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Approaches to the Synthesis of Heptitol Derivatives via Stereocontrolled Functionalization of Cycloheptatrienone Using Organo-Iron Chemistry

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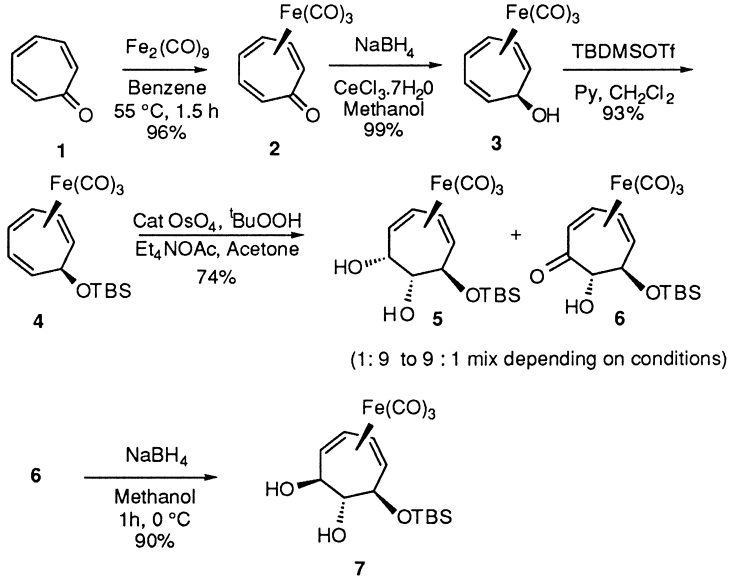
Abstract—A stereo-chemically defined, differentially protected polyhydroxylated heptanedial derivative was prepared by the stereo- and regio-controlled functionalization of cycloheptatrienone, followed by cleavage of the ring to afford the acyclic derivative in high yields.

Introduction

The stereo-controlled synthesis of polyhydroxylated heptanes is a very desirable goal because of its potential application as, or in the synthesis of, glycosidase inhibitors[1] and in the synthesis of compounds related to anti-tumor substances such as swansonine,[2] and also because of the potential use of heptitol derivatives in the construction of C-glycosides.[3] Stereo- and regio- controlled attachment of substituents to a carbocyclic ring, followed by cleavage of the ring, offers a useful approach to stereo-control. This then allows access to acyclic subunits that can be used to prepare important intermediates in the synthesis of sugar molecules with defined stereo- and regio-chemistry.

Previous studies[4,5] in our laboratories have established that a variety of reactions can be performed on a carbon–carbon double bond in the presence of a diene-$Fe(CO)_2L$ moiety.



Scheme 1.

Keywords: heptitol; cycloheptatrienone; acyclic.
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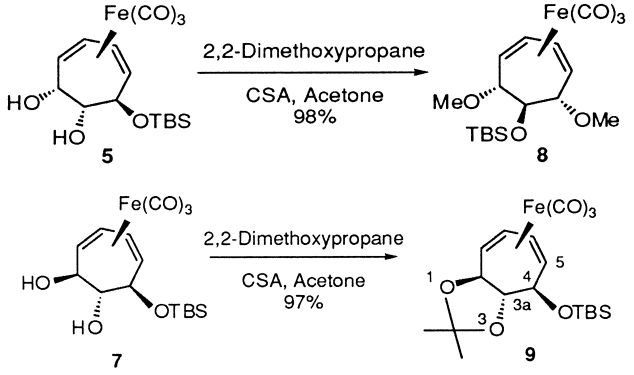


Scheme 2.

Besides using the $Fe(CO)_2L$ group as an efficient protecting group for the diene, the stereo-chemical directing effect and the ability of the $Fe(CO)_2L$ to stabilize carbocations has been used effectively to construct polyfunctional cyclo-heptenes.[6] In addition, tropone-$Fe(CO)_3$ **2** has been prepared in optically pure form by resolution[7] and has reasonable configurational stability so that any syntheses of heptitols starting from this complex can, in principle, lead to enantio-merically pure materials, provided that racemization does not occur during reactions of **2** and that the products of such stereo-controlled reactions are also configurationally stable.

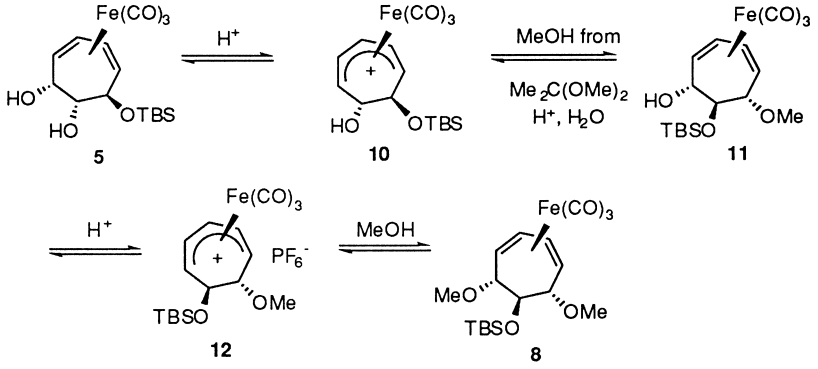
Results and Discussion

Racemic **2** was prepared according to the literature pro-cedure.[8] Stereo-controlled reduction of **2** under Luche conditions followed by protection of the hydroxyl group gives the (*tert*-butyldimethylsilyloxy)cyclo-heptatriene complex **4** (Scheme 1).[4]

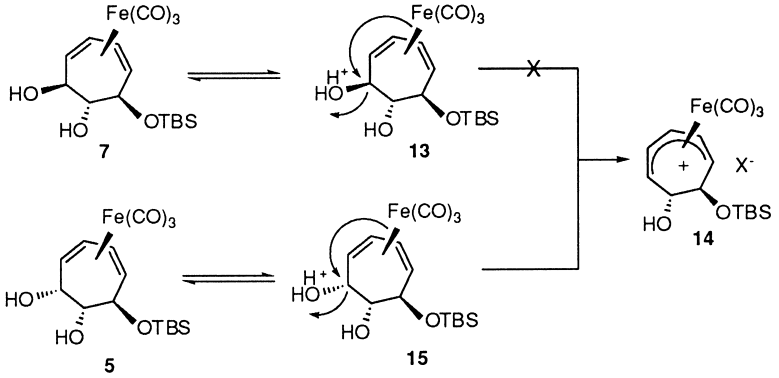
Previous studies[4] on catalytic osmylation of **4** showed the formation of a mixture of diol **5** and ketol **6**. The ratio of **5** to **6** varies widely depending upon the reaction conditions, longer reaction time and lower concentration favoring the ketol. In the present study, the latter conditions were employed, as we were interested in further investigations of the chemistry of **6**. Since it is difficult to separate **5** from **6** by flash chromatography, the mixture was reacted directly with sodium borohydride to give diols **5** and **7** which can be separated easily.

The *cis* and *trans* diols (**5** and **7**) behave very differently on treatment with catalytic quantities of camphorsulfonic acid in a 1:1 mixture of acetone and 2,2-dimethoxypropane. The *cis* diol rearranges to give a symmetrical dimethoxy product **8**[4] whereas *trans* diol **7** gives acetonide derivative **9** under similar conditions (Scheme 2).

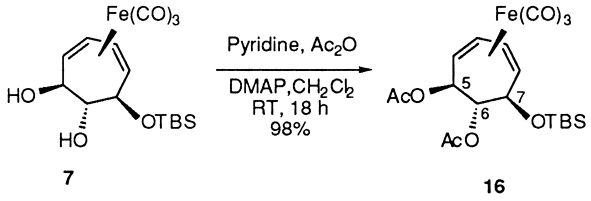
The *cis*-diol **5** under acidic conditions undergoes facile metal-assisted elimination of the protonated *exo*-hydroxyl



Scheme 3.



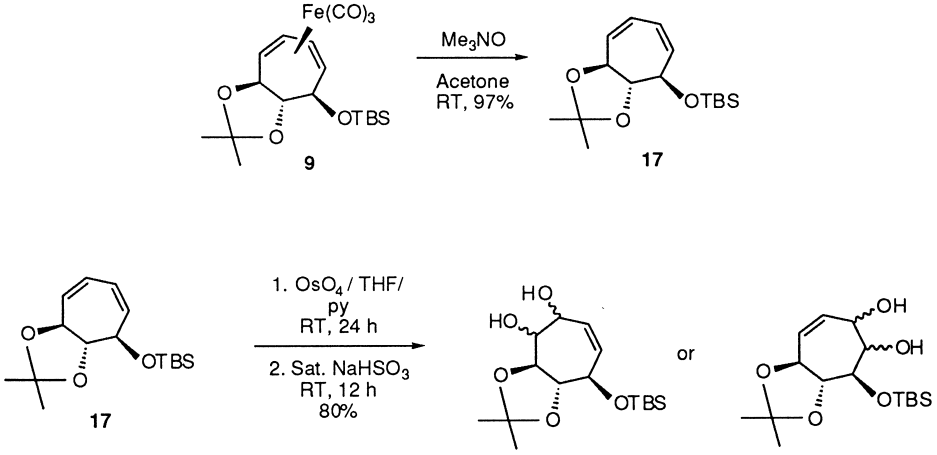
Scheme 4.



Scheme 5.

group in the pseudo-allylic position. Here, the iron attacks in an S_N2 type fashion to form an intermediate dienyl complex. The byproduct, water, in this reaction in the presence of acid converts 2,2-dimethoxypropane to methanol and acetone. Nucleophilic attack of methanol on the intermediate dienyl complex, controlled by both the metal and OTBS group (Scheme 3), gives the monomethoxy derivative **11**.[5] The other hydroxyl group of **11** undergoes similar reaction to give, ultimately, the symmetrical dimethoxy derivative **8**.

In the case of the *trans* diol this type of metal-assisted elimination to give the dienyl intermediate is not possible, because the pseudo-allylic hydroxyl group is now *syn* to the metal, which can no longer provide anchimeric assistance for loss of water. Thus acetonide derivative **9** is formed instead. This different behavior of **5** and **7** is illustrated in Scheme 4.



Scheme 6.

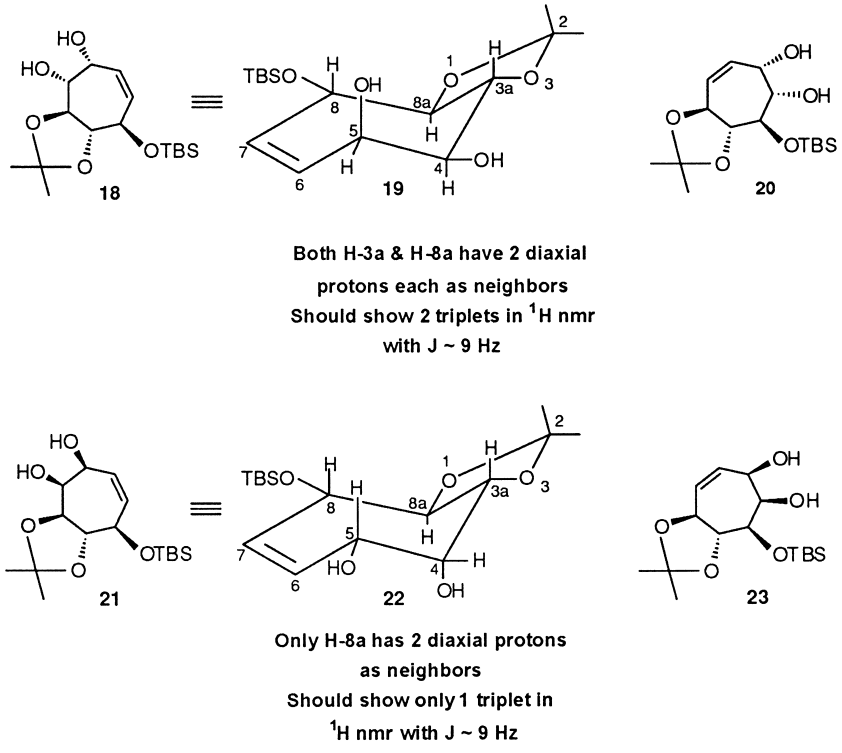


Figure 1. Possible products of dihydroxylation of **17**.

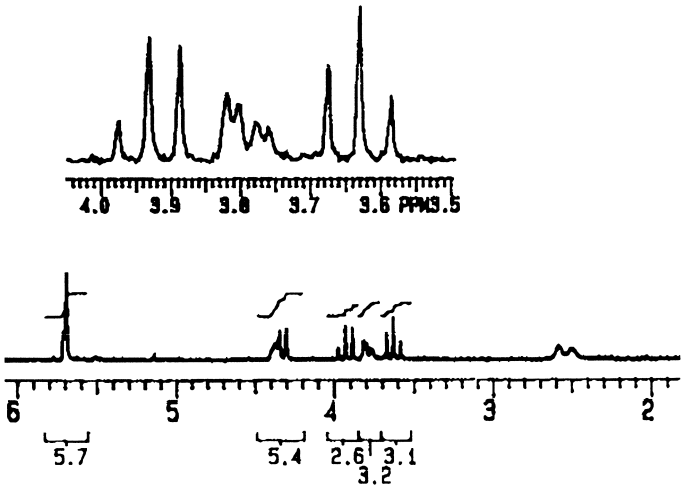


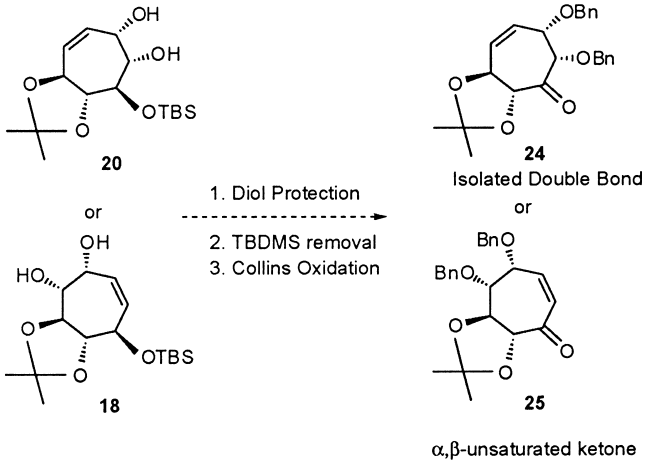
Figure 2. ^{1}H NMR spectrum of **18** (δ 2 to 6 region).

Assignment of the ^{1}H NMR spectrum of the acetonide derivative **9** in both $CDCl_3$ and C_6D_6 proved difficult because of similarity of resonances due to the C*H*-OR protons. Examination of the diacetate derivative **16** provided an avenue for making the required assignments, in particular the H-7 (corresponds to H-4 in **9**) resonance. As expected, the ^{1}H NMR spectrum of diacetate derivative **16** showed a shift in the position of H-5 and H-6 protons to lower field (δ 4.79 and 4.49 ppm, respectively, compared with 2.91 and 2.78 for **9**), while H-7 (corresponds to H-4 in **9**) is at δ 3.55 in **9** compared to 3.79 ppm in **16**. Comparison of COSY spectra of the diol **7**, diacetate derivative **16** and acetonide derivative **9** enabled unambiguous assignment of peaks in the proton spectra of these complexes, provided in the Experimental Section (Scheme 5).

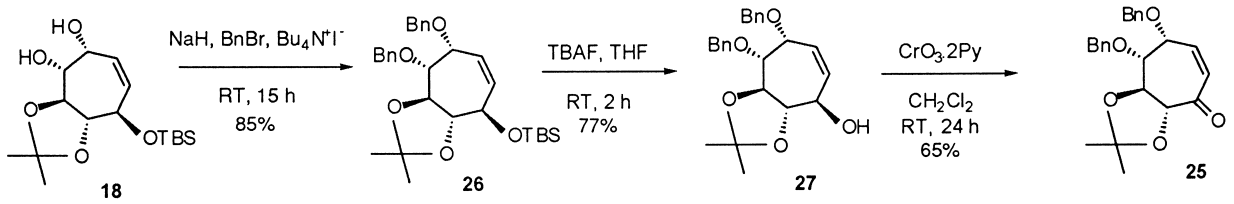
Decomplexation of the acetonide derivative **9** using trimethylamine-*N*-oxide in acetone at room temperature for 3 h afforded the cycloheptadiene derivative **17** in 97% yield (Scheme 6). The diene **17** is unsymmetrically functionalized on sp^3 carbons C-5 and C-7 and we were interested in determining whether it would show any regio- and stereo-selectivity during stoichiometric osmylation reaction. Out of a total of four possible stereo-isomeric diols, we found to our delight that the reaction is completely stereo-selective and regio-specific, giving a single product in 80% yield. The next step was to determine the regio- and stereo-chemistry of the product (see Scheme 6).

The stereo-chemical aspect was easily addressed by using ^{1}H NMR spectroscopy. Fig. 1 shows the four possible products of the dihydroxylation reaction. Compounds **18** and **20** have the same relative stereo-chemistry, as do **21** and **23**. Careful examination of the conformational drawing **19** shows that both H-3a and H-8a have two diaxal protons as neighbors, which should result in two sets of triplets with J=9 Hz in the ^{1}H NMR spectrum. Examining **22** shows that only H-8a has one set of two diaxial protons (H-3a and H-8) as neighbors, and should show only one triplet with J=9 Hz in the ^{1}H NMR spectrum. In the event the former was observed (Fig. 2, triplets at 3.93 and 3.62), indicating that osmylation occurs *trans* to the C–O bond at either the 5, 6 or 7, 8 double bonds and since osmylation of a double bond results in a *cis* diol, our product is either **18** or **20** depending on the regio-chemistry of the reaction.

It was not possible to establish the regio-chemistry of the osmylation reaction directly from the NMR spectrum of the



Scheme 7.



Scheme 8.

product. Therefore, we devised a scheme of simple chemical transformations to address this problem (Scheme 7). Protection of the diol (**18** or **20**) followed by TBDMS removal should give an alcohol that can be further oxidized to ketone. The ketone resulting from this set of transformations would either be an α,β-unsaturated ketone **25** (from **18**) or one with an isolated double bond **24** (from **20**). The structure of the ketone should be readily assignable from its ^{1}H NMR spectrum.

The actual outcome of this set of transformations is detailed in Scheme 8. The dibenzyl derivative **26** was prepared in 85% yield by stirring the diol with sodium hydride, benzyl bromide and catalytic amounts of tetrabutylammonium iodide for 15 h at room temperature. The silyl protecting group was selectively removed using TBAF in THF for 3 h affording **27** in 77% yield. Collins oxidation of the alcohol **27** afforded the ketone **25** in 65% yield (Scheme 8). The resulting product was in fact an α,β-unsaturated ketone, easily identified by its NMR spectrum; vinyl protons at δ 6.69 and 6.07 ppm are consistent with this structure, but not with **24**. It may be noted that the COSY spectrum of the diol **18** is also consistent with this assignment.

The outcome of this reaction can be rationalized by inspection of the energy minimized structure of diene **17** (Fig. 3). The acetonide ring imparts rigidity to the molecule, making it conformationally less mobile. It is apparent from the structure that of the two double bonds **a** and **b**, double bond **a** is sterically more accessible to the approach of osmium tetraoxide than is double bond **b**, at which the bulky *tert*-butyldimethylsilyloxy group provides considerable steric hindrance. Based on these observations the regiochemical outcome of stoichiometric osmylation should be at the double bond adjacent to the acetonide group. Careful examination of the model also indicates that the approach of osmium tetraoxide on bond **a** from face **A**, where the attack would be *trans* to the adjacent acetonide C–O bond, would be more favorable than from face **B**. It should be noted that the stereo-chemical outcome of this reaction parallels that observed for simple allylic ethers.[9]

The exceptional stereo- and regio-control observed during this dihydroxylation reaction provides a useful approach for the construction of differentially protected acyclic heptitol derivatives. Ozonolysis of the double bond of cycloheptene derivative **26** proved to be very clean and efficient. The dibenzyl derivative **26** was treated with excess ozone–oxygen mixture at −78°C in a 1:1 mixture of dichloromethane and methanol, followed by in situ treatment with dimethyl sulfide to give the heptanedial derivative **28** in essentially quantitative yield. Thus we were able to accomplish a very efficient synthesis of a highly functionalized heptitol derivative with excellent stereo-control (Scheme 9).

Conclusions

We have shown that highly stereo-selective multiple hydroxylation of a seven-membered carbocyclic system

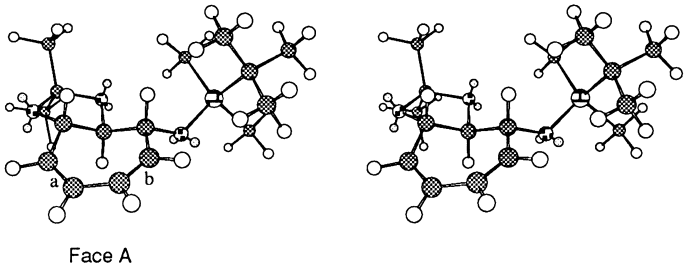
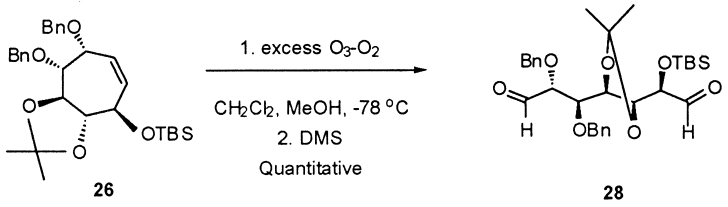


Figure 3. Stereoview of energy minimized structure of diene **17**.



Scheme 9.

can be achieved by using the directing and protecting capacities of a tricarbonyliron moiety attached to a cycloheptadiene. Resistance to acid-promoted rearrangement can be established by judicious control of the stereo-chemistry of hydroxyl substituents that are alpha to the diene-$Fe(CO)_3$ unit, which allows the efficient preparation of a differentially protected, stereo-defined trihydroxycycloheptadiene (**17**). The latter molecule undergoes osmylation with remarkable stereo- and regio-control to afford a pentahydroxy cycloheptene which can be cleaved to produce a heptanedial system. Further investigations of this chemistry and its applications in the synthesis of biologically important target molecules will form the basis of future studies in our laboratories.

Experimental

General

All reactions were carried out under an anhydrous, deoxygenated argon atmosphere. Tetrahydrofuran and diethyl ether were freshly distilled from sodium/benzophenone prior to use; dichloromethane from calcium hydride, acetone and methanol from anhydrous calcium sulfate. All other solvents were used as purchased. All non-volatile compounds were freed from residual solvents by exposure to high vacuum prior to analysis. Infrared spectra were recorded in CH_2Cl_2 solution, unless otherwise noted, on a Nicolet Impact FT-IR spectrometer in sodium chloride chambers. ^{1}H NMR spectra were recorded on a 200 MHz, or 300 MHz Varian Gemini in $CDCl_3$ solution unless otherwise noted, and were referenced either to the solvent or to TMS. Mass spectra were recorded in-house on a Kratos MS25A instrument.

Tricarbonyl[(5-8-η)-[(3a*S*,4*R*,8a*S*)-2,2-dimethyl-4,8a-dihydro-3aH-cyclohepta[d][1,3]-dioxol-4-yl]*tert*-butyldimethylsilyl ether]iron (9). To a stirred solution of the diol **7** (277 mg, 0.698 mmol, 1 equiv.) in 24 mL of 1:1 acetone and 2,2-dimethoxypropane was added camphorsulfonic acid (84.3 mg, 0.52 mmol, 0.52 equiv.). The reaction mixture was stirred at RT for 2 h and the progress of the reaction was monitored by tlc at definite intervals. After 2 h, the tlc of reaction mixture showed the disappearance of starting material, and the reaction mixture was diluted with 5 mL of ether. The organic layer was washed with water (2×5 mL), brine (1×5 mL), dried ($MgSO_4$) and evaporated to give the crude product which was then purified by flash chromatography (10% ethyl acetate/hexanes) to provide the title compound as a yellow solid (294 mg, 97% yield). Mp: 89°C; TLC R_f=0.48 (10% EtOAc/hexanes); IR ($CDCl_3$): 2054 (s), 1985 (s) cm^{-1}; ^{1}H NMR (300 MHz) δ, ppm: 5.45 (dd, *J*=7.5, 4.7 Hz, 1H, H-7), 5.01 (dd, *J*=8.6, 4.8 Hz, 1H, H-6), 3.55 (d, *J*=8.1 Hz, 1H, H-4), 3.05 (d, *J*=7.5 Hz, 1H, H-8), 2.94–2.88 (m, 2H, H-1, H-3a), 2.78 (d, *J*=8.9 Hz, 1H, H-8a), 1.40 (s, 3H, CH_3-acetonide), 1.28 (s, 3H, CH_3-acetonide), 0.92 (s, 9H, Si-^{t}Butyl), 0.09 (s, 6H, Si–CH_3); ^{13}C NMR (75 MHz) δ, ppm: 210.1, 110.0, 88.7, 86.7, 85.9, 72.0, 70.5, 67.4, 55.4, 26.9, 26.8, 25.8, 18.1, −4.9, −4.4; HRMS (EI, 23 eV): calcd for $C_{17}H_{28}FeO_4Si$ (M^+-2CO) 380.1106; found 380.1107.

Tricarbonyl[(1-4-η)-[5-*endo*-6-*exo*-diacetoxy-7-*endo*-(*tert*-butyldimethylsilyl)oxy]cyclohep-ta-1,3-diene]iron (16). To a solution of the diol complex **7** (11 mg, 0.063 mmol, 1 equiv.) in 3 mL of CH_2Cl_2 was added pyridine (102 μL, 1.26 mmol, 20 equiv.), DMAP (2.9 mg, 0.024 mmol, 0.38 equiv.), followed by acetic anhydride (36 μL, 0.38 mmol, 6 equiv.). The reaction mixture was stirred at room temperature for 24 h, diluted with 15 mL of ether and the ether solution was washed with water (2×15 mL), brine (1×15 mL) and dried ($MgSO_4$). The solvent was removed at reduced pressure and the crude product was purified by flash chromatography (30% EtOAc/hexanes) to give the product as pale yellow oil (32 mg, 98%). Mp: 84°C; TLC R_f=0.35 (30% EtOAc/hexanes); IR: 2058 (s), 1997 (s), 1749 (s) cm^{-1}; ^{1}H NMR (300 MHz) δ, ppm: 5.39–5.25 (m, 2H, H-2, H-3), 4.79 (t, *J*=4.6 Hz, 1H, H-5), 4.49 (dt, *J*=4.6 Hz, 1.0 Hz, 1H, H-6), 3.79 (t, *J*=4.6 Hz, 1H, H-7), 2.81–2.71 (m, 2H, H-1, H-4), 2.09 (s, 3H, OAc), 1.99 (s, 3H, OAc), 0.90 (s, 9H, Si-^{t}Butyl), 0.09 (s, 3H, Si–CH_3), 0.05 (s, 3H, Si–CH_3); ^{13}C NMR (50 MHz) δ, ppm: 209.8, 170.3, 169.1, 88.4, 87.9, 73.8, 68.6, 67.0, 61.0, 54.5, 25.7, 21.1, 21.0, 18.2, −4.8, −4.9; HRMS (EI, 23 eV): calcd. for $C_{18}H_{25}FeO_6Si$ (M^+-CH_3COO) 420.0770; found 421.0779; calc for $C_{17}H_{28}FeO_5Si$ (M^+-3CO) 396.1055; found 396.1057.

(3a*S*,4*R*,8a*S*)-2,2-Dimethyl-4,8a-dihydro-3aH-cyclohepta[d][1,3]dioxol-4-yl-*tert*-butyldimethylsilyl ether and enantiomer (17). To a stirred solution of diene complex **9** (294 mg, 0.673 mmol, 1 equiv.) in freshly distilled acetone (3.0 mL) at 0°C was added an ice-cooled solution of 404 mg of anhydrous trimethylamine-*N*-oxide (5.38 mmol, 8 equiv.) in acetone. The solution was stirred at 0°C for 5 min, allowed to warm to room temperature and stirred for 3 h while the reaction progress was monitored by tlc. The reaction mixture was then diluted with ether (10 mL), filtered through Celite, and the Celite pad was further washed with 30 mL of ether. The combined organic solution was washed with water (2×20 mL), brine (1×20 mL), dried ($MgSO_4$) and evaporated to give the crude product which was then purified by flash chromatography (10% ethyl acetate/hexanes) to provide the title compound as a pale yellow oil (193.3 mg, 97% yield). TLC R_f=0.52 (10% EtOAc/hexanes); IR ($CDCl_3$): 2944 (s), 2866 (m), 1378 (m), 1247 (s), 1092 (s), 847 (s) cm^{-1}; ^{1}H NMR (200 MHz) δ, ppm: 5.92–5.43 (m, 4H, H-5, H-6, H-7, H-8), 4.79 (d, *J*=8.9 Hz, 2H, H-4, H-8a), 3.93 (broad triplet, *J*=8.8 Hz, 1H, H-3a), 1.39 (s, 6H, CH_3-acetonide), 0.87 (s, 9H, Si-^{t}Butyl), 0.09 (s, 6H, Si–CH_3); ^{13}C NMR (75 MHz) δ, ppm: 132.6, 130.4, 122.9, 122.6, 109.5, 80.5, 75.6, 74.3, 26.9, 26.8, 25.8, −4.3, −4.8; HRMS (EI, 23 eV): calcd for $C_{16}H_{28}FeO_3Si$ (M^+) 296.1808; found 296.1796; calcd for $C_{15}H_{25}FeO_3Si$ ($M^+ - CH_3$) 281.1573; found 281.1574.

(3a*S*,4*R*,5*R*,8*R*,8a*S*)-8-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-4,5,8,8a-tetrahydro-3aH-cyclohepta[d][1,3]-dioxole-4,5-diol and enantiomer (18). To a stirred solution of the diene **17** (26.2 mg, 0.089 mmol, 1 equiv.) in 0.28 mL pyridine was added 1.13 mL of 0.0786 M (1 g in 50 mL of THF) osmium tetraoxide solution (22.5 mg, 0.089 mmol, 1 equiv.) in THF. The reaction mixture was stirred at room temperature for 24 h and then quenched by the

addition of 3 mL of aqueous saturated sodium bisulfite solution. Stirring was continued for another 16h, the solution was filtered through Celite, and the Celite pad was further washed with 20 mL of ether. The organic layer was separated and washed with water (2×15 mL), brine (1×15 mL), dried ($MgSO_4$) and evaporated to give the crude product which was purified by flash chromatography (30% ethyl acetate/hexanes) to provide the title compound as pale yellow oil (24 mg, 80% yield). TLC R_f=0.36 (30% EtOAc/hexanes); IR ($CDCl_3$): 3353 (s), 2956 (s), 1081 (s) cm^{-1}; ^1H NMR (200 MHz) δ, ppm: 5.71–5.68 (m, 2H, H-6, H-7), 4.38–4.37 (m, 1H, H-5), 4.32 (d, J=8.9 Hz, 1H, H-8), 3.93 (t, J=8.9 Hz, 1H, H-3a), 3.79 (dd, J=8.7, 3.6 Hz, 1H, H-4), 3.62 (t, J=8.9 Hz, 1H, H-8a), 2.58 (broad d, J=1.9 Hz, 1H, OH), 2.50 (broad d, J=2.3 Hz, 1H, OH), 1.39 (s, 6H, CH_3-acetonide), 0.88 (s, 9H, Si-^{t}Butyl), 0.09 (s, 6H, Si–CH_3); ^{13}C NMR (75 MHz) δ, ppm: 136.6, 126.5, 80.3, 76.8, 76.5, 72.6, 71.9, 67.2, 27.0, 26.9, 25.8, −4.9; HRMS (EI, 23 eV): calcd for $C_{16}H_{31}O_5Si$ (MH^+) 331.1941; found 331.1945; calcd for $C_{15}H_{27}O_5Si$ (M^+-CH_3) 315.1628; found 315.1604.

(3a*S*,4*R*,5*R*,8a*R*)-4,5-Di(benzyloxy)-2,2-dimethyl-4,5,8,8a-tetrahydro-3aH-cyclohepta[d][1,3]dioxol-8-one and enantiomer (25). To a stirred solution of the alcohol **27** (6 mg, 0.02 mmol, 1 equiv.) in 1 mL of dichloromethane at 0°C was added 19.3 μL pyridine (0.24 mmol, 12 equiv.). This was followed by the addition of chromium (VI) trioxide (11.6 mg, 0.12 mmol, 6 equiv.) and the solution was vigorously stirred for 15 min. (Caution: The order of addition of chromium trioxide to pyridine should be followed strictly as the reverse order of addition may result in fire and explosion.) The temperature was raised to room temperature and the solution was stirred for 24 h followed by the addition of 5 mL of ether. The solution was filtered through Celite and the Celite pad was further washed with 10 mL of ether. The organic layer was washed with water (3×15 mL), brine (1×15 mL), dried ($MgSO_4$) and evaporated to give the crude product which was then purified by flash chromatography (5% ethyl acetate/hexanes) to provide the title compound as a colorless oil (3.9 mg, 65% yield). TLC R_f=0.26 (30% EtOAc/hexanes); IR: 2924 (s), 1695 (s), 1078 (s) cm^{-1}; ^1H NMR (200 MHz) δ, ppm: 7.37–7.16 (m, 10H, Ar-H), 6.69 (ddd, J=12.5, 4.0, 1.4 Hz, 1H, H-6), 6.07 (dd, J=12.4, 2.3 Hz, 1H, H-7), 4.80 (d, J=2.0 Hz, 1H, CH_2-benzyl), 4.49 (s, 2H, CH_2-benzyl), 4.36–4.33 (m, 1H, H-5), 4.30 (d, J=10.6 Hz, 1H, H-8a), 4.15 (dt, J=4.3, 1.2 Hz, 1H, H-4), 3.96 (dd, J=10.4, 4.1 Hz, 1H, H-3a), 1.41 (s, 3H, CH_3-acetonide), 1.38 (s, 3H, CH_3-acetonide); ^{13}C NMR (50 MHz) δ, ppm: 129.5, 128.6, 128.4, 128.2, 127.9, 127.7, 82.1, 81.0, 80.0, 79.9, 71.2, 29.7, 26.9, 26.3, −1.1; HRMS (EI, 23 eV): calcd for $C_{17}H_{19}O_5$ (M^+) 303.1232; found 303.1229.

(3a*S*,4*R*,5*R*,8*R*,8a*S*)-4,5-Di(benzyloxy)-8-(*tert*-butyldimethylsilyloxy)-2,2-dimethyl-4,5,8,8a-tetrahydro-3aH-cyclohepta[d][1,3]dioxole and enantiomer (26). To a stirred solution of the diol **18** (20 mg, 0.06 mmol, 1 equiv.) in 1 mL of freshly distilled THF at room temperature was added 60% sodium hydride in mineral oil (7.2 mg, 0.181 mmol, 3 equiv.). The cloudy suspension was stirred for 5 min and tetrabutyl ammonium iodide (2.3 mg, 0.006 mmol, 0.1 equiv.) was added, followed by the addition of benzyl bromide (57.3 μL, 0.48 mmol, 8 equiv.) via a syringe. The reaction mixture was stirred for 15 h (monitored via tlc) and then diluted with 10 mL of ether. The organic layer was washed with water (2×5 mL), brine (1×5 mL), dried ($MgSO_4$) and evaporated to give the crude product which was then purified by flash chromatography (7% ethyl acetate/hexanes) to provide the title compound as a colorless oil (26 mg, 85% yield). TLC R_f=0.31 (10% EtOAc/hexanes); IR: 2944 (s), 2865 (s), 1728 (w), 1089 (s), 852 (m) cm^{-1}; ^1H NMR (200 MHz) δ, ppm: 7.42–7.26 (m, 10H, Ar-H), 5.70 (d, J=3.6 Hz, 2H, H-6, H-7), 4.82 and 4.70 (AB quartet, J_{AB}=12.5 Hz, 2H, CH_2-benzyl), 4.58 and 4.47 (AB quartet, J_{AB}=12.1 Hz, 2H, CH_2-benzyl), 4.38 (d, J=8.7 Hz, 1H, H-8), 4.20 (t, J=3.2 Hz, 1H, H-5), 4.04 (dd, J=9.4, 6.9 Hz, 1H, H-3a), 3.80–3.68 (m, 2H, H-4, H-8a), 1.42 (s, 3H, CH_3-acetonide), 1.41 (s, 3H, CH_3-acetonide), 0.90 (s, 9H, Si-^{t}Butyl), 0.11 (s, 6H, Si–CH_3); ^{13}C NMR (50 MHz) δ, ppm: 134.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.6, 127.4, 108.7, 80.3, 79.7, 78.6, 74.4, 72.8, 72.1, 70.8, 29.7, 27.1, 27.0, 25.9, 18.4, 1.0, −4.4, −4.9; HRMS (EI, 23 eV): calcd for $C_{30}H_{42}O_5Si$ (M^+) 510.2801; found 510.2805.

(3a*S*,4*R*,5*R*,8*R*,8a*S*),-4,5-Di(benzyloxy)-2,2-dimethyl-4,5,8,8a-tetrahydro-3aH-cyclohepta-[d][1,3]dioxo-8-ol and enantiomer (27). To a stirred solution of the dibenzyl derivative **26** (20 mg, 0.05 mmol, 1 equiv.) in 2 mL of freshly distilled THF at 0°C was added 1 M solution of tetrabutyl ammonium fluoride solution (150 μL, 0.15 mmol, 3 equiv.) in THF. The reaction mixture was stirred at 0°C for 5 min and then the temperature was allowed to rise to ambient. After stirring the solution for 3 h, 5 mL of ether was added and the organic layer was throughly washed with water (5×5 mL), brine (1×5 mL) and dried ($MgSO_4$). The solvent was evaporated to give the crude product which was purified via flash chromatography (15% EtOAc/hexanes) to give the alcohol **27** (12 mg, 77% yield). TLC R_f=0.27 (15% EtOAc/hexanes); IR: 3435 (s), 2923 (s), 1073 (s) cm^{-1}; ^1H NMR (300 MHz) δ, ppm: 7.39–7.24 (m, 10H, Ar-H), 5.81–5.78 (m, 2H, H-6, H-7), 4.84–4.45 (m, 5H, AB quartet of CH_2-benzyl, H-5), 4.24 (t, J=8.6 Hz, 1H, H-3a), 4.17 (dd, J=5.56, 2.7 Hz, 1H, H-4), 3.63–3.53 (m, 2H, H-8, H-8a), 1.46 (s, 3H, CH_3-acetonide), 1.44 (s, 3H, CH_3-acetonide); ^{13}C NMR (50 MHz) δ, ppm: 138.5, 138.0, 134.9, 128.3, 128.2, 128.1, 127.7, 127.6, 127.4, 108.9, 80.2, 78.8, 78.4, 73.5, 72.2, 70.8, 70.7, 27.1, 26.9; HRMS (EI, 23 eV): calcd for $C_{24}H_{28}O_5$ (M^+) 396.1937; found 396.1921; calcd for $C_{24}H_{29}O_5$ (MH^+) 397.2015; found 397.2001.

(2*R*,3*R*)-2,3-Di(benzyloxy)-3-{(4*R*,5*S*)-5-[(*R*)-1-(*tert*-butyldimethylsilyloxy)-1-formylmethyl]-2,2-dimethyl-1,3-dioxolan-4-yl}propanal (28). A solution of dibenzyl derivative **27** (14 mg, 0.027 mmol, 1 equiv.) in 0.5 mL of CH_2Cl_2 and 0.5 mL of methanol was cooled to −78°C. Ozonized oxygen gas was bubbled through the reaction mixture until a blue color persisted (approx 10 min). While still at −78°C the system was flushed with argon and 5.2 μL of dimethyl sulfide was added (0.058 mmol, 2.1 equiv.). The solution was then stirred at −78°C for 1 h, then at ice bath temperature for 1 h and finally at room temperature for 2h. The solvent was removed and 5 mL of ether was added. The organic layer was washed

with water (5×5 mL), brine (2×5 mL), dried ($MgSO_4$), evaporated and chromatographed (20% EtOAc/hexanes) to give the product (14.5 mg, 99% yield). TLC R_f=0.34 (20% EtOAc/hexanes); IR: 2930 (s), 2857 (s), 1736 (s), 1456 (s), 1090 (s) cm^{-1}; ^1H NMR (300 MHz) δ, ppm: 9.77 (s, 1H, CHO), 9.57 (s, 1H, CHO), 7.35–7.27 (m, 10H, aromatic-H), 4.79–4.49 (m, 5H, CH_2-benzyl, H-3), 4.31 (dd, J=8.1, 3.9 Hz, 1H, H-2), 4.18 (d, J=3.3 Hz, 1H, H-1'), 3.97 (t, J=3.6 Hz, 1H, H-4), 3.89 (d, J=2.2 Hz, 1H, H-5), 1.38 (s, 3H, CH_3-acetonide), 1.37 (s, 3H, CH_3-acetonide), 0.90 (s, 9H, Si-^{t}Butyl), 0.03 (s, 3H, Si–CH_3), −0.04 (s, 3H, Si–CH_3); ^{13}C NMR (50 MHz) δ, ppm: 202.2, 201.2, 137.0, 128.5, 128.3, 128.1, 127.9, 110.3, 83.7, 75.6, 73.2, 73.1, 29.6, 27.0, 26.9, 26.7, 25.7, 18.2, −4.6, −5.1; HRMS (EI, 23 eV): calcd for $C_{29}H_{39}O_7Si$ (M^+-CH_3) 527.2466; found 527.2469.

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