens are allylic and are part of an ether subunit; consequently, these hydrogens should be susceptible to free radical reactions, and treatment with NBS under standard bromination conditions (dibenzoyl peroxide, tungsten lamp irradiation) gave a mixture of epimeric bromides **55**. These were hydrolyzed with aqueous silver nitrate to an aldehyde acid which, though it existed largely as a mixture of epimeric hydroxy lactones (OH instead of Br in **55**), was easily trapped as the methyl ester **56** by reaction with diazomethane.

During hydrolysis the acetylenic trimethylsilyl group is lost, but it would eventually have had to be removed and so its loss at this stage was of no consequence. The overall yield from **54** to **56** was 77%—a value that is most satisfactory in view of the fact that several transformations have been performed in one operation on a rather complex and sensitive structure.

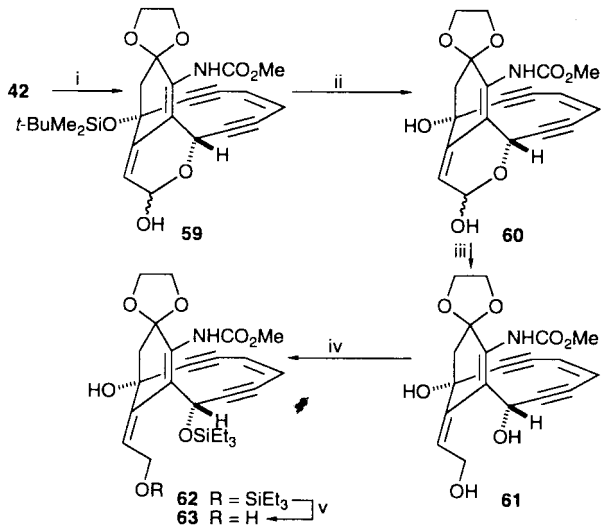
We were now ready to introduce the second acetylene. Naturally, we intended to use the cerium salt of trimethylsilylacetylene, but we had no idea of what stereochemical outcome to expect, and so we really were very pleased to find that a single compound (**57**) was formed in excellent yield (91%) and with the desired *syn* stereochemistry. When we removed the acetylenic trimethylsilyl group, the product (**58**) was, of course, identical to the material obtained by the first route. Two points need to be made about the formation of **58**. The first is that, during the desilylation, epimerization occurs at C(9), but this problem was handled in the same way as in the first route: the undesired *anti* bisacetylene was treated with tetrabutylammonium acetate to obtain an equilibrium mixture of the *syn* and *anti* isomers, so that the yield of the desired *syn* material was 71% from **57** after one recycling.

The second point also concerns stereochemistry. Up to this point we have been dealing with racemic compounds, but representing them by a single enantiomer. In the two routes, the first acetylene [at C(5)] has a different stereochemical relationship to the nitrogen function, being in one case *syn* (*cf.* **23**) and in the other *anti* (*cf.* **47**). However, all the stereogenic centers in **47** except C(5) are ultimately converted into sp^2 hybridization, and so both racemic monoacetylenes give the same *racemic* product, *i.e.* **58** and **39** are identical, but are drawn in different ways merely to emphasize the *initial* relationship between the C(5) acetylene and the nitrogen. Later on we were able to make good use of this stereochemical outcome in order to prepare optically pure material.

Formation of (±)-calicheamicinone

By the time we had made the cyclic enediyne **42** Danishefsky and coworkers[7a] and Nicolaou and coworkers[8] had shown how substances of very similar structure could be converted into calicheamicinone, and we used a method similar to theirs.

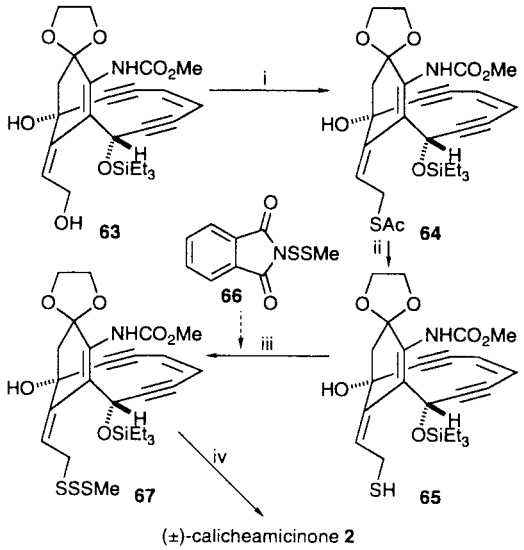
Lactone **42** was first reduced with DIBAL-H (Scheme 15) to a mixture of lactols (**59**) and then the silicon protecting group was removed in the usual way (**42** → **59** → **60**). The DIBAL-H



Scheme 15 *Reagents and conditions*: i, DIBAL-H, CH_2Cl_2, 98%; ii, Bu_4NF, THF, 94%; iii, $NaBH_4$, MeOH, 76%; iv, Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, 95%; v, AcOH, THF, H_2O, 94%.

reduction must be done before desilylation in order to avoid solubility problems with the desilylated lactone and, in turn, desilylation must precede installation of the trisulfide because the latter is sensitive to tetrabutylammonium fluoride. Thus, the timing of the last two reactions is critical. Lactols **60** were further reduced with sodium borohydride to triol **61**, and at this point it was necessary to protect the secondary hydroxy group so as to block its participation in a subsequent Mitsunobu reaction. Selective protection was achieved by silylating both the primary and secondary hydroxy groups and then storing the resulting product (**62**) in a mixture of acetic acid, THF and water. Under these conditions the primary allylic hydroxy group was released (**62** → **63**), and the stage was set to introduce the trisulfide unit.

The primary hydroxy group was replaced by a thioacetyl group, under typical Mitsunobu conditions (Scheme 16, **63** → **64**), and the free thiol was then liberated by treatment with



Scheme 16 *Reagents and conditions*: i, *i*-PrO_2CN = NCO_2Pr-*i*, Ph_3P, AcSH, 94%; ii, DIBAL-H, CH_2Cl_2; iii, *N*-(methyldithio)phthalimide, CH_2Cl_2, 88% from **64**; iv $TsOH·H_2O$, THF, H_2O, 84%.

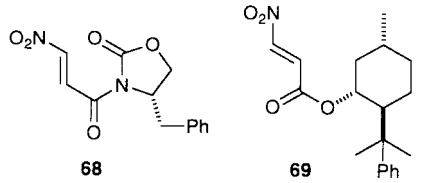
DIBAL-H. The next step proved to be troublesome until we recognized that freshly chromatographed thiol must be used. As soon as that was established, we found that treatment of **65** with an eight-fold excess of reagent **66** gave the desired trisulfide **67** in 88% yield over the two steps from **64**. Finally, the remaining protecting groups were removed by mild acid hydrolysis, affording (84%) racemic calicheamicinone as a white foam.

Synthesis of optically pure and crystalline (−)-calicheamicinone

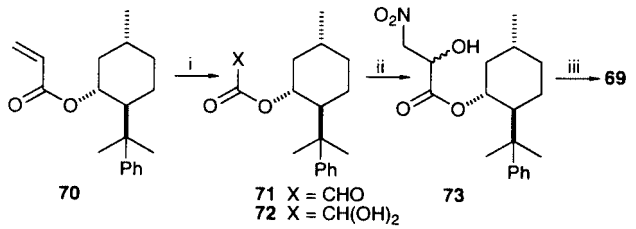
In the two syntheses of racemic calicheamicinone described above, the stereochemical relationship between the first acetylene and the nitrogen is different, but both modes of acetylide addition ultimately lead to the same *racemic* product. However, if the initial Diels–Alder adduct is made optically pure, then each route would give a different enantiomer of calicheamicinone. Moreover, the *absolute* stereochemistry of the initial Diels–Alder adduct is immaterial—provided it is known—since calicheamicinone of natural or unnatural stereochemistry can be reached from either enantiomer of the Diels–Alder adduct simply by selecting one or other of the two routes. With this unusual situation as background, we set out to prepare optically pure calicheamicinone,[5] a task for which the only new problem was the preparation of the Diels–Alder adduct in optically pure form and the determination of its absolute configuration.

In our initial Diels–Alder reaction (*cf.* Scheme 1) we had used the *methyl* ester of β-nitroacrylic acid; consequently, nitroacrylates such as **68** and **69** were obvious candidates for use in an asymmetric Diels–Alder reaction.

Our first choice was the oxazolidinone derivative **68**, but we were unable to prepare it. Perhaps we were too impatient but, in



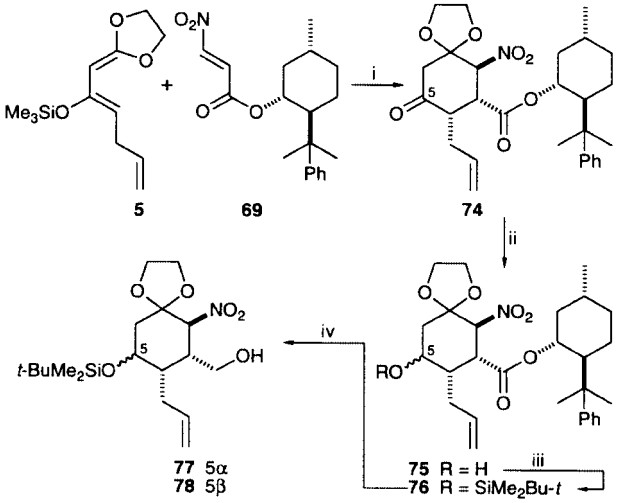
any event, our second choice—the 8-phenylmenthol derivative **69**—served the desired purpose admirably. Preparation of **69** was initially problematic, but it did not take long to devise an acceptable route (Scheme 17).



Scheme 17 *Reagents and conditions*: i, $NaIO_4$, OsO_4, H_2O, dioxane, 98%; ii, $MeNO_2$, alumina, 90%; iii, MsCl, Et_3N, 89%.

Optically pure 8-phenylmenthol[18] was acylated with acryloyl chloride and the double bond in the product **70**[19] was cleaved by the Lemieux–Johnson method to provide a mixture of the glyoxylate **71** and its hydrate **72**. This mixture underwent a Henry reaction with nitromethane in the presence of neutral alumina[20] to give a mixture of nitro alcohols (**71**, **72** → **73**), which was easily dehydrated by mesylation and spontaneous elimination.

For the asymmetric Diels–Alder reaction the diene component **5** was again generated *in situ*; it reacts smoothly with the optically pure nitroacrylate to give, after mild acid workup, the ketone **74** in slightly higher yield than for the *methyl* ester—64 versus 56%. X-Ray analysis of the ketone showed that the absolute configuration was as drawn in Scheme 18. The C(5)



Scheme 18 *Reagents and conditions*: i, THF, −78 °C, 35 min, then aqueous NH_4Cl, 4 h, 64% based on **11**; ii, $NaBH_4$, MeOH, 99%; iii, *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 100%; iv, DIBAL-H, CH_2Cl_2, −78 to −30 °C, 52% for **77** and 27% for **78**.

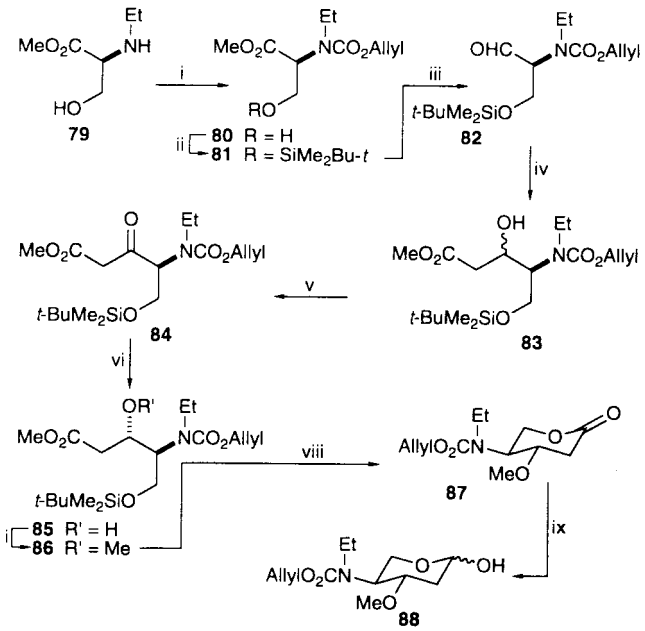
carbonyl was reduced as before to a mixture of epimeric alcohols, and these were then silylated (**74** → **75** → **76**). Finally, the chiral auxiliary was removed by treatment with DIBAL-H, first at −78 °C and then at −30 °C. With proper temperature control the two optically pure alcohols **77** (52% from ketone **74**) and **78** (27%) can be obtained, and the chiral auxiliary is recovered (96%). Alcohols **77** and **78** correspond to the racemic compounds used earlier (see Scheme 3), and the absolute configuration of ketone **74** indicated that the second route (Schemes 11–14) developed with racemic material would lead to calicheamicinone of natural configuration. Accordingly, the earlier experiments were repeated using both **77** and **78**; the sequence afforded (−)-calicheamicinone. Our material was crystalline, and we were able to obtain the first X-ray crystallographic data for calicheamicinone.

Synthesis of model compounds representing the sugar units

Once the aglycone had been completed we began work on the sugars and the aromatic unit. We arbitrarily decided to make each of the sugars from materials in the chiral pool—but excluding other sugars—or by asymmetric synthesis.

Synthesis of a ring E model

Our starting material for the ring E unit (see structure **1**) was serine, which is easily converted[21] into the *N*-ethyl ester **79**. *N*-Carbamoylation and silylation of the remaining hydroxy group (see Scheme 19) gave the fully protected derivative **81** (**79** → **80** → **81**). DIBAL-H reduction furnished aldehyde **82**, and

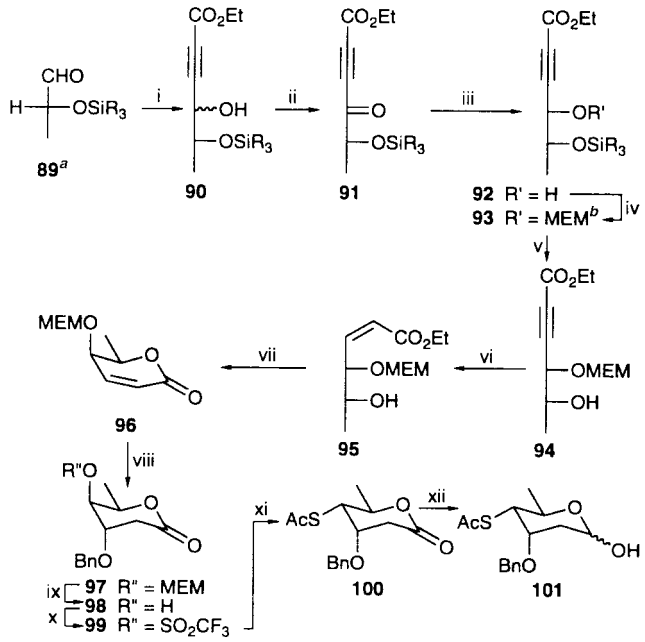


Scheme 19 *Reagents and conditions*: i, allyl chloroformate, K_2CO_3, THF, water, 0 °C, 94%; ii, *t*-$BuMe_2SiOTf$, imidazole, DMF, 97%; iii, DIBAL-H (added over 1 h), CH_2Cl_2, −78 °C, 30 min; iv, SmI_2, THF, −78 °C, MeO_2CCH_2Br, 1 h, 56% from **81**; v, PCC, 4 Å molecular sieves, CH_2Cl_2, 1 h; vi, $NaBH_4$, MeOH, 0 °C, 83% from **83**; vii, $MeOSO_2CF_3$, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, reflux, 82%; viii, 3:1:1 AcOH–THF–water, 24 h; azeotrope with PhMe; PhMe, AcOH, 80 °C, 5 h, 86%; ix, DIBAL-H, CH_2Cl_2, −78 °C, 88%.

condensation with methyl bromoacetate, mediated by samarium iodide,[22] served to generate the required carbon skeleton (**82** → **83**). The condensation gave a mixture of isomers with the major one having a stereochemistry at the hydroxy-bearing carbon opposite[23] to that required. Consequently, an oxidation-reduction sequence (**83** → **84** → **85**) was needed to adjust the stereochemistry; alcohol **85** was obtained in 89% ee. Methylation and desilylation then led directly to lactone **87**, and DIBAL-H reduction gave the lactols **88**, corresponding to a protected version of the ring E sugar of calicheamicin γ_1^I.[24]

Synthesis of a ring B model

Synthesis of the ring B unit began with methyl (*R*)-lactate, which was converted by silylation and reduction into aldehyde **89** (Scheme 20), following a literature procedure.[25] Addition of the magnesium acetylide derived from ethyl propiolate afforded



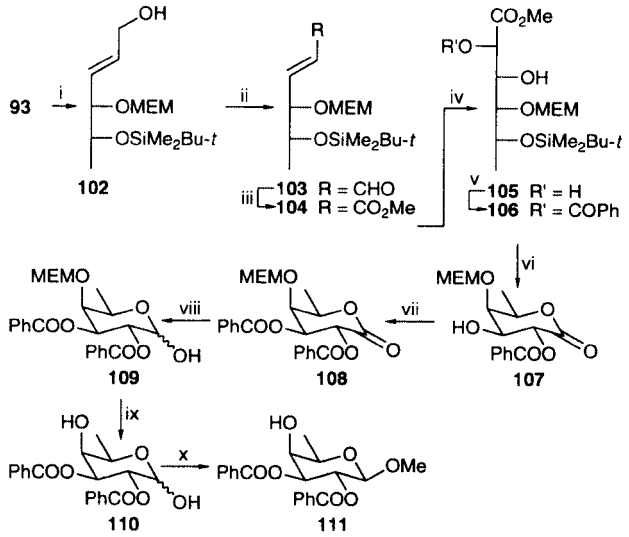
Scheme 20 [a]R_3 = Me_2Bu-*t*. [b]MEM = $CH_2OCH_2CH_2OMe$. *Reagents and conditions*: i, $EtO_2CC{\equiv}CMgBr$, THF, HMPA, **89** in CH_2Cl_2, −78 °C, 72%; ii, Jones reagent; iii, K-Selectride, THF, −78 °C, 68% from **90**; iv, MEMCl, *i*-Pr_2NEt, CH_2Cl_2, 86%; v, 48% aqueous HF, MeCN, 94%; vi, 5% Pd–$BaSO_4$, quinoline, H_2, 1 atm, 86%; vii, PhMe, AcOH, 80 °C, 95%; viii, BnOH, $Hg(OAc)_2$, $HClO_4$, 2 days; then THF, aqueous pH 8 buffer, $NaBH_4$, 52% overall, 71% corrected for recovered **96**; ix, Me_3SiCl, NaI, MeCN, 86%; x, $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2; xi, AcSK, DMF, 48% from **98**; xii, DIBAL-H, CH_2Cl_2, −95 °C, 90%.

a 9.6 : 1 mixture of alcohols **90**, in which the minor isomer was the desired one.[25] Accordingly, the alcohols were subjected to Jones oxidation (**90** → **91**) and then treated with K-Selectride, so as to generate the required stereochemistry (**91** → **92**).[25] The hydroxy group was now protected as its MEM ether, and the other oxygen was deprotected with aqueous HF in acetonitrile (**92** → **93** → **94**). Semihydrogenation gave the *Z* alkene **95**, which lactonized (**95** → **96**) on heating in the presence of acetic acid. At this point, treatment with benzyl alcohol and mercuric acetate served to effect alkoxymercuration of the double bond, and reduction with sodium borohydride released the desired benzyloxy lactone **97**.[26] The C(4) oxygen was next deprotected with iodotrimethylsilane, generated *in situ*, and sulfonylated with triflic anhydride (**97** → **98** → **99**). These operations took the route to a point where a thioacetyl group could be introduced by S_N2 inversion, using potassium thioacetate in DMF (**99** → **100**). Finally, DIBAL-H reduction at −95 °C gave the lactols **101** (94%), the thioacetyl group remaining intact. Lactols **101** represent a model of the ring B sugar unit of calicheamicin γ_1^I.[27]

Synthesis of a ring A model

Our ring A model is one having a hydroxy group at C(4) that can be converted into a leaving group (for displacement by a hydroxylamine nitrogen), a C(2) hydroxy group for glycosylation with a suitable ring E precursor, and C(1) blocked as a methyl glycoside. Structure **111** satisfies these requirements, and the route we used to prepare it should allow differential protection of the C(2) and C(3) oxygen functions.

Intermediate **93**, used in the synthesis of the ring B model, served as the starting point for the ring A model. The acetylenic ester unit was converted by reduction ($LiAlH_4$) and oxidation into aldehyde **103** (see Scheme 21), and the latter was converted in one step into the *E* olefinic ester **104**. The double bond was then hydroxylated, giving as the major product (80% yield) the desired diol **105**, this structural assignment being made after ring closure. Selective benzoylation of the C(2) hydroxy group



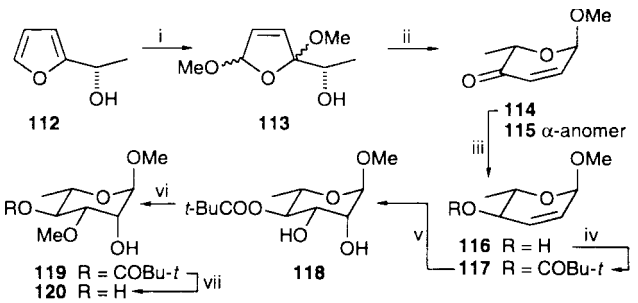
Scheme 21 *Reagents and conditions*: i, $LiAlH_4$, THF, 83%; ii, MnO_2, hexane; iii, MnO_2, NaCN, MeOH, AcOH, 87% from **102**; iv, OsO_4, NMO, *t*-BuOH, 8:1 acetone–water, 78% (isolated) plus an isomer (16%); v, PhCOCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, room temperature, 84%; vi, Bu_4NF, THF, AcOH, 92%; vii, PhCOCl, pyridine, DMAP, CH_2Cl_2, 98%; viii, DIBAL-H in CH_2Cl_2, THF, −78 °C, 87%; ix, Me_3SiCl, NaI, MeCN, −20 °C; x, $(MeO)_3CH$, camphorsulfonic acid, MeOH, reflux, 78% from **109**.

afforded **106** and, when the silyl group was removed, under standard conditions, spontaneous lactonization occurred, generating lactone **107**. For convenience in this model study we chose to mask the C(3) hydroxy group as a benzoate (**107** → **108**). At that point, DIBAL-H reduction selectively modified the lactone carbonyl, providing a mixture of lactols (**109**), and the C(4) oxygen was deprotected, using iodotrimethylsilane, generated as before, *in situ*. Finally, the anomeric position was blocked as a methyl glycoside (**110** → **111**).[28]

Synthesis of a ring D model

We arbitrarily decided to prepare our ring D model by asymmetric synthesis rather than from rhamnose; consequently, our route, which is closely related to prior methods,[24f] is longer than that starting with a preformed sugar, but does offer additional possibilities for incorporating isotopic labels.

The (*S*) furyl alcohol **112**[29] (Scheme 22) was prepared by asymmetric[29,30] transfer hydrogenation from the corresponding

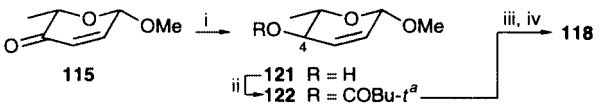


Scheme 22 *Reagents and conditions*: i, Br_2, MeOH, −40 °C, 89%; ii, HCO_2H, MeOH, 61% **114**, 20% **115**; iii, $LiAlH_4$, Et_2O, −50 °C, then warm to room temperature, 94%; iv, *t*-BuCOCl, pyridine, DMAP, CH_2Cl_2, 93%; v, OsO_4, *t*-BuOH, NMO, 9:1 acetone–water, 97%; vi, Bu_2SnO, 10 : 1 MeOH–PhH, reflux 70 min, cool, MeI, 45 °C, 17 h, 95%; vii, $LiOH{\cdot}H_2O$, 4 : 1 MeOH–water, 5 days, 85 or 95%, corrected for recovered **119**.

ketone. Following a literature procedure,[31] bromination in methanol (**112** → **113**) and treatment with formic acid then gave a mixture of the desired pyranosidulose **114**[32] (61%) and the α-anomer (20%), both of which were used in the synthesis, as described below.

Reduction of the ketone with lithium aluminium hydride proceeded[31] with the required stereochemical result in high yield (**114** → **116**, 94%). At this point, the optical purity of the compound was confirmed by NMR comparison of its Mosher ester with corresponding material made from racemic **112**. The C(3) hydroxy group was now protected as its pivaloyl ester, and dihydroxylation, under standard conditions, produced diol **118**, which could be selectively and efficiently (95%) methylated[33] (Bu_2SnO, MeI) on the C(3) oxygen (**118** → **119**). Mild basic hydrolysis gave diol **120**. Both **119** and **120** serve as models for the D ring.[34]

The ring closure step from **113** afforded as a byproduct the α-anomer **115** in 20% yield, but the stereochemistry could be adjusted (Scheme 23), so that some of this material could be used for the main sequence of Scheme 22.

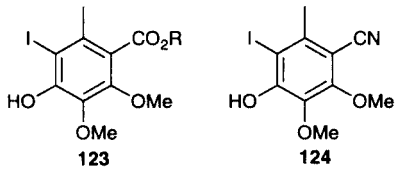


Scheme 23 [a]Yield of C(4) epimer 22%. *Reagents and conditions*: i, $NaBH_4$, THF, water, 0 °C; ii, *t*-BuCOCl, pyridine, DMAP, $CHCl_3$, 66% **116**, 22% for the C(4) anomer; iii, camphorsulfonic acid, MeOH; iv, OsO_4, *t*-BuOH, NMO, 9:1 acetone–water, 75% from **115**.

Reduction of ketone **115** with sodium borohydride, and pivaloylation gave **122** as the predominant product. Without purification, this was subjected to conditions for acetal exchange, so as to form mainly the α-glycal. Finally, dihydroxylation gave pure **118** in 75% overall yield from **122**. We did not investigate the use of other hydride agents, in an attempt to improve the isomer ratio (*ca*. 3:1) in the first step.

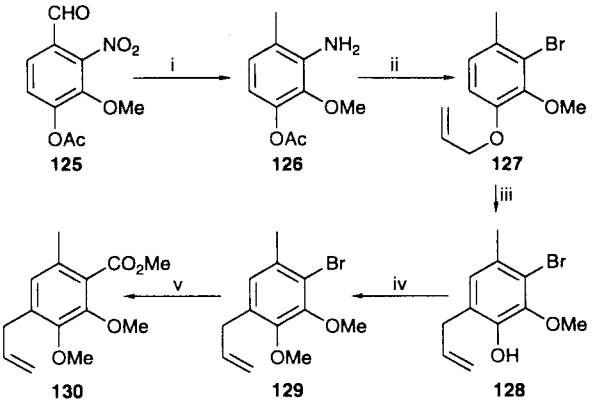
Synthesis of the aromatic unit

The carbohydrate domain of calicheamicinone is interrupted by the hexasubstituted benzene, which is flanked by a monosaccharide and a trisaccharide. Before we began our own work,[6] methods had been published for making the parent aromatic system **123** (R = H),[35] the corresponding ester **123** (R = Me),[21,35] and the nitrile **124**.[24f] We prepared ester **123** (R = Me) by two routes, using very simple reactions. Both routes lead to compound **130** (Scheme 24), from which the target is easily reached, as described below.

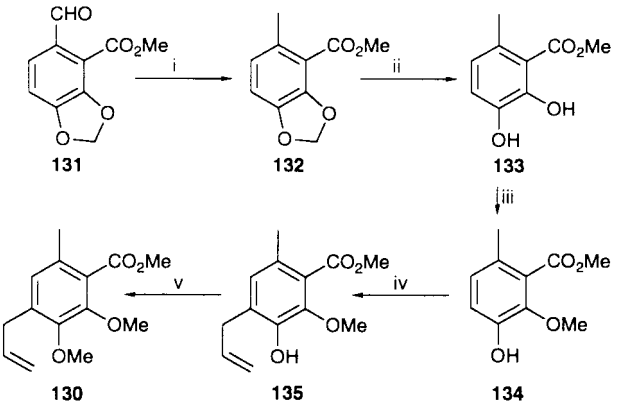


Our first route begins with the known nitro acetate **125**[36] (Scheme 24), which is available in good yield from vanillin by acetylation (Ac_2O, aqueous NaOH; 94%) and nitration (fuming HNO_3; 83%). Catalytic hydrogenation served to reduce both the nitro and formyl groups, and in this way the required methyl and amino functions are introduced (**125** → **126**). Sandmeyer reaction, acetate hydrolysis, and allylation of the resulting phenol then gave the bromo allyl ether **127**. This rearranged in high yield when heated in refluxing decalin, to produce the *ortho* allyl phenol **128**, which was methylated under standard conditions. Finally, halogen–metal exchange and acylation with methyl chloroformate gave **130**, which is an advanced intermediate common to both the routes we developed to the aromatic ring.

The second route (Scheme 25) starts with piperonal. The derived cyclohexylimine (*ca*. 97%) is easily converted into aldehyde ester **131** by lithiation and treatment with methyl chloroformate (88%).[37] Hydrogenolysis again converts the formyl group into a methyl, and then the phenolic hydroxy



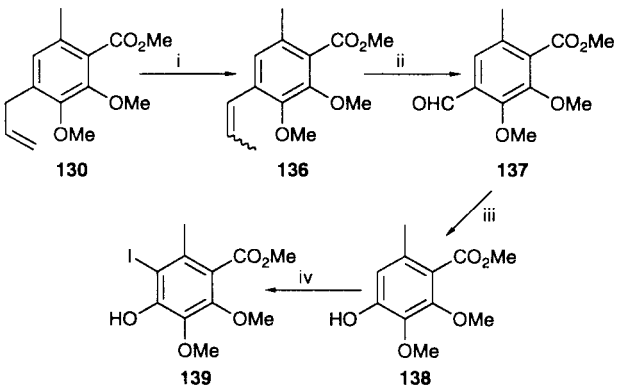
Scheme 24 *Reagents and conditions*: i, AcOH, MeOH, Pd-C, H_2, 93%; ii, (a) $NaNO_2$, HCl, CuBr, (b) MeOH, KOH, heat, 81%, (c) K_2CO_3, allyl bromide, acetone, 96%; iii, refluxing decalin (*ca*. 190 °C), 91%; iv, K_2CO_3, Me_2SO_4, acetone, 92%; v, *n*-BuLi, THF, MeOCOCl, 81%.



Scheme 25 *Reagents and conditions*: i, AcOH, MeOH, Pd–C, H_2, 93%; ii, $AlBr_3$, EtSH, 93%; iii, Li_2CO_3, MeI, DMF, 71%, after correction for recovered **133** (30%); iv, (a) K_2CO_3, allyl bromide, acetone, 92%, (b) refluxing decalin (*ca*. 190 °C), 86%; v, K_2CO_3, Me_2SO_4, acetone, 97%.

groups were released by the action of aluminium tribromide in ethanethiol. The critical next step (**133** → **134**) involved selective methylation of the C(2) hydroxy group. This was accomplished[38] by using methyl iodide and lithium carbonate in DMF at room temperature and, under these conditions, it was possible to isolate the desired monomethyl ether **134** in acceptable yield (50%, or 71%, after correction for recovered **133**). The remaining hydroxy group was then allylated as before, and Claisen rearrangement gave the new phenol **135**. This was then methylated (**135** → **130**), bringing the sequence to a point that overlaps with the first route.

Having a supply of **130** in hand, we had next to degrade the allyl pendant to a formyl group (Scheme 26). To this end, the



Scheme 26 *Reagents and conditions*: i, $RhCl_3·3H_2O$, EtOH, heat, 89%; ii, OsO_4, $NaIO_4$, *t*-BuOH, CCl_4, H_2O, 83%; iii, MCPBA, CH_2Cl_2, then MeOH, KOH, water, 81%; iv, ICl, CH_2Cl_2, 95%.

double bond was shifted into conjugation with the aromatic ring, using rhodium trichloride in refluxing ethanol,[39] and oxidative cleavage of the product (**136**) under Lemieux–Johnson conditions gave aldehyde **137**. At that point, Baeyer–Villiger oxidation and base hydrolysis produced the known phenol **138**,[35] which reacted with iodine monochloride to afford in 95% yield the target **139**—a substance that represents the aromatic unit of calicheamicin.

Conclusion

Our synthetic work has led to each of the subunits of calicheamicin γ_1^I, including the first preparation of *crystalline* (−)-calicheamicinone, for which the molecular dimensions were established by X-ray analysis. At several points a remarkable level of stereoselectivity was observed with alkynyl cerium reagents, and the stereochemical aspects of the synthesis of **2** are very unusual.

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