

Communications to the Editor

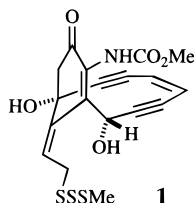
Synthesis of (±)-Calicheamicinone by Two Related Methods

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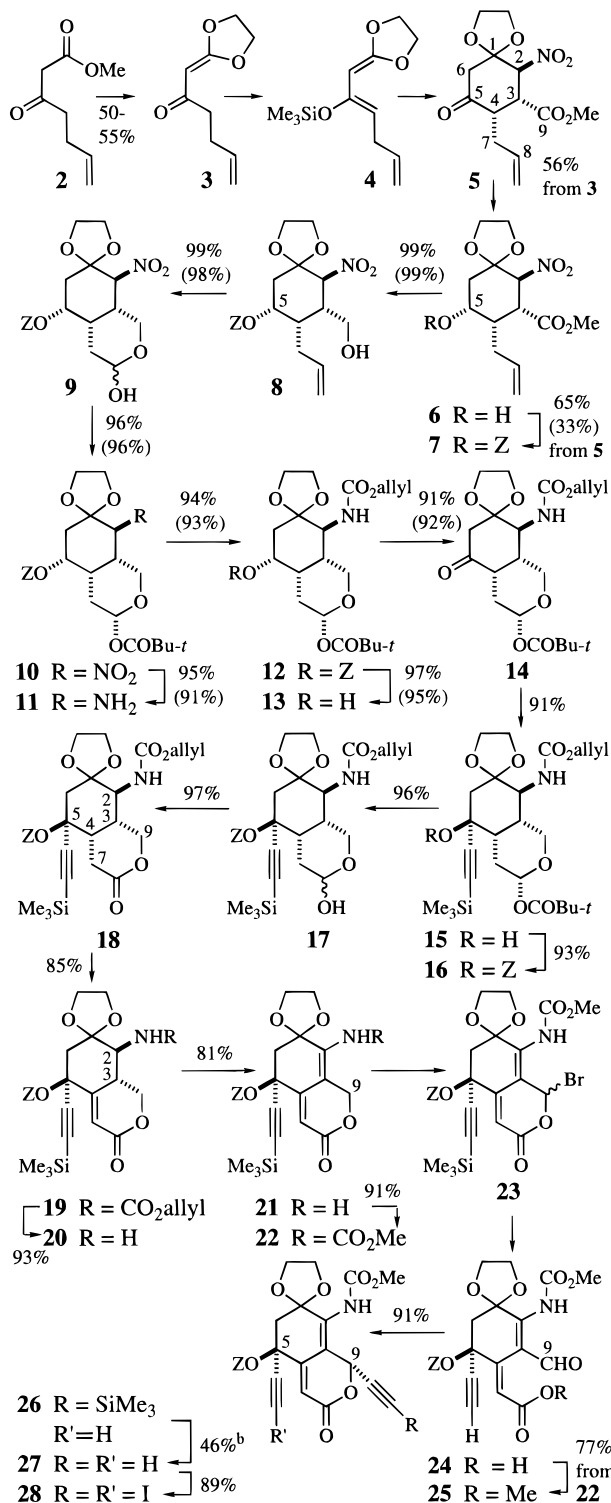
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We report the synthesis of (±)-calicheamicinone (**1**),¹ the aglycon (in racemic form) of the antitumor agent² calicheamicin γ_1 .¹ Ester exchange of β -keto ester **2** with $\text{ClCH}_2\text{CH}_2\text{OH}$ [Ti-



(*OPr-i*)₄, 63%], followed by treatment with K_2CO_3 , gave⁵ ketene acetal **3** (80–87%) (Scheme 1). Deprotonation [$(\text{Ph}_2\text{MeSi})_2\text{NLi}^6$] to the *Z*-enolate⁷ and trapping with Me_3SiCl afforded triene **4**, which underwent Diels–Alder cycloaddition with methyl (*E*)-3-nitropropenoate⁸ (**4** → **5**; 56% from **3**). Reduction of **5** with NaBH_4 gave a 2:1 mixture of C(5) epimeric alcohols [only the major one (**6**) is shown]. These were separated after silylation [*t*-BuMe₂SiOTf, 2,6-lutidine, 65% (from **5**) of 5 α -isomer **7**, and 33% (from **5**) of corresponding 5 β -isomer⁹]. Both isomers were independently converted into **14** by identical routes; only the procedure for the major isomer is shown, but yields for the 5 β -series are also given in the scheme. Reduction (DIBAL-H; 99%) of ester **7** generated primary alcohol **8**, and the carbon–carbon double bond of **8** was then cleaved (OsO_4 , NaIO_4 ; 99%). The resulting equilibrium mixture of lactols (**9**) afforded (96%) a single pivaloate (**10**) in the presence of *t*-BuCOCl and pyridine. Next, the nitro group was reduced¹⁰ (NiCl_2 , NaBH_4 , ultrasound, 95%) and protected (allyloxycarbonyl chloride, pyridine; 94%) (**10** → **11** → **12**). Desilylation (**12** → **13**; TBAF; 97%) and PCC oxidation (**13** → **14**; 91%) now set the stage for introduction of the first acetylene unit (**14** → **15**⁹). This was

Scheme 1^a



^a Z = SiMe₂Bu-*t*; yields in brackets refer to 5 β series. ^b Yield after equilibration: 71% (see text).

accomplished by reaction with cerium trimethylsilylacetylide¹¹ (1:1.2 $\text{Me}_3\text{SiC}\equiv\text{CLi}$, CeCl_3 , THF, -78°C ; 91%), the acetylene being introduced *anti* to the nitrogen. Protection of the hydroxyl group (**15** → **16**; *t*-BuMe₂SiOTf, 2,6-lutidine; 93%), removal of the pivaloyl group (**16** → **17**; DIBAL-H; 96%), and Collins oxidation (**17** → **18**; 97%) then brought the work to a point

(1) (a) Haseltine, J. N.; Paz Cabal, M.; Mantlo, N. B.; Iwasawa, N.; Yamashita, D. S.; Coleman, R. S.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1991**, *113*, 3850. (b) Smith, A. L.; Pitsinos, E. N.; Hwang, C.-K.; Mizuno, Y.; Saimoto, H.; Scarlato, G. R.; Suzuki, T.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1993**, *115*, 7612. (c) Aiyer, 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.

(2) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Siegel, M. M.; Morton, G. O.; Ellestad, G. A.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 985.

(3) Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982**, 138.

(4) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

(5) cf.: (a) Broadhurst, M. D. *J. Org. Chem.* **1985**, *50*, 1117. (b) Eid, C. N., Jr.; Konopelski, J. P. *Tetrahedron* **1991**, *47*, 975.

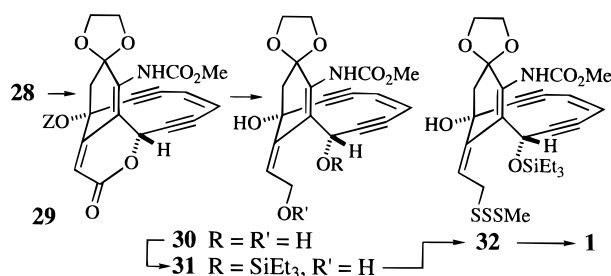
(6) Made from the amine (BuLi, THF, 0°C ; 20 min); Zhinkin, D. Y.; Mal'nova, G. N.; Gorislavskaya, Zh. V. *J. Gen. Chem. USSR* **1968**, *38*, 2702.

(7) cf.: Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526.

(8) Danishefsky, S.; Prisbylla, M. P.; Hiner, S. *J. Am. Chem. Soc.* **1978**, *100*, 2918. cf.: Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400. Banville, J.; Brassard, P. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1852. Schechter, H.; Conrad, F.; Daulton, A. L.; Kaplan, R. B. *J. Am. Chem. Soc.* **1952**, *74*, 3052.

(9) Structure confirmed by x-ray analysis.

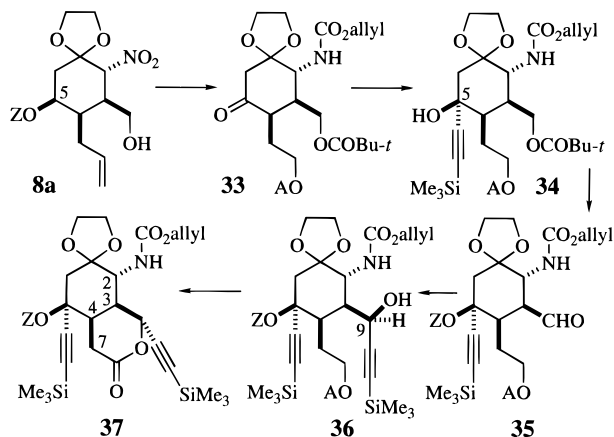
(10) Osby, J. O.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 6413.

Scheme 2^a

where we needed to introduce double bonds at C(4)–C(7) and C(2)–C(3) and attach an acetylene unit at C(9).

Compound **18** was desaturated at C(4)–C(7) [**18** → **19**; LDA, PhSeBr; dimethyldioxirane; 85%], deprotected at nitrogen [**19** → **20**; Pd(PPh₃)₄, dimedone; 93%], desaturated at C(2)–C(3) [**20** → **21**; *t*-BuOCl, DBU; 81%], and methoxycarbonylated (**21** → **22**; triphosgene, pyridine; MeOH; 91%). Next, free radical bromination at C(9) [**22** → **23**; NBS, (PhCO)₂O₂, 100 W tungsten lamp], followed by hydrolysis (H₂O, AgNO₃, **23** → **24**¹³) and esterification (CH₂N₂), gave aldehyde ester **25** (77% from **22**). This reacted with cerium trimethylsilylacetylide (1:1.3 Me₃SiC≡CLi, CeCl₃, THF, –78 °C), affording **26** (91%). Finally, desilylation (TBAF) yielded **27**⁹ (46%). During this step, epimerization occurs at C(9); however, treatment of the easily separated *anti*-isomer¹⁴ (42% isolated from **26**) with Bu₄NOAc gives quantitatively a 6:4 mixture in favor of **27**. Therefore, by equilibrating the *anti*-diyne once, it is possible to convert **26** into **27** in 71% yield.

The acetylenic hydrogens of **27** were now replaced by iodine (**27** → **28**; NIS, AgNO₃; 89%), and the cyclic enediyne was then generated¹⁵ (Scheme 2, **28** → **29**; 72%) by Pd-mediated condensation with (*Z*)-1,2-bis(trimethylstannyl)ethene¹⁶ [Pd(PPh₃)₄, 60 °C]. From **29**, the last steps were guided by established^{1a,b,17} principles. Reduction with DIBAL (98%), desilylation (TBAF, 94%), and further reduction (76%) with NaBH₄ gave triol **30**. Silylation of the primary and secondary hydroxyls (Et₃SiOTf, 2,6-lutidine, 95%) and selective hydrolysis (3:6:1 AcOH, THF, H₂O; 94%) then afforded allylic alcohol **31**, from which point elaboration of the trisulfide (**31** → **32**) was accomplished^{1a,18} by successive reaction with diisopropyl azodicarboxylate, Ph₃P, and AcSH (94%) and DIBAL-H and *N*-(methylthio)phthalimide (88% over two steps). Finally, acid

Scheme 3^a

hydrolysis (TsOH, H₂O, 84%) served to disengage the two remaining protecting groups and so give synthetic (±)-calicheamicinone (**1**).^{1a,b}

We have also converted racemic **8** (represented in Scheme 3 by the enantiomer **8a**) into ketone **33** by procedures^{19,20} of the type used in the first route. Treatment of **33** with cerium trimethylsilylacetylide (1:1.4 Me₃SiC≡CLi, CeCl₃; THF, –78 °C; 91%) serves to introduce the acetylene *syn* to the nitrogen (**33** → **34**), and further elaboration^{20,21} took the route as far as aldehyde **35**. This reacts with cerium trimethylsilylacetylide (1:1.3 Me₃SiC≡CLi, CeCl₃, THF, –78 °C) to give alcohol **36** (71%),²² which is easily convertible^{20,23} into lactone **37** and then, by a procedure^{20,24} similar to that used earlier, into **27**.

The only stereogenic center in **18** and **34** that is preserved after elaboration to (±)-calicheamicinone is C(5). Therefore, in a synthesis of material with the natural stereochemistry (as actually depicted in diagram **1**), intermediates corresponding to **5** with (2*S*) absolute configuration would have to be processed as in Scheme 1, while the reactions of Scheme 3 would be used for the (2*R*)-isomer.

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Supporting Information Available: Spectral data for most compounds and annotated flow chart for the second route (42 pages). Ordering information is given on any current masthead page.

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(19) OH → OCOBu-*t*; CH=CH₂ → CHO → CH₂OH → CH₂OCH₂-OC₆H₄OMe-*p*; NO₂ → NH₂ → NHCO₂allyl; CHOSiMe₂Bu-*t* → CHOH → C=O. The C(5) epimer of **8a** was also converted into **33**.

(20) See supporting information for details of these efficient procedures.

(21) OH → OSiMe₂Bu-*t*; CH₂OCOBu-*t* → CH₂OH → CHO.

(22) The C(9) epimer (18%) is convertible (PCC; NaBH₄; ca. 90% overall) into an 11.6:1 isomer mixture in favor of **36**.

(23) OH → OCOCH₂Cl; CH₂OCH₂OC₆H₄OMe-*p* → CH₂OH → CHO; OCOCH₂Cl → OH; Collins oxidation of lactols.

(24) Desaturation at C(4)–C(7), nitrogen deprotection, desaturation at C(2)–C(3), nitrogen methoxycarbonylation, acetylene desilylation.

(11) cf.: (a) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, 25, 4233. (b) Suzuki, M.; Kimura, Y.; Terashima, S. *Chem. Lett.* **1984**, 1543. (c) Jung, P. M. J.; Burger, A.; Biellmann, J.-F. *Tetrahedron Lett.* **1995**, 36, 1031.

(12) Kunz, H.; Unverzagt, C. *Angew. Chem., Int. Edn. Engl.* **1984**, 23, 436.

(13) The SiMe₃ group is removed during hydrolysis. Compound **24** exists as two hydroxyl lactones, epimeric at C(9).

(14) C≡CH units at C(5) and C(9) *anti*.

(15) cf.: Shair, M. D.; Yoon, T.; Danishefsky, S. J. *J. Org. Chem.* **1994**, 59, 3755. Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, 115, 4419. Barrett, A. G. M.; Boys, M. L.; Boehm, T. L. *J. Chem. Soc., Chem. Commun.* **1994**, 1881. Pattenden, G.; Thom, S. M. *Synlett* **1993**, 215.

(16) Mitchell, T. N.; Amamria, A.; Killing, H.; Rutschow, D.; J. *Organomet. Chem.* **1986**, 304, 257.

(17) Magnus, P.; Lewis, R. T.; Bennett, F. J. *Chem. Soc., Chem. Commun.* **1989**, 916 and references therein.

(18) CH₂OH → CH₂Sac → CH₂SH → CH₂SSSMe.