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Estramycins : a Potential Acyclic Diyl Precursor Derived from Estradiol

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***Abstract** : The estradiol derived enyne **2** is obtained via a nine step sequence starting from estrone. Key-steps involve the opening of the α-epoxide **7** and the 1,2-addition of propargylmagnesium bromide on the allene ketone **10**. The allylic alcohol **2** possesses the required functionalities for yielding, after dehydratation, the unsaturated core structure that is expected to cycloaromatize via Myers cyclization. So far, however, this elimination reaction has been unsuccessful.*

Recently the discovery of a novel class of anticancer antibiotics from bacterial source has opened new perspectives in cancer chemotherapy. These natural derivatives, presently consisting of neocarzinostatin, the esperamycin and calicheamycin families, dynemycin, kedarcidin, and C-1027, exert their biological activity through DNA cleavage. The latter is effected by diradicals that are generated from cyclic polyunsaturated core structures upon suitable activation.[1]

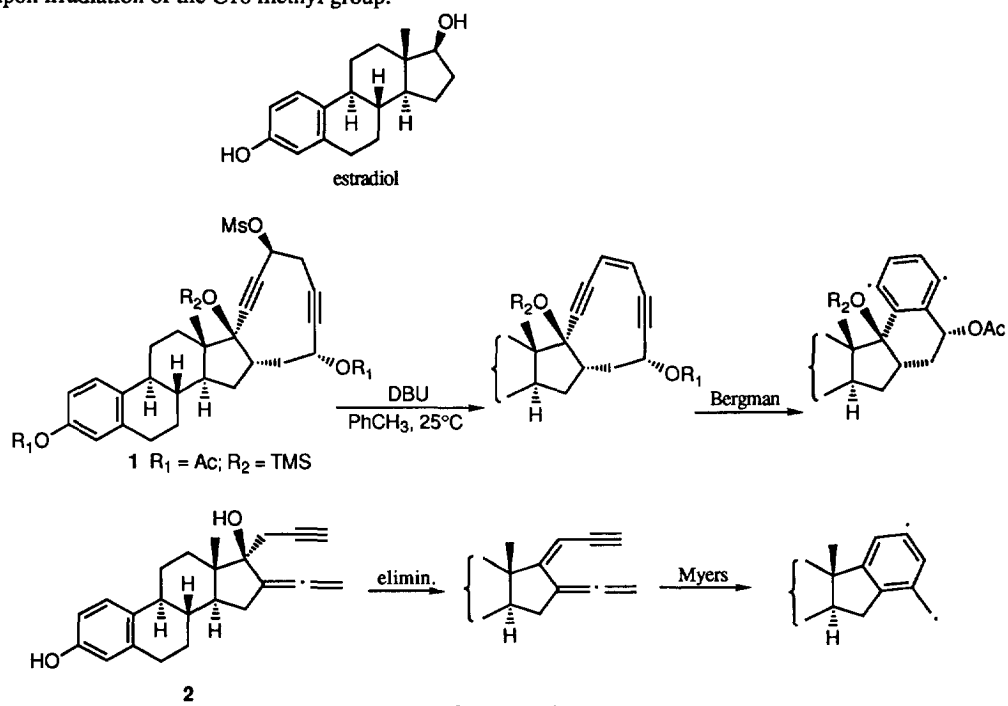
With the aim of developing site specific chemotherapeutic agents diyl-based DNA cleaving agents have been conceived in which the core of the diradical precursor is tethered to known minor groove DNA binding agents and DNA intercalators.[2] Also, a new family of artificial enediynes (taxamycins) has been reported in which the unsaturated core is comprised within a structure with known antitumor activity, as taxol.[3]

In the latter context we have initiated a program in which we want to study the chemotherapeutic potential of estramycins, derivatives in which the diradical precursor core is incorporated into estradiol. Since human mammary cancers are usually rich in estrogen receptor, estrogens, and estradiol in particular, are potential vectors to transfer cytotoxic agents into the nuclei of receptor rich cells.[4] Along this line we have recently reported on the synthesis of mesylate **1** which was eliminated to the corresponding cyclic 10-membered enediyne ring derivative, the disappearance of which through Bergman cyclization[5] at 25°C had been estimated at $t_{1/2}$ = 108 min (Scheme 1).[6]

In the present paper we wish to describe the synthesis of the estradiol derivative **2** which we conceived as a pontentially useful chemotherapeutic agent (Scheme 1). Indeed, diol **2** is only substituted at positions 16 and 17α which are known not to interfere too much in the binding to the estrogen receptor.[7] Furthermore, the elimination of the tertiary 17-hydroxy group can be considered as an easy process, even if a stereoselectivity problem about the 17,20-double bond stereochemistry can arise, and would generate a hepta-3,5,6-triene-1-yne unsaturated core that should collapse to generate a σ,π-diradical according to the Myers cyclization.[8]

The synthesis of the estradiol derivative **2** is shown in scheme 2. After protection of the phenolic hydroxyl group in estrone as the *tert*-butyldimethylsilyl ether **4** (*tert*-butyldimethylsilyl chloride and imidazole in DMF; 92 % yield),[9] the latter is converted to the 16,17-ene derivative **6** according to the method of Shapiro and Heath, involving the elimination of hydrazone **5** (tosylhydrazine in dichloromethane-isopropanol in the presence

of acetic acid, 98 % yield) with an excess of methyllithium (82 % yield).[10,11] Epoxidation of alkene **6** with *m*-chloroperoxybenzoic acid in a two-phase system at pH = 8 in a phosphate buffer solution and dichloromethane gave selectively the 16α,17α-epoxide in 92 % yield. Evidence for the α-stereochemistry of the epoxide, expected on steric grounds, rests on a strong nOe enhancement of both the H16 and H17 signals of **7** upon irradiation of the C18 methyl group.

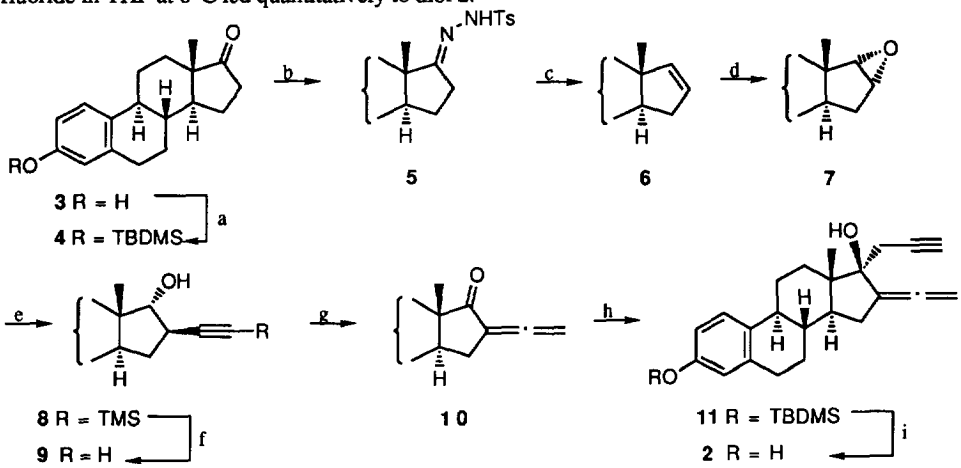


Scheme 1

Ring opening of the epoxide **7** is expected to be troublesome because the nucleophile must attack from the sterically hindered β-side. When **7** was treated with lithium (trimethylsilyl)acetylide, no reaction occurred. Exposure of the epoxide to lithium acetylide ethylenediamine complex only gave rise to desilylation.[12] Reaction with diethyl(trimethylsilyl)ethynyl aluminum in toluene,[13] prepared via addition of diethylaluminum chloride to lithium (trimethylsilyl)acetylide at 0°C, led on the other hand to a complex mixture in which the desired **8** could not be detected. Eventually, the required β-hydroxyalkyne **8** was obtained in 34 % isolated yield (along with 26 % starting epoxide) using the alkynyl borane according to Yamaguchi :[14] the (trimethylsilyl)ethynyl borane reagent was prepared *in situ* by the addition of boron trifluoride etherate to a solution of lithium (trimethylsilyl)acetylide in THF at -78°C and reacted with epoxide **7** (-78°C to room temperature overnight). The removal of the trimethylsilyl group in **8** was effected without any concomittant cleavage of the phenol silyl ether according to the procedure of Arens :[15] sequential reaction with silver nitrate and potassium cyanide in water-ethanol-dichloromethane gave **9** in 97 % yield. The oxidation of the secondary alcohol was cleanly effected using Swern's dimethyl sulfoxide-trifluoroacetic anhydride reagent in dichloromethane (-70°C to -50°C, followed by addition of excess triethylamine)[16] and led to the isomerized allene-ketone **10** in 77 % yield.

Finally, reaction of the conjugated ketone **10** with propargylmagnesium bromide in diethyl ether led to the desired allene-alcohol **11** in 93 % yield.[17] The expected C17-β-hydroxy configuration was further

confirmed by ^1H NMR : the pyridine-induced solvent shift of the C18 angular methyl group, relative to chloroform was found to be quite large in accord with a *cis*-relation between the HO- and Me-groups, i.e. $\Delta(\delta CDCl_3\text{-}\delta C_5D_5N) = -0.18$ ppm.[18] Final deprotection of the A-ring phenolic alcohol with tetrabutylammonium fluoride in THF at 0°C led quantitatively to diol **2**.



[a] TBDMSCl, imidazole, DMF, r.t., 3.5 h (92 %); [b] p-$MeC_6H_4SO_2NHNH_2$, HOAc, i-PrOH, CH_2Cl_2, 40°C, 22 h (98 %); [c] MeLi, ether, 0°C → r.t., 12 h (82 %); [d] mCPBA, phosphate buffer pH = 8, CH_2Cl_2, r.t., 3.5 h (92 %); [e] $HC{\equiv}CSiMe_3$, n-BuLi, $BF_3.OEt_2$, THF, -78°C → 0°C, 6.5 h (51 % based on recovery); [f] $AgNO_3$/KCN, EtOH, CH_2Cl_2, H_2O, -50°C → r.t., 0.5 h (97 %); [g] $(CF_3CO)_2O$, DMSO, -70°C → 50°C, 0.5 h; Et_3N, CH_2Cl_2, -50°C → r.t., 0.5 h (77 %); [h] $BrMgCH_2C{\equiv}CH$, ether, THF, -40°C → -20°C, 1 h (93 %); [i] TBAF, THF, r.t. (100 %).

Scheme 2

Much to our surprise the tertiary hydroxyl group at C17 was found very reluctant to eliminate. Under a variety of elimination conditions[19] **11** reacted only very slowly and led to complex reaction mixtures in which the expected elimination product(s) or a subsequent Bergman cyclization product could not be detected. Despite this failure, derivative **2** possesses an interesting structure (cf. substitution at C17-α and C16) with respect to possible agonist or antagonist acrivity.[7] Results of the biological evaluation will be reported in due course.

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11. Satisfactory analytical and spectroscopic (IR, ^{1}H NMR, MS) data were obtained for all compounds. Relevant ^{1}H NMR data (360 MHz, $CDCl_3$) follow :
for **4** : 7.12 (1H, d, 8.4 Hz), 6.62 (1H, dd, 8.4, 2.6 Hz), 6.57 (1H, d, 2.6 Hz), 2.85 (2H, m), 2.50 (1H, m), 2,24 (1H, m), 2.19 - 1.35 (11H, m), 0.97 (9H, s), 0.82 (3H, s), 0.18 (6H, s) ppm
for **5** : 7.85 (2H, d, 8.1 Hz), 7.31 (2H, d, 8.3 Hz), 7.11 (1H, d, 8.4 Hz), 6.61 (1H, dd, 8.4, 2.6 Hz), 6.54 (1H, d, 2.6 Hz), 2.80 (2H, m), 2.42 (3H, s), 2.37 - 1.85 (5H, m), 1.90 (2H, m), 1.57 (1H, br), 1.52 - 0.98 (6H, m), 0.97 (9H, s), 0.82 (3H, s), 0.18 (6H, s) ppm
for **6** : 7.12 (1H, d, 8.4 Hz), 6.62 (1H, dd, 8.4, 2.6 Hz), 6.56 (1H, d, 2.6 Hz), 5.92 (1H, m), 5.75 (1H, m), 2.84 (2H, m), 2.30 (2H, m), 2.22 (1H, m), 2.02 (1H, m), 1.91 (2H, m), 1.65 - 1.40 (5H, m), 0.98 (9H, s), 0.79 (3H, s), 0.19 (6H, s) ppm
for **7** : 7.09 (1H, d, 8.4 Hz), 6.60 (1H, dd, 8.4, 2.6 Hz), 6.54 (1H, d, 2.6 Hz), 3.40 (1H, d, 3.0 Hz), 3.17 (1H, d, 3.0 Hz), 2.82 (2H, m), 2.34 (1H, m), 2.21 (1H, m), 2.01 (1H, m), 1.80 (2H, m), 1.72 (1H, m), 1.55 (2H, m), 1.41 (2H, m), 1.32 - 1.12 (1H, m), 0.97 (9H, s), 0.77 (3H, s), 0.18 (6H, s) ppm
for **8** : 7.13 (1H, d, 8.4 Hz), 6.62 (1H, dd, 8.4, 2.6 Hz), 6.55 (1H, d, 2.6 Hz), 3.90 (1H, m), 2.80 (2H, m), 2.66 (1H, m), 2.32 (2H. m), 2.20 (1H, m), 1.86 (1H, m), 1.78 - 1.20 (8H, m), 0.98 (9H, s), 0.90 (3H, s), 0.18 (6H, s), 0.13 (9H, s) ppm
for **9** : 7.13 (1H, d, 8.4 Hz), 6.62 (1H, dd, 8.4, 2.5 Hz), 6.55 (1H, d, 2.5 Hz), 3.92 (1H, m), 2.82 (2H, m), 2.65 (1H, m), 2.33 (2H, m), 2.21 (1H, m), 2.20 (1H, d, 2.7 Hz), 1.88 (1H, m), 1.77 - 1.63 (8H, m), 0.97 (9H, s), 0.91 (3H, s), 0.19 (6H, s) ppm
for **10** : 7.12 (1H, d, 8.4Hz), 6.62 (1H, dd, 8.4 , 2.6 Hz), 6.57 (1H, d, 2.6 Hz), 5.21 (1H, d, 2.6Hz), 5.20 (1H, d, 2.6 Hz), 2.86 (2H, m), 2.76 (1H, m), 2.41 (2H, m), 2.28 (1H, m), 1.99 (2H, m), 1.65 - 1.40 (5H, m), 0.98 (9H, s), 0.96 (3H, s), 0.19 (6H, s) ppm
for **11** : 7.11 (1H, d, 8.4 Hz), 6.61 (1H, dd, 2.6, 8.4 Hz), 6.55 (1H, d, 2.6 Hz), 5.04 (1H, m), 4.92 (1H, m), 2.81 (2H, m), 2.70 (1H, dd, A of ABX, 2.5, 16.6 Hz), 2.57 (1H, dd, B of ABX, 2.5, 16.6 Hz), 2.53 (1H, m), 2.34 (1H, m), 2.22 (2H, m), 2.05 (1H, t, X of ABX, 2.5 Hz), 1.86 (1H, m), 1.81 (1H, m), 1.60 - 1.49 (5H, m), 1.35 (1H, m), 0.97 (12H, 2s), 0.18 (6H, s) ppm
for **2** : 7.14 (1H, d, 8.4 Hz), 6.63 (1H, dd, 2.7, 8.4 Hz), 6.56 (1H, d, 2.7 Hz), 5.04 (1H, m, A of AB), 4.91 (1H, m, B of AB), 4.60 (1H, broad, -OH), 2.83 (2H, m), 2.70 (1H, dd, A of ABX, 2.6, 16.6 Hz), 2.57 (1H, dd, B of ABX, 2.6, 16.6 Hz), 2.53 (1H, m), 2.35 (1H, m), 2.22 (2H, m), 2.05 (1H, t, X of ABX, 2.6 Hz), 1.91 - 1.79 (2H, m), 1.62 - 1.20 (6H, m), 0.97 (3H, s) ppm
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19. The following reaction conditions were investigated : (a) Burgess reagent ($MeO_2CNSO_2NEt_3$), toluene, 50°C; (b) Martin sulfurane ($[C_6H_5C(CF_3)_2O]_2S(C_6H_5)_2$), CH_2Cl_2, -35°C → r.t., 14 h; or CCl_4, -50° → 60°C; (c) MsCl, DMAP, H_2O, CH_2Cl_2, r.t.; (d) MsCl, Et_3N, CH_2Cl_2, DBN; (e) *n*-BuLi/LiBr, MsCl, THF, -60°C → r.t.; (f) $POCl_3$, DMAP, CH_2Cl_2, 0°C → r.t.; (g) Tf_2O, Py, DMAP, CH_2Cl_2, -50°C → r.t.; (h) Ph_3P, DEAD (EtOOC-N=N-COOEt), THF, reflux.

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