Pergamon

Tetrahedron Letters 41 (2000) 8063–8067

TETRAHEDRON LETTERS

Regioselective oxidations of equilenin derivatives catalyzed by a rhodium(III) porphyrin complex—contrast with the manganese(III) porphyrin

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Received 27 July 2000; revised 14 August 2000; accepted 16 August 2000

Abstract

Equilenin acetate and dihydroequilenin acetate were oxidized with iodosobenzene and a rhodium(III) porphyrin catalyst. The selectivity of the reactions differs from that with the corresponding Mn(III) catalyst, or from that of free radical chain oxidation. © 2000 Published by Elsevier Science Ltd.

We have described the oxidation and amination reactions of equilenin acetate **1** catalyzed by a manganese porphyrin **2**, carrying four pentafluorophenyl substituents, in methylene chloride solution.[1] Oxidation, using iodosobenzene as the reagent, afforded the C6 phenol **3** as the major product (74%) while the axial C11 benzylic alcohol **4** was a minor product (26%). No hydroxylation occurred at the other benzylic position, C14, and even with 25 catalytic turnovers the alcohol **4** was not oxidized to a ketone. With 57% conversion of starting material, only these two products were formed in quantitative overall yield. With the same catalyst **2**, tosylamidation of **1** using Ph–I=N–Ts afforded only the axial tosylamide **5**, with no attack on the naphthalene ring (with varying amounts of moisture, the Mn=NTs intermediate partially hydrolyzed to Mn=O and gave some of the oxygenation products). We invoked an explanation in which the Mn=O intermediate performs oxygen atom transfer to the naphthalene ring to form the phenol, while the benzylic hydroxylation and tosylamidation reactions involve hydrogen abstraction to form a benzylic radical that is then captured with stereoelectronic control to form axial products.

To explore these interesting selectivities further, we have examined related reactions catalyzed by the rhodium(III) analog **6**[2,3] of catalyst **2**. No phenol was formed on oxidation of **1** with one equivalent of iodosobenzene and 0.001 equivalents of catalyst **6**, only benzylic ketone **7**[4] (43%) and alcohol **8**[5] (57%) in quantitative overall yield with ca. 40% conversion. Neither of these

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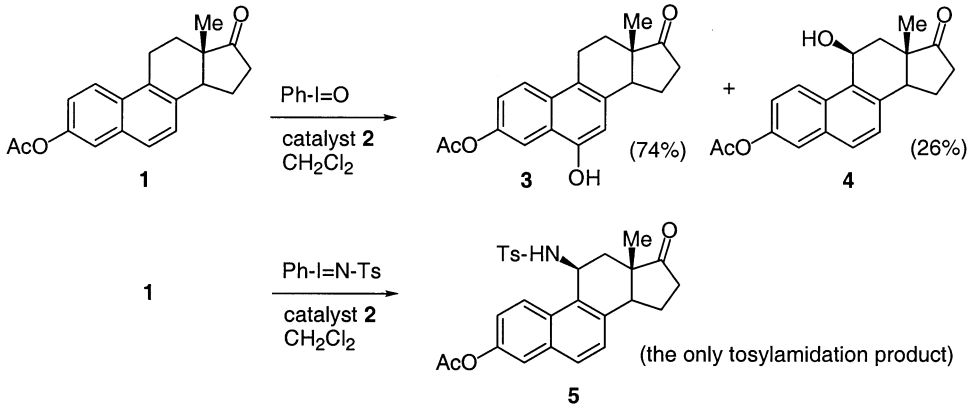
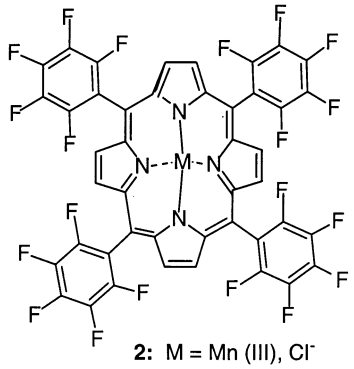
PII: S0040-4039(00)01402-7

products had been formed with catalyst **2**. We also examined the oxidation of dihydroequilenin diacetate **9**[6] with iodosobenzene and rhodium catalyst **6**. Again an 11-keto product **10**[7] was formed, but not the 14-hydroxy compound. In contrast to our findings with the manganese catalyst **2**, the rhodium catalyst **6** did not catalyze any amidation of the steroid with Ph–I=N–Ts, but instead the catalyst was rapidly destroyed by the reagent.

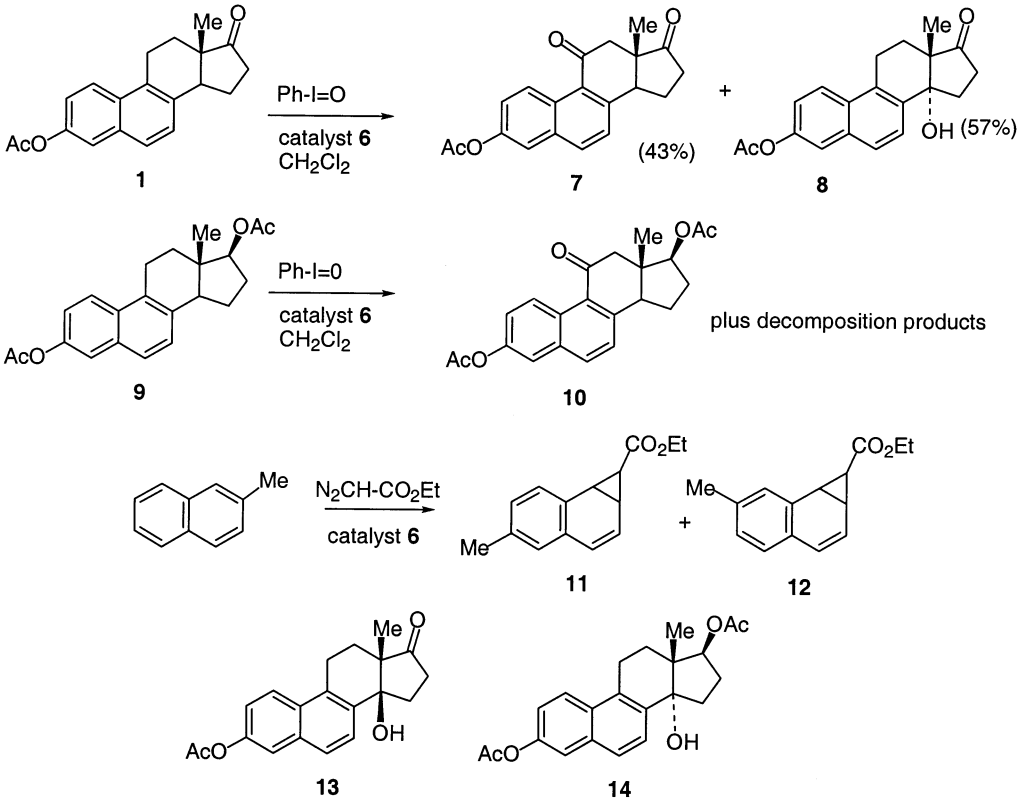




Rhodium(III) porphyrins are known to catalyze carbon–carbon bond formations between carbenes (generated from diazo compounds) and olefins to form cyclopropanes.[8–10] They also catalyze the insertion of carbenes into the C–H bonds of saturated compounds.[11] In both cases the substrates were used as solvent. We examined the reaction of ethyl diazoacetate with a concentrated solution of **1** in $CHCl_3$ with catalyst **6**, but under anaerobic conditions there was no reaction. We found that ethyl diazoacetate in 2-methylnaphthalene solution did form two cyclopropane products, **11** and **12**.[12,13] Presumably the problem with **1** was that it was diluted in solvent, not neat. However, when oxygen was present the same reaction conditions with **1** afforded the two isomeric 14-hydroxy steroids, **8** and **13**,[14,15] in a 1:1 ratio. Under the same conditions substrate **9** afforded only the 14-α-hydroxy steroid **14**.[16] In both cases no oxidation occurred when the diazo compound was omitted.

Some sense can be made of these varied reactions. Apparently manganese catalyst **2** forms a phenol **3** by oxygen addition from the Mn=O intermediate to the naphthalene ring, the dominant reaction. In contrast, the presumed Rh=O intermediate[17] formed from rhodium catalyst **6** is selective for benzylic oxidation, not oxygen transfer. Also, catalyst **2** does not

oxidize the benzylic alcohol **4** to a ketone, presumably because it cannot remove the equatorial hydrogen at C11 in **4**, but rhodium catalyst **6** oxidizes that alcohol more readily than it oxidizes the substrate, so only the ketones **7** and **10** are seen as C11 products.



Two different mechanisms for benzylic oxidation seem to be operating. The hydroxylations at C14 with ethyl diazoacetate in air must be free radical chain oxidations, and indeed we find that heating substrate **9** in benzene under reflux with azo-bis-isobutyronitrile in air without catalysts afforded the same 14-α-hydroxy product **14**, with no identified product from oxidation at C11. A presumed intermediate hydroperoxide must be converted to this carbinol, probably on workup or during chromatographic isolation. However, in our catalytic oxidations of **1** with catalyst **2** and of substrate **9** with both catalysts we see benzylic reaction at C11, not C14.

This contrast may reflect a steric difference between hydrogen atom removal by the small oxygen radical intermediate in the oxygen reactions and the bulky M=O intermediate in the catalyzed reactions. However, another possibility is that some of the metal–porphyrin catalyzed benzylic oxidations may involve electron transfer from the naphthalene system, followed by proton loss from the benzylic position to yield a benzylic radical. Such a mechanism can make sense of the finding that hydroxylation by catalyst **6** occurs preferentially at C14 in the ketone **1**, while it occurs exclusively at C11 with substrate **9**. By this mechanism, product is determined by the preferential loss in the cation radical of **1** of the more acidic C14 proton, which is nearer the carbonyl dipole, but without the ketone group the cation radical of **9** deprotonates at C11.

Regardless of the detailed reasons for these results, the contrast in behavior of the two different catalysts **2** and **6** is striking. Also, it is clear that the two catalysts have different useful selectivities. With equilenin acetate **1** the manganese catalyst produces amidation only at C11, in

product **5**. With dihydroequilenin acetate **9**, the rhodium catalyst directs selective oxidation to form the 11-keto derivative **10**, along with some oxidative decomposition products. Thus for selective functionalizations in the equilenin series, both catalysts have a role.

Acknowledgements

This work has been supported by the NIH and the NSF. J.Y. acknowledges support from a Bristol-Myers Squibb Graduate Fellowship and an EPA NCERQA STAR Graduate Fellowship.

References

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2. Rhodium porphyrin **6** was synthesized using a similar procedure to that reported by Wayland et al.[3] A 0.24 mM solution of 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin(TFPP-H_2) in 100 ml of 1,2-dichloroethane was charged with 1.83 mmol NaOAc under argon. $Rh_2(CO)_4Cl_2$ (0.32 mmol) dissolved in 20 ml of 1,2-dichloroethane was added dropwise to the porphyrin solution under argon. The solution was heated at reflux under argon for 48 h. After cooling to room temperature, 90 mg of I_2 was added and the solution was stirred for 5 h. The solution was then concentrated and filtered to remove the inorganic salts. The product was isolated by column chromatography using chloroform as eluent to give the bright red RhTFPPI in 94% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.99 ppm (singlet). ^{19}F NMR (300 MHz, $CDCl_3$): δ (ppm) −135 (2F, m, *ortho* to porphyrin), −150 (1F, t, *para* to porphyrin), −160 (2F, m, *meta* to porphyrin). UV–vis (CH_2Cl_2): λ 414 (Soret), 543, 577 nm.
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4. Compound **7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.36 (1H, d, C6-H), 8.00 (1H, d, C1-H), 7.55 (1H, d, C4-H), 7.46 (1H, d, C7-H), 7.40 (1H, dd, C2-H), 3.44 (1H, dd, C14-H), 2.97 (1H, d, C12-H), 2.74 (1H, d, C12-H), 2.67–2.48 (3H, m, C15-H and C16-H's), 2.38 (3H, s, acetate Me), 2.18 (1H, m, C15-H), 0.85 (3H, s, C18-Me). ESI-MS: m/z 323 (M+1). Product **7** indicated a loss of both C11 protons present in starting material **1**. The two protons at C12 were shifted from 2.23 and 1.92 ppm in **1** to 2.97 and 2.74 ppm in **7**. COSY spectra showed that the C12 protons in **7** had no couplings other than geminal coupling. HSQC spectra indicated that both of the assigned protons at C12 were attached to the same carbon. COSY also indicated that the C14, C15, and C16 H's present in **1** were all still present in **7**. Finally, the large shift of the C6-H at δ 7.68 in **1** to 9.36 in **7** could be attributed to a deshielding effect from a conjugated ketone at the C11 position.
5. Compound **8**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (1H, d, C1-H), 7.80 (1H, d, C7-H), 7.74 (1H, d, C6-H), 7.55 (1H, d, C4-H), 7.29 (1H, dd, C2-H), 3.15 (2H, m, C11-H's), 2.59 (1H, m, C16-H), 2.50 (1H, m, C16-H), 2.36 (3H, s, acetate Me), 2.34 (2H, m, C15-H's), 2.05 (1H, m, C12-H), 1.81 (1H, m, C12-H), 1.18 (3H, s, C18-Me). FAB-MS: m/z 325 (M+1), 307 (M−H_2O+1). ^{1}H NMR, COSY, and HSQC spectra of product **8** indicated that all carbons and protons present in **1** were retained in **8** except for the C14 proton. The downfield shifts of the C7 proton from 7.32 ppm in **1** to 7.80 in **8** as well as the angular methyl group from 0.80 ppm in **1** to 1.18 ppm in **8** are consistent with oxidation at the C14α position. Furthermore, the downfield shift of the C15α proton from 2.04 ppm in **1** to 2.34 ppm in **8** was consistent with a C14α hydroxylation.
6. Compounds **1** and **9** were synthesized from the commercially available equilenin and dihydroequilenin (Steraloids, Inc.) by acylation with acetic anhydride in pyridine under standard conditions. All products were isolated by column chromatography and characterized by ^{1}H NMR, COSY, HSQC and MS.
7. Compound **10**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.44 (1H, d, C6-H), 7.98 (1H, d, C1-H), 7.57 (1H, d, C4-H), 7.37 (1H, dd, C2-H), 7.34 (1H, d, C7-H), 5.03 (1H, t, C17-H), 3.24 (1H, dd, C14-H), 2.94 (1H, d, C12-H), 2.70 (1H, d, C12-H), 2.51 (1H, m, C16-H), 2.37 (1H, m, C15-H), 2.36 (3H, s, C3-acetate), 2.10 (3H, s, C17-acetate), 2.01 (1H, m, C15-H), 1.80 (1H, m, C16-H), 0.79 (3H, s, C18-Me). ESI-MS: m/z 367 (M+1). Similar characterization and arguments were made to identify compound **10** as for compound **7**.
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12. Compounds **11** and **12** were produced as a 1:1 mixture. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33–6.95 (3H, m, C1-H, C2-H, and C4-H), 6.36 (1H, m, vinyl H adjacent to the aromatic ring), 6.25 (1H, m, H adjacent to the cyclopropyl ring), 4.20 (2H, q, ethyl H's), 3.05 (1H, m, cyclopropyl H adjacent to the aromatic ring), 2.62 (1H, m, cyclopropyl H), 2.35 (3H, s, Me on one isomer), 2.32 (3H, s, Me on other isomer), 1.26 (3H, t, ethyl H's), 0.86 (1H, m, H α to the ester). ESI-MS: 229 (M+1). These products are similar to those reported for cyclopropanation of naphthalene with $CuSO_4$ and ethyl diazoacetate.[13]
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14. Compound **13**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (1H, d, C1-H), 7.69 (1H, d, C7-H or C6-H), 7.72 (1H, d, C7-H or C6-H), 7.56 (1H, d, C4-H), 7.32 (1H, dd, C2-H), 3.23 (1H, dt, C11-H), 2. 88 (1H, m, C11-H), 2.55–2.44 (2H, m, C16-H's), 2.36 (3H, s, acetate Me), 2.34 (1H, m, C15-H), 2.22 (1H, m, C12-H), 2.08 (1H, m, C15-H), 1.96 (1H, m, C12-H), 1.35 (3H, s, C18-Me). FAB-MS: m/z 325 (M+1), 307 (M$-H_2O$+1). The ^{1}H NMR, COSY, and HSQC spectra were very similar for compound **13** and compound **8**. One major difference was the greater downfield shift in the angular methyl to δ 1.35 ppm in **13**. Hydroxylations at 14β are known to produce larger downfield shifts than 14α hydroxylations.[15]
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16. Compound **14**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (1H, d, C1-H), 7.78 (1H, d, C7-H or C6-H), 7.70 (1H, d, C7-H or C6-H), 7.52 (1H, d, C4-H), 7.26 (1H, dd, C2-H), 5.12 (1H, dd, C17-H), 3.19 (2H, m, C11-H's), 2.36–2.30 (2H, m, C16-H and C15-H), 2.35 (3H, s, C3-acetate), 2.14 (3H, s, C17-acetate), 2.12 (1H, m, C15-H), 1.97 (1H, m, C16-H), 1.89 (1H, m, C12-H), 1.81 (1H, m, C12-H), 1.07 (3H, s, C18-Me). FAB-MS: m/z 368 (M+), 351 (M$-H_2O$+1). High resolution FAB-MS (368.21) indicated an elemental composition of $C_{22}H_{24}O_5$. Similar characterization and arguments were made to identify compound **14** as for compound **8**.
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