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Recent Applications of the Simple Hydrocarbon Cyclooctatetrene as a Starting Material for Complex Molecule Synthesis

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Abstract: Cyclooctatetraene [COT], a simple non-aromatic cyclic polyene, is capable of undergoing a variety of oxidation and cycloaddition reactions to afford polycyclic structures. In addition, complexation of COT or the cycloaddition products with transition metals facilitates bond formation. Recent developments in the reactivity of COT and application to the synthesis of naturally occurring and non-naturally occurring compounds is reviewed.

Keywords: Cyclooctatetraene, Oxidation, Cycloaddition, Synthesis

1. Introduction

The use of simple, relatively inexpensive hydrocarbons as starting materials for the synthesis of complex molecules relies on efficient methods for their oxidation and/or functionalization. This
review will primarily deal with recent accounts of the reactivity of the parent hydrocarbon cyclooctatetraene, particularly in relationship to its use as a starting material for organic synthesis.

The hydrocarbon cyclooctatetraene, “COT” (1, Scheme 1) was first prepared via a multistep sequence from pseudo-pelletierine (2) by Willstatter [1]. Reppe later reported a Ni-catalyzed cyclotetramerization of acetylene [2]. Eventually the ability to obtain large quantities of this hydrocarbon by this direct route, lead to a period in which the reactivity of this polyolefin was exploited for the preparation of a variety of architecturally interesting molecules such as basketene, snoutene and diazatwistene. Some have termed this period as “the renaissance in cyclooctatetraene chemistry” [3].

Cyclooctatetraene may also be prepared from 1,5-cyclooctadiene (3) by double deprotonation with butyl lithium to afford the cyclooctadiene dianion 4, which can be oxidized with CdCl$_2$ [4a], or HgCl$_2$ [4b], (t-BuO)$_2$, [4c] or 1,2-dibromoethane [4d] (Scheme 2). Similarly, deprotonation with potassium, followed by oxidation with dry oxygen or iodine gave 1 [5]. Alternatively, addition of two equivalents of bromine to 3 gave a mixture of tetrabromides, meso-5 and dl-5, which upon phase transfer dehydrobromination gave cyclooctatetraene [6]. Other methods for the metal mediated synthesis of substituted cyclooctatetraenes have recently been reviewed [7].

2. Reactions of Cyclooctatetraene That Maintain an 8-Membered Ring

Photolysis of diethyl azomalonate in the presence of 1 gave the bicyclo[6.1.0]nonatriene product 7 (87%) along with bicyclo[4.2.1]nonatriene 8 (13%, Scheme 3) [8]. Product 7 is believed to arise via 1,2-addition of the singlet carbene species generated from the diazomalonate, while 8 is proposed to arise via 1,4-addition of the small amount of triplet carbene which is formed during the photolysis. Notably, addition of benzophenone as a photosensitizer led to increasing amounts of the 1,4-addition product 8, such that 50 mole % of benzophenone led to exclusive formation of 8.
Reppe, et al. reported that the reaction of 1 with perbenzoic acid afforded a mono-oxide [2a]. While there was initially some disagreement on the structure of the mono-oxide, Cope, et al. eventually provided chemical and NMR spectral evidence to support structure 9 (Chart 1) [9a]. The presence of three remaining double bonds in 9 allowed for the possible formation of polyepoxides if excess oxidizing agent is used. The ratio of these products depended on the nature and number of equivalents of the epoxidizing agent. In 1999 Murray, et al., reported a detailed study of the reaction of 1 with dimethyl dioxirane [DMDO] (Table 1) [9b]. The use of three equivalents of DMDO gave a mixture of diepoxides 10a, 10b, 10c, triepoxides 11a, 11c, and tetraepoxide 12a (5:4:3:12:54:21 ratio), while use of six equivalents gave only tetraepoxides 12a and 12b (87:13 ratio). Since this reaction presumably occurs in a stepwise fashion, the epoxidation fate of each of the individual di- and triepoxides were examined. In this case, epoxidation of 10a led to the formation of triepoxide 11a and tetraepoxide 12b, along with unreacted starting material. Finally epoxidation of triepoxide 11a gave exclusively 12b, while separate epoxidation of 11b or 11c gave exclusively 12a. The structural identity of the triepoxides and tetraepoxides were established by single crystal X-ray diffraction.

Nucleophilic addition to cyclooctatetraene epoxide 9 generally results in the formation of ring rearranged products (e.g. 13, Scheme 4). Recently, Pineschi and coworkers demonstrated that ring opening of 9 with organocuprates resulted in an $S_N2$´ epoxide opening to afford 4-alkyl- or 4-aryl-2,5,7-cyclooctatrienols 14 (Table 2) [10]. In addition, reaction of 9 with dimethyl-, diethyl, or dibutylzinc, in the presence of Cu(OTf)$_2$ and an optically active phosphoramidite ligand (e.g. 15 or 16) proceeded in an enantioselective fashion (Table 3) [10b].

Attempts to acylate ent-14 gave mixtures of two diastereomeric bicyclo[4.2.0]octadienyl acetates 17 and 18 (Scheme 5) [10b]. This transformation is proposed to occur by acylation of 14, followed by a [3,3] sigmatropic rearrangement and subsequent 6π–electrocyclic ring closure.
3. Reactions of Cyclooctatetraene Producing Cyclobutanes/Cyclobutenes

Generally cyclooctatetraene does not undergo Diels-Alder reactions. This is in part due to the tub-like structure of the cyclic polyene. A 6-\(\pi\) electrocyclic ring closure of 1 can afford the bicyclo[4.2.0]octa-2,4,7-triene 23 valence tautomer, however the equilibrium concentration of 23 is relatively small (ca. 0.01% @ 100 °C), and thus this valence tautomer can only be trapped with highly reactive dienophiles such as maleic anhydride, maleimide, \(N\)-phenyl-1,2,4-triaza-3,5-dione, dimethyl acetylenedicarboxylate, tetracyanoethylene, or \(trans\)-1,2-dibenzylethylene to give 24-26 (Scheme 6). Recently, 24a and 26a were found to cause halfmaximal inhibition of ethylene binding in yeast cells expressing the ethylene receptor protein ETR1 at concentrations below 0.1 \(\mu\)M [11].

Mehta and Vidya have utilized 24a as a starting material for the synthesis of “oxa bowls” (Scheme 7) [12]. These compounds are of interest as constrained analogs of crown ethers.

To this end, reduction of 24a gave the diol 27, which upon dehydration with pyridinium \(p\)-toluenesulfonate gave the tetrahydrofuran derivative 28. Ozonolysis of 27 or 28, followed by treatment of the putative tetraaldehydes with acidic resin gave the polycyclic ethers 29 and 30 respectively. These authors did not report any data concerning the ability of these ions to coordinate to metal cations.

In the mid-20th century, Reppe [9a] and Cope [13] reported that oxidation of cyclooctatetraene with bromine or mercuric acetate gives the 7,8-disubstituted bicyclo[4.2.0]octa-2,4-diene derivatives 31 and 32 respectively (Scheme 8). Due to the low temperature at which these reactions are run, and the rate of these oxidations, the mechanism for formation of 31/32 clearly does not proceed via the intermediacy of 23. Paquette has reviewed the use of bicyclic building blocks 31/32, prior to 1975, for the synthesis of polycyclic molecules [3]. Since that time, a number of natural products, derivatives, or molecules of theoretical interest have been prepared beginning from these readily available starting materials.
3.1. Synthesis bis-Homoconduritols and bis-Inositols

Balci and co-workers utilized cyclooctatetraene as a precursor to bis-homoconduritols as potential glycosidase inhibitors [14]. Tetraphenylporphyrin (TPP) sensitized photooxygenation of 31 gave the endoperoxide 33 (Scheme 9). Cleavage of the endoperoxide with thiourea and acetylation with Ac₂O gave the corresponding diacetate 34. Epoxidation with m-CPBA afforded a single diastereomer. Reductive debromination of 35 proceeded smoothly with Zn-DMSO to give epoxydiacetate 36. Trans ring-opening was accomplished in acidified acetic anhydride to provide the tetraacetate 37, which upon treatment with methanolic ammonia gave tetaol 38 which possessed the configuration of the conduritol-F family. Alternatively dihydroxylation of 34 with KMnO₄, followed by reaction with acetic anhydride gave the tetraacetate 39 as a single isomer, albeit in attenuated yield (Scheme 10). In a similar fashion to the preparation of 36 from 35, reductive debromination of 39 with zinc metal, and deacetylation afforded tetaol 41 having the configuration of conduritol-D.

Inositols or cyclohexanehexols are useful in the study of intracellular communication. Kara and Balci synthesized inositol analogues from 1 [15]. Tetraphenylporphyrine (TPP) mediated photooxygenation of 32 gave the endoperoxide 42 (Scheme 11). Cleavage of the endoperoxide and acetylation yielded the tetraacetate 43. cis-Dihydroxylation with KMnO₄ provided the diol, which was converted into the hexaacetate 44 by treatment with acetic anhydride. Deprotection of the hexaacetate with ammonia in methanol gave the desired bis-homoinositol 45 in near quantitative yield.

Balci and co-workers have also used 1 as a precursor to aminocyclitols in their research of glycosidase inhibitors [16]. Cleavage of the endoperoxide 42 with thiourea followed by in situ reaction with toluenesulfonyl isocyanate gave the biscardamate 46 (Scheme 12). Palladium catalyzed cyclization of biscardamate 46 occurred in a regioselective fashion to afford the oxazolidinone 48. The authors proposed that the R* carbamate was selectively ionized, rather than the S* carbamate, due to steric hindrance of the endo
acetate group. Dihydroxylation of 48 with KMnO₄ followed by acetylation gave the tetraacetate 49. Removal of the acetyl groups with H₂SO₄ provided the desired aminocyclitol 50 in 84% yield.

3.2. Synthesis of (±)-Pentacycloanammoxic Acid

Pentacycloanammoxic acid (51b, Scheme 13) is a pentacyclic ladderane C₂₀ fatty acid present in the membranes of ammonia oxidizing bacteria as its glycerol ester [17]. It is believed that membranes constituted from these ladderane lipids are more dense and exhibit a lower permeability compared to other membranes. Machetti and Corey reported a synthesis of the methyl ester (±)-51a which utilized 1 for formation of three of the cyclobutane rings [18a]. Diels-Alder cycloaddition of 31 with dibenzyl azodicarboxylate in benzene at 80°C afforded 52. Chemoselective reduction of the olefin, followed by reductive elimination of the dibromide afforded cyclobutene 53. Photo [2+2] cycloaddition of 53 with cyclopentenone gave the pentacyclic ketone 54 in 40% yield, based on recovered starting material (“borsm”). Reductive removal of the Cbz groups, followed by O₂ oxidation of the hydrazine afforded 55. Protection of the ketone as its dimethoxy ketal, subsequent photolysis to affect the loss of N₂, and deprotection of the ketal gave pentacyclic ketone 56, albeit in very low yield. Diazo transfer by the method of Regitz [19] afforded the diazoketone 57 which underwent photo-Wolff rearrangement to yield a 3:1 mixture of endo- and exo-methyl esters. The mixture of diastereomers were transformed into the exo-aldehyde 58 by a reduction–oxidation–epimerization sequence. The synthesis of (±)-51a was completed by Wittig olefination, diimide reduction and diazomethane esterification. Machetti and Corey subsequently reported a synthesis of (+)-51a which utilized (R)-4-dimethylphenylsilyl-2-cyclopentenone as a chiral starting material [18b].

3.3. Synthesis of the C1-C10 Segment of Roxiticin

(+)-Roxaticin (59, Scheme 14) is a polyene macrolide isolated from an unidentified streptomyces, whose structure was determined by X-ray crystallography [20]. The first laboratory synthesis of 59 was reported by Mori and co-workers [21] and subsequently Evans and Connell completed their own synthesis [22]. Cleavage of the acetyl...
groups from bicyclo[4.2.0]octadiene 32 by LiAlH₄ reduction gave the corresponding diol which undergoes a 2-electron oxidative ring fragmentation and olefin isomerization to afford the dialdehyde 60. Due to the instability of 60 it was immediately reacted with the sodium salt of triethyl phosphonoacetate to give the monoester-monoaldehyde, which was treated with excess NaBH₄ to afford alcohol 61 in 60% yield. Conversion of the allylic alcohol to the allylic bromide followed by Arbuzov reaction afforded phosphonate 62. The endgame of the roxaticin synthesis involved Horner-Wadsworth-Emmons olefination of aldehyde 63 with the anion derived from 62, ester hydrolysis, Yamaguchi macrolactonization protocol and finally ketal deprotection.

4. Synthesis And Reactions Of Bicyclo[4.2.1]Nona-2,4,7-Trien-9-One

Reaction of the cyclooctatetraene dianion with dimethyl carbamoyl chloride gives bicyclo[4.2.1]nona-2,4,7-trien-9-one (64, Scheme 15) [23]. This product arises via initial acylation of the dianion, followed by intramolecular attack of the remaining anionic charge on the amide carbonyl.

Generation of the bridgehead enolate of 64 by treatment with KHMDS or LTMP led to the formation of a self-condensation product 65 (Scheme 16) [24]. Alternatively, addition of 64 to excess base in the presence of trimethylsilyl chloride gave an inseparable mixture of 66 and 67; the latter appears to arise via a transannular [4+2] cycloaddition of 66. If only 1.1 equivalent of base is used, along with inverse addition (i.e. addition of base to ketone/TMSCl), then the mono-silylated product 68 is obtained, along with a mixture of bis-silylated products 66/67. Use of chiral base 69 gave (−)-68 in a highly enantioselective fashion; the absolute configuration of (−)-68 was determined by single crystal X-ray diffraction.

Reaction of mono-silyl ketone (−)-68 with Bu₄N⁺ Ph₃SiF²⁻ and an electrophile resulted in formation of the monosubstituted products 70 (Scheme 17). The yields for aldol condensation products (70d/70e) were generally greater than for the organohalide electrophiles.
4.1. Synthesis Cyclooctitols

In 2002, Mehta and Pallavi used 1 to prepare a series of racemic polyols from a pure hydrocarbon source (Scheme 18) [25]. Baeyer-Villiger oxidation of 64 afforded the racemic bicyclic lactone 71 in 60% yield. Catalytic dihydroxylation with OsO₄ gave the diol 72 with complete regio- and stereocontrol. Direct acylation of the diol proceeded with rearrangement to yield lactone 73, which upon reduction and acylation gave the tetracetylated diene 74. This compound served as a key intermediate for the preparation of tetaols 75 and 76, and octaol 77. Alternatively, catalytic reduction of 73 gave a mixture of mono-unsaturated lactone 78 and saturated lactone 79 (Scheme 19). Hydride reduction of 79 gave the same saturated tetraol 75 as previously prepared. Similarly reduction of 78 gave the unsaturated tetraol 80 which could be selectively protected as the acetonide 81. Hydroboration-oxidation of 81, followed by peracetylation gave a separable mixture of triacetates 82, 83, and 84 whose structures were assigned on the basis of NMR spectral data or X-ray crystal structure. Hydrolysis of each gave the corresponding pentaols.

Finally, osmium catalyzed dihydroxylation of the unsaturated tetraacetate 85 (prepared from 80), followed by acetylation proceeded in a non-stereoselective fashion to afford an equimolar, but separable, mixture of hexaacetates 86 and 87 (Scheme 20). Separate hydrolysis of each gave the corresponding hexaols.

4.2. Synthesis (±)-β-allose

Mehta and Pallavi prepared (±)-β-allose from the cyclooctatetraene derived synthon 71 via a lengthy sequence of manipulations (Scheme 21) [26]. Regiocontrolled and stereocontrolled dihydroxylation with catalytic OsO₄ followed by acetonide protection gave 88. Hydride reduction of 88 afforded the cyclooctadienediol 89, which was selectively protected at the primary alcohol with TBSCI. Ozonolysis followed by PCC oxidation of the intermediate lactol yielded the bicyclic lactone 90. Lactone ring opening with methoxide followed by mixed acetal formation gave 91. Reduction of the ester functionality and further protecting group manipulation afforded 92.
The primary alcohol of 92 was converted into a terminal alkene via mesylate formation and β-elimination to generate 93. Ozonolysis gave a hemiacetal (94), which upon reduction with NaBH4 gave diol 95. Racemic β-allose 96 was realized after acetonide deprotection.

5. METAL-CATALYZED/METAL-MEDIATED REACTIONS

5.1. Cycloadditions of Cyclooctatetraene

As indicated previously, cyclooctatetraene generally does not undergo Diels-Alder reactions due to the tub-like structure of the cyclic polyene. However, the complexation of 1 to transition metals may result in modified chemical reactivity. Rigby, et al., demonstrated that higher-order photochemically induced cycloadditions can be achieved using chromium tricarbonyl polyenes. Toward this end, photolysis of (η⁶-cyclooctatetraene)-Cr(CO)₃ 97 with electron-deficient olefins, 2,3-dimethyl-1,3-butadiene, or dimethylacetylenedicarboxylate afforded the bicyclo[4.2.2]deca-2,4,6-trienes 98-99 or bicyclo[4.2.2]deca-2,4,6,8-tetraene 100 respectively (Scheme 22) [27].

In a similar fashion, reaction of the bis-alkyne Mo cations 101a/b with cyclooctatetraene afforded the bicyclo[4.2.2]deca-2,4,6,8-tetraenes 102a/b in moderate yield (Scheme 23) [28]. In the case of the bis-2-butyne complex 101c, reaction with 1 gave the neutral (η³-allyl) (η⁴-diene)molybdenum complex 103a, whose structure was determined by single crystal X-ray diffraction. Hydride abstraction from 103a with trityl cation gave the bis-diene cation 104. The cation 104 underwent regioselective nucleophilic attack with NaBH₃CN or LiCuPh₂ to afford 103a or b respectively.

Buono and co-workers have reported a cobalt catalyzed cycloaddition of alkynes to cyclooctatetraene that gave predominantly bicyclo[4.2.2]deca-2,4,7,10-tetraenes 105 (Scheme 24) [29]. For certain monosubstituted alkynes (e.g. propargyl trimethylsilane or ethynylcyclohexene), the isomeric 9-alkenylbicyclo[4.2.1]nona-1,4,6-triene 106 is formed as a minor product. The reduction of Co(2+) with Zn metal is accelerated by ZnI₂ [30].
Coordination of 1 to Co(1+) is proposed to afford the η⁶ complex 107 (Scheme 25). Two pathways are possible from 107. One involves coordination of the alkyne with a change in the hapticity of the COT ligand from η⁶ to η⁴ (i.e. 108). Alternatively, coordination of the alkyne may effect the generation of a 2-butene-1,4-diyl structure (i.e. 109). Insertion of the alkyne into either of these complexes eventually generates 112, which upon reductive elimination gives 105 and regenerates the catalytically active species.

While not a metal mediated/catalyzed reaction, the thermal reaction of 1 with 2-(thiomethyl)acrylonitrile (113) is included here due to the bicyclo[4.2.2]deca-2,4,7-trienes 114a/b which are formed (Scheme 26) [31]. These compounds were characterized by NMR spectroscopy and mass spectrometry. Oxidation of the mixture gave a mixture of sulfoxides 115a/b, which upon thermolysis gave the nitrile 116.

The authors proposed that bicyclic adducts 114a/b were formed by electrocyclic closure of 1 to bicyclo[4.2.0]octa-2,4,7-triene 23 which underwent Diels-Alder cycloaddition with 113 to generate the diastereomeric tricyclo[4.2.2.0⁴,⁵]decadienes 117 (Scheme 27). Homolytic C–C bond cleavage of 117 led to the captodative stabilized diradical 118.

A cyclobutenylmethyl radical rearrangement and diradical collapse gave 114a/b.

5.2. Reactions of Cyclooctatetraene-Metal Complexes with Electrophiles and/or Nucleophiles

Tricarbonyl(cyclooctatetraene)iron (119, Scheme 28) was one of the first metal complexes prepared from 1 [32]. The reaction of 119 with a variety of electrophiles has been reported; for example, Vilsmeier-Hack formylation gives (formylcyclooctatetraene) Fe(CO)₃ (120). In comparison, reactions with other electrophiles led to a wide variety of cationic iron complexes via skeletal rearrangements. Protonation of 119 or its phosphine ligated analogs afforded (bicyclo[5.1.0]octadienyl)iron cations 121 [33]. Similarly, reaction
with p-nitrophenyl diazonium salt gave the 7-p-nitrophenyl substituted (bicyclo[5.1.0]octadienyl)iron cation 122, however reaction with pyridine led to the aryl substituted COT complex 123 [34]. In contrast, Friedel-Crafts acylation of 119, followed by anion metathesis gave the (bicyclo[3.2.1]octadienyl)Fe(CO)₃⁺ cations 124 [35]. The structural assignment of the 8-acyl substituted cation (124a) was eventually confirmed by X-ray crystal structure [35c]. Reaction of 119 with cyclopropenium cations afforded the (tricyclo[6.3.0.0⁵,1¹]nonadienyl)Fe(CO)₃⁺ cations 125 [36]. The structure of 125 was deduced from the X-ray crystal structure of the neutral complex derived from reaction with sodium borohydride. Finally, reaction of 119 with tropylium cation, in the presence of pyridine, gave the styrylcycloheptatriene complex 126 [37].

The rearranged skeletons afforded by these transformations have been utilized to prepare (carboxycycloalkyl)glycines. For example, nucleophilic attack of phthalimide anion on 121b proceeds in a stereoselective fashion (Scheme 29) [38a]. Removal of the metal afforded (bicyclo[5.1.0]octa-3,5-dien-2-yl)phthalimide 127 which was transformed into 2-[(2′-carboxycyclopropyl)glycine 128 in 4 steps. This sequence of reactions fixes the relative stereochemistry at three contiguous centers. The spectral data for this compound matched that for the natural product, which inhibits glutamate transport. In a similar fashion, 2-[(3′-carboxycyclopentyl) glycine 130 was prepared from the bicyclic cation 124b (Scheme 30) [38b].

Heck and co-workers have reported on the nucleophilic addition to (η⁶-cyclooctatetraene)FeCp⁺ cation 131 which afforded the substituted neutral (η⁵-cyclooctatrienyl)FeCp complexes 132 (Scheme 31) [39]. Protonation of 132 gave (η⁶-cyclooctatriene)FeCp⁺ cations 133, which can undergo subsequent addition of a second nucleophile. In all of the cases examined, the second nucleophilic addition proceeded at the less sterically hindered triene carbon, to yield the disubstituted (η⁵-cyclooctatrienyl)FeCp complexes 134. Finally protonation of complexes 134 gave the cis-5,7-disubstituted-1,3-cyclooctadienes 135.

Shornschusen and Heck have reported on the reaction of disubstituted cyclooctadienes 135 (n = m = 1, n = m = 2) with
Grubbs’ 1st generation catalyst (Scheme 32) [39b]. In both of these cases, the ring rearrangement metathesis products 136a and 136b were isolated; none of the bicycloalkatriene ring closing metathesis products (i.e. 137) were observed.

Prior to examining the (cyclopentadienyl)iron ligated cation 131, Heck’s group had previously examined the sequential addition of malonate nucleophiles to the (cyclopentadienyl)ruthenium ligated cation 138 (Scheme 33) [40]. The overall transformation led to the same product 135aa’ in good overall yield, however several new intermediates (compared to the iron mediated pathway) were detected and spectroscopically characterized. Thus, while initial nucleophilic addition to 138 gave ruthenium complex 139 (similar to iron complex 132), the (1,2,3,4,5-η5) complex 139 underwent a slow haptotropic rearrangement to the more stable (1,2,3,6,7-η5-cyclooctatrienyl)RuCp complex 140. Protonation of 140 initially generated a (1,2,3,4,6,7-η6)-cyclooctatriene)RuCp+ cation (141), which is isomerized by a 1,5-hydride migration to give the (1,2,3,4,5-η5)-cation 142 (similar to iron cation 133). Eventually, protonolysis of 143 gave 135aa’. If this final protonation is conducted in acetonitrile as solvent, the RuCp(CH3CN)3+ cation is generated, which can be recycled to the starting material 138.

5.3. Metal-Catalyzed/Mediated Reactions of Cyclooctatetraene Valence Isomers

Tricyclo[4.2.2.02,5]deca-3,7,9-triene 25 has been utilized as a cyclobutadiene synthon. Gibson has demonstrated that Pauson-Khand cyclopentenone annulation of 25, with terminal alkynes, occurred preferentially on more strained cyclobutene ring to yield the pentacyclic enones 145 in moderate to good yields (Scheme 34) [41]. Pyrolysis of 145 afforded the bicyclo[3.2.0]hepta-3,6-dien-1-ones 146. If the sequence was conducted as a one-pot reaction, the overall yields range from 70-98%.

Recently, Wender and co-workers reported the Rh-catalyzed [2+2+2] cycloaddition of 25 with dienes to afford the corresponding tetracyclic products 147 (Scheme 35) [42]. These authors proposed a mechanism involving oxidative cyclization of 25 to afford a
metallotetracyclic intermediate 148. Insertion of one of the C=C of the diene into the Rh-carbon bond generated 149, which upon reductive elimination gave the product.

In contrast, Gandolfi and co-workers found that cycloaddition of 25 with 1,3-dipoles proceeded at both of the disubstituted alkenes. In order to improve the regioselectivity for this reaction, they prepared the (tricarbonyl)iron complex 150 (Scheme 36) [43]. Cycloaddition of 150 with nitrile oxides, nitrile imines, or dimethyl diazomethane proceeded on the less hindered face of the uncoordinated olefin to give 151-153 respectively. Demetallation of these complexes with trimethylamine oxide gave the free ligands in good isolated yields (80-95%).

Conclusion

While the preparation of cyclooctatetraene was reported nearly 100 years ago, this simple, non-aromatic hydrocarbon continues to be a useful starting material for the synthesis of naturally-occurring and non-natural structures. This synthetic utility is the result of a variety of oxidation, cycloaddition or carbonylation reactions of the parent hydrocarbon. In addition reactions of COT with stoichiometric transition metal reagents or catalyzed by metals results in the formation of a variety of novel hydrocarbon skeletons. Clearly COT can continue to serve as an outstanding, yet simple, starting material for diversity oriented synthesis. Studies in this direction show tremendous potential for the preparation of molecules with beneficial biological activity.

Acknowledgements

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References


[10] (a) Del Moro, F.; Crotti, P.; Di Bussolo, V.; Macchia, F.; Pineschi, M. Catalytic enantioselective desymmetrization of COT-Monoepoxide. Maximum deviation from coplanarity for an SN2'-Cuprate alkylation.


Charts and Schemes

![Scheme 1](chart.png)

Scheme 1.
Scheme 2.

Scheme 3.
Table 1. Epoxidation of COT and Epoxide Products

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Equiv.</th>
<th>DMDO</th>
<th>Product(s) (Ratio)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td>3</td>
<td>10a + 10b + 10c + 11a + 11c + 12a (5:4:3:12:54:21)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>6</td>
<td>12a + 12b (87:13)</td>
</tr>
<tr>
<td>10a</td>
<td></td>
<td>4</td>
<td>11a + 12b + 10a (81:10:9)</td>
</tr>
<tr>
<td>11a</td>
<td></td>
<td>6</td>
<td>12b only (&gt;99% yield)</td>
</tr>
<tr>
<td>11b</td>
<td></td>
<td>2</td>
<td>12a only (100% yield)</td>
</tr>
<tr>
<td>11c</td>
<td></td>
<td>2</td>
<td>12a only (100% yield)</td>
</tr>
</tbody>
</table>

Chart 1.
Scheme 4.

**Table 2.  Ring Opening of Cyclooctatetraene Monoepoxide**

<table>
<thead>
<tr>
<th>conditions</th>
<th>R</th>
<th>14:13</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me₂CuLi, Et₂O</td>
<td>4S Me</td>
<td>&lt;2 : 98</td>
<td>70%</td>
</tr>
<tr>
<td>MeMgBr/CuCN (cat)</td>
<td>Me</td>
<td>62 : 38</td>
<td>62%</td>
</tr>
<tr>
<td>MeCuCN(MgBr)</td>
<td>Me</td>
<td>&gt;98 : 2</td>
<td>88%</td>
</tr>
<tr>
<td>Me₂CuCN(MgBr)₂</td>
<td>Me</td>
<td>82 : 18</td>
<td>–</td>
</tr>
<tr>
<td>EtMgBr/CuCN (cat)</td>
<td>Et</td>
<td>94 : 6</td>
<td>75%</td>
</tr>
<tr>
<td>PhCuCN(MgBr)</td>
<td>Ph</td>
<td>&gt;96 : 4</td>
<td>40%</td>
</tr>
</tbody>
</table>
Table 3. Enantioselective Monoepoxide Opening of Cyclooctatetraene

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Ring</th>
<th>Opening</th>
<th>Yield of 14</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me₂Zn/Cu(OTf)₂, 3% 15</td>
<td>Me</td>
<td>65%</td>
<td>&gt;90%</td>
<td></td>
</tr>
<tr>
<td>Et₂Zn/Cu(OTf)₂, 3% 15</td>
<td>Et</td>
<td>90%</td>
<td>86%</td>
<td></td>
</tr>
<tr>
<td>n-Bu₂Zn/Cu(OTf)₂, 3% 15</td>
<td>n-Bu</td>
<td>78%</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>Me₂Zn/Cu(OTf)₂, 3% 16</td>
<td>Me</td>
<td>81%</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>Et₂Zn/Cu(OTf)₂, 3% 16</td>
<td>Et</td>
<td>91%</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>n-Bu₂Zn/Cu(OTf)₂, 3% 16</td>
<td>n-Bu</td>
<td>95%</td>
<td>96%</td>
<td></td>
</tr>
</tbody>
</table>

a The major enantiomer has the 1S,4S- absolute configuration.

b The major enantiomer has the 1R,4R- absolute configuration.

![Chemical structures](image-url)
Scheme 5.

Scheme 6.

24a, X = CH, Y = O
24b, X = CH, Y = NH
24c, X = N, Y = NPh

25

26a, X = Y = CN
26b, X = C(O)Ph
Y = H
Scheme 7.

Scheme 8.
Scheme 9.

Scheme 10.
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Scheme 11.

Scheme 12.
Scheme 13. Cbz = CO₂CH₂Ph; "bornyl" = based on recovered starting material.

Scheme 14.
Scheme 15.

Scheme 16.
Scheme 17.
NOT THE PUBLISHED VERSION; this is the author’s final, peer-reviewed manuscript. The published version may be accessed by following the link in the citation at the bottom of the page.

Scheme 18.
Scheme 19.
Scheme 20.
Scheme 22.
Scheme 23.
Scheme 24.
Scheme 25.

Scheme 26.
Scheme 27.

Scheme 28.
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Scheme 29.

Scheme 30.

Scheme 31.

Mini-Reviews in Organic Chemistry, Vol. 9, No. 1 (2012): pg. 31-43. DOI. This article is © Bentham Science Publishers and permission has been granted for this version to appear in e-Publications@Marquette. Bentham Science Publishers does not grant permission for this article to be further copied/distributed or hosted elsewhere without the express permission from Bentham Science Publishers.
**Scheme 32.** [G-I = (PCy$_3$)$_2$Cl$_2$Ru=CHPh].

**Scheme 33.** (E = CO$_2$Me).
Scheme 34.

Scheme 35.
**Scheme 36.**

$\text{Fe}_2(\text{CO})_9 \text{ ether}$

25 $\xrightarrow{}$ 150 (60%)

$\text{C}_\text{R} \text{ N} \text{ O}^{-} + \text{PhN} \equiv \text{N} \equiv \text{R}$

$\xrightarrow{}$ 

$\text{Me}_2\text{C} \equiv \text{N} \equiv \text{N}$

151a, $\text{R} = \text{Ph}$ (82%)

152 (82%)

153 (81%)

151b, $\text{R} = 2,6\text{-Cl}_2\text{C}_6\text{H}_3$ (95%)

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