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Oxidative Functionalization of Unactivated Carbon-Hydrogen Bonds in Heptacyclo[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}.0^{10,14}]tetradecane (HCTD)

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Abstract. Gif-type reactions have been used to perform direct oxidative functionalization of the title compound (HCTD, **1**). Thus, GoAgg^{III} and GoAgg^{IV} promoted oxidations of **1** afford 1-(2'-pyridyl)heptacyclo[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}.0^{10,14}]tetradecane [i. e., 1-(2'-pyridyl)HCTD, **2**] in 6-10% isolated yield. In addition to **2**, GoAgg^{V} promoted oxidation of **1** produced heptacyclo[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}.0^{10,14}]tetradecan-7-one (HCTD-7-one, **3**) and 1-(4'-pyridyl)HCTD (**4**) in low isolated yield. Finally, oxidation of **1** performed by using an Fe^{II}-*t*-BuOOH system afforded several products, including hexacyclo[6.6.0,0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}]tetradecane-10,14-dione (**6**) and 14-hydroxyhexacyclo[6.6.0,0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}]-tetradecan-10-one (**7**), both of which resulted via oxidative cleavage of the C(1)-C(2) σ-bond in **1**.
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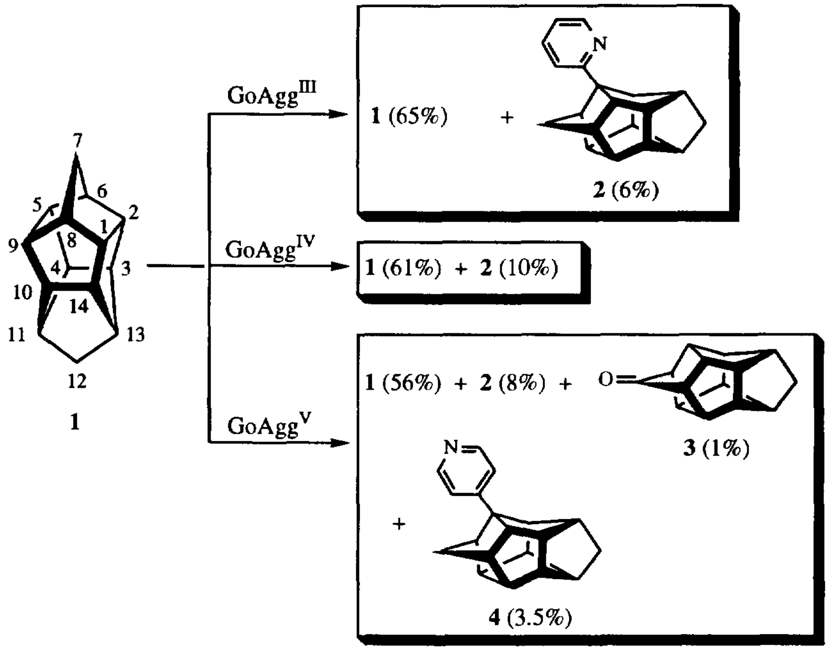
Introduction. As part of a long-term research program which is concerned with the synthesis and chemistry of novel polycarbocyclic "cage" compounds,[1] we have continuing need for specifically-substituted cage molecules which bear oxygen-containing functional groups (e. g., alcohols, ketones) for use as synthetic intermediates. One such compound is heptacyclo[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}.0^{10,14}]tetradecan-7-one (HCTD-7-one, **3**, Scheme 1), which previously has been prepared in our laboratory in 1.7% overall yield by application of a tedious and highly time-consuming seven-step synthesis.[2] Chow and co-workers[3] have reported a three-step synthesis that affords **3**, albeit in low overall yield.

Recently, it was shown[4] that Gif-type oxidants can be used for direct regioselective oxidative functionalization of heptacyclo[8.4.0.0^{2,7}.0^{3,5}.0^{4,8}.0^{9,13}.0^{12,14}]tetradecane ("Binor-S"). Thus, under standard GoAgg^{III} oxidation conditions,[5,6] Binor-S can be oxidized regiospecifically to 6-oxo-Binor-S in 8% yield (10% conversion). In view of this highly encouraging result, it was of interest to investigate the use of Gif-type reactions to effect the corresponding oxidative functionalization of heptacyclo[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}.0^{10,14}]tetradecane (HCTD, **1**) in a single synthetic step. Even if the resulting yield of, e. g., HCTD-7-one (**3**) proved to be only a few percent, this one-step oxidation of **1** nevertheless might prove to be competitive with our existing seven-step route.[2]

It should be noted that direct, highly selective acylation occurs when solutions of **1** in CH_3CN are irradiated in the presence of a catalytic amount of either $Na_4W_{10}O_{32}$ or $[(n\text{-}Bu)_4N]_4W_{10}O_{32}$.[7] The ensuing reaction results in selective formation of 1-acetyl-HCTD (i. e., functionalization of HCTD occurs preferentially at the 1-position rather than at the 7-position; the latter is required if the objectives of the present study are to be met).[7]

Gif-type Oxidative Functionalization of 1. Three standard Gif-type methods were employed for oxidative functionalization of **1**, i. e. GoAgg^{III}, GoAgg^{IV}, and GoAgg^{V}.[5,8] The results thereby obtained are shown in Scheme 1. In general, application of these procedures afforded 1-(2'-pyridyl)HCTD (**2**) as the major reaction product. A small amount (*ca.* 1%) of HCTD-7-one (**3**) along with 1-(4'-pyridyl)HCTD (**4**) also were produced when GoAgg^{V} was employed as the oxidizing agent.

Scheme 1



The structures of pyridyl-substituted HCTDs, i. e., **2** and **4**, were established via analysis of their ^{1}H and ^{13}C NMR spectra (see the Experimental Section). Thus, e. g., the ^{1}H NMR spectrum of **4** displays resonance signals which correspond to 15 aliphatic protons (δ 1.75-2.92) and four aromatic protons (δ 7.17-8.43). The downfield signals, which consist of an AB pattern (J_{AB} = 4.2 Hz), can be assigned to the pyridyl ring protons in **4**. The corresponding proton noise-decoupled ^{13}C NMR spectrum of **4** consists of 14 aliphatic carbon signals (δ 42.1-67.6) and three aromatic carbon signals [δ 121.5 (d), 149.5 (d), 157.7 (s)], consistent with the suggested structure for this compound.

Oxidative Functionalization of 1 with an Fe^{II}-*t*-BuOOH System. Oxidative functionalization of **1**, when performed by using Fe^{II}-*t*-BuOOH under conditions which have been described previously (Method A),[8] afforded six oxidation products in addition to recovered **1** (42%). Interestingly, in addition to HCTD-3-one (**3**, 2%) and 1-pyridyl-substituted HCTDs [i. e., **2** (7%), **4** (4%), and **5** (0.8%)], two additional products were obtained, **6** (13%) and **7** (2%; see Scheme 2), both of which resulted via concomitant oxidative cleavage of the C(1)-C(2) σ-bond in **1**. Products **6** and **7** were identified readily simply via comparison of their IR, ^{1}H NMR, and ^{13}C NMR spectra with corresponding literature values.[3] It should be noted that this procedure affords a greater *isolated* yield of **6** by starting with **1** than was achieved previously[3] via multistep synthesis.

Fe^{II}-*t*-BuOOH promoted oxidative functionalization of **1** was also performed in the presence of ascorbic acid[8] but without HOAc (Method B). Application of this procedure produced an improved yield of **3** (i. e., 3.4%, with 42% recovery of unreacted **1**; see the Experimental Section).

Oxidative Functionalization of 1 with an Fe^{II}-H_2O_2 System. Oxidative functionalization of **1** was also performed by using Fe^{II}-H_2O_2. Two procedures were employed which differed only in the ratio of pyridine:HOAc employed in each experiment. The results thereby obtained are summarized in Table 1.

Scheme 2

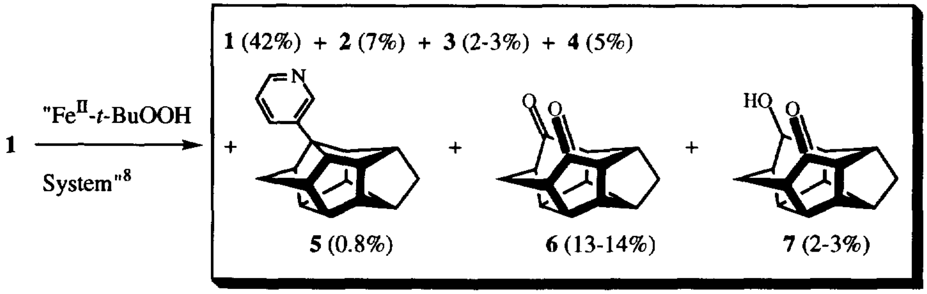


Table 1. Fe^{II}-H_2O_2 Promoted Oxidative Functionalization of 1

Conditions	**Products (% yields)**
Method A: $Fe(ClO_4)_2$, LiCl, picolinic acid, ascorbic acid, 30% aqueous H_2O_2, 10:1 pyridine-HOAc	**1** (63% recovered) + **2** (3.3%) + **3** (1.4%) + **4** (2.2%) + **5** (0.8%) + **6** (4.5%); (no **7** was obtained)
Method B: $Fe(ClO_4)_2$, LiCl, picolinic acid, ascorbic acid, 30% aqueous H_2O_2, 30:1 pyridine-HOAc	**1** (71% recovered) + isomeric mixture of **2** + **4** + **5** (individual isomers not separated; 6.7%) + **3** (2.2%) + **6** (8.1%) + **7** (0.8%).

Discussion. Although the absolute yields of **3** obtained via oxidative functionalization of **1** by using either Gif-type oxidants[5,8], Fe^{II}-*t*-BuOOH[9], or Fe^{II}-H_2O_2[9] are low (*ca.* 1-3%), these results nevertheless compare favorably with the overall yield of **3** obtained by using our previously published seven-step procedure.[2] Among the various methods that were examined for oxidative functionalization of **1**, the use of Fe^{II}-H_2O_2 (Method B, Table 1) appears to offer the best route for synthesizing **3**. The absolute yield of **3** thereby obtained was found to be 2.2%. However, since 71% of unreacted **1** was recovered (and subsequently can be recycled), this result represents a 7.6% overall conversion of **1** into **3**.

In addition, it should be noted that **3** produced via Gif-type oxidative functionalization of **1** is accompanied only by recovered **1** and by isomeric pyridyl-substituted HCTDs (i. e., **2**, **4**, and **5**). The latter materials are basic; hence, they can be removed effectively via extraction with dilute aqueous HCl. The remaining neutral compounds (i. e., **1**, **3**, **6**, and **7**) can be separated conveniently via column chromatography. Thus, despite the relatively poor absolute yield of **3** obtained via these reactions, the application of Gif-type oxidants for oxidative functionalization of **1** does offer some distinct advantages *vis-à-vis* existing routes that have been used for this purpose.

The results shown in Scheme 2 suggest that the Fe^{II}-*t*-BuOOH system[9] is considerably more reactive than are the other Gif-type oxidants that were employed in this study. Importantly, this procedure affords diketone **6** in synthetically useful quantities (i. e., 13-14% isolated yield).

The results described above have interest for the preparative chemistry of this type of difficultly-accessible compounds. They also have interest in terms of the theory of Gif chemistry. By taking a recent paper[10] as a convenient summary, it follows that $GoAgg^{III}$ (pyridine-HOAc-H_2O_2, with picolinic acid added as ligand) operates within the Fe^{III}-Fe^{V} manifold and displays radical chemistry only in special cases (e. g. for reaction at a tertiary C-H bond in adamantane). The radical intermediate in such reactions can be detected by coupling to pyridine.[11]

The $GoAgg^{IV}$ and $GoAgg^{V}$ systems use *t*-BuOOH as oxidant. These systems proceed mainly via radical chemistry, and the Gif nomenclature is no longer appropriate.[12] This same statement applies to the Fe^{II}-*t*-BuOOH systems.[9,12] The two Fe^{II}-H_2O_2 systems operate in the Fe^{II}-Fe^{IV} manifold,[13] wherein initial attack of the iron reagent on the hydrocarbon is not radical in character but instead is Gif-like. The selectivity of this species is very similar to that displayed by the corresponding reagent in the Fe^{III}-Fe^{V} manifold. However, in the case of Fe^{II}-H_2O_2 systems, the initial Fe^{II}-carbon bond fragments rapidly to Fe^{III} and a carbon radical.

When considering the results obtained in the present study, we must bear in mind that the objective is preparative chemistry rather than mechanistic chemistry. The mass balances of the seven reaction reported herein are *ca.* 70, 70, 70, 60, 60, 70, and 85%, respectively. Thus, considerable over-oxidation has taken place to furnish minor by-products. Furthermore, the first-formed oxidation products may be oxidized to other products that are not characterized.

From a theoretical standpoint, the most surprising result to emanate from the present study is that which was obtained by using $GoAgg^{III}$ conditions (i. e., the first system studied; see Scheme 1), where the only product characterized is a substituted pyridine, **2**. Of course, due its inertness toward oxidation and its ability to complex with excess HOAc, we expect that **2** is better able to resist over-oxidation than is the desired ketone (**3**).

The last two experiments, i. e., those which employ Fe^{II}-H_2O_2 systems (Table 1), do afford ketone **3**, but the major products of these reactions are diketone **6** and its congener, **7**. Products of this type have not been seen before in Gif chemistry.

Experimental Section

Melting points are uncorrected. High-resolution mass spectra were obtained by personnal at the Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln, NE. Elemental microanalyses were performed by personnel at M-H-W Laboratories, Phoenix, AZ.

$GoAgg^{III}$ Promoted Oxidative Functionalization of 1.[8] To a mixture of **1** (0.92 g, 5.0 mmol), pyridine (15 mL), $FeCl_3 \cdot 6H_2O$ (54 mg, 0.20 mmol), and HOAc (0.5 mL) was added picolinic acid (73.8 mg, 0.60 mmol), and the resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was cooled to 0-5 °C via application of an external ice-water bath. To the cooled reaction mixture was added dropwise with stirring 30% aqueous H_2O_2 (1.0 mL) during 3 minutes. After the addition of H_2O_2 had been completed, the external cold bath was removed. The reaction mixture was stirred at ambient temperature for 18 h, at which time the extenal ice-water bath was replaced, and the stirred reaction mixture was acidified via careful dropwise addition of 25% aqueous H_2SO_4. The resulting acidified mixture was transferred into a separatory funnel and then was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed sequentially with saturated aqueous $NaHCO_3$ solution (2 x 20 mL) and water (30 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. The residue, a brown solid, was purified via column chromatography on silica gel by using a 0-10% EtOAc-hexane gradient elution scheme.

The first chromatography fraction contained recovered starting material (**1**, 600 mg, 65%). Continued elution of the chromatography column afforded a second fraction which contained **2** (i. e., 1-(2'-pyridyl)heptacyclo-$[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}.0^{10,14}]$tetradecane, 80 mg, 6%) as a colorless oil; IR (film) 2946 (s), 2862 (m), 1588 (m), 1470 (m), 1429 (w), 745 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 1.73-1.90 (m, 4 H), 2.48-2.64 (m, 9 H), 2.83-2.92 (m, 2 H), 6.99-7.12 (m, 1 H), 7.22-7.47 (m, 1 H), 7.48-7.67 (m, 1 H), 8.48-8.62 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 42.0 (t), 42.6 (t), 51.0 (d), 51.4 (d), 51.9 (d), 52.2 (d), 53.2 (d), 53.35 (d), 53.4 (d), 54.0 (d), 55.7 (d), 60.3 (d), 61.6 (d), 70.5 (s), 120.3 (d), 120.6 (d), 135.9 (d), 148.7 (d), 167.0 (s); mass spectrum (70 eV), m/z (relative intensity) 261 (molecular ion, 100), 156 (11.8), 32 (10.6), 28 (45.6); Anal. Calcd for $C_{19}H_{19}N$: M_r^+ 261.1517. Found (high-resolution mass spectrometry): M_r^+ 261.1509.

GoAgg^{IV} Promoted Oxidative Functionalization of 1.[8] A solution of **1** (920 mg, 5.0 mmol), $Fe(NO_3)_3{\cdot}9H_2O$ (202 mg, 0.50 mmol), and HOAc (3.0 mL) in pyridine (30 mL) was stirred at ambient temperature for 5 minutes. 90% Aqueous *t*-BuOOH solution (1.1 mL, 10 mL) was added, and the resulting mixture was heated at 60 °C for 18 h. The reaction mixture was allowed to cool gradually to room temperature and then was transferred into a separatory funnel. Methylene chloride (30 mL) was added, and the resulting mixture was shaken with saturated $Cu^{II}SO_4$ solution (7 x 20 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue thereby obtained was purified via column chromatography on silica gel by using a 0-5% EtOAc-hexane gradient elution scheme.

The first chromatography fraction contained recovered starting material (**1**, 558 mg, 61%). Continued elution of the chromatography column afforded a second fraction which contained **2** (92 mg, 10%). The IR, ^1H NMR, and ^{13}C NMR spectra of **2** thereby are identical in all respects with the corresponding spectra obtained via GoAgg^{III} oxidation of **1** (*vide supra*).

GoAgg^{V} Promoted Oxidative Functionalization of 1.[8] A solution of **1** (920 mg, 5.0 mmol), $Fe^{III}(NO_3)_3{\cdot}9H_2O$ (202 mg, 0.50 mmol), and HOAc (3.0 mL) in pyridine (30 mL) was stirred at ambient teperature for 5 minutes. Picolinic acid (185 mg, 1.5 mmol) was added, and the resulting mixture was stirred at ambient temperature for 30 minutes. To the reaction mixture was added 90% aqueous *t*-BuOOH solution (1.1 mL, 10 mL), and the resulting mixture was stirred at ambient temperature for 18 h. Workup of the reaction was performed as described above for the corresponding GoAgg^{III} oxidation of **1** (*vide supra*). The residue thereby obtained was purified via column chromatography on silica gel by eluting with 5% EtOAc-hexane.

The first chromatography fraction contained recovered starting material (**1**, 517 mg, 56%). Continued elution of the chromatography column afforded a second fraction which contained **2** (100 mg, 8%). The IR, ^1H NMR, and ^{13}C NMR spectra of **2** thereby are identical in all respects with the corresponding spectra obtained via GoAgg^{III} oxidation of **1** (*vide supra*).

Continued elution of the chromatography fraction afforded a third fraction, which, when concentrated *in vacuo*, afforded pure **3** (i. e., heptacyclo$[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}.0^{10,14}]$tetradecan-7-one, 8 mg, 1%) as a colorless microcrystalline solid: mp 199-200.5 °C (lit.[2] mp 200-201 °C). The IR, ^1H NMR, and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra reported previously for authentic **3**.[2]

Subsequently, a final (fourth) chromatography fraction was collected which, when concentrated *in vacuo*, afforded **4** (i. e., 1-(4'-pyridyl)heptacyclo$[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}.0^{10,14}]$tetradecane, 45 mg, 3.5%) as a colorless oil; IR (film) 2946 (vs), 2857 (m), 1596 (s), 1540 (w), 1404 (w), 1288 (w), 704 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 1.75-1.92 (m, 4 H), 2.44-2.72 (m, 10 H), 2.86 (d, J = 4.4 Hz, 1 H), 7.17 (*A*B, J_{AB} = 6.1 Hz, 2 H), 8.43 (A*B*, J_{AB} = 6.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 42.1 (t), 42.7 (t), 51.2 (d), 51.6 (d), 52.0 (d), 52.1 (d), 52.9 (d), 53.1 (d), 53.4 (d), 53.8 (d), 54.2 (d), 62.1 (d), 62.3 (d), 67.6 (s), 121.5 (d), 149.5 (d), 157.7 (s); mass spectrum (70 eV), *m/z* (relative intensity) 261 (molecular ion, 29.1), 207 (73.4), 73 (50.1), 55 (50.5), 44 (100). Anal. Calcd for $C_{19}H_{19}N$: M_r^+ 261.1518. Found (high-resolution mass spectrometry): M_r^+ 261.1513. This material solidified upon long standing at ambient temperature to afford a colorless microcrystalline solid: mp 72-73 °C. This solid was further purified via preparative tlc (silica gel stationary phase) by eluting with 20% EtOAc-hexane. Pure **4** was thereby obtained as a colorless microcrystalline solid: mp 76.0-77.5 °C. Anal. Calcd for $C_{19}H_{19}N$: C, 87.31; H, 7.33. Found: C, 87.54; H, 7.06.

Oxidative Functionalization of 1 Performed By Using an Fe^{II}-*t*-BuOOH System.[9] **Method A.** A solution of pyridine (17 mL) and HOAc (1.7 mL) was placed in a flask which was fitted with a gas bubbling tube, and O_2 gas was bubbled through this solution at ambient temperature. To this solution were added sequentially $Fe^{II}(ClO_4)_2{\cdot}6H_2O$ (323 mg, 0.89 mmol), **1** (984 mg, 5.34 mmol), LiCl (174 mg, 4.11 mmol), and picolinic acid (267 mg, 2.17 mmol). Subsequently, 70% aqueous *t*-BuOOH (1.03 g, 8.0 mmol) was added portionwise (10 x 100 mg, each portion added at 15 minute intervals) to the reaction mixture, and the resulting mixture was stirred at ambient temperature for 4 days. The reaction was quenched via addition of 25% aqueous H_2SO_4 (75 mL), and the resulting aqueous suspension was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed sequentially with saturated aqueous $NaHCO_3$ (30 mL) and water (30 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by using a 0-30% EtOAc-hexane gradient elution scheme.

The first chromatography fraction contained recovered starting material (**1**, 415 mg, 42%). Continued elution of the chromatography column afforded a second fraction which contained **2** (94 mg, 7%). The IR, ^1H NMR, and ^{13}C NMR spectra of **2** thereby are identical in all respects with the corresponding spectra obtained via GoAgg^{III} oxidation of **1** (*vide supra*).

Continued elution of the chromatography fraction afforded a third fraction, which, when concentrated *in vacuo*, afforded pure **3** (22 mg, 2%) as a colorless microcrystalline solid: mp 195-197 °C (lit.[2] mp 200-201 °C). The IR, ^1H NMR, and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra reported previously for authentic **3**.[2]

This was followed by a fourth chromatography fraction; when concentrated *in vacuo*, this fraction afforded **5** [i. e., 1-(3'-pyridyl)heptacyclo[$6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}.0^{10,14}$]tetradecane, 11 mg, 0.8%] as a colorless oil; IR (film) 2950 (vs), 2864 (s), 1733 (m), 1569 (w), 1479 (m), 1458 (m), 1412 (m), 1297 (m), 1023 (m), 806 (m), 790 (m), 714 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.79-1.85 (m, 4 H), 2.46-2.75 (m, 10 H), 2.90 (d, J = 4.4 Hz, 1 H), 7.17 (dd, J = 8.0, 4.6 Hz, 1 H), 7.58 (dt, J = 8.0, 2.0 Hz, 1 H), 8.36 (dd, J = 4.6, 1.1 Hz, 1 H), 8.56 (d, J = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 42.1 (t), 42.8 (t), 51.2 (d), 51.5 (d), 52.1 (d), 52.2 (d), 53.0 (d), 53.1 (d), 53.5 (d), 53.8 (d), 54.4 (d), 62.3 (2 C, d), 70.6 (s), 123.2 (d), 133.7 (d), 146.2 (d), 147.9 (d), 151.6 (s). Anal. Calcd for $C_{19}H_{19}N$: M_r^+ 261.15175. Found (high-resolution mass spectrometry): M_r^+ 261.15183.

A fifth chromatography fraction was collected, which, when concentrated *in vacuo*, afforded pure **4** (60 mg, 5%) as a colorless microcrystalline solid: mp 76.0-77.5 °C. The IR, ^1H NMR, and ^{13}C NMR spectra of **4** thereby are identical in all respects with the corresponding spectra obtained via GoAgg^V oxidation of **1** (*vide supra*).

Subsequently, a sixth chromatography fraction was collected. When concentrated *in vacuo*, this fraction afforded pure hexacyclo[$6.6.0,0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}$]tetradecane-10,14-dione, (i. e., **6**, 152 mg, 13%) as a colorless microcrystalline solid: mp 292-293 °C (lit.[3a] mp 293.5-294.5 °C). The IR, ^1H NMR, and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra reported previously for authentic **6**.[3a]

Finally, the last (seventh) chromatography fraction was collected and subsequently was concentrated *in vacuo*. Pure 14-hydroxyhexacyclo[$6.6.0,0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}$]tetradecan-10-one (i. e., **7**, 25 mg, 2%) was thereby obtained as a colorless microcrystalline solid: mp 288-290 °C (lit.[3a] mp 291-292 °C). The IR, ^1H NMR, and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra reported previously for authentic **7**.[3a]

Method B. A solution of pyridine (20 mL) was placed in a flask which was fitted with a gas bubbling tube, and O_2 gas was bubbled through this solution at ambient temperature. To this solution were added sequentially $Fe^{II}(ClO_4)_2{\cdot}6H_2O$ (253 mg, 0.70 mmol), **1** (859 mg, 4.66 mmol), LiCl (148 mg, 3.5 mmol), picolinic acid (258 mg, 2.10 mmol), and ascorbic acid (123 mg, 0.70 mmol). Subsequently, 70% aqueous *t*-BuOOH (1.26 g, 9.8 mmol) was added portionwise to the reaction mixture (10 x 90 mg, each portion added at 15 minute intervals, followed by 4 x 90 mg portions, which were added at 24 h intervals), and the resulting mixture was stirred at ambient temperature for 5 days. The reaction was quenched via addition of 25% aqueous H_2SO_4 (80 mL), and the resulting aqueous suspension was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed sequentially with saturated aqueous $NaHCO_3$ (30 mL) and water (30 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. To the residue was added 5% aqueous HCl (25 mL), and the resulting aqueous suspension was stirred at ambient temperature for 2 h. The aqueous suspension was extracted with Et_2O (5 x 20 mL).The combined ethereal extracts were set aside, and the aqueous layer was rendered basic via careful addition of saturated aqueous $NaHCO_3$ (25 mL), and the resulting suspension was extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts wre washed with water (30 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Analysis of the ^1H and ^{13}C NMR spectra of the residue thereby obtained (153 mg, 12.6%) revealed that it consisted exclusively of a mixture of three isomeric pyridyl-substituted HCTDs (i. e., **2**, **4**, and **5**). The combined ethereal extracts (*vide supra*) were washed with water (30 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by using a 0-40% EtOAc-hexane gradient elution scheme. The first chromatography fraction contained recovered starting material (**1**, 358 mg, 42%). Continued elution of the chromatography column afforded fractions which contained the following products (collected sequentially): **3** (31 mg, 3.4%), **6** (140 mg, 14%), and **7** (26 mg, 2.6%).

Oxidative Functionalization of 1 Performed By Using an Fe^{II}-H_2O_2 System.[9] **Method A.** A solution of pyridine (20 mL) and glacial HOAc (2.0 mL) was placed in a flask which was fitted with a gas bubbling tube, and O_2 gas was bubbled through this solution at ambient temperature. To this solution were added sequentially $Fe^{II}(ClO_4)_2 \cdot 6H_2O$ (330 mg, 0.91 mmol), **1** (1.01 g, 5.48 mmol), LiCl (174 mg, 4.11 mmol), and picolinic acid (303 mg, 2.45 mmol). Subsequently, 30% aqueous H_2O_2 (931 mg, 8.22 mmol) was added portionwise to the reaction mixture (10 x 93 mg, each portion added at 15 minute intervals) followed by ascorbic acid (160 mg, 0.91 mg, which was added portionwise to the reaction mixture (5 x 32 mg, each portion added at 30 minute intervals), and the resulting mixture was stirred at ambient temperature for 3 days. It was noted that a solid precipitated gradually during the reaction; thus, pyridine (4 mL) was added after the reaction had proceeded for 24 h in order to redissolve this precipitate. The reaction was quenched via addition of 25% aqueous H_2SO_4 (80 mL), and the resulting aqueous suspension was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed sequentially with saturated aqueous $NaHCO_3$ (30 mL) and water (30 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. The residue thereby obtained was purified via column chromatography on silica gel by using a 0-30% EtOAc-hexane gradient elution scheme. The first chromatography fraction contained recovered starting material (**1**, 636 mg, 63%). Continued elution of the chromatography column afforded fractions which contained the following products (collected sequentially): **2** (47 mg, 3.3%), **3** (15 mg, 1.4%), **5** (6 mg, 0.4%), **4** (32 mg, 2.2%), and **6** (53 mg, 4.5%).

Method B. A solution of pyridine (30 mL) and glacial HOAc (1.0 mL) was placed in a flask which was fitted with a gas bubbling tube, and O_2 gas was bubbled through this solution at ambient temperature. To this solution were added sequentially $Fe^{II}(ClO_4)_2 \cdot 6H_2O$ (296 mg, 0.82 mmol), **1** (905 mg, 4.91 mmol), LiCl (156 mg, 3.68 mmol), picolinic acid (272 mg, 2.21 mmol), and ascorbic acid (144 mg, 0.82 mmol). Subsequently, 30% aqueous H_2O_2 (1.17 mg, 10.3 mmol) was added portionwise to the reaction mixture (10 x 83 mg, each portion added at 15 minute intervals (10 x 83 mg, each portion added at 15 minute intervals, followed by 4 x 83 mg portions, which were added at 24 h intervals), and the resulting mixture was stirred at ambient temperature for 5 days. The reaction was quenched via addition of 25% aqueous H_2SO_4 (120 mL), and the resulting aqueous suspension was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed sequentially with saturated aqueous $NaHCO_3$ (30 mL) and water (30 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. To the residue was added 5% aqueous HCl (25 mL), and the resulting aqueous suspension was stirred at ambient temperature for 2 h. The aqeuous suspension was extracted with Et_2O (5 x 20 mL).The combined ethereal extracts were set aside, and the aqueous layer was rendered basic via careful addition of saturated aqueous $NaHCO_3$ (25 mL), and the resulting suspension was extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts wre washed with water (30 mL), dried ($MgSO_4$), and filtered through a Celite® pad. The residue was washed with a small quantity of CH_2Cl_2, and the combined filtrates were concentrated *in vacuo*. Analysis of the ^1H and ^{13}C NMR spectra of the residue thereby obtained (86 mg, 6.7%) revealed that it consisted exclusively of a mixture of three isomeric pyridyl-substituted HCTDs (i. e., **2**, **4**, and **5**). The combined ethereal extracts (*vide supra*) were washed with water (30 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by using a 0-40% EtOAc-hexane gradient elution scheme. The first chromatography fraction contained recovered starting material (**1**, 640 mg, 71%). Continued elution of the chromatography column afforded fractions which contained the following products (collected sequentially): **3** (21 mg, 2.2%), **6** (85 mg, 8.1%), and **7** (8 mg, 0.8%).

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