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Estramicins: a Novel Cyclic Diyl Precursor Derived from Estradiol

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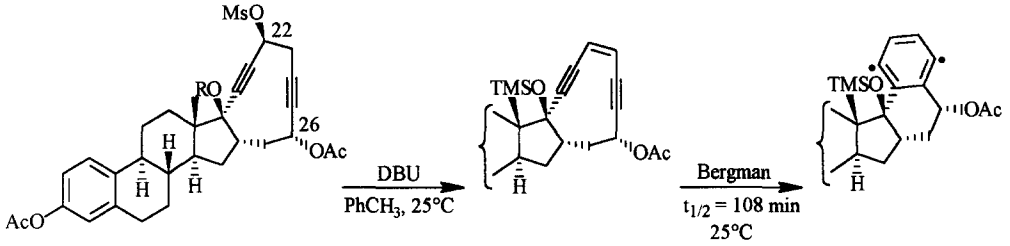
Abstract: The estradiol derived ynone **2** is obtained via a 13 step sequence starting from estrone. One of the key-steps involves the addition to estrone derivative **3** of the lithio derivative **8**. Obtention of the latter in enantiomerically pure form involves the lipase mediated kinetic resolution of racemic alcohol (±) **5**. The triethylamine induced elimination of dimesylate **15** leads to the Bergman precursor **16**, the cyclization of which at 25°C is estimated at $t_{1/2}$ = 20 min. © 1997 Elsevier Science Ltd.

New perspectives in cancer chemotherapy have recently been opened through the discovery of a new class of anticancer antibiotics from a bacterial source that presently includes the esperamicins, calicheamicins, dynemicin and the neocarzinostatin, kedarcidin and C-1027 chromophores.[1] These natural compounds exert their biological activity through DNA cleavage which is effected by diradicals that are generated from cyclic polyunsaturated core structures upon suitable activation.[2] For the purpose of developing site specific chemotherapeutic agents diyl-based DNA cleaving agents have been synthesized in which the core of the diradical precursor is linked to known minor groove DNA binding agents and DNA intercalators.[3] A derivative in which the unsaturated core is embedded within a structure with known antitumor activity has also been reported.[4]

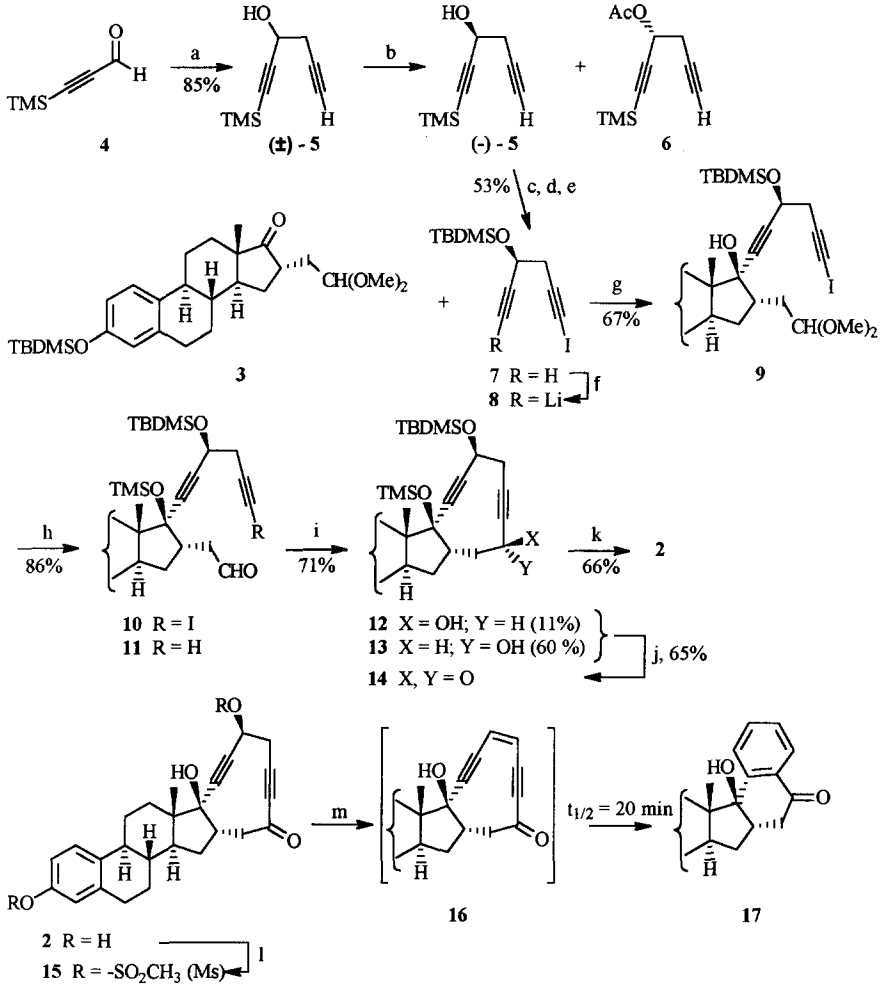
Recently we became interested in the development of estramicins, derivatives with a chemotherapeutic potential in which the diradical precursor core is incorporated into estradiol.[5a,b] The latter is a potential vector to transfer cytotoxic agents into the nuclei of human mammary cancer cells since these are usually rich in estrogen receptor.[6,7,8] In this context we recently reported on the elimination of methanesulfonate **1a** which led to the required cyclic enediyne core that was found to further cyclize via the Bergman process at 25°C with a half life of 108 min (Scheme 1).[9,5a]



1a R = -Si(CH$_3$)$_3$ (TMS); **1b** R = H

Scheme 1

Although the diradical formation proceeds at a useful rate the above process suffers from important limitations: (i) the elimination conditions require the C17-hydroxyl group to be protected; treatment of the unprotected derivative **1b** with a large excess of DBU proved unsatisfactory.[10] Since the free β-orientated C17-hydroxyl group is necessary for recognition by the receptor[11] the development of a similar precursor, in which the generation of the central (*Z*)-double bond would occur more readily and in the presence of a free C17-hydroxyl group, is mandatory; (ii) the synthesis of derivative **1** involved a scheme that was unselective for the stereocenters at C22 and at C26 hence requiring a difficult separation by chromatography.[5a] We now wish to report a solution to both shortcomings with the synthesis of ynone **2**, a more suitable substrate for the generation of a Bergman precursor.



[a] $BrMgCH_2C{\equiv}CH$, Et_2O, -30°C → rt, overnight; [b] lipase PS (Amano), vinylacetate, 30°C, 6 days; [c] TBDMSCl, imidazole, CH_2Cl_2, rt, overnight; [d] nBuLi, I_2, THF, -78°C, 3 h; [e] $AgNO_3$/KCN, EtOH/H_2O/CH_2Cl_2, 0°C → rt, 30 min; [f] $LiN(TMS)_2$, THF, -78°C, 1 h; [g] THF, -78°C → rt, 4 h; [h] TMSOTf, 2,6-lutidine, CH_2Cl_2, -78°C, 1 h; [i] $CrCl_2$/$NiCl_2$, THF, rt, 5h; [j] Dess- Martin periodinane, CH_2Cl_2, rt, 1.5 h; [k] HF (aq. 48% wt), CH_2Cl_2/CH_3CN, 0°C → rt, 5 h; [l] MsCl (4 eq), Et_3N (5 eq), cyclohexadiene (10 eq), C_3D_6O, rt; [m] MsCl (0.8 eq), Et_3N (1.6 eq), C_3D_6O, rt

Scheme 2

The synthesis of the estradiol derivative **2** is shown in scheme 2 and proceeds via the addition of the enantiomerically pure lithiated derivative **8** on the known estrone derivative **3**.[3a] Central in the synthesis of the diyne derivative stands the kinetic resolution of alcohol **(±)-5** that is obtained by Grignard addition of propargylmagnesium bromide to the known 3-trimethylsilyl-1-propynal **4**.[12,13] The resolution was effected via esterification of the alcohol with vinylacetate using Lipase PS of Amano.[14] After chromatographic separation the required alcohol **(-)-5** was obtained in 43% yield (ee>95%)[15] next to acetate **6** (39% yield).[13] The absolute stereochemical assignment rests on the application of Mosher's model on the corresponding *O*-methylmandelate esters of **5**.[16] The further transformation of **(-)-5** into the lithiated derivative **8** involved: (i) protection of the hydroxyl group with *tert*-butyldimethylsilyl chloride and imidazole in dichloromethane (93% yield); (ii) iodination via *n*-butyllithium deprotonation followed by the addition of iodine at -78°C (quantitative); (iii) selective

desilylation using silver nitrate and potassium cyanide in ethanol-water-dichloromethane (57%);[17] (iv) deprotonation using lithium hexamethyldisilazide in tetrahydrofuran (-78°C).

In analogy with the synthetic scheme leading to **1**,[5a] the addition of **8** to **3** occurred from the α-side leading to **9** in 67% isolated yield.[13,18] Protection of the C17-hydroxyl group as trimethylsilyl ether using trimethylsilyl trifluoromethanesulfonate and 2,6-lutidine in dichloromethane led to concomitant acetal deprotection.[19] The resulting iodoalkyne-aldehyde **10** was contaminated with up to 40% deiodinated derivative **11** which was recovered after the cyclization stage.[13] Cyclization was effected using the intramolecular version of Nozaki's chromium(II)/nickel(II) salt mediated coupling of haloalkynes with aldehydes,[20] a method that is especially useful when dealing with enolizable aldehydes, and led to a 1:6 mixture of the diastereomeric alcohols **12** and **13** in 71% yield (based on the 60% iodide content of the starting material).[13] Both alcohols can be separated by column chromatography and led via oxidation with Dess-Martin periodinane in dichloromethane to the same ynone **14** (65% yield).[13,21,22] Full deprotection was effected using aqueous hydrofluoric acid and gave the desired **2** in 66% isolated yield.[13,23]

The generation of the enediyne core from **2** and subsequent Bergman cyclization were followed by ^{1}H-NMR. When **2** was treated with methanesulfonyl chloride (4 equiv) and triethylamine (5 equiv) in the presence of 1,4-cyclohexadiene in acetone-d_6 the bis-mesylate **15** was formed.[13] Upon further addition of methanesulfonyl chloride (0.8 equiv) and triethylamine (1.6 equiv) the AB pattern for the hydrogen atoms of the (*Z*)-enediyne system in **16** (δ = 6.54, 6.31 ppm; J = 9.65 Hz) appeared. By following their disappearance a half-life value of 20 min was determined. From the rather complex reaction mixture the expected aromatic ketone (R = Ms) **17** was isolated in low yield (10%).[13]

The greater reactivity of the conjugated ynone precursor **16** compared to the reduced substrate derived from **1a** is in line with results that have been reported for chinone derived cyclic enediyne systems.[24] The results of the biological evaluation will be reported in the full account.

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for **2**: 7.07 (1H, d, J=8.47 Hz); 6.53 (1H, dd, J=8.44, 2.60 Hz); 6.46 (1H, d, J=2.55 Hz); 4.90 (1H, t, J=6.17 Hz); 2.93 (1H, ABd, J=17.84, 6.00 Hz); 2.64 (1H, ABd, J=17.85, 6.20 Hz); 0.91 (3H, s) ppm
for **(±)-5**: 4.51 (1H, broad t, J=5.98 Hz); 2.65 (1H, ABdd, J=16.75, 5.39, 2.63 Hz); 2.60 (1H, ABdd, J=16.75, 6.61, 2.63 Hz); 2.20 (1H, broad s); 2.11 (1H, t, J=2.62 Hz); 0.18 (9H, s) ppm
for **6**: 5.51 (1H, t, J=6.32 Hz); 2.67 (2H, dd, J=6.31, 2.63 Hz); 2.11 (3H, s); 2.05 (1H, t, J=2.64 Hz); 0.17 (9H, s) ppm
for **7**: 4.48 (1H, ddd, J=7.11, 6.25, 2.03 Hz); 2.76 (1H, ABd, J=16.63, 7.14 Hz); 2.72 (1H, ABd, J=16.59, 6.22 Hz); 2.44 (1H, d, J=2.03 Hz); 0.91 (9H, s); 0.15 (3H, s); 0.14 (3H, s) ppm
for **9**: 7.13 (1H, d, J=8.48 Hz); 6.61 (1H, dd, J=8.47, 2.45 Hz); 6.54 (1H, d, J=2.51 Hz); 4.60 (1H, t, J=6.67 Hz); 4.51 (1H, m); 3.37 (3H, s, OCH_3); 3.35 (3H, s, OCH_3); 2.75 (2H, d, J=6.68 Hz); 0.97 (9H, s); 0.94 (3H, s); 0.90 (9H, s); 0.18 (6H, s), 0.14 (3H, s); 0.13 (3H, s) ppm
for **10**: 9.85 (1H,broad s); 7.12 (1H, d, J=8.46 Hz); 6.61 (1H, dd, J=8.43, 2.57 Hz); 6.54 (1H, d, J=2.50 Hz); 4.59 (1H, t, J=6.77 Hz); 0.97 (9H, s); 0.90 (9H, s); 0.89 (3H, s); 0.18 (15H, s); 0.14 (3H, s); 0.13 (3H, s) ppm
for **11**: 9.82 (1H, broad d, J=1.95 Hz); 7.11 (1H, d, J=8.49 Hz); 6.61 (1H, dd, J=8.45, 2.54 Hz); 6.54 (1H, d, J=2.46 Hz); 4.60 (1H, t, J=6.68 Hz); 2.63 (1H, ABdd, J=16.38, 6.85, 2.64 Hz); 2.58 (1H, ABdd, J=16.27, 6.43, 2.63 Hz); 2.04 (1H, t, J=2.60 Hz); 0.98 (9H, s); 0.91(12H, s); 0.18 (15H, s); 0.16 (3H, s); 0.15 (3H, s) ppm
for **12**: 7.14 (1H, d, J=8.51 Hz); 6.63 (1H, dd, J=8.37, 2.61 Hz); 6.55 (1H, d, J=2.55 Hz); 4.80 (1H, dd, J=8.16, 6.76 Hz); 4.41 (1H, m); 2.58 (1H, ABdd, J=16.47, 6.63, 3.20 Hz); 2.50 (1H, broad dd, J=16.27, 8.24 Hz); 0.97 (9H, s); 0.92 (3H, s); 0.90 (9H, s); 0.31 (9H, s); 0.19 (6H, s); 0.15 (3H, s); 0.10 (3H, s) ppm
for **13**: 7.13 (1H, d, J=8.14 Hz); 6.62 (1H, dd, J=8.44, 2.65 Hz); 6.55 (1H, d, J=2.61 Hz); 4.85 (1H, dd, J=8.59, 6.76 Hz); 4.53 (1H, m); 2.63 (1H, ABdd, J=16.31, 6.76, 1.26 Hz); 2.47 (1H, ABdd, J=16.08, 8.60, 3.32 Hz); 0.98 (9H, s); 0.90 (9H, s); 0.87(3H, s); 0.23 (9H, s); 0.18 (6H, s); 0.14 (3H, s); 0.11 (3H, s) ppm
for **14**: 7.12 (1H, d, J=8.45 Hz); 6.62 (1H, dd, J=8.40, 2.52 Hz); 6.55 (1H, d, J=2.44 Hz); 4.91 (1H, t, J=6.41 Hz); 2.82 (1H, ABd, J=17.39, 6.32 Hz); 2.69 (1H, ABd, J=17.40, 6.54 Hz); 0.98 (9H, s); 0.92 (9H, s); 0.87(3H, s); 0.22 (9H, s); 0.19 (6H, s); 0.16 (3H, s); 0.13 (3H, s) ppm
for **15**: 7.30 (1H, d, J=8.64 Hz); 7.04 (1H, dd, J=8.67, 2.69 Hz); 7.00 (1H, broad s); 5.67 (1H, t, J=6.46 Hz); 3.19 (3H, s); 3.13 (3H, s); 0.94 (3H, s) ppm
for **17**: 7.84 (1H, dd, J=7.70, 1.10 Hz); 7.64 (1H, dd, J=8.05, 1.31 Hz); 7.61 (1H, dt, J=6.85, 1.32 Hz); 7.43 (1H, dt, J=7.82, 1.39 Hz); 7.20 (1H, d, J=8.63 Hz); 6.99 (1H, dd, J=8.60, 2.40 Hz); 6.94 (1H, d, J=2.44 Hz); 3.10 (3H, s); 1.18 (3H, s) ppm
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