Synthesis of the Enediyne Aglycon (±)-Calicheamicinone

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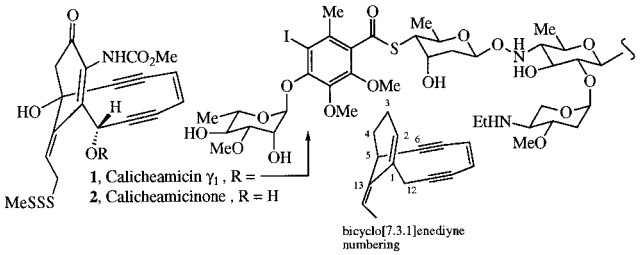
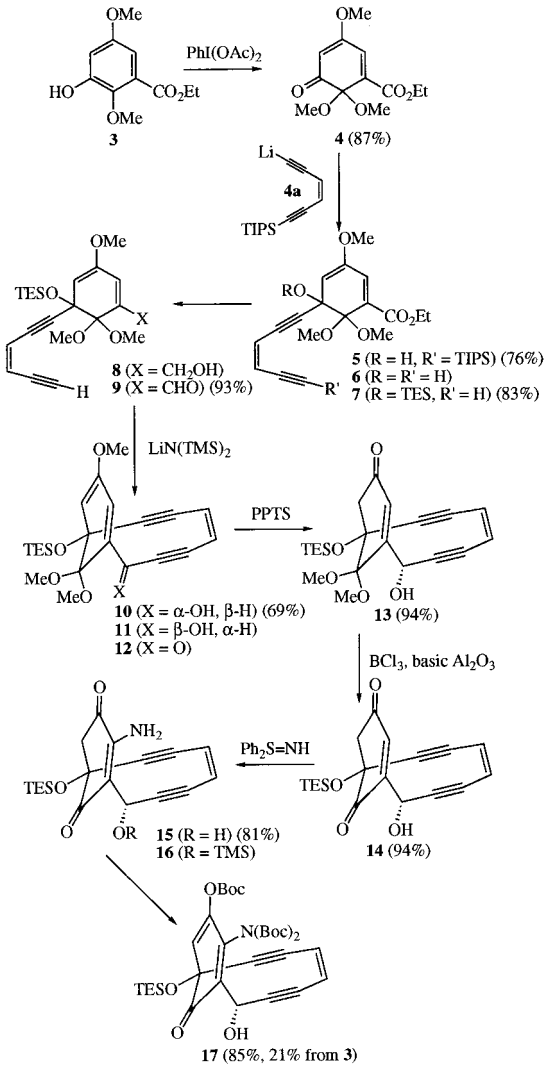
The unusual structure, potent antitumor activity, and *in vitro* mechanism of action of calicheamicin **1** has attracted a great deal of attention (Scheme 1).[1] To date, four syntheses of the aglycon calicheamicinone **2** have been reported by the groups of Danishefsky,[2] Nicolaou,[3] and Clive (2 reports).[4] The former two groups have also synthesized calicheamicin.[5,6] Our own synthetic studies, based upon an $\eta^2Co_2(CO)_6$−propargylic aldol cyclization to form the 10-membered enediyne ring, produced **15** [TBS instead of TES] (Scheme 2) as the pivotal intermediate, but not in sufficient quantities to readily explore the full range of protection−deprotection options that were necessary to complete the synthesis of **2**.[7] Consequently, it was decided to examine a different route that would supply gram amounts of **15**. While there is a substantial literature describing the various strategies that have been developed for the synthesis of **2**, it is notable that the potentially most direct approach, namely one based upon an *o*-quinone monoketal has not been reported.[8] The Danishefsky route most closely parallels a quinone monoketal strategy but uses the Becker−Adler spiro-epoxide reaction,[9] which requires deletion of one carbon atom (C-14) and replacement by a two-carbon side chain (C-14,15).

The phenol **3** was prepared from commercially available 5-methoxysalicylic acid in four standard steps.[10] Oxidation of **3** with $PhI(OAc)_2$/MeOH[11] gave the *o*-quinone monoketal **4** (87%), which was treated with **4a** to give **5** (76%) (Scheme 2). Removal of the TIPS group to give **6** and protection of the tertiary hydroxyl group as a TES ether resulted in **7** (83% from **5**). Reduction of **7** using DIBAL-H/toluene gave **8**, which on oxidation with Dess−Martin (D−M) periodinane[12] gave the aldehyde **9** (93% from **7**). Exposure of **9** to $LiN(TMS)_2$/THF at −78 °C gave **10** and **11** (1:4), which were directly oxidized (D−M) to the crystalline ketone **12**. Reduction with DIBAL-H/toluene at −78 °C produced the desired 12α-alcohol **10** (69% from **9**; **11** could not be detected by ^{1}H NMR). Treatment of **10** with PPTS in aqueous dioxane at 60 °C gave **13** (94%), which on exposure to BCl_3/CH_2Cl_2/heptane and workup with basic Al_2O_3/CH_2Cl_2 gave **14** (94%).[13]

Scheme 1



Scheme 2



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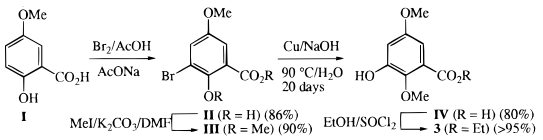
(10) Bromination of **I** gave **II**, which was converted into **III**. Prolonged exposure of **III** to Cu/NaOH/H_2O gave **IV**, which on treatment with EtOH/$SOCl_2$ provided **3** (overall yield 59%).



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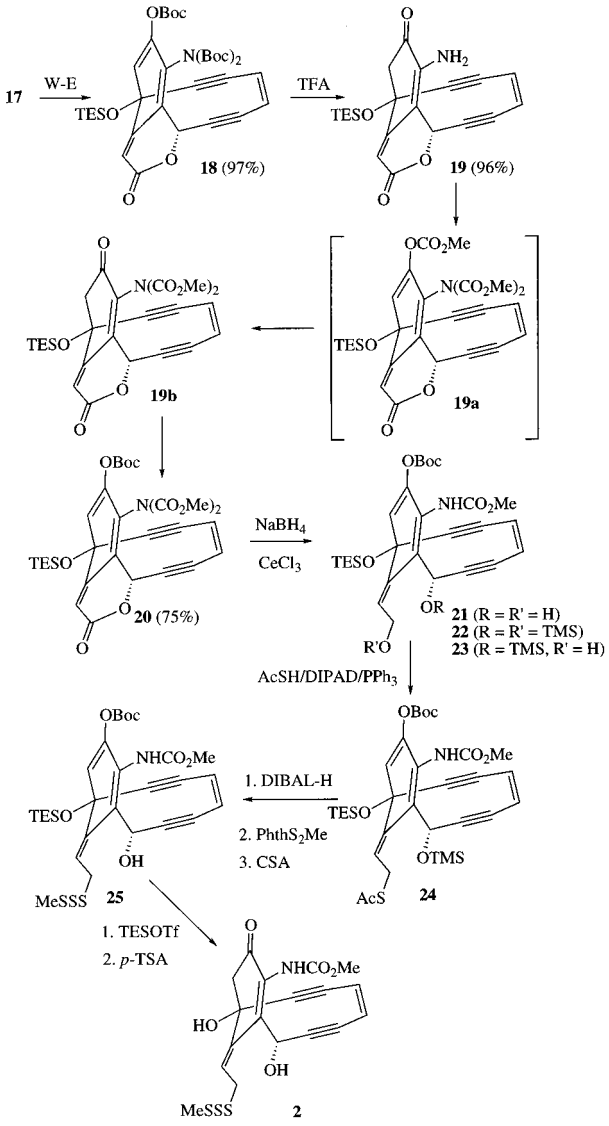
Treatment of **14** with $Ph_2S{=}NH$/THF gave the 2-amino adduct **15** (81%, on 4 g scale).[14] All attempts to ketalize the C-3 carbonyl group of **15** (and closely related intermediates) were unsuccessful (preventing correlation with the other syntheses); consequently, recourse was made to an enol carbonate protecting group strategy. Treatment of **15** with TMSCN gave **16**, which was immediately exposed to $Boc_2O/Et_3N/DMAP/CH_2Cl_2$ followed by citric acid/MeOH to give the adduct **17** (85%).[15] The use of methyl carbonate/carbamate protecting groups was precluded at this stage due to their lability under the Wadsworth−Emmons reaction conditions.

Intermolecular Wadsworth−Emmons[16] reaction [$(MeO)_2POCH_2CO_2Me/LiN(TMS)_2$/THF −78 °C to 25 °C] of **17** gave **18** (97%), (Scheme 3).[17] While the tris-Boc protection had served its purpose in the previous step, it was too robust to allow deprotection without degradation of the trisulfide in late stage intermediates. Consequently, **18** was treated with CF_3CO_2H/CH_2Cl_2 (1:1) to give **19** (96%) and reprotected by sequential treatment with $MeO_2CCl/Et_3N/DMAP/CH_2Cl_2$ followed by $Boc_2O/Et_3N/DMAP/CH_2Cl_2$ to give **20** (75%). By analogy to the protection of **16**, it is thought that **19** undergoes *O*-acylation followed by intramolecular *N*-acyl transfer (twice) to give **19a**, which on workup undergoes enol carbonate hydrolysis to give **19b**. Reduction of the lactone **20** with $NaBH_4/CeCl_3{\cdot}7H_2O/MeOH/CH_2Cl_2$ gave the diol **21**, which was selectively protected (TMSCN followed by $AcOH/H_2O$/THF) to give **23** (81%, via **22**). Standard Mitsunobu conditions (AcSH/PPh_3/DIPAD/THF/0 °C) provided the thioacetate **24** (72%), which was reductively cleaved (DIBAL-H/THF/−78 to −10 °C) and treated *in situ* with the Harpp reagent PhthSSMe[18] to give **25** (65%) after desilylation. Deprotection of the enol Boc group with TESOTf/2,6-lutidine/CH_2Cl_2 (71%), followed by removal of the two TES-groups with *p*-TSA/THF/H_2O at 55 °C provided **2** (50%).

The synthesis of **2** from 5-methoxysalicylic acid requires 28 steps, involving the chromatographic purification of nine intermediates, in an overall yield of 1.4% at an average of 86% per step. This results in the most efficient synthesis to-date (Danishefsky 22 steps, 0.2%, Nicolaou 34 steps, 0.2%, and Clive 37 steps, 0.9%). The opportunity to modify the route to provide an enantioselective synthesis of **2** is possible by the application of asymmetric induction methodology for the conversion of **4** into **5**[19] and through well-precedented enzymatic resolution of **14**.[20]

Scheme 3



Acknowledgment. Dedicated to Sir Derek Barton (1918−1998). The National Institutes of Health (CA 50512), The Robert A. Welch Foundation and Merck Research Laboratories are thanked for their support of this research. Drs. Nicolaou and Clive are thanked for copies of spectral data of **2**.

Supporting Information Available: Complete spectral information for compounds **2**−**25** (excluding **4a**, **11**, **19a**, and **22**) and **II**−**IV** (10 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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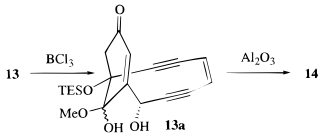
(13) The hemiketal **13a** is the first formed product when **13** is treated with BCl_3. The subsequent work-up with Al_2O_3 produces **14**. We have observed stable hemiketals in simpler model compounds. Magnus, P.; Bennett, F. *Tetrahedron Lett.* **1989**, *30*, 3637. See also ref 17.



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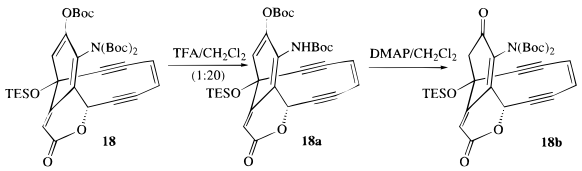
(15) The unusual formation of the bis-carbamate **17** can be explained by the following observation. Treatment of **18** with TFA gave **18a**, which when exposed to $DMAP/CH_2Cl_2$ rapidly underwent enol carbonate → bis-carbamate rearrangement to give **18b**.



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