Communications to the Editor

Synthesis of (±)-Calicheamicinone by Two Related Methods

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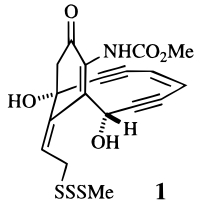
We report the synthesis of (±)-calicheamicinone (**1**),[1] the aglycon (in racemic form) of the antitumor agent[2] calicheamicin γ_1[1]. Ester exchange[3] of β-keto ester **2**[4] with $ClCH_2CH_2OH$ [Ti-



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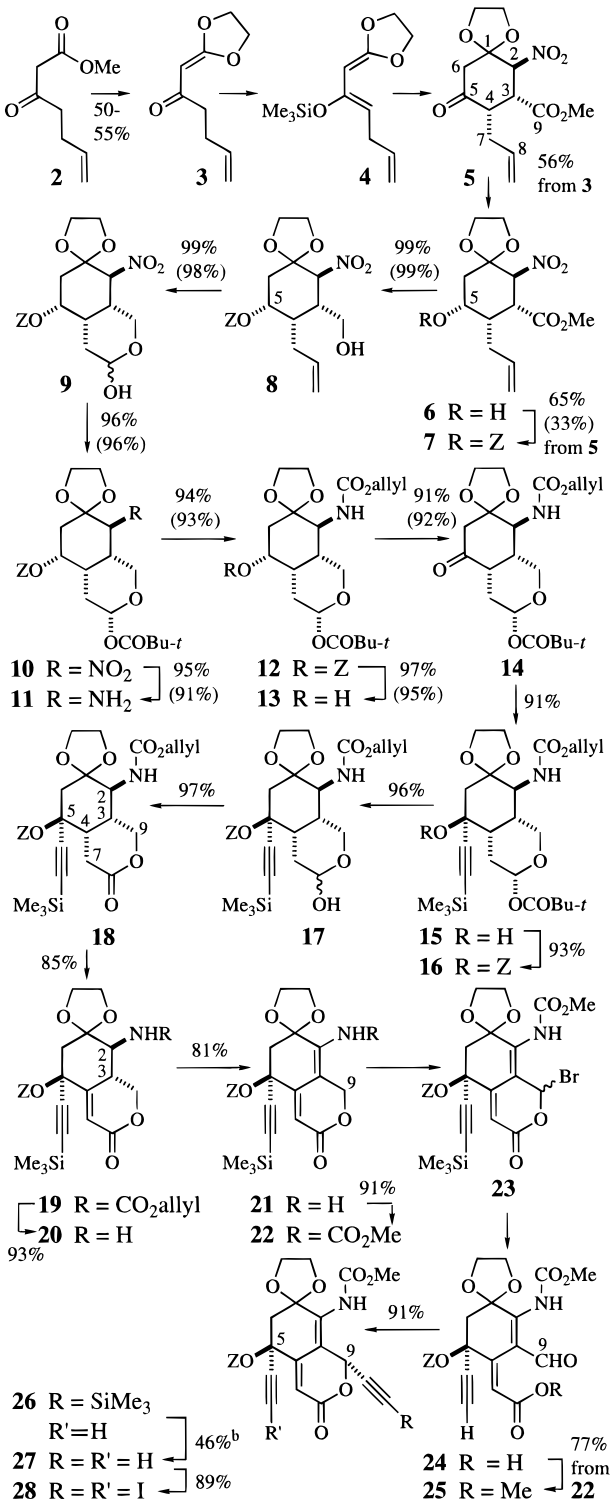
$(OPr\text{-}i)_4$, 63%], followed by treatment with K_2CO_3, gave[5] ketene acetal **3** (80−87%) (Scheme 1). Deprotonation [$(Ph_2MeSi)_2NLi$[6]] to the *Z*-enolate[7] and trapping with Me_3SiCl afforded triene **4**, which underwent Diels−Alder cycloaddition with methyl (*E*)-3-nitropropenoate[8] (**4** → **5**[9]; 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*-$BuMe_2SiOTf$, 2,6-lutidine, 65% (from **5**) of 5α-isomer **7**, and 33% (from **5**) of corresponding 5β-isomer[9]]. Both isomers were independently converted into **14** by identical routes; only the procedure for the major isomer is shown, but yields for the 5β-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 reduced[10] ($NiCl_2$, $NaBH_4$, 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 = $SiMe_2Bu$-*t*; yields in brackets refer to 5β series. [b] Yield after equilibration: 71% (see text).

accomplished by reaction with cerium trimethylsilylacetylide[11] (1:1.2 $Me_3SiC{\equiv}CLi$, $CeCl_3$; THF, −78 °C; 91%), the acetylene being introduced *anti* to the nitrogen. Protection of the hydroxyl group (**15** → **16**; *t*-$BuMe_2SiOTf$, 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.; Gorislavskya, 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.

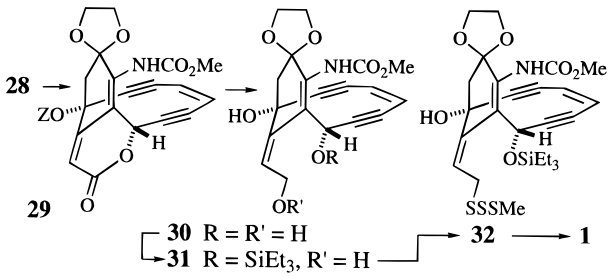
(8) Danishefsky, S.; Prisbylla, M. P.; Hiner, S. *J. Am. Chem. Soc.* **1978**, *100*, 2918. *cf.*: Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400. Banville, J.; Brassard, P. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1852. Schechter, H.; Conrad, F.; Daulton, A. L.; Kaplan, R. B. *J. Am. Chem.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

(9) Structure confirmed by x-ray analysis.

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

S0002-7863(96)00200-4 CCC: $12.00

Scheme 2[a]



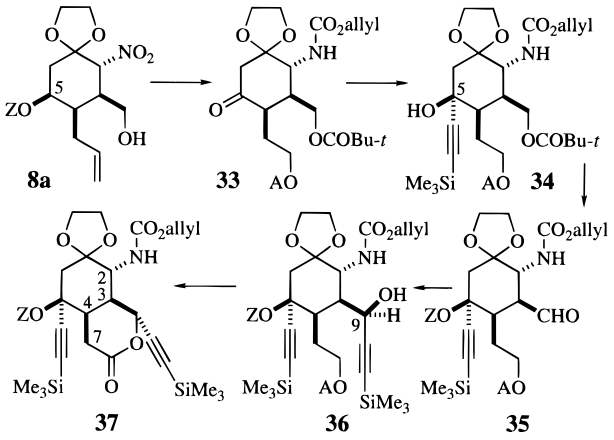
[a] Z = $SiMe_2Bu$-*t*.

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**; $Pd(PPh_3)_4$, dimedone;[12] 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, $(PhCO)_2O_2$, 100 W tungsten lamp], followed by hydrolysis (H_2O, $AgNO_3$, **23** → **24**[13]) and esterification (CH_2N_2), gave aldehyde ester **25** (77% from **22**). This reacted with cerium trimethylsilylacetylide (1:1.3 $Me_3SiC{\equiv}CLi$, $CeCl_3$, 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*-isomer[14] (42% isolated from **26**) with Bu_4NOAc 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, $AgNO_3$; 89%], and the cyclic enediyne was then generated[15] (Scheme 2, **28** → **29**; 72%) by Pd-mediated condensation with (*Z*)-1,2-bis(trimethylstannyl)ethene[16] [Pd-$(PPh_3)_4$, 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 $NaBH_4$ gave triol **30**. Silylation of the primary and secondary hydroxyls (Et_3SiOTf, 2,6-lutidine, 95%) and selective hydrolysis (3:6:1 AcOH, THF, H_2O; 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, Ph_3P, and AcSH (94%) and DIBAL-H and *N*-(methyldithio)phthalimide (88% over two steps). Finally, acid

Scheme 3[a]



[a] Z = $SiMe_2Bu$-*t*; A = $CH_2OC_6H_4OMe$-*p*.

hydrolysis (TsOH, H_2O, 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 $Me_3SiC{\equiv}CLi$, $CeCl_3$; 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 $Me_3SiC{\equiv}CLi$, $CeCl_3$, 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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(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 $SiMe_3$ 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) CH_2OH → CH_2SAc → CH_2SH → CH_2SSSMe.

(19) OH → OCOBu-*t*; CH═CH_2 → CHO → CH_2OH → CH_2OCH_2-OC_6H_4OMe-*p*; NO_2 → NH_2 → $NHCO_2$allyl; $CHOSiMe_2Bu$-*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 → $OSiMe_2Bu$-*t*; CH_2OCOBu-*t* → CH_2OH → CHO.

(22) The C(9) epimer (18%) is convertible (PCC; $NaBH_4$; ca. 90% overall) into an 11.6:1 isomer mixture in favor of **36**.

(23) OH → $OCOCH_2Cl$; $CH_2OCH_2OC_6H_4OMe$-*p* → CH_2OH → CHO; $OCOCH_2Cl$ → OH; Collins oxidation of lactols.

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