A Rapid Entry into the Dynemicin Core Structure: Remarkable Solvent Effect on an η^2-Hexacarbonyldicobalt Propargylic Cation Cyclization

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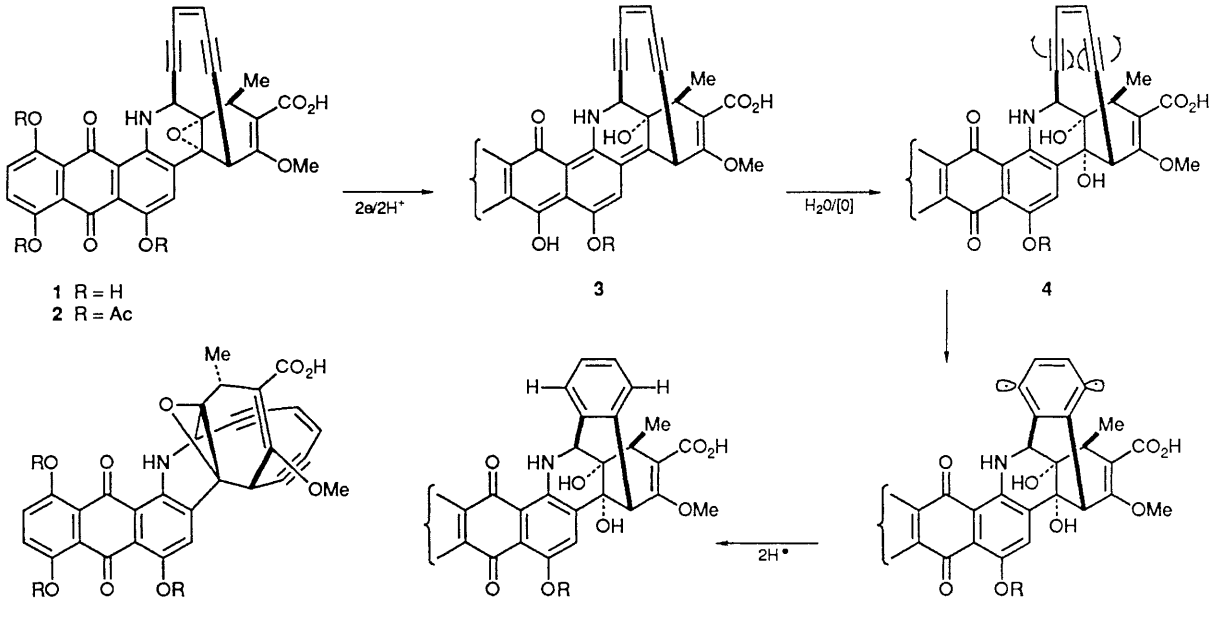
3-(*tert*-Butyldimethylsilyloxy)quinoline **8** on treatment with the diynene **9** gave the diynene **10** (64%), and deprotection of **10** gave **11** (88%) which was converted into the η2-$Co_2(CO)_6$ adduct **12**; treatment of **12** with $(CF_3SO_2)_2O$ in CH_2Cl_2–$MeNO_2$ at −10°C gave the cyclized product **13** (43%), and decomplexation of **13** using I_2–THF produced the stable azabicyclo[7.3.1]tridecadiynene core structure **7** of the antitumour antibiotic dynemicin **1**.

Dynemicin **1** is the latest antitumour antibiotic to be added to the growing list of diynene natural products.[1] It exhibits extraordinary potent antimicrobial and antitumour activity, and moreover it shows little *in vivo* toxicity. The derived triacetate **2** is even more impressive. It has been speculated that dynemicin undergoes bioreductive activation with concomitant epoxide ring opening to give the extended quinone methide **3**. Hydration of **3** followed by Bergman cycloaromatization of the diol leads to the diyl **5** which can abstract hydrogen to provide the adduct **6**.[2,3] Consequently if dynemicin, or one of the subsequent adducts **3**, **4** and **5** is bound to DNA,[4] the diyl is fully capable of back-bone scission (Scheme 1).

As an extension of our studies on the related antitumour agents esperamicin–calicheamicin[5] we report the synthesis of the core tetrahydroquinoline diynene structure **7**† using η^2-hexacarbonyldicobalt acetylene complexes (Scheme 2).[6] Treatment of the *tert*-butyldimethylsilyl ether of 3-hydroxyquinoline **8**[7] with the magnesioacetylide **9**‡ in the presence of methyl chloroformate gave, in a completely regiospecific reaction,[8] the dihydroquinoline **10** (64%). Selective deprotection of the tetrahydropyran-2-yl (THP) ether to give **11** (88%) was accomplished using the Grieco procedure (pyridinium tosylate–EtOH).[9] Complexation of **11** with $Co_2(CO)_8$ gave **12** (54%) along with some complexation at the other acetylene (*ca.* 15%) and bis-complexation. Surprisingly when the alcohol **12** was exposed to trifluoromethanesulphonic anhydride–2,6-di-*tert*-butyl-4-methylpyridine (DBMP) in CH_2Cl_2 at −10°C, conditions that convert both **14** and **15** into **16** (59%) and **17** (77%) respectively,§ a rapid transformation took place to give the ether **20** (69%). None of the desired adduct **13** could be detected.

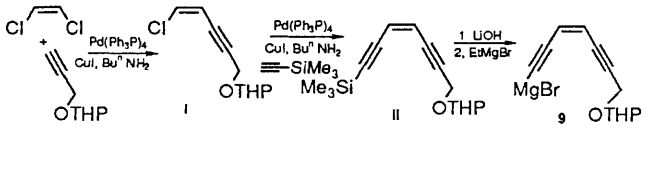
We reasoned that the alcohol **12**, being somewhat more polar than **14** or **15**, could be intermolecularly hydrogen bonded. As a consequence ionization of the hydroxy group to the η^2-$Co_2(CO)_6$ propargylic (prop-2-ynylic) cation takes place when it is solvated by unionized molecules of **12** (in



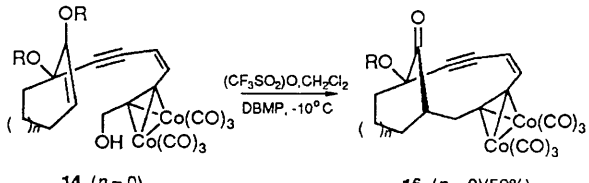
Scheme 1

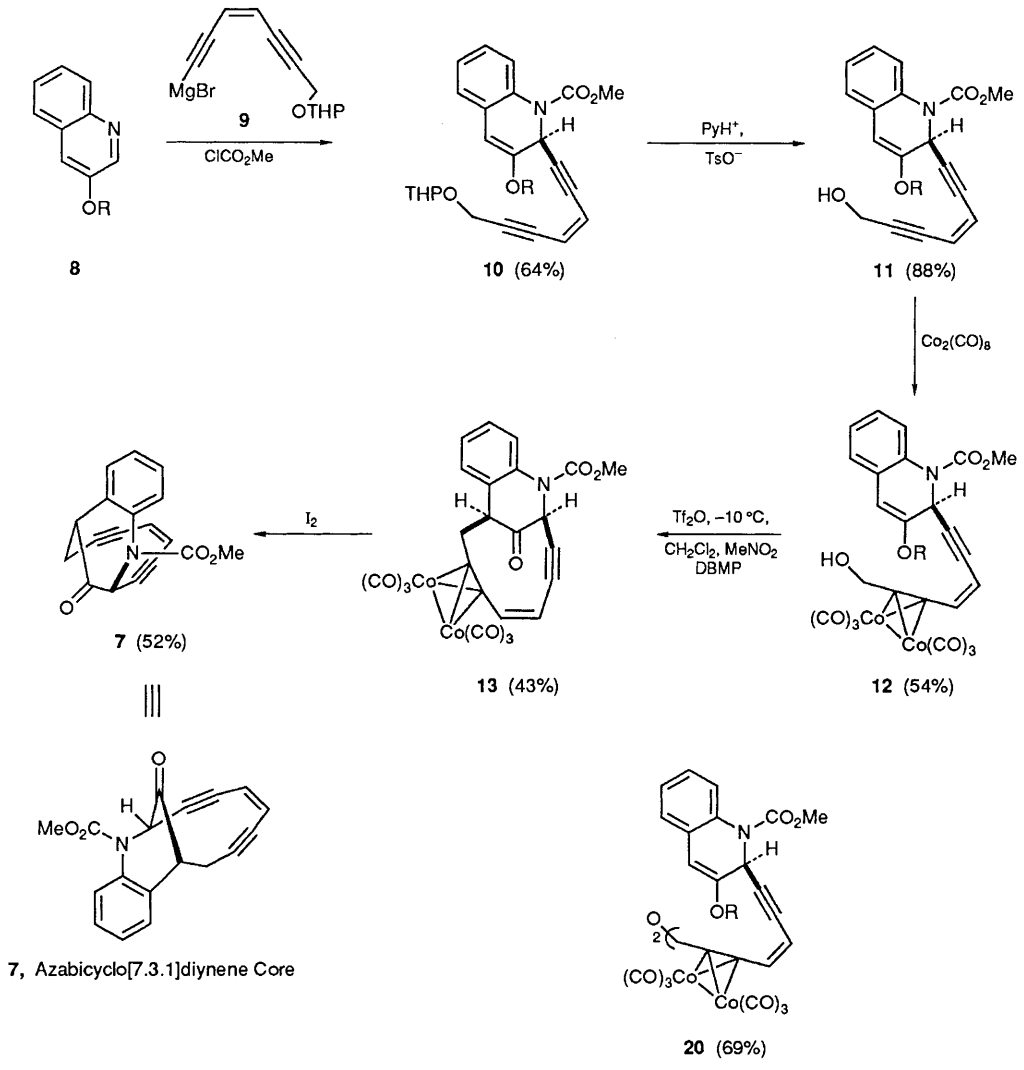
† Satisfactory spectroscopic data were obtained for all new compounds, and high-resolution mass spectra were consistent with the molecular formulae for **7**, **11**, **12**, **13**, **20** and **21**.

‡ *Z*-Dichloroethylene was converted into **9** using the sequence shown below.

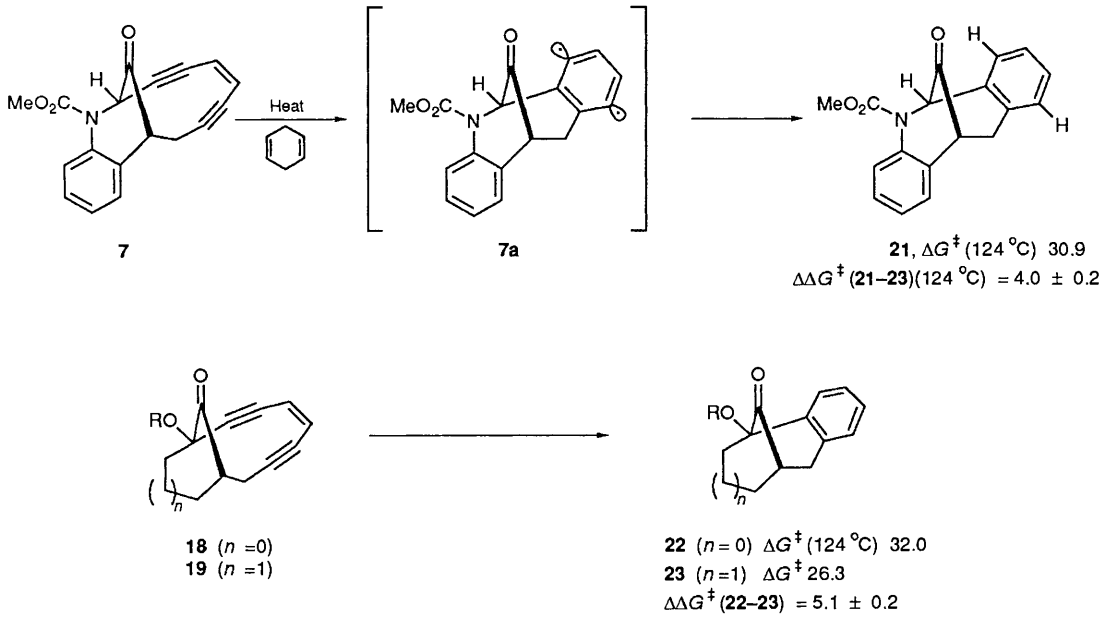


§ The conversions of **14** and **15** into **16** and **17** respectively, proceed without complications involving *sym*-ether formation. Unpublished results from this laboratory.





Scheme 2 Py = pyridine; Ts = *p*-$MeC_6H_4SO_2$; Tf = CF_3SO_2



Scheme 3 ΔG values in kcal mol^{-1}

CH_2Cl_2).[10] This solvate collapses to the ether **20** faster than intramolecular enol ether trapping to give **13**. Clearly a cation solvating solvent is required. Treatment of **12** with $(CF_3SO_2)_2O$–DBMP in $MeNO_2$ (ϵ, 35.9)–CH_2Cl_2 (ϵ, 8.9) (1 : 2) at −10 °C gave the cyclized product **13** (43%), and none of the ether **20**. Presumably nitromethane solvates the η^2-$Co_2(CO)_6$ propargylic cation protecting it from bimolecular ether formation. Oxidation decomplexation of **13** using I_2–tetrahydrofuran (THF) gave **7** (52%) [partial ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (1H, s), 5.79–5.62 (2H, AB, J_{AB} 9.46 Hz), 3.84 (3H, s), 3.75–3.72 (1H, m), 3.35–3.45 (1H, m), 3.34–3.26 (1H, m); ABX, J_{AB} 17.9, J_{AX}/J_{BX} 4.9 and 3.2 Hz].

The dynemicin core azabicyclo[7.3.1]tridecadiynene unit **7** proved to be remarkably resistant to cycloaromatization. It required heating in cyclohexa-1,4-diene at 124 °C for 18 h to convert it into **21** (84%), giving an approximate $\Delta G^{\ddagger}$ 30.9 kcal mol^{-1}, $\Delta\Delta G^{\ddagger}$ (**21** − **23**) at 124 °C, 4.0 kcal mol^{-1} (1 cal = 4.184 J). This should be compared to the conversion of **18** and **19** into **22** and **23** respectively (Scheme 3).[11] The presence of three additional trigonal atoms in **7** (*cf.* **19**) makes the transition state leading to the diyl **7a** more strained. We are extending this strategy to more highly functionalized azabicyclo[7.3.0]diynenes.

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