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

Kevin W. Glaeske[a] and William A. Donaldson[b,*]

[a]*Department of Chemistry, Wisconsin Lutheran College, 8800 West Blue Mound Road, Milwaukee, WI 53226-4699, USA*

[b]*Department of Chemistry, Marquette University, P. O. Box 1881, Milwaukee, WI 53201-1881 USA*

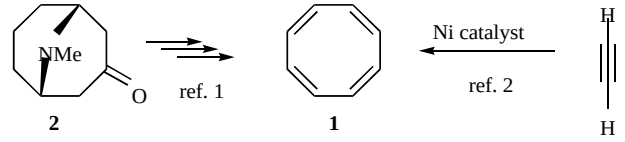
Abstract: Cyclooctatetraene [COT], a simple non-aromatic cyclic polyene, is capable of undergoing a variety of oxidation and cycloaddition reactions to afford polycyclic structures. In addition, complexation of COT or the cycloaddition products with transition metals facilitates bond formation. Recent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

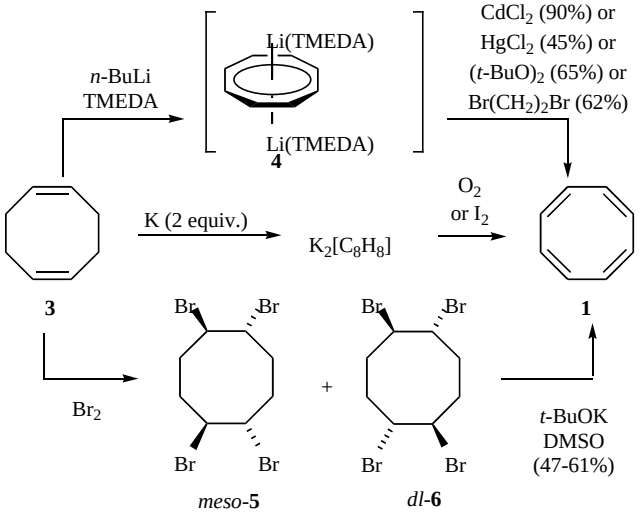
The use of simple, relatively inexpensive hydrocarbons as starting materials for the synthesis of complex molecules relies on efficient methods for their oxidation and/or functionalization. This review will primarily deal with recent accounts of the reactivity of the *parent* hydrocarbon cyclooctatetraene, 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].



2 **1**

Scheme 1.

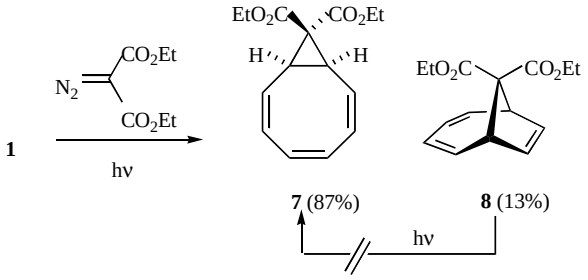


Scheme 2.

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], $(t\text{-}BuO)_2$, [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**.



Scheme 3.

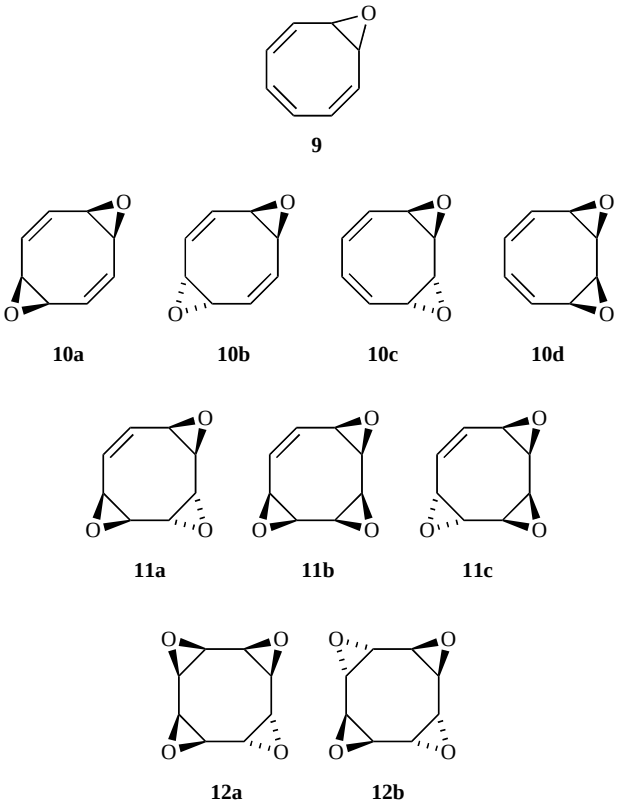
Reppe, *et al.* reported that the reaction of **1** with perbenzoic acid afforded a mono-oxide [2a]. While there was initially some disagreement on the structure of the mono-oxide, Cope, *et al.* eventually provided chemical and NMR spectral evidence to support structure **9** (Chart 1) [9a]. The presence 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

*Address correspondence to these authors at the Department of Chemistry, Marquette University, P. O. Box 1881, Milwaukee, WI 53201-1881 USA; Tel: 414-288-7374; Fax: 414-288-7065; E-mail: william.donaldson@marquette.edu

1875-6298/12 $58.00+.00

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.

Table 1. Epoxidation of COT and Epoxide Products

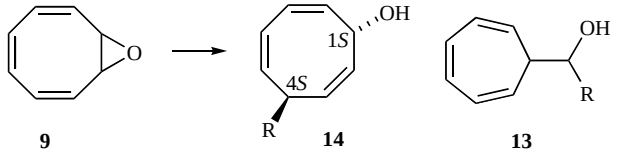


9 **10a** **10b** **10c** **10d** **11a** **11b** **11c** **12a** **12b**

Chart 1.

substrate	equiv. DMDO	product(s) (ratio)
1	3	**10a**+**10b**+**10c**+**11a**+**11c**+**12a** (5:4:3:12:54:21)
1	6	**12a**+**12b** (87:13)
10a	4	**11a**+**12b**+**10a** (81:10:9)
11a	6	**12b** only (>99% yield)
11b	2	**12a** only (100% yield)
11c	2	**12a** only (100% yield)

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].



9 **14** **13**

Scheme 4.

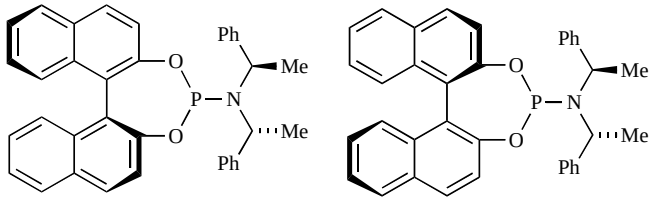
Table 2. Ring Opening of Cyclooctatetraene Monoepoxide

conditions	R	**14:13**	yield
Me_2CuLi, Et_2O	4*S* Me	<2: 98	70%
MeMgBr/CuCN (cat)	Me	62 : 38	62%
MeCuCN(MgBr)	Me	>98 : 2	88%
$Me_2CuCN(MgBr)_2$	Me	82 : 18	–
EtMgBr/CuCN (cat)	Et	94 : 6	75%
PhCuCN(MgBr)	Ph	>96 : 4	40%

Table 3. Enantioselective Ring Opening of Cyclooctatetraene Monoepoxide 9

conditions	R	yield of **14**	ee
$Me_2Zn/Cu(OTf)_2$, 3% **15**	Me	65%	>90%[a]
$Et_2Zn/Cu(OTf)_2$, 3% **15**	Et	90%	86%[a]
n-$Bu_2Zn/Cu(OTf)_2$, 3% **15**	*n*-Bu	78%	82%[a]
$Me_2Zn/Cu(OTf)_2$, 3% **16**	Me	81%	94%[b]
$Et_2Zn/Cu(OTf)_2$, 3% **16**	Et	91%	93%[b]
n-$Bu_2Zn/Cu(OTf)_2$, 3% **16**	*n*-Bu	95%	96%[b]

[a]The major enantiomer has the 1*S*,4*S*- absolute configuration.
[b]The major enantiomer has the 1*R*,4*R*- absolute configuration.

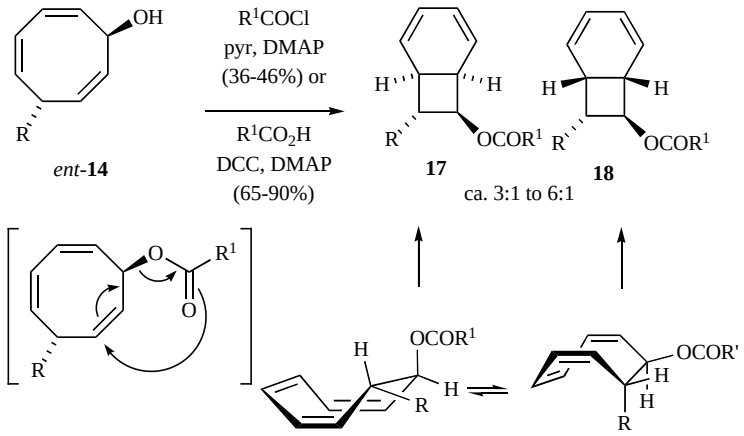


(*S*,*S*,*R*)-**15** (*R*,*R*,*R*)-**16**

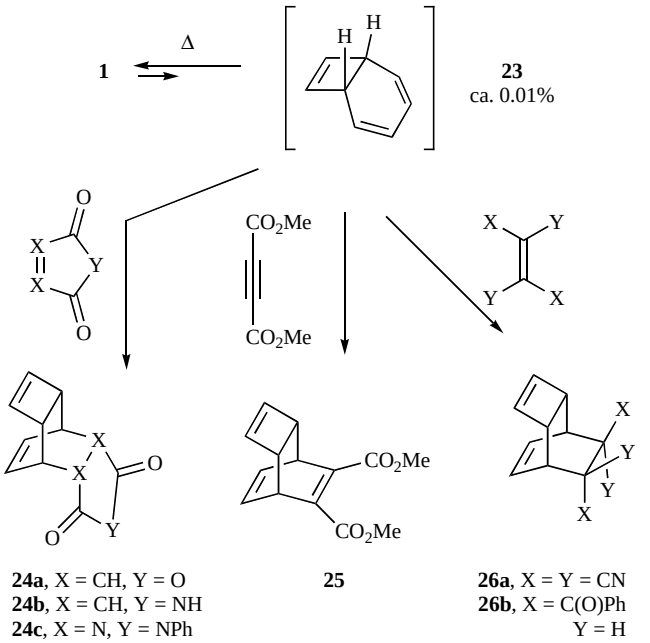
Attempts to acylate *ent*-**14** gave mixtures of two diastereomeric bicyclo[4.2.0]octadienyl acetates **17** and **18** (Scheme **5**) [10b]. This transformation is proposed to occur by acylation of **14**, followed by a [3,3] sigmatropic rearrangement and subsequent 6π–electrocyclic ring closure.

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-π 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-dibenzoylethylene to give **24**-**26** (Scheme **6**). Recently, **24a** and **26a** were found to cause half-maximal inhibition of ethylene binding in yeast cells expressing the ethylene receptor protein ETR1 at concentrations below 0.1 μM [11].



Scheme 5.

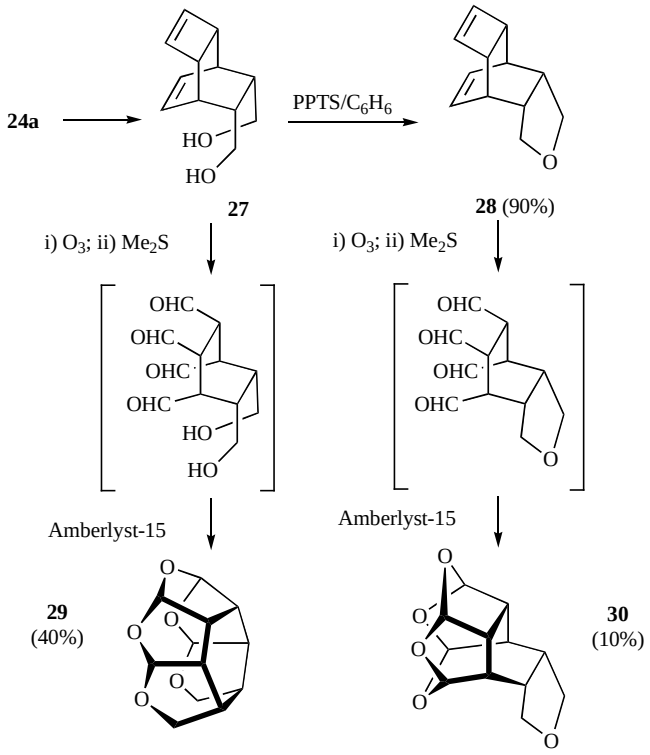


Scheme 6.

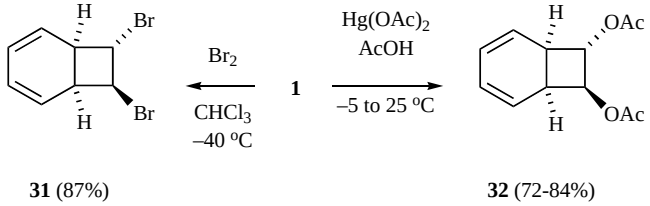
Mehta and Vidya have utilized **24a** as a starting material for the synthesis of "oxa bowls" (Scheme **7**) [12]. These compounds are of interest as constrained analogs of crown ethers.

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.



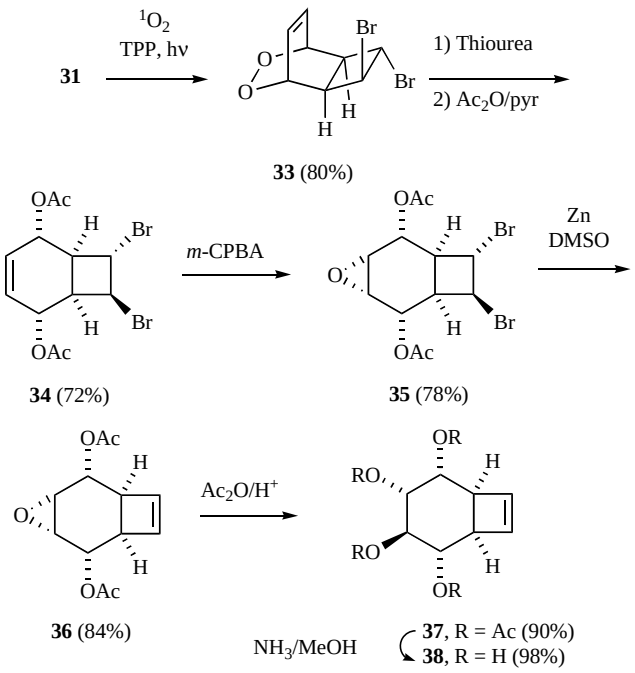
Scheme 7.



Scheme 8.

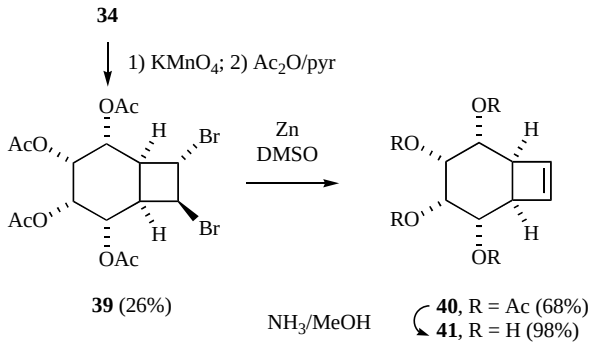
3.1. Synthesis bis-Homoconduritols and bis-Inositols

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 Ac_2O gave the corresponding diacetate **34**. Epoxidation with *m*-CPBA afforded a



Scheme 9.

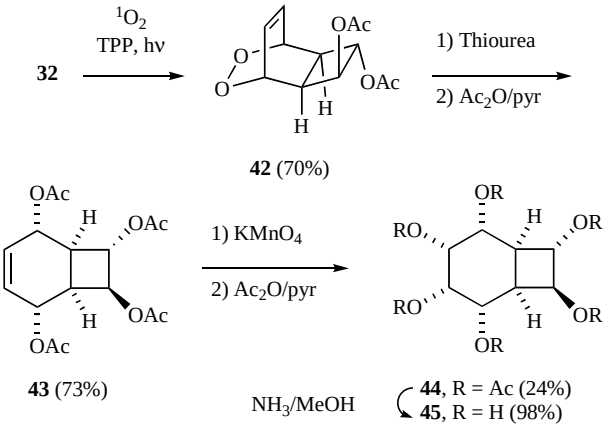
single diastereomer. Reductive debromination of **35** proceeded smoothly with Zn-DMSO to give epoxydiacetate **36**. Trans ring-opening was accomplished in acidified acetic anhydride to provide the tetraacetate **37**, which upon treatment with methanolic ammonia gave tetraol **38** which possessed the configuration of the conduritol-F family. Alternatively dihydroxylation of **34** with $KMnO_4$, 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 tetraol **41** having the configuration of conduritol-D.



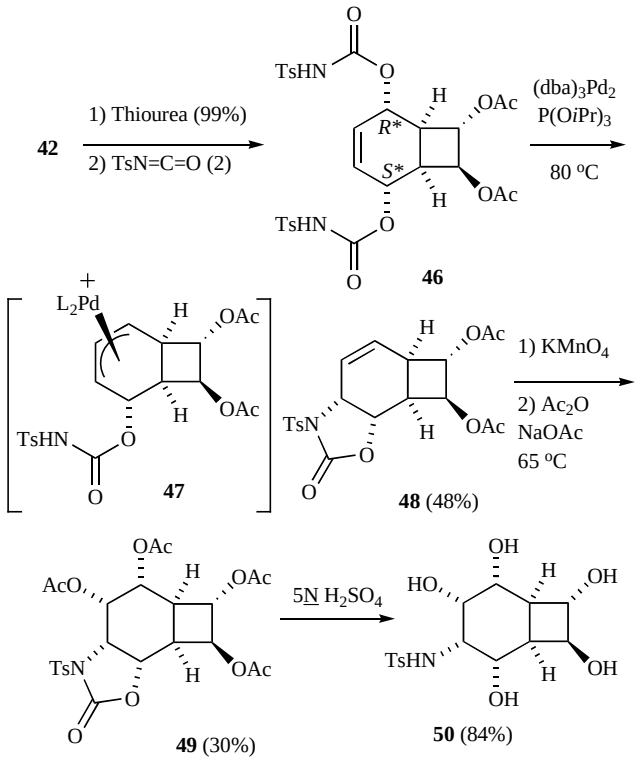
Scheme 10.

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 $KMnO_4$ 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 biscarbamate **46** (Scheme **12**). Palladium catalyzed cyclization of biscarbamate **46** occured 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 $KMnO_4$ followed by acetylation gave the tetraacetate **49**. Removal of the acetyl groups with H_2SO_4 provided the desired aminocyclitol **50** in 84% yield.



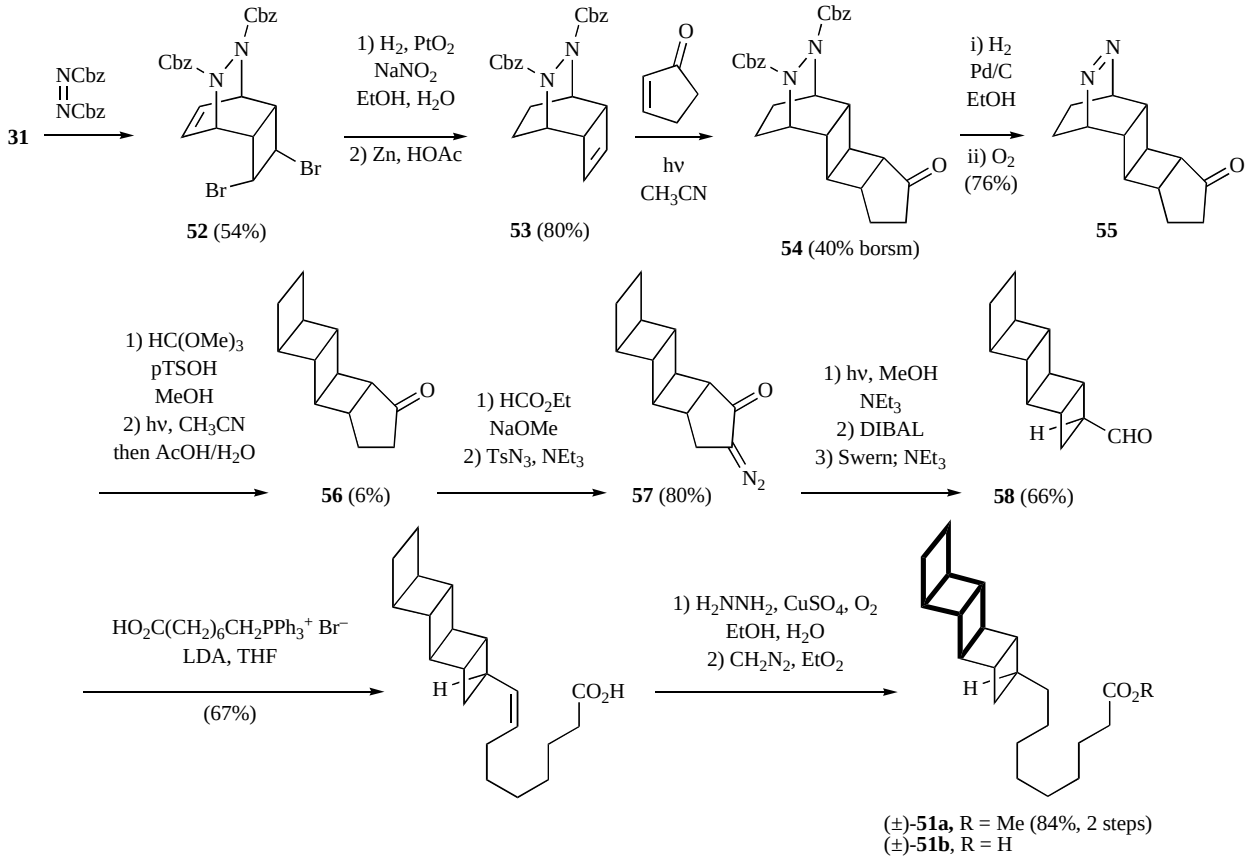
Scheme 11.



Scheme 12.

3.2. Synthesis of (±)-Pentacycloanammoxic Acid

Pentacycloanammoxic acid (**51b**, Scheme **13**) is a pentacyclic ladderane C_{20} 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

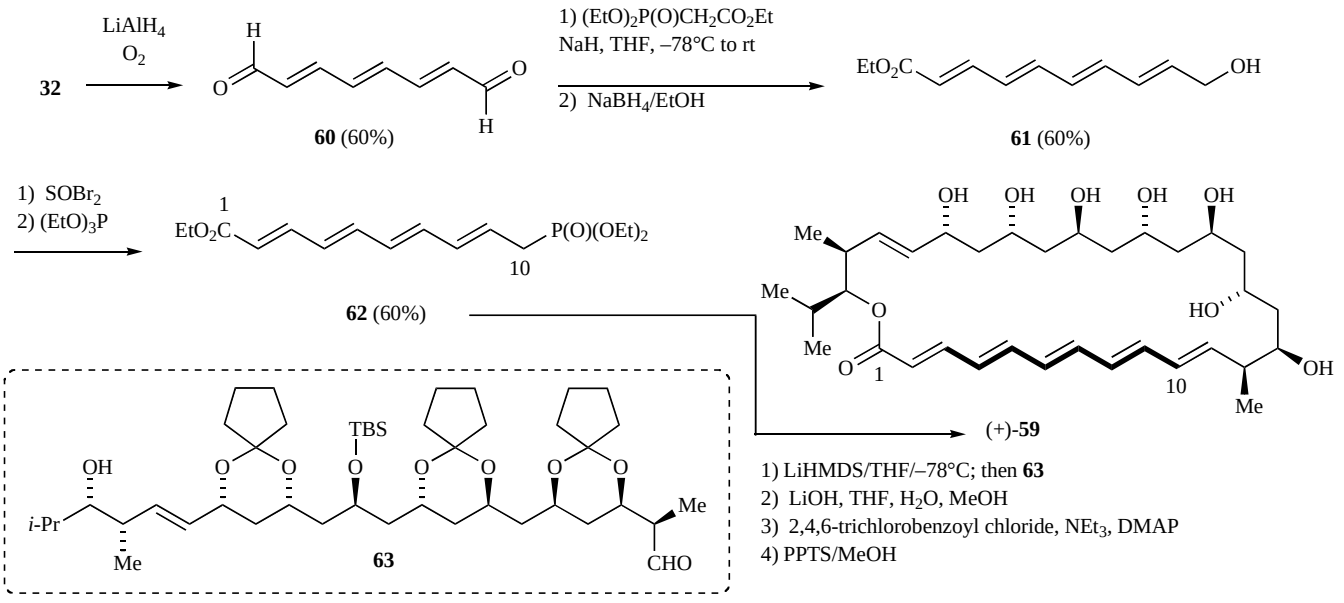


Scheme 13. Cbz = CO_2CH_2Ph; "borsm" = based on recovered starting material.

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 O_2 oxidation of the hydrazine afforded **55**. Protection of the ketone as its dimethoxy ketal, subsequent photolysis to affect the loss of N_2, 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 streptomycete, whose structure was determined by X-ray crystallography [20]. The first laboratory

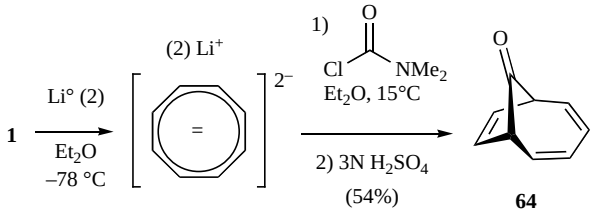


Scheme 14.

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 $LiAlH_4$ 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 $NaBH_4$ 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.

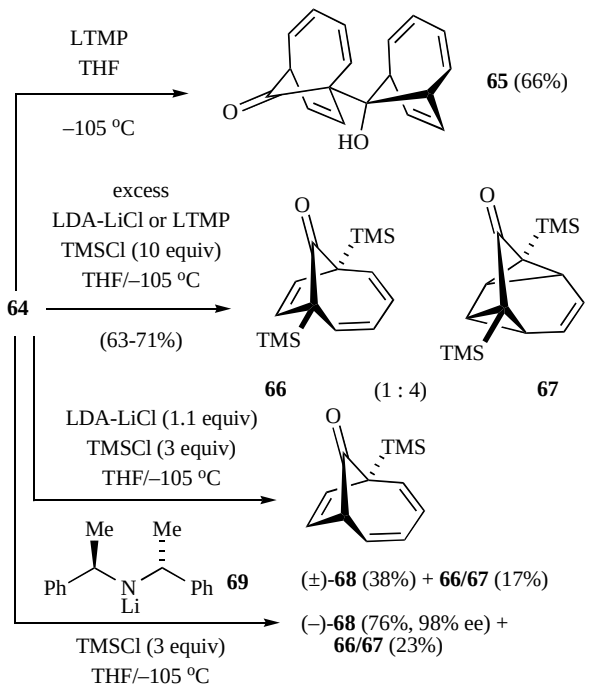
4. SYNTHESIS AND REACTIONS OF BICYCLO[4.2.1] NONA-2,4,7-TRIEN-9-ONE

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.



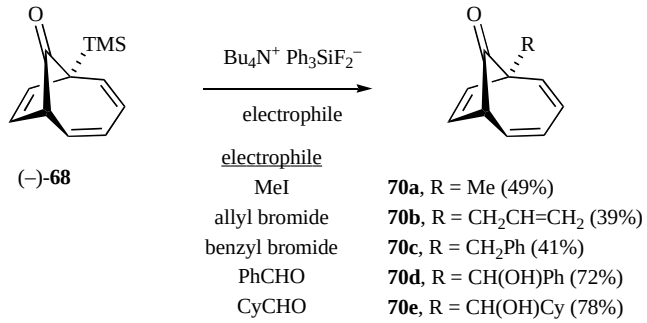
Scheme 15.

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.



Scheme 16.

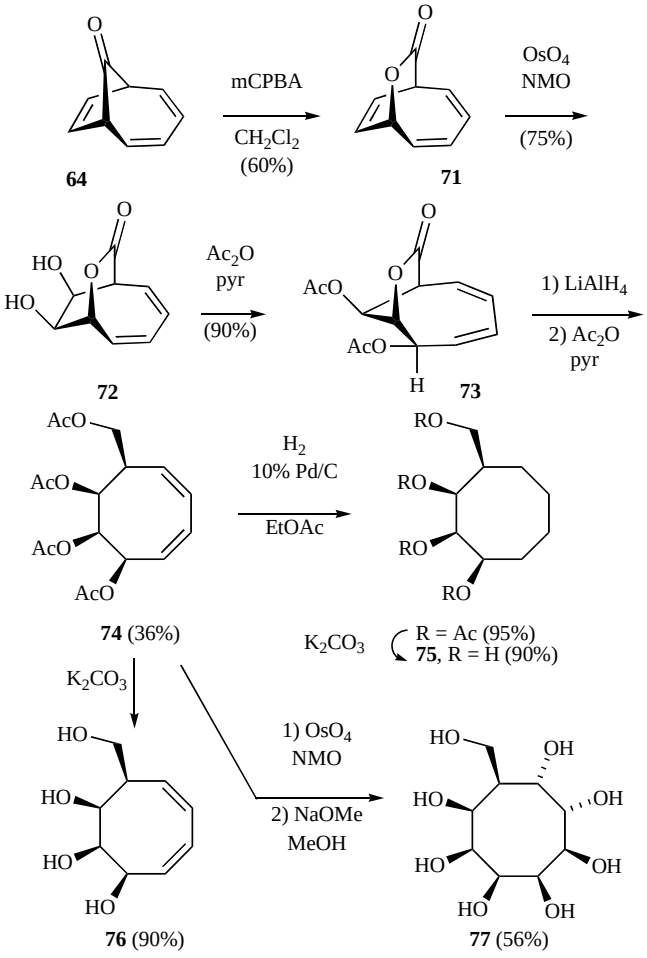
Reaction of mono-silyl ketone (–)-**68** with Bu_4N^+ $Ph_3SiF_2^-$ and an electrophile resulted in formation of the monosubstituted products **70** (Scheme **17**). The yields for aldol condensation products (**70d**/**70e**) were generally greater than for the organohalide electrophiles.



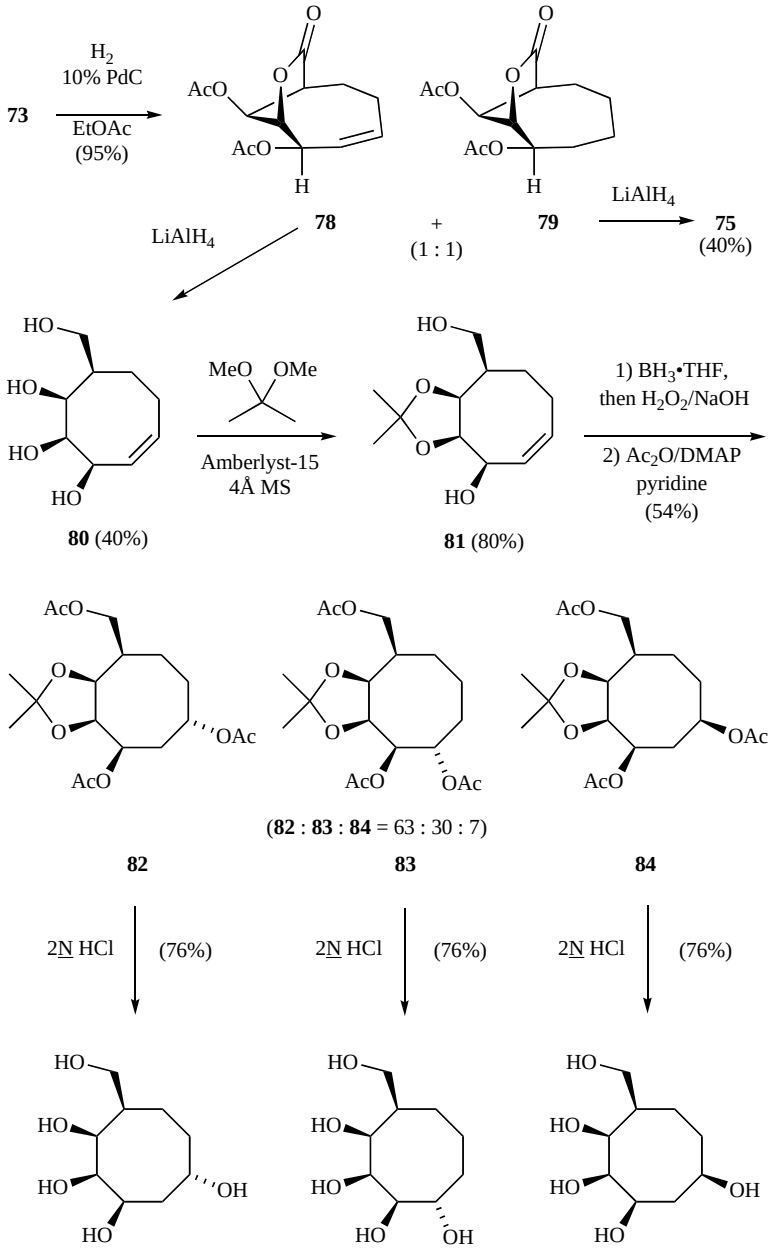
Scheme 17.

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 OsO_4 gave the diol **72**



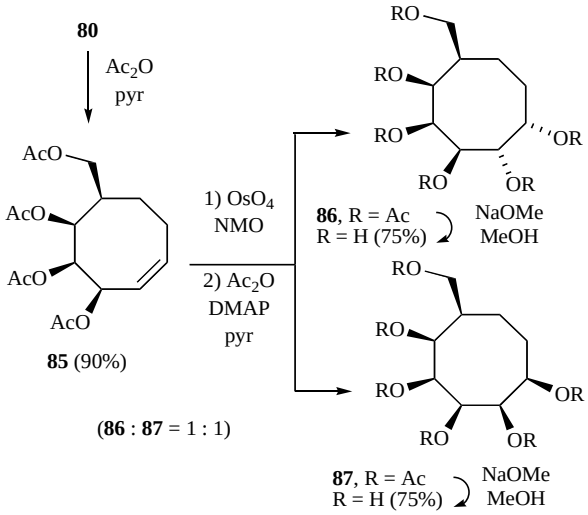
Scheme 18.



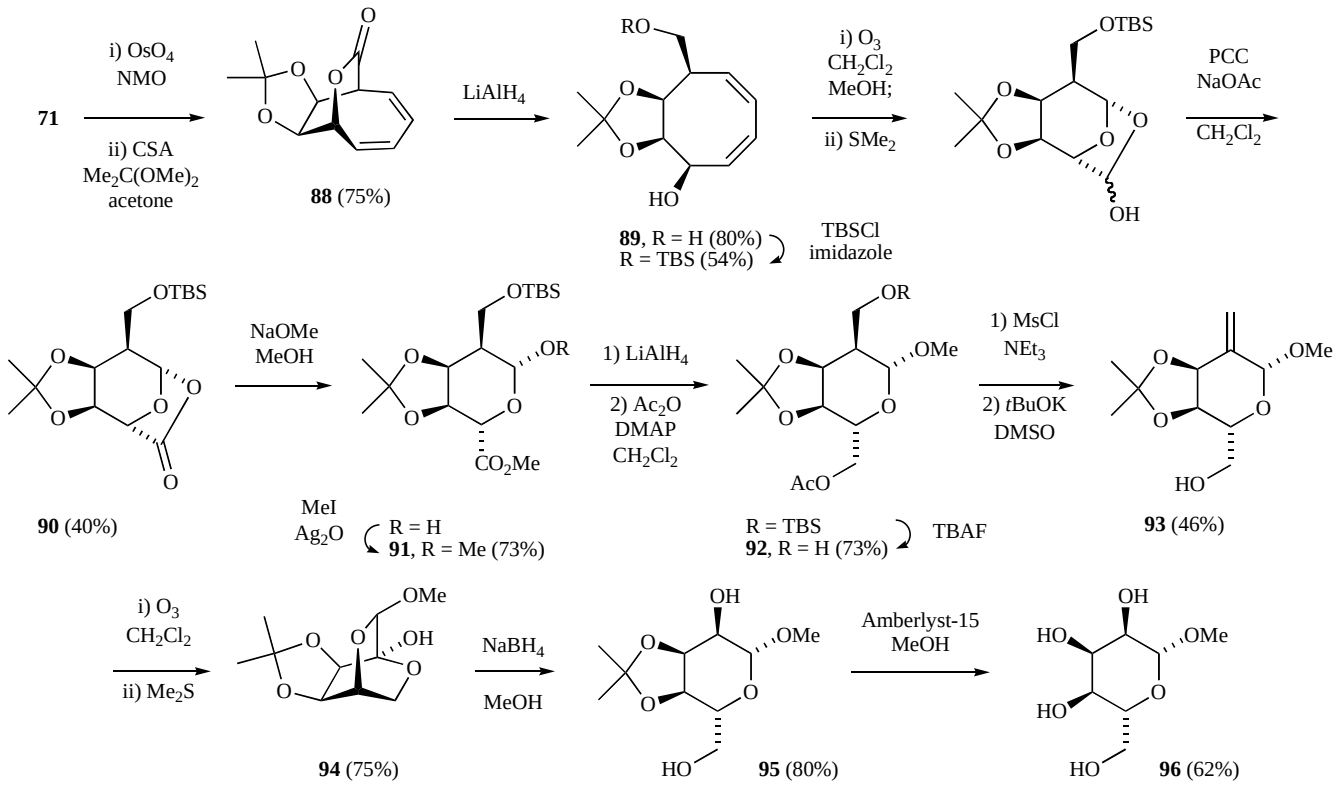
Scheme 19.

with complete regio- and sterocontrol. 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 tetraols **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.



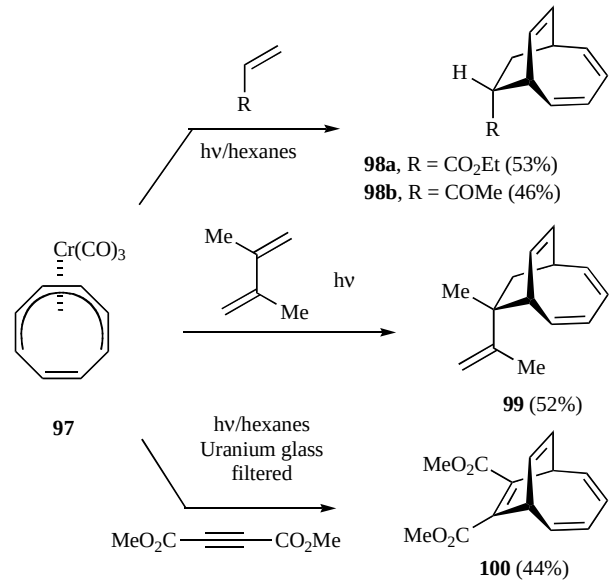
Scheme 20.



Scheme 21.

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 OsO_4 followed by acetonide protection gave **88**. Hydride reduction of **88** afforded the cyclooctadienediol **89**, which was selectively protected at the primary alcohol with TBSCl. 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 $NaBH_4$ gave diol **95**. Racemic β-allose **96** was realized after acetonide deprotection.



Scheme 22.

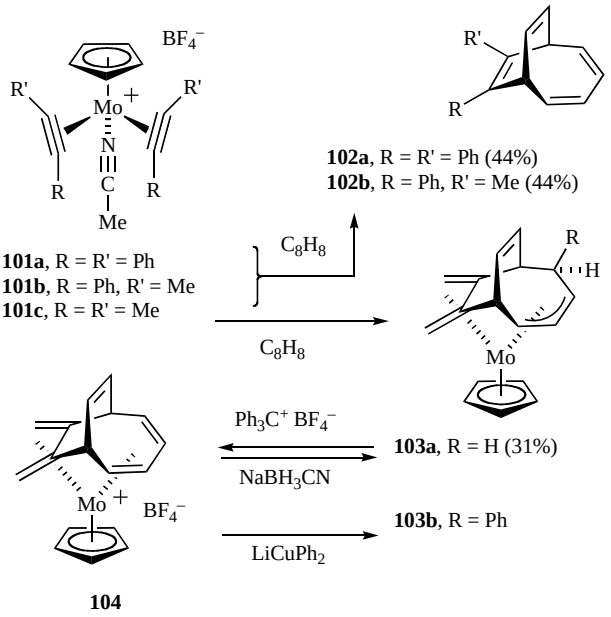
5. METAL-CATALYZED/METAL-MEDIATED REACTIONS

5.1. Cycloadditions of Cyclooctatetraene

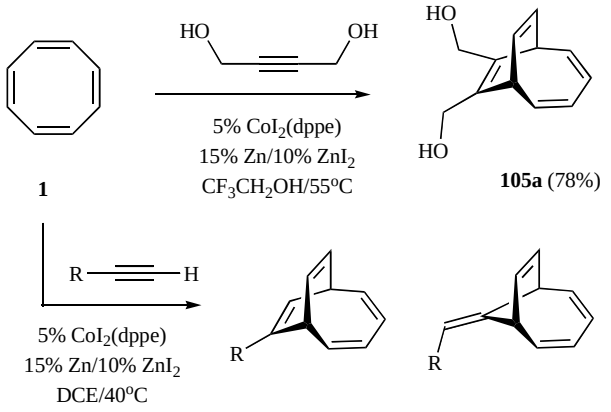
As indicated previously, cyclooctatetraene generally does not undergo Diels-Alder reactions due to the tub-like structure of the cyclic polyene. However, the complexation of **1** to transition metals may result in modified chemical reactivity. Rigby, *et al.*, demonstrated that higher-order photochemically induced cycloadditions can be achieved using chromium tricarbonyl polyenes. Toward this end, photolysis of (η^6-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 (η^3-allyl) (η^4-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 $NaBH_3CN$ or $LiCuPh_2$ 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-alkenyl-bicyclo[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 ZnI_2 [30].



Scheme 23.

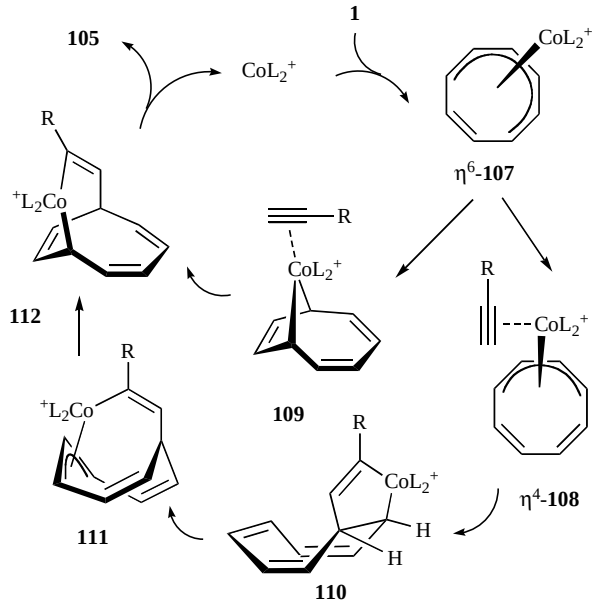


R	products	yield
Ph	**105b** (1 : 0) **106b**	70%
n-Bu	**105c** (1 : 0) **106c**	61%
$SiMe_3$	**105d** (1 : 0) **106d**	89%
CH_2SO_2Ph	**105e** (1 : 0) **106e**	71%
CH_2CH_2OAc	**105f** (1 : 0) **106f**	56%
CH_2SiMe_3	**105g** (72:28) **106g**	51%
1-cyclohexenyl	**105h** (89:11) **106h**	52%

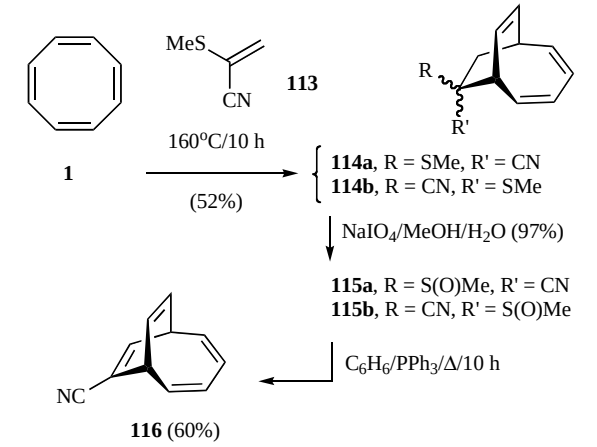
Scheme 24.

Coordination of **1** to Co(1+) is proposed to afford the η^6-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 η^6 to η^4 (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**.

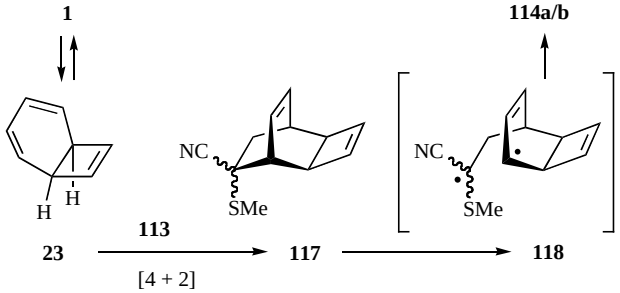


Scheme 25.



Scheme 26.

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.$0^{2,5}$]decadienes **117** (Scheme **27**). Homolytic C–C bond cleavage of **117** led to the captodative stabilized diradical **118**.

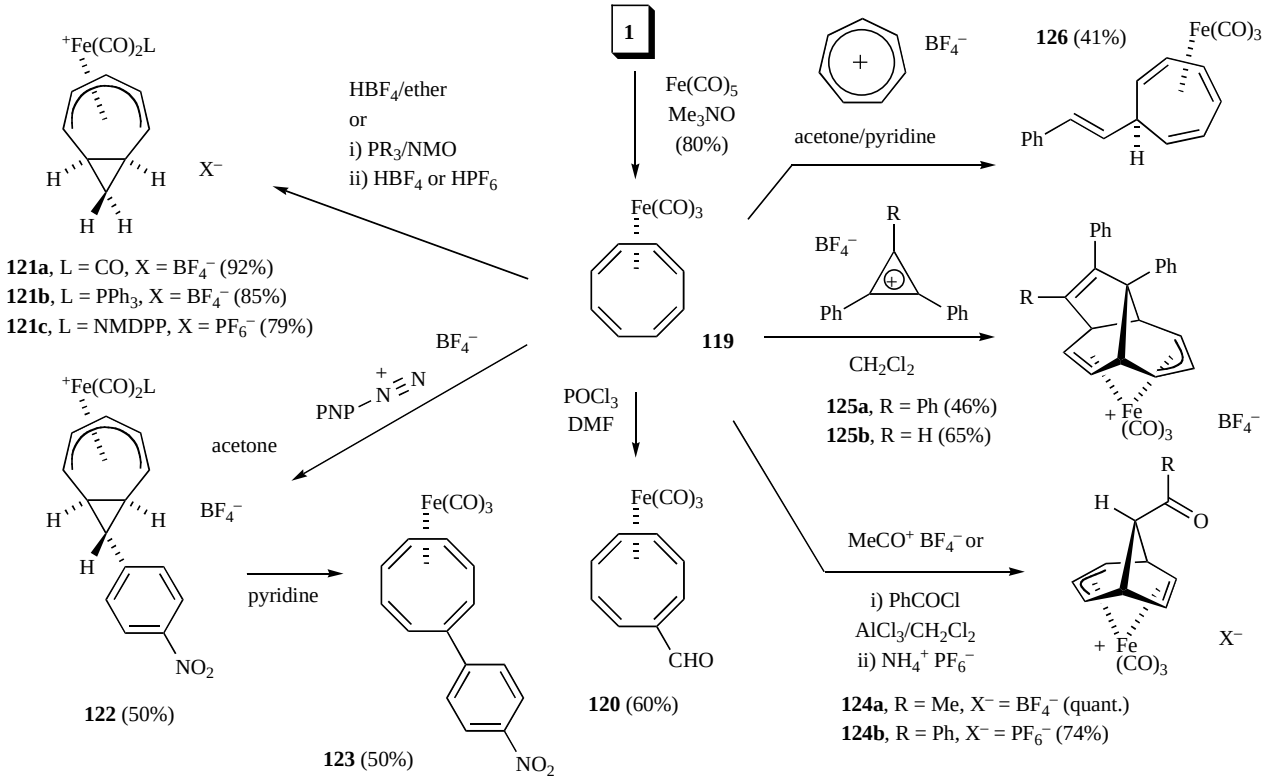


Scheme 27.

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

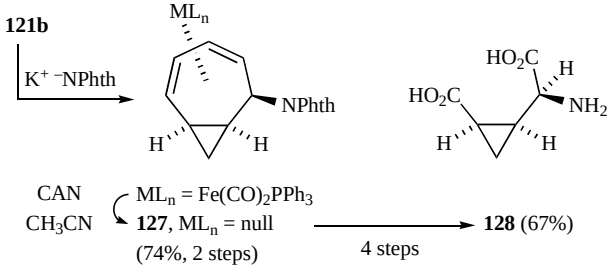
5.2. Reactions of Cyclooctatetraene-Metal Complexes with Electrophiles and/or Nucleophiles

Tricarbonyl(cyclooctatetraene)iron (**119**, Scheme **28**) was one of the first metal complexes prepared from **1** [32]. The reaction of



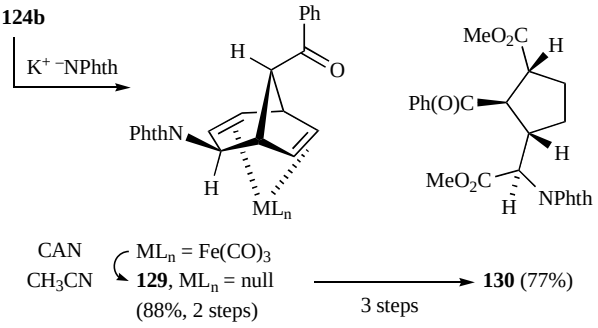
Scheme 28.

119 with a variety of electrophiles has been reported; for example, Vilsmeyer-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*-nitrophenyldiazonium 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.$0^{5,11}$]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].



Scheme 29.

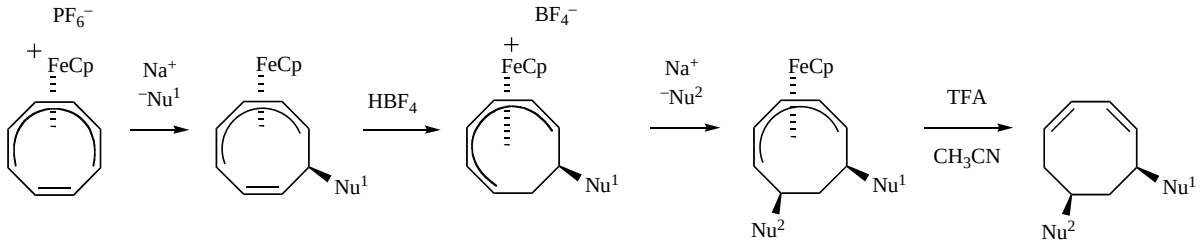
The rearranged skeletons afforded by these transformations have been utilized to prepare (carboxycycloalkyl)glycines. For example, nucleophilic attack of phthalimide anion on **121b** proceeds in a stereoselective fashion (Scheme **29**) [38a]. Removal of the metal afforded (bicyclo[5.1.0]octa-3,5-dien-2-yl)phthalimide **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].



Scheme 30.

Heck and co-workers have reported on the nucleophilic addition to (η^6-cyclooctatetraene)$FeCp^+$ cation **131** which afforded the substituted neutral (η^5-cyclooctatrienyl)FeCp complexes **132** (Scheme **31**) [39]. Protonation of **132** gave (η^6-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 (η^5-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**

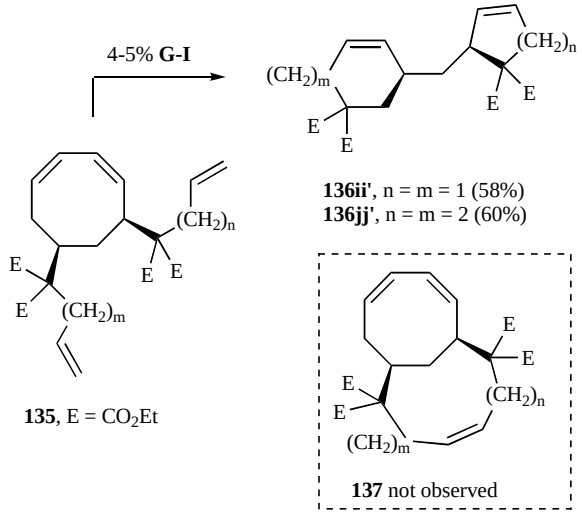


131 **132** (34-92%) **133** (67-99%) **134** (34-90%) **135** (41-76%)

Nu^1 = $CH(EWG)_2$, $CR(EWG)_2$; EWG = CO_2Me, CO_2Et, CN, C(O)Me; R = Et, Ph, $(CH_2)_nCO_2Et$, $(CH_2)_nCH{=}CH_2$
Nu^2 = $CH(EWG)_2$, $CR(EWG)_2$; EWG = CO_2Me, CO_2Et, CN; R = Ph, $(CH_2)_nCH{=}CH_2$

Scheme 31.

were isolated; none of the bicycloalkatriene ring closing metathesis products (i.e. **137**) were observed.



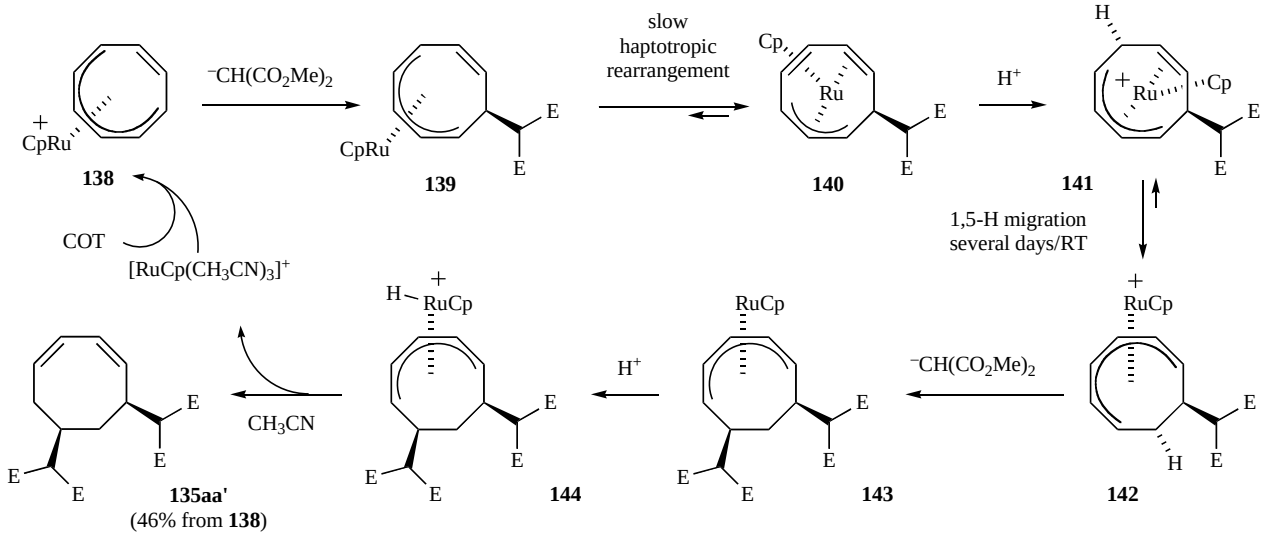
Scheme 32. [**G-I** = $(PCy_3)_2Cl_2Ru{=}CHPh$].

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-η^5) complex **139** underwent a slow haptotropic rearrangement to the more stable (1,2,3,6,7-η^5-cyclooctatrienyl)RuCp complex **140**. Protonation of **140** initially generated a (1,2,3,4,6,7-η^6)-cyclooctatriene)$RuCp^+$ cation (**141**), which is isomerized by a 1,5-hydride migration to give the (1,2,3,4,5-η^5)- cation **142** (similar to iron cation **133**). Eventually, protonolysis of **143** gave **135aa'**. If this final protonation is conducted in acetonitrile as solvent, the $RuCp(CH_3CN)_3^+$ cation is generated, which can be recycled to the starting material **138**.

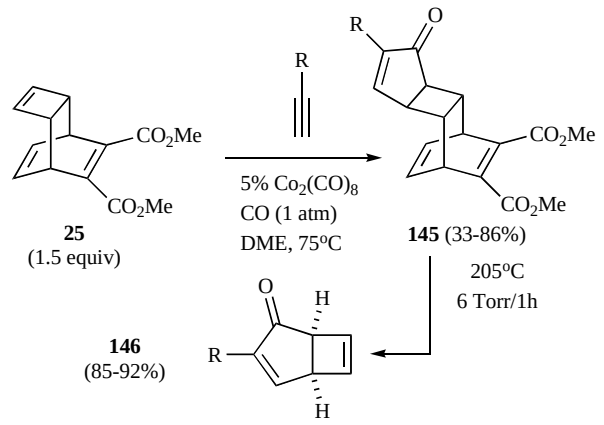
5.3. Metal-Catalyzed/Mediated Reactions of Cyclooctatetraene Valence Isomers

Tricyclo[4.2.2.$0^{2,5}$]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

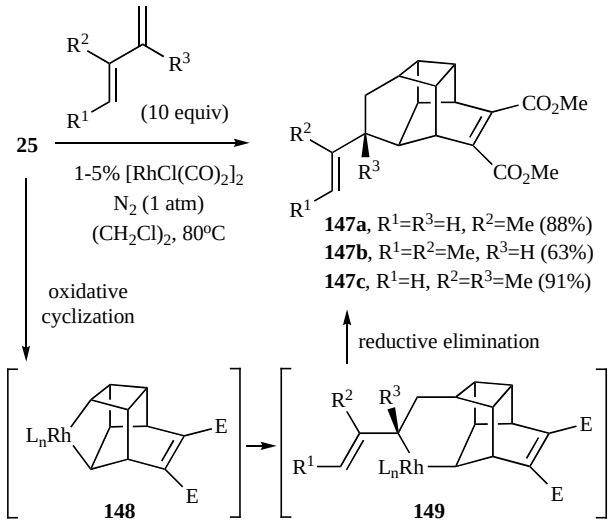


Scheme 33. (E = CO_2Me).



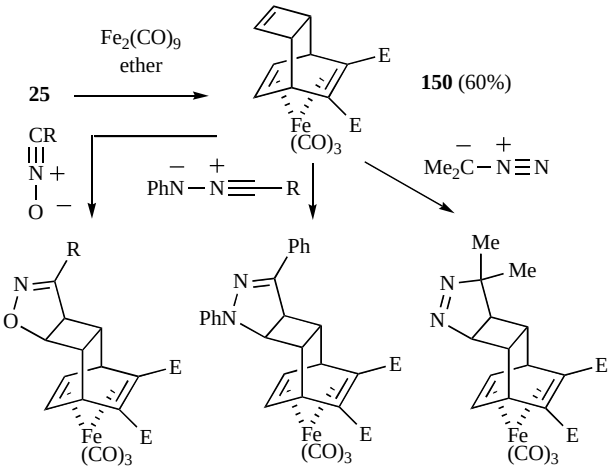
Scheme 34.

of the C=C of the diene into the Rh-carbon bond generated **149**, which upon reductive elimination gave the product.



Scheme 35.

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].



Scheme 36.

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

K. W. G. would like to thank Wisconsin Lutheran College for a sabbatical leave during which time portions of this manuscript were written. W.A.D. thanks the NIH, NSF, and Marquette University for partial support of his group's work on (cyclooctatetraene)$Fe(CO)_3$ complexes.

REFERENCES

[1] Willstatter, R.; Waser, E. Cyclo-octane Series. V. Cyclo-octatetraene. *Ber. Dtsch. Chem. Ges.* **1912**, *44*, 3423-3445. (b) Willstatter, R.; Heidelberger, M. Cyclo-octane Series. VI. Cyclo-octatetraene. *Ber. Dtsch. Chem. Ges.* **1913**, *46*, 517-527.

[2] (a) Reppe, W.; Schichting, O.; Klager, K.; Toepel, T. Cyclizing polymerization of acetylene I. Cyclo-octatetraene. *Justus Liebigs Ann. Chem.* **1948**, *560*, 1-92. (b) Barnes, C. E. Cyclo.ovrddot.octatetraene. U.S. Patent 2 579 106; CA 46: 39223. (c) Canale, A. J.; Kincaid, J. F. Cyclo.ovrddot.octatetraene. U.S. Patent 2 613 231; CA 47: 44714. (d) Matsuzawa, K.; *et al.* Cyclo.ovrddot.octatetraene. Japanese Patent 29 002 967; CA 49: 84432.

[3] Paquette, L. A. The renaissance in cyclooctatetraene chemistry. *Tetrahedron* **1975**, *31*, 2855-2883.

[4] (a) Gausing, W.; Wilke, G. Facile preparation of cyclooctatetraene from 1,5-Cyclooctadiene by metalation and oxidation. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 371-372. (b) Wetzsel, T. G.; Dehnen, S.; Roesky, P. W. A multifunctional substituted cyclooctatetraene as a ligand in organosamarium chemistry. *Organometallics* **1999**, *18*, 3835-3842. (c) Gottfriedsen, J.; Miloslavina, A.; Edelmann, F. T. Cyclooctatetraene made easy. *Tetrahedron Lett.* **2004**, *45*, 3583-3584. (d) Majumder, S.; Odom, A. L. Simple and convenient one-pot synthesis of cyclooctatetraene. *Tetrahedron Lett.* **2008**, *49*, 1771-1772.

[5] Simons, L. H.; Lagowski, J. J. Cyclooctatetraene dianion from 1,5-cyclooctadiene. A synthesis in the presence of naphthalene radical anion. *Tetrahedron Lett.* **2002**, *43*, 1771-1773.

[6] Detert, H.; Rose, B.; Mayer, W.; Meier, H. Preparation of 1,5-cyclooctadiyne and 1,3,5,7-cyclooctatetraene from 1,5-cyclooctadiene. *Chem. Ber.* **1994**, *127*, 1529-1532.

[7] Wang, C.; Xi, Z. Metal mediated synthesis of substituted cyclooctatetraenes. *Chem. Commun.* **2007**, 5119-5133.

[8] Pan, W.; Hendrick, M. E.; Jones, Maitland, Jr. Triplet carbenes and cyclooctatetraene. 1,4-Addition is more common than we thought. *Tetrahedron Lett.* **1999**, *40*, 3085-3088.

[9] (a) Cope, A. C.; Moore, P. T.; Moore, W. R. Cyclic Polyolefins. XLIII. Derivatives of Bicyclo[3.3.0]oct-1(5)-ene. *J. Am. Chem. Soc.* **1958**, *80*, 5505-5507. (b) Murray, R. W.; Singh, M.; Rath, N. P. The reaction of cyclooctatetraene with dimethyldioxirane. *Tetrahedron* **1999**, *55*, 4539-4558.

[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 S_N2'-Cuprate alkylation. *Org. Lett.* **2003**, *5*, 1971-1974. (b) Pineschi, M.; Del Moro, F.; Crotti, P.; Macchia, F. Simple synthetic transformations of highly enantio-enriched 4-Alkyl-2,5,7-cyclooctatrienols into functionalized Bicyclo[4.2.0]octa-2,4-dienes and 2,6-Cyclooctadienones. *Eur. J. Org. Chem.* **2004**, 4614-4620.

[11] Pirrung, M. C.; Bleecker, A. B.; Inoue, Y.; Rodriguez, R. I.; Sugawara, N.; Wada, T.; Zou, Y.; Binder, B. M. Ethylene receptor antagonists: strained alkenes are necessary but not sufficient. *Chem. Biol.* **2008**, *15*, 313-321.

[12] Mehta, G.; Vidya, R. Oxa bowls: Studies Toward Hexaoxa-[6]-peristylane. Synthesis of a *Seco*-Derivative of Hexaoxa-[6]-peristylane. *J. Org. Chem.* **2001**, *66*, 6913-6918.

[13] (a) Cope, A. C.; Brug, M. Cyclic Polyolefins. XIX. Chloro and bromocyclooctatetraenes. *J. Am. Chem. Soc.* **1952**, *74*, 168-172. (b) Cope, A. C.; Nelson, N. A.; Smith, D. S. Cyclic Polyolefins. XXXI. Cycloheptatriene and Bicyclo[4.2.0]octa-2,4-diene derivatives from cyclooctatetraene and Mercuric Acetate *J. Am. Chem. Soc.* **1954**, *76*, 1100-1104.

[14] Kelebekli, L.; Kara, Y.; Balci, M. Stereospecific synthesis of a new class of compounds: bis-homoconduritol-A, -D, and -F. *Carbohydr. Res.* **2005**, *340*, 1940-1948.

[15] Kara, Y.; Balci, M. A new and stereospecific synthesis of an inositol analogue: bis-homoinositol. *Tetrahedron* **2003**, *59*, 2063-2066.

[16] Kelebekli, L.; Çelik, M.; Sahin, E.; Kara, Y.; Balci, M. Stereospecific synthesis of a new class of aminocyclitol with the conduramine D-2 configuration. *Tetrahedron Lett.* **2006**, *47*, 7031-7035.

[17] Damste, J. S. S.; Strous, M.; Pijpstra, W. I. C.; Hopmans, E. C.; Greenevasen, J. A. J.; van Duin, A. C. T.; van Niftrik, L. A.; Jetten, M. S. M. Linearly concatenated cyclobutane lipids form a dense bacterial membrane. *Nature* **2002**, *419*, 708-712.

[18] (a) Mascitti, V.; Corey, E. J. Total synthesis of (±)-pentacycloanammoxic Acid. *J. Am. Chem. Soc.* **2004**, *126*, 15664-15665. (b) Mascitti, V.; Corey, E. J. Enantioselective synthesis of pentacycloanammoxic acid. *J. Am. Chem. Soc.* **2006**, *128*, 3118-3119.

[19] Regitz, M. Recent synthetic methods in diazo chemistry. *Synthesis* **1972**, 351-373.

[20] (a) Maehr, H.; Yang, R.; Hong, L. N.; Liu, C. M. Hatada, M. H. Todaro, L. J. Microbial products. 9. Roxaticin, a new oxo pentaene antibiotic. *J. Org. Chem.* **1989**, *54*, 3816-3819. (b) Maehr, H.; Yang, R.; Hong, L. N.; Liu, C. M. Hatada, M. H. Todaro, L. J. Microbial products. 9. Roxaticin, a new oxo pentene antibiotic. *J. Org. Chem.* **1990**, *55*, 3704 (*erratum*)

[21] (a) Mori, Y.; Asai, M.; Kawade, J.-I.; Okumura, A.; Furukawa, H. Total synthesis of the polyene macrolide roxaticin. *Tetrahedron Lett.* **1994**, *35*, 6503-6506. (b) Mori, Y.; Asai, M.; Okumura, A.; Furukawa, H. Total synthesis of the polyene macrolide antibiotic roxaticin. 1. Synthesis of the polyol fragment of roxaticin using a four-carbon chain extension strategy. *Tetrahedron* **1995**, *51*, 5299-5314. (c) Mori, Y.; Asai, M.; Kawade, J.-I.; Okumura, A.; Furukawa, H. Total synthesis of the polyene macrolide antibiotic roxaticin. II. Total synthesis of roxaticin. *Tetrahedron* **1995**, *51*, 5315-5330.

[22] Evans, D. A.; Connell, B. T. Synthesis of the Antifungal Macrolide Antibiotic (+)-Roxaticin *J. Am. Chem. Soc*., **2003**, *125*, 10899-10905.

[23] Antkowiak, T.A.; Sanders, D.C.; Trimitsis, G.B.; Press, J.B.; Shechter, H. Synthesis and chemistry of bicyclo[4.2.1]nona-2,4,7-triene-9-one and of bicyclo[4.2.1]nona-2,4,7-trien-9-yl intermediates. *J. Am. Chem. Soc*., **1972**, *94*, 5366-5373.

[24] Hayes, C. J.; Simpkins, N. S.; Kirk, D. T.; Mitchell, L.; Baudoux, J.; Blake, A. J.; Wilson, C. Bridgehead Lithiation-Substitution of Bridged Ketones, Lactones, Lactams, and Imides: Experimental observations and computational insights. *J. Am. Chem. Soc.* **2009**, *131*, 8196-8210.

[25] Mehta, G.; Pallavi, K. From hydrocarbons to polyols. Cyclooctatetraene to novel cyclooctitols. *Chem. Comm*. **2002**, 2828-2929.

[26] Mehta, G.; Pallavi, K. From cyclic polyenes to carbohydrates: synthesis of the hexose sugar β-allose and its 2C-branched homologue from cyclooctatetraene. *Tetrahedron Lett*. **2004**, *45*, 3865-3867.

[27] Rigby, J. H.; Scribner, S.; Heeg, M. J. Chromium(0)-promoted higher-order cycloadditions of 1,3,5-cyclooctatriene and cyclooctatetraene. *Tetrahedron Lett.* **1995**, *36*, 8569-8572.

[28] Bourner, D. G.; Brammer, L.; Green, M.; Moran, G.; Orpen, A. G.; Reeve, C.; Schaverien, C. J. A Molybdenum-centered (6+2)π Addition of Alkynes to Cyclo-octatetraene and Cycloheptatriene; Structural Evidence for an Arrested 1,3-Hydrogen Shift. *J. Chem. Soc., Chem. Commun*. **1985**, 1409-1411.

[29] Achard, M.; Mosrin, M.; Tenaglia, A.; Buono, G. Cobalt(I)-Catalyzed [6+2] Cycloadditions of Cyclooctatetra(tri)ene with Alkynes. *J. Org. Chem.* **2006**, *71*, 2907-2910.

[30] Ma, B.; Snyder, J. K. Development of a new cobalt catalyst system for the [4+2+2] cycloadditions of functionalized norbornadienes and butadiene. *Organometallics* **2002**, *21*, 4688-4695.

[31] Boucher, J.-L.; De Riggi, I.; Stella, L. A Novel Entry to the Bicyclo[4.2.2]decatriene and tetraene systems: The unexpected 1,4-cycloaddition of 2-(Methylthio)acrylonitrile to cyclooctatetraene. *J. Org. Chem.* **1997**, *62*, 6077-6079.

[32] Manuel, T. A.; Stone, F. G. A. Cyclo-octatetraene-iron complexes. *Proc. Chem. Soc.* **1959**, 90.

[33] (a) Davison, A.; McFarlane, W.; Pratt, L.; Wilkinson, G. 941. The protonation of tricarbonylcyclo-octatetraeneiron and some related compounds. *J. Chem. Soc.* **1962**, 4821-4829. (b) Johnson, B. F. G.; Lewis, J.; Randall, G. L. P. Reactivity of co-ordinated ligands. Part VI. Electrophilic substitution and addition reactions of co-ordinated cyclo-octatetraene. *J. Chem. Soc. (A)* **1971**, 422-429. (c) Brookhart, M.; Davis, E. R.; Harris, D. L. Low-temperature protonation of cyclooctatetraeneiron tricarbonyl and methylcyclooctatetraeneiron tricarbonyl. Generation and observation of cycloctatrienyliron tricarbonyl cations. *J. Am. Chem. Soc.* **1972**, *94*, 7853-7858.

[34] Connelly, N. G.; Lucy, A. D.; Whiteley, M. W. The reaction of co-ordinated cyclo-octatetraene with arenediazonium ions: azo-coupling *vs.* arylation. *J. Chem. Soc. Dalton Trans.* **1983**, 111-115.

[35] (a) Charles, A. D.; Diversi, P.; Johnson, B. F. G.; Karlin, K. D.; Lewis, Rivera, A. V.; Sheldrick, G. M. Tricarbonyl[8-acetyl 2-4:6-7-η-bicyclo[3.2.1]octadienylium]iron, a novel rearrangement in the acylation of η-$C_8H_8Fe(CO)_3$. *J. Organomet. Chem.* **1977**, 128, C31-C34. (b) Charles, A. D.; Diversi, P.; Johnson, B. F. G.; Lewis, J. Friedel-Crafts acylation of tricarbonyl(cyclo-octatetraene)iron. Preparation and reactions of (8-acylbicyclo[3.2.1]octadienylium)tricarbonyliron hexafluorophosphates. *J. Chem. Soc. Dalton Trans.* **1981**, 1906-1917. (c) Rivera, A. V.; Sheldrick, G. M. {2-4:6-7-η-(8-Acetylbicyclo[3.2.1]octadienyl)}tricarbonyliron hexafluorophosphate. *Acta Cryst.* **1978**, *34*, 1716-1718.

[36] Broadley, K.; Connelly, N. G.; Graham, P. G.; Howard, J. A. K.; Risse, W.; Whiteley, M. W.; Woodward, P. Annelation of ring-opened arylcyclopropenium ions to co-ordinated cyclo-octatetraene, and the X-ray crystal structure of [$Fe(CO)_3$(σ,η^3-$C_{11}H_9Ph_3$)]. *J. Chem. Soc. Dalton Trans.* **1985**, 777-781.

[37] Broadley, K.; Connelly, N. G.; Mills, R. M.; Whiteley, M. W.; Woodward, P. Synthesis of styrylcycloheptatriene derivatives *via* the electrophilic addition of tropylium ions to [$Fe(CO)_3$(η^4-C_8H_8)]: X-ray crystal structure of tricarbonyl(1-4-η-7-styrylcyclohepta-1,3,5-triene)iron. *J. Chem. Soc. Dalton Trans.* **1984**, 683-688.

[38] (a) Wallock, N. J.; Donaldson, W. A. Reactivity of (Bicyclo[5.1.0]octadienyl)iron(1+) Cations: Application to the Synthesis of *cis*-2-(2'-Carboxycyclopropyl)glycines. *J. Org. Chem.* **2004**, *69*, 2997-3007. (b) Chaudhury, S.; Lindeman, S.; Donaldson, W. A. Generation of molecular complexity from cyclooctatetraene: synthesis of a protected 2-(3'-carboxy-2'-benzoylcyclopentyl)glycine. *Tetrahedron Lett.* **2007**, *48*, 7849-7852.

[39] (a) Reimelt, O.; Heck, J. From coordinated cyclooctatetraene to *cis*-5,7-disubstituted cycloocta-1,3-diene by iteratively applied nucleophilic and electrophilic addition. *Organometallics* **2003**, *22*, 2097-2107. (b) Schorshusen, S.; Heck, J. Metal-mediated transformations of cyclo-octatetraene to novel methylene-bridged, bicyclic compounds. *Organometallics* **2007**, *26*, 5386-5394.

[40] Heck, J.; Lange, G.; Beimelt, O. Iterative nucleophilic and electrophilic additions to coordinated cyclooctatetraene: An efficient route to *cis*-5,7-Disubstituted 1,3-Cyclooctadienes. *Angew. Chem. Int. Ed*. **1998**, *37*, 520-522.

[41] Gibson, S. E.; Mainolfi, N.; Kalindjian, S. B.; Wright, P. T. A Cyclo-butadiene equivalent in the catalytic pauson-khand reaction. *Angew. Chem. Int. Ed.* **2004**, *43*, 5680-5682.

[42] Wender, P. A.; Croatt, M. P.; Kuhn, B. Rhodium(I)-Catalyzed [2+2], [2+2+2], and [2+2+2+2] cycloadditions of dienes or alkynes with a Bis-ene *Organometallics* **2009**, *28*, 5841-5844.

[43] Freccero, M.; Gandolfi, R.; Sarzi-Amade, M. Site specificity in 1,3-Dipolar cycloadditions to a polycyclic polyene induced by complexation with tricarbonyliron. *Heterocycles* **1998**, *49*, 415-426.

Received: January 01, 2011 Revised: June 20, 2011 Accepted: June 22, 2011