Short Synthesis of the Dynemicin Core Structure: Unusual Bridgehead Enolate Reactivity

Philip Magnus,* David Parry, Theodore Iliadis, Shane A. Eisenbeis and Robin A. Fairhurst

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712, USA

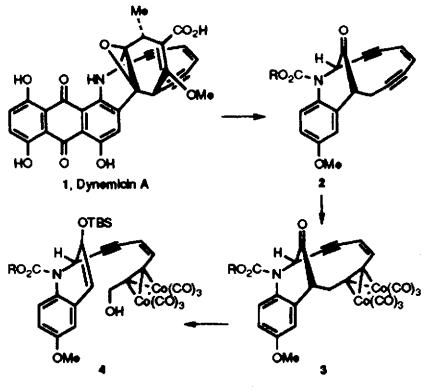
The dynemicin core azabicyclo[7.3.1]enediyne **2** is readily synthesized in five steps from the quinolines **9** or **13**; the chemistry of the core enediyne is dominated by its ready enolization.

The unusual structure and potent antitumour activity of dynemicin A **1** have made it a topical subject for synthetic and molecular modelling/recognition studies.† As an extension of our research on esperamicin and calicheamicin, we have applied the key η^2-$Co_2(CO)_6$–propargyl cation cyclization strategy for the synthesis of cyclic ten-membered ring enediynes to the synthesis of the azabicyclo[7.3.1]enediyne core structure **2**, Scheme 1.[1]

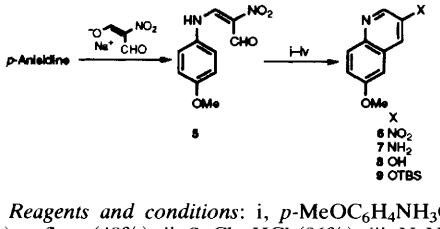
The η^2-$Co_2(CO)_6$–propargyl alcohol complex **4** should ionize under electrophilic conditions to give **3**, which upon oxidative decomplexation provides an exceptionally short route to the azabicyclo[7.3.1]enediyne **2**.

3-Hydroxy-6-methoxyquinoline **8** is not a known compound, and the common methods for synthesizing quinolines are not readily applicable to those with 3-hydroxy substituents.[2] *p*-Anisidine hydrochloride was treated with sodium nitromalonaldehyde to give the enamine **5** (>95%). Heating *p*-anisidine hydrochloride and the enamine **5** in acetic acid in the presence of a catalytic amount of 3,5-dimethylthiophenol gave 3-nitro-6-methoxyquinoline **6** (48%).[3] Reduction of **6** using $Sn^{II}Cl_2$ gave 3-amino-6-methoxyquinoline **7** (86%). Standard diazotization conditions and hydrolysis gave the phenol **8** (95%). Treatment of **8** with *tert*-butyldimethylsilyl-chloride–imidazole–DMF gave **9** (91%), (Scheme 2).

Treatment of the quinoline **9** with the magnesioacetylide **9a** in the presence of 1-adamantyl chloroformate gave, in a completely regiospecific reaction, the dihydroquinoline **10** (75%).[4] Deprotection of the THP ether to give **11** (89%) was accomplished using the Grieco procedure (pyridinium tosylate–EtOH).[5] Complexation of **11** with $Co_2(CO)_8$ in THF gave **4** (59%) along with some complexation at the other acetylene **12** (33%) and traces of bis-complexation. The regioisomers **4** and **12** could be separated by chromatography over silica gel. The undesired regioisomer **12** can be recycled by ceric ammonium nitrate (CAN) oxidation to give **11** (76%). All attempts to make this complexation more selective did not improve the above ratio. The uncomplexed propargyl alcohol **11**, and the η^2-$Co_2(CO)_6$-isomer **12** do not cyclize to the dynemicin core structure using the conditions described below.



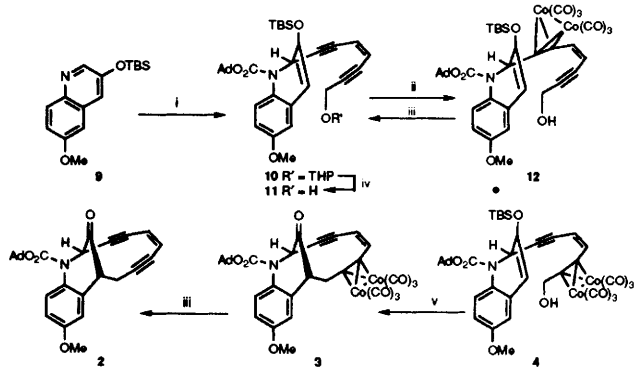
Scheme 1



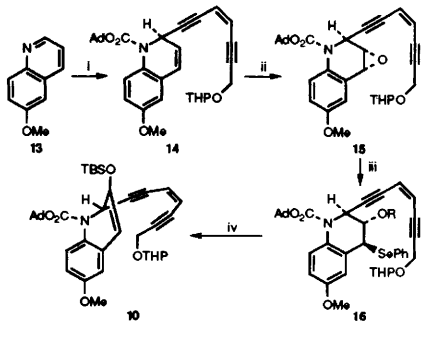
Scheme 2 *Reagents and conditions*: i, *p*-$MeOC_6H_4NH_3Cl$–AcOH–ArSH (cat), reflux, (48%); ii, $SnCl_2$–HCl (86%); iii, $NaNO_2$–H_2SO_4 (95%); iv, Bu^tMe_2SiCl–DMF (91%)

Treatment of the cobalt adduct **4** with triflic anhydride in 2-nitropropane containing 2,6-di-*tert*-butyl-4-methylpyridine at −10 °C for 30 min gave **3**. Direct oxidative work-up by (CAN) oxidation gave the cyclized enediyne **2** (53%, for the two steps), (Scheme 3).[6] We have used other chloroformates such as $ClCO_2Me$, $ClCO_2(CH_2)_2Cl$, $ClCO_2$menthyl and $ClCO_2$-cholesteryl for the above sequence. Only the adamantyl carbamate was readily removed under conditions that did not destroy the enediyne.[7] While the route to the azabicyclo[7.3.1]enediyne core structure **2** is short (5 steps from **9**), the 3-silyloxyquinoline **9** is tedious to make, and lacks flexibility for more substituted systems. Consequently, we examined a route from the commercially available 6-methoxyquinoline **13**.

Treatment of **13** with the enediyne Grignard reagent MgBrC≡C–C=C–C≡COTHP **9a** in the presence of 1-ada-



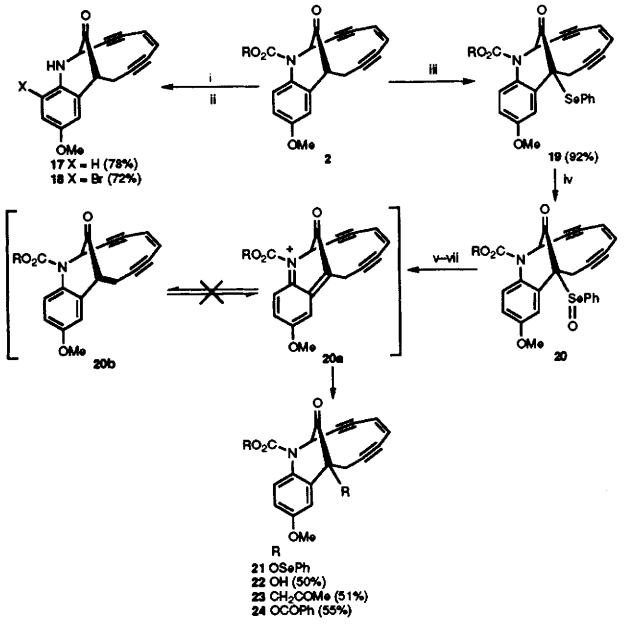
Scheme 3 *Reagents and conditions*: i, AdO_2CCl, **9a**; ii, $Co_2(CO)_8$–THF; iii, $Ce(NH_4)_2(NO_2)_6$–acetone; iv, pyridinium tosylate–EtOH; v, Tf_2O–2-nitropropane–2,6-di-*tert*-butyl-4-methylpyridine at −10 °C for 30 min. Tf = triflate, Ad = 1-adamantyl.



Scheme 4 *Reagents*: i, AdO_2CCl, **9a**; ii, MCPBA–$NaHCO_3$–CH_2Cl_2; iii, PhSeSePh–$NaBH_4$ then TBSCl–DMF–imidazole; iv, MCPBA–$NaHCO_3$–CH_2Cl_2, pyridine (50%)

mantyl chloroformate gave the dihydroquinoline **14** (78%). Epoxidation of **14** with *m*-chloroperoxybenzoic acid (MCPBA)–$NaHCO_3$–CH_2Cl_2 gave the epoxide **15** as a single stereoisomer.‡ The epoxide **15** was opened with $(PhSe)_2$–$NaBH_4$ to give **16** (R = H), and the newly generated hydroxy group protected as the TBS derivative **16** (98%, R = TBS).[8] Oxidation of the selenide **16** (R = TBS) using MCPBA followed by *syn*-elimination gave **10**, thus avoiding the synthesis of **9** (Scheme 4).

The adamantyl carbamate was removed by treatment of **2** with trifluoroacetic acid (TFA) in dichloromethane to give the amine **17** (78%).[9] Surprisingly, the amine was cleanly brominated (Br_2–$CHCl_3$) to give **18** (72%). Even exposure of **17** to excess bromine for extended periods of time did not disrupt the enediyne functionality.§ The bridged ketone **2** was readily enolized using $LiN(SiMe_3)_2$–THF at −78 °C, quenching with PhSeBr gave the bridgehead selenide **19** (92%). The X-ray structure of **2** shows that the bridgehead proton is in the plane of the π orbitals of the carbonyl group, and therefore ideally aligned for enolization. Oxidation of **19** (MCPBA) gave the selenoxide **20** which was sufficiently stable to be isolated. Heating **20** at 40 °C resulted in rearrangement to the selenite ester **21**, and eventually the alcohol **22** (50%). If **20** is heated in the presence of the trimethylsilyl enol ether of acetone, the bridgehead acetonyl compound **23** (68%) was formed. These transformations indicate that iminiumquinomethide **20a** is formed from **20**, and does not lose a proton to form the α,β-unsaturated ketone **20b**. The formation of the iminiumquinomethide intermediate **20a** is completely analogous to the chemistry exhibited by dynemicin, and speculated to be an intermediate formed from opening of the epoxide in **1**.



Scheme 5 *Reagents and conditions*: i, CF_3CO_2H–CH_2Cl_2 (78%); ii, Br_2–$CHCl_3$ (72%); iii, $LiN(SiMe_3)_2$–THF–PhSeBr, −78 °C (92%); iv, MCPBA–CH_2Cl_2, 78 °C; v, CH_2Cl_2 25–40 °C (**21** and **22**, 50%); vi, acetone–$SiMe_3$ enol ether–TMSOTf, 0 °C (**23**, 51%); vii, $LiN(SiMe_3)_2$–THF–$(PhCOO)_2$, −78 °C (**24**, 55%)

In summary, the route to **2** takes five steps from **9** and **9a** and proceeds in an overall 15% yield. This provides sufficient quantities for the more meaningful *in vivo* screening.

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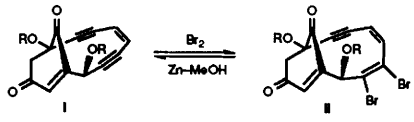
Footnotes

† See refs. 1 of preceding paper.

‡ If the epoxidation of **14** with MCPBA is carried out without $NaHCO_3$, a mixture (1 : 1) of stereoisomeric epoxides is formed.

§ This result is in contrast to the reactivity exhibited in the esperamicin series. The compound **i** reacted with bromine to give **ii** (unknown vinyl bromide stereochemistry), which regenerated **i** when treated with Zn–MeOH (unpublished work).



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