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Synthesis of The Diaza Analogue of Ellagic Acid

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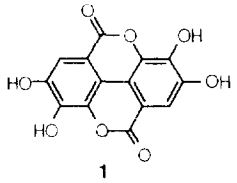
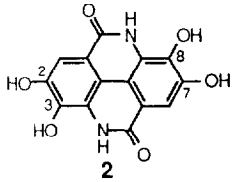
Abstract: The novel diaza analogue **2** of DNA-gyrase inhibitor ellagic acid **1** was synthesized via the Ullmann coupling of methyl 2-bromo-3-nitroveratrate **6** which, in turn, was prepared by a 7-step synthesis from 2-bromopiperonal **10** requiring a contrived, regiospecific 3-nitration as a crucial step. Analogue **2** was two-fold as potent a DNA-Gyrase inhibitor as **1**

Ellagic acid **1** is a polyphenolic dilactone widely occurring in various plants. It has been reported[1] to have antihemorrhagic, hypotensive, sedative, antineoplastic, antimutagenic as well as antioxidant properties. Recently, in the course of our efforts to identify novel, nonquinolone type DNA-gyrase inhibitors, our laboratories have reported[2] the potent DNA-gyrase inhibitory properties of **1**. Herein we describe the synthesis of its novel diaza analogue **2**, which was found to be twice as potent a DNA-gyrase inhibitor[3] as **1**.

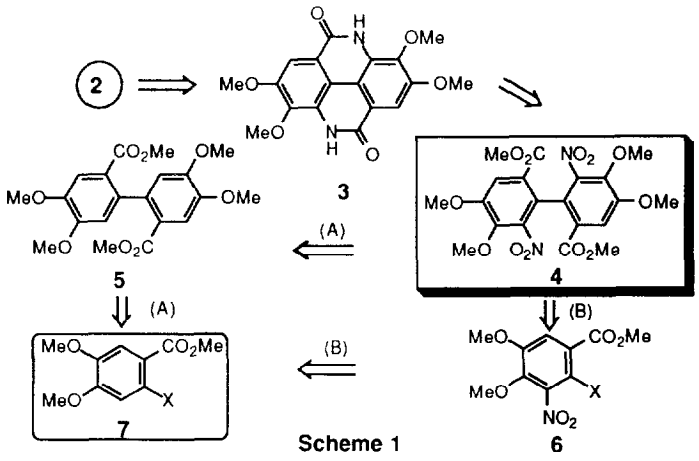


1



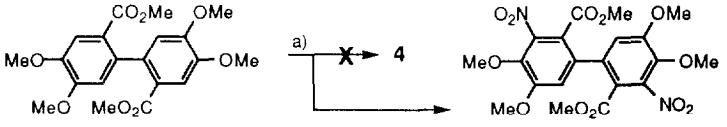
2

Although the unsubstituted[4] dilactam skeleton structure of **2** as well as several substituted derivatives, including the 2,7-dihydroxy derivative,[5] are known, the exact 2,3,7,8-tetrahydroxy derivative **2** has never before been described, signifying the potential synthetic difficulties in constructing the correct oxygen substitution pattern of **2**. Retrosynthetically, two possible approaches were envisaged (Scheme 1) for the synthesis of the pivotal synthon **4** from the same starting material **7**, leading to the protected precursor **3** of **2**. The first approach (A) to **4** involved nitration of the biaryl diester **5**,[6] readily obtained from **7** via either reductive diazonium salt coupling[6] (**7a**, X = NH_2) or the Ullmann coupling[7] (**7c**, X = halogen). In the alternate approach (B), nitration of monoaryl compound (**7b,c**, X = NHAc, halogen) to **6** (X = NH_2⇒halogen) would precede the Ullmann coupling to obtain **4**. Although several newer, milder biaryl coupling methods are now available,[8] majority of them are either incompatible or give poor yields with the highly hindered, contiguously substituted phenyl derivatives such as **6** for which the Ullmann method still remains the best.



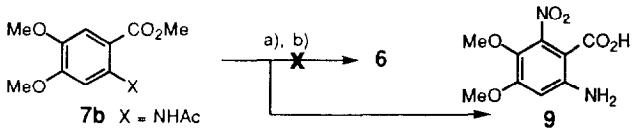
Scheme 1

Unfortunately, in attempted approach A (Scheme 2), nitration of **5** with $CuNO_3/Ac_2O$[9] at 0° gave the wrong nitro regioisomer **8** making it a dead-end situation.



Reagents: a) $CuNO_3$, Ac_2O, 0° **Scheme 2**

Similarly, in approach B (Scheme 3), nitration of acid **7b** with HNO_3/Ac_2O at 0°, followed by alkaline hydrolysis again gave the undesired nitro regioisomer **9**,[10] presenting yet another stumbling block.



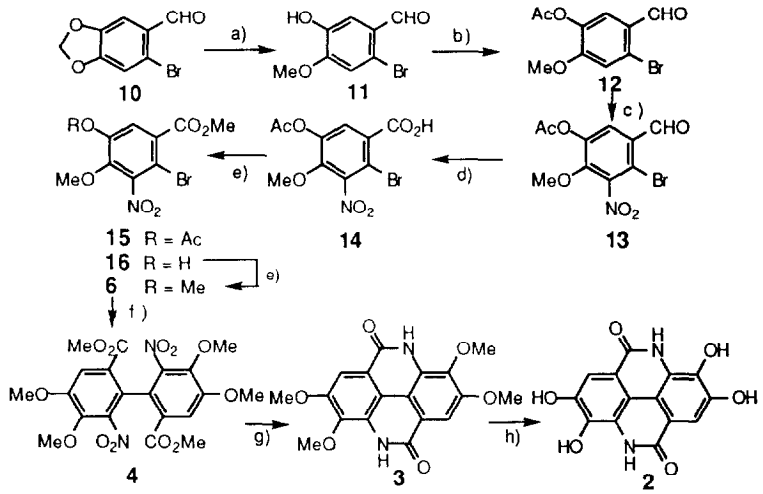
Reagents: a), HNO_3, Ac_2O, 0°; b) NaOH/Δ

Scheme 3

The regiochemistry of the nitro products **8** and **9** was evident in the NMR spectra[17] showing the 5-H only slightly deshielded relative to the corresponding more shielded Ar-H in their respective starting materials. In the desired **4** and **6**, subsequently prepared unequivocally (*vide infra*), the 6-H was found, as expected, equally or more deshielded than the lowest field Ar-H of the respective starting materials.

Regioselective 3-nitration of structures such as **7** (e.g.**7c**, X = halogen), hitherto unachieved, then became a crucial and challenging goal. The problem was overcome by replacing the 5-MeO with an AcO moiety which

deactivated C-6 sufficiently to force the otherwise disfavored 3-nitration in such a system. Thus, nitration of the 5-acetoxy aldehyde **12**[11a] (Scheme 4) with >99% HNO_3 (all other grades of HNO_3, with or without Ac_2O, failed) at 0° afforded the desired 3-nitrobenzaldehyde **13** in good yield (72%).[12] The precursor 2-bromobenzaldehyde **11**[11] was more conveniently prepared from 6-bromopiperonal **10** with NaOMe/DMSO[13]. Following the Jones oxidation[14] of the aldehyde **13** to the acid **14** (75%), diazomethane esterification in $MeOH/Et_2O$ gave a mixture of **15** (37%), **16** (34%) and **6** (13%), which was separated by silica gel chromatography . The formation of **16** and **6** from **14** with diazomethane was traced to the presence of moisture in MeOH causing partial hydrolysis of the 5-acetoxy group to **16** and methylation with excess diazomethane to **6**. Ullman coupling of **6** with freshly prepared copper powder[15] at 240° afforded **4** in 88% yield. However, acetate **15**, under similar conditions, decomposed at 220°. Reduction of **4** with Fe/AcOH[16] yielded the dilactam **3** (41%), which was demethylated to **2**[17] (>95%) with pyridine hydrochloride at 210°.



Reagents: a) NaOMe, DMSO, RT; b) Ac_2O, Pyr, 80°; c) >99% HNO_3, 0°; d) CrO_3, H_2SO_4, acetone, 0-5° ; e) MeOH, Et_2O, CH_2N_2, RT; f) Cu, 240°, 0.5 hr; g) Fe, AcOH, reflux, 1 hr.; h) Pyr.HCl, 210°, 5 hr.

Scheme 4

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17. All new compounds were characterized by NMR (300 MHz , ppm), IR (KBr, cm^{-1}) , MS (DCI , m/z) and combustion analysis. **2** , mp >300° ; ^{1}H NMR (DMSO-d6) 10.36 (s, 2H) , 7.50 (s, 2H) ; ^{13}C NMR, (DMSO-d6) 160.3, 145.5, 135.2 , 122.7, 114.8, 112.1, 106.9 ; IR 1629, 1642 ; MS 301 (MH^+) . **3** , mp >300° ; ^{1}H NMR (DMF / NaOD) 8.35 (s, 2H), 4.02 and 4.03 (each s, each 3H) ; IR 3200-2800, 1661; MS 357 (MH^+). **4** , mp 203-204° (Et_2O/Hexane) ; ^{1}H NMR ($CDCl_3$) 7.72 (s, 2H), 3.99 (s, 12H), 3.72 (s, 6H) ; ^{13}C NMR ($CDCl_3$) 164.5, 152.6, 43.8, 125.7, 121.2, 115.4, 62.2, 56.4, 52.5 ; IR 1733, 1607; MS 481 (MH^+). **5**, mp 193-195° (MeOH) ; ^{1}H NMR (DMSO-d6) 7.40 (s, 2H), 6.75 (s, 2H), 3.84 (s, 6H), 3.79 (s, 6H), 3.52 (s, 6H) ; ^{13}C NMR (DMSO-d6) 166.1, 151.0, 147.0, 136.8, 120.9, 113.7, 112.3, 55.7, 55.6, 51.4 ; IR 1625, 1600; MS 391 (MH^+). **6** , mp 120-121°(Et_2O /hexane) ; ^{1}H NMR ($CDCl_3$) 7.51 (s, 1H), 3.99 (s, 3H), 3.95 (s, 6H) ; ^{13}C NMR ($CDCl_3$) 164.9, 151.9, 115.9, 62.4, 56.6, 52.9 ; IR1742, 1547 ; MS 322 (MH^+1Br). **13** , mp 95-96° (Et_2O / pentane) ; ^{1}H NMR ($CDCl_3$) 10.23 (s, 1H), 7.81 (s, 1H), 4.02 (s, 3H), 2.39 (s, 3H) ; ^{13}C NMR ($CDCl_3$) 188.1, 167.6, 149.2, 143.1, 129.1, 126.2, 114.6, 62.66, 20.6 ; IR 2879 , 1771 , 1700 ; MS 320 (MH^+, 1Br). **14** , mp 209-210° (Et_2O / pentane) ; ^{1}H NMR (DMSO-d6) 14.00 (br s, 1H), 7.98 (s, 1H), 3.95 (s, 3H), 2.38 (s, 3H) ; ^{13}C NMR (DMSO-d6) 168.3, 164.9, 145.8, 141.8, 129.1, 128.3, 108.7, 62.82 , 20.6 ; IR 3238 , 1746 , 1600 ; MS 336 (MH^+, 1Br). **15** , mp 86-87° (Et_2O / hexane) ; ^{1}H NMR (CDCl3) 7.79 (s, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 2.38 (s, 3H) ; IR 1784 , 1740 , 1600 ; MS 348 (M^+, 1Br). **16** , mp 164-165° (Et_2O / hexane) ; ^{1}H NMR ($CDCl_3$) 7.57 (s, 1H), 5.89 (s, 1H), 3.97 (s, 3H), 3.94 (s, 3H); ^{13}C NMR ($CDCl_3$) 164.7, 148.5, 128.8, 120.0, 103.2, 62.8, 60,1, 53.0 ; IR 3368, 1696 , 1598 , 1549 ; MS 308 (M^+, 1Br).

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