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Intramolecular Carboxylate Capture of an Intermediate in Aromatic Electrophilic Substitution. The 8,9,10,11-tetrahydro-7.11-methano-7H-cycloocta[*de*]naphthalene-9-*endo*-carboxylic acid System.

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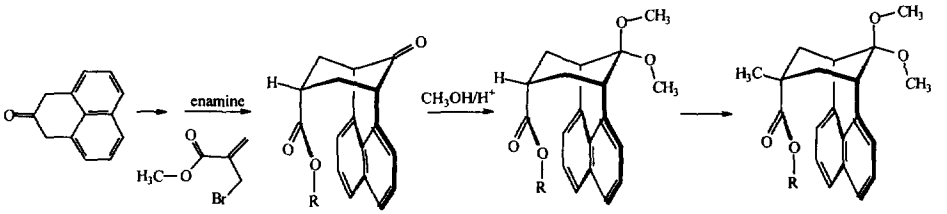
Abstract: The α, α'-annelation of the enamine of 1,3-dihydro-2-phenalenone with methyl α-(bromomethyl)acrylate affords an aromatic bicyclic framework, methyl 8,9,10,11-tetrahydro-7,11-methano-12-keto-7H-cycloocta(*de*)-naphthalene-9-*endo*-carboxylate having the ester function positioned over the aromatic ring. The 9-*exo*-methyl-12, 12-dimethoxy ketal carboxylate anion derivative reacts with excess Br_2 in aqueous solution affording the bromo lactone epoxide derived through capture of the intermediate of electorphilic attack on the naphthalene ring, 12, 12-dimethoxy-2, 3-*endo*-epoxy-11a-*endo*-hydroxy-1-*exo*, 4-dibromo-7, 11-methano-9-methyl-11a, 1, 2, 3, 4, 8, 9, 10, 11-octahydro-7 H-cycloocta [*de*] naphthalene-9-*endo*-carboxylic acid δ lactone. © 1997 Elsevier Science Ltd.

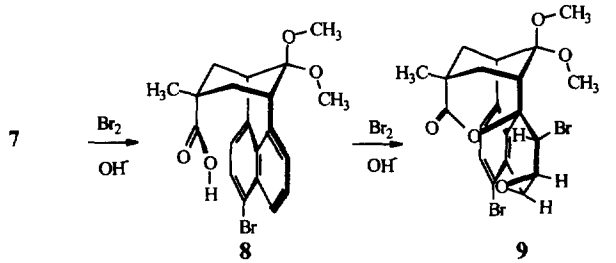
We have recently described the straightforward synthesis of methyl 8,9,10,11-tetrahydro-7,11-methano-12-keto-7H-cycloocta[*de*]naphthalene-9-*endo*-carboxylate[2, 3] [**3**] through the α, α'-annelation[4,5] of the enamine of 1,3-dihydro-2-phenalenone[6–9] [**1**] with methyl α-(bromomethyl)acrylate[10] [**2**]. The resulting bicyclic ester **3** was easily converted to the corresponding 12,12-dimethoxy ketal **4** with methanol and *p*TsOH and after



1 **2** **3** **4** R=CH_3, **5** R=H **6** R=CH_3, **7** R=H

formation of the anion α to the ester[LDA with HMPA in THF], this was alkylated with methyl iodide. The ester was transformed into the acid by KOH in refluxing ethylene glycol. The methyl group was introduced to prevent isomerization during hydrolysis. The resulting *endo*-bicyclic acid structure [**7**, X-ray, see ref 2] has the carboxyl group lying in the face of and within about 3 Å of the aromatic naphthalene ring. The dimeric hydrogen bonded acid has stacked aromatic rings and a "sandwiching" of the dimer carboxyl groups between those rings. This characteristic leads to a variety of very interesting chemistries.

Upon treatment of an aqueous solution of the sodium salt of acid **7** with 1 equiv. of bromine at room temperature (rt), there was obtained, almost instantly and in almost quantitative yield, the 3-substituted *mono* bromide **8**[11]. This was in contrast to the very slow reaction of the corresponding ester **6** with excess bromine in acetic acid. After 2 days at rt only a 54% yield of the corresponding 3-bromo ester[12] was obtained with recovery of unreacted starting ester. The conspicuous rate difference between the ester and carboxylate anion suggested there was perhaps some assistance by the carboxylate anion in the electrophilic aromatic attack by



bromine.[13] In the course of experiments to explore and expand the observation, an excess of aqueous Br_2 was added to aqueous solutions of both the anions **7** and **8**. In both cases there resulted the immediate precipitation of the same, pale yellow solid. This substance no longer contained a carboxylic acid function. After chromatography (hexane:ethyl acetate; 3:1), a 66-85% yield (yield depending upon starting material) of a light yellow crystalline compound, mp 197-198°C (dec.) was obtained. The MS [469, 421, 375, 343, 313, 204, 139, 84, 49] and HRMS [found 497.9701] pointed to a formula $C_{20}H_{20}BrO_5$ [calcd for 497.9677] and combined with the ^1H NMR, ^{13}C NMR and FT IR[14] signified a remarkable transformation. There was clearly both the loss of the aromatic character of the naphthalene system and the formation of a δ-lactone combined with the introduction of another oxygen and a bromine. An X-ray crystallographic study [Figure 1] determined the structure as 12, 12-dimethoxy-2,3-*endo*-epoxy-11a-*endo*-hydroxy-1-*exo*,4-dibromo-7, 11-methano-9-methyl-11a, 1, 2, 3, 4, 8, 9, 10, 11-octahydro-7H-cycloocta[*de*]naphthalene-9-*endo*-carboxylic acid δ lactone [**9**].

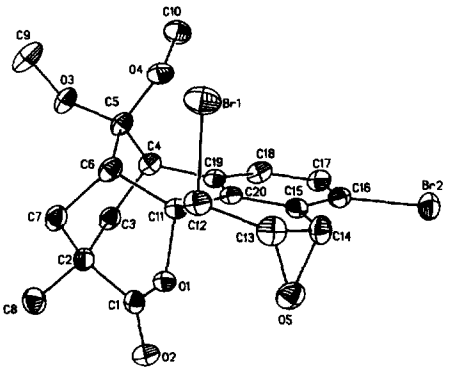
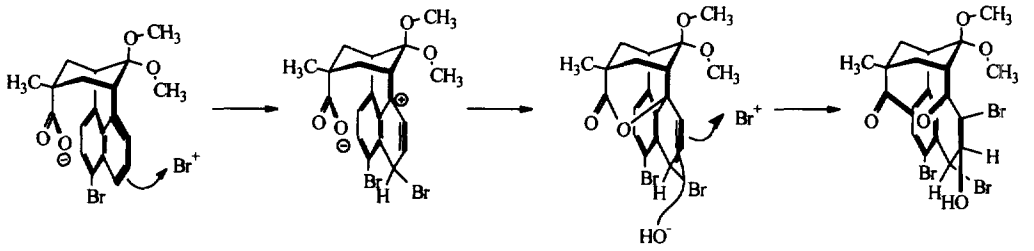


Figure 1: Compound 9

One rational mechanistic scenario for formation of lactone **9** from the 3-bromo acid **8** involves electrophilic attack of halogen on the 4 position of the naphthalene ring with capture of the allylic cation at position 11a by the neighboring carboxylate forming the unstrained δ-lactone[**12**]. Attack of Br^+ on the resulting 1, 2 double bond from the least hindered *exo* face followed by the requisite *trans* hydration of the resulting bromonium ion with OH^- at the 2 position from the *endo* face sets the stage[**13**] for intramolecular displacement of the 3-halogen by the neighboring 2-OH group resulting in the production of the *endo* epoxide[**9**]. We believe, because of the rate observations, that both the bromination of the unsubstituted carboxylate **7** and the 3-bromo carboxylate **8** anions follow much the same path involving a δ-lactone intermediate. However in the case of the unsubstituted naphthalene **7**, the intermediate lactone decomposes through base abstraction of the 3 proton with fragmentation of the δ-lactone and rearomatization of the 3-bromonaphthalene ring to give derivative **8**.



10 **11** **12** **13**

In the conversion of **8** to **9**, with a bromine substituted at the 3 position, subsequent substitution at position 4 [**11**] affords intermediate **12**. Elimination of the proton at 4 and fragmentation of the lactone (and return to the aromatic naphthalene) is inhibited in this example because of the resulting steric *peri* interactions between the two bromine atoms now at positions 3 and 4.

Though carbocation/neighboring aromatic participation within such frameworks[4e] is well established, the capture of the cationic intermediates in aromatic substitution by a neighboring nucleophile with loss of aromatic character is much less common.

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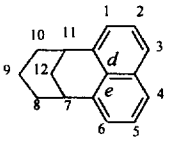
3 The *CA* numbering of the ring system is:



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11 Compound **8**: 86% yield as a light yellow solid; mp 274-275°C; FT IR (KBr) 2938, 2921, 1696, 1317, 1134, 1113, 1059; ^{1}H NMR ($CDCl_3$) δ 7.80 (d, *J* = 8.5 Hz, 1H), 7.54 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.35 (dd, *J* = 8.5, 7.5 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.16 (dd, *J* = 7.5, 1.0 Hz, 1H), 3.45-3.38 (m, 2H), 3.33 (s, 3H), 2.94 (s, 3H), 2.42-2.33 (m, 2H), 1.92 (dt, *J* = 13.8, 4.3 Hz, 2H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 180.8, 137.74, 137.66, 130.9, 130.7, 129.8, 127.2, 125.7, 125.2, 124.9, 120.3, 100.1, 47.6, 47.5, 41.8, 41.7, 38.4, 38.2, 30.6.; MS: 404 (M+), 341, 245, 165; HRMS: Calcd. for $C_{20}H_{221}BrO_4$: 404.0623. Found: 404.0621.

12 Isolated as the ketone methyl 3-bromo-12-oxo-8,9,10,11-tetrahydro-7,11-methano-7H-cycloocta[*de*]-naphthalene-9-*endo*-carboxylate. A white solid; mp 140-141°C; FT IR (KBr) 2949, 1596, 1724, 1442, 1247, 1204, 1071; ^{1}H NMR ($CDCl_3$) δ 8.14 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.62 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.34 (d, *J* = 7.1 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 3.87-3.84 (m, 2H), 3.04-3.00 (m, 2H), 2.64-2.59 (m, 1H), 2.63 (s, 3H), 2.54-2.48 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 210.4, 172.2, 137.4, 137.0, 131.2, 130.7, 130.4, 128.2, 126.2, 125.8, 125.1, 121.2, 52.4, 52.3, 51.3, 38.0, 37.9, 34.5; MS: 358 (M+), 272, 245, 191, 165; HRMS Calcd. for $C_{18}H_{15}BrO_3$ $(M)^+$: 358.0204. Found: 358.0205.

13 Bromination of the ketone **3** leads to the same substitution.

14 Compound **9**: FT IR [(KBr) 3020, 2959, 2934, 1729, 1216, 755. ^{1}H NMR ($CDCl_3$) δ 7.54 (d, *J* = 8.1 Hz, 1H), 7.04 (d, *J* = 8.1 Hz, 1H), 4.80 (d, *J* = 2.2 Hz, 1H), 4.66 (d, *J* = 4.0 Hz, 1H), 4.14 (dd, *J* = 4.0, 2.2 Hz, 1H), 3.30-3.27 (m, 2H), 3.26 (s, 3H), 3.18-3.16 (m, 1H), 2.80 (s, 3H), 2.09 (dd, *J* = 14.1, 5.7 Hz, 1H), 1.97-1.88 (m, 2H), 1.78-1.73 (m, 1H), 1.22 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 177.8, 138.1, 134.5, 133.6, 130.6, 129.8, 125.6, 100.5, 80.4, 55.1, 50.7, 49.6, 47.6, 47.0, 42.5, 40.9, 37.4, 35.9, 32.7, 26.2.

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