Tropone and Tropolone Chemistry

What follows are excerpts from references I was able to obtain dealing with aspects of this chemistry. I'm doing this as a service to those who are interested in this subject. Rather than letting my search for information remain in my saved pdf files, I will present it here in figures copied from the indicated references, or if too unwieldy, give you the reference for your review.

Pauson, P. L. (1955). Tropones and tropolones. *Chemical Reviews*, *55*(1), 9-136.

By far a monumental detailed description of the literature through 1954. This review is based on 492 references! If you search for tropones and tropolones on Google Scholar you will find 1910 hits. Even today anyone claiming to know this chemistry must study this review.

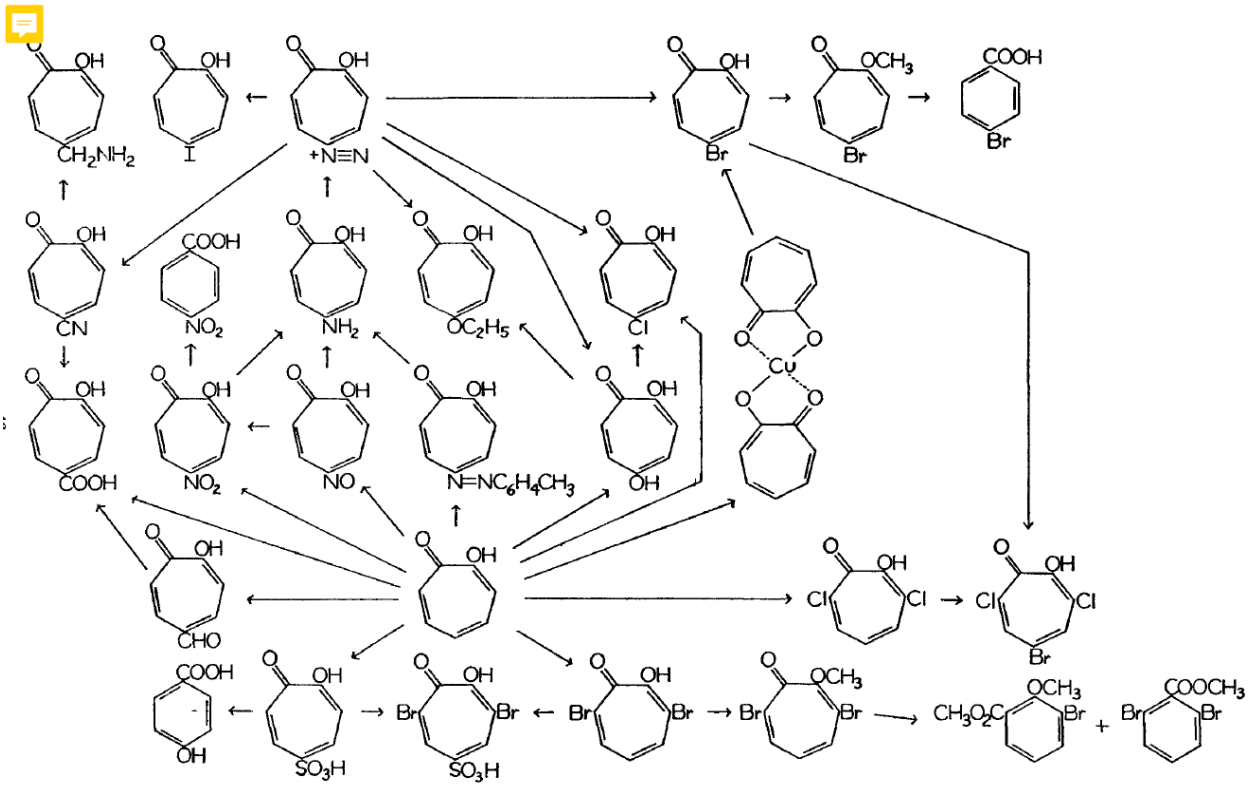
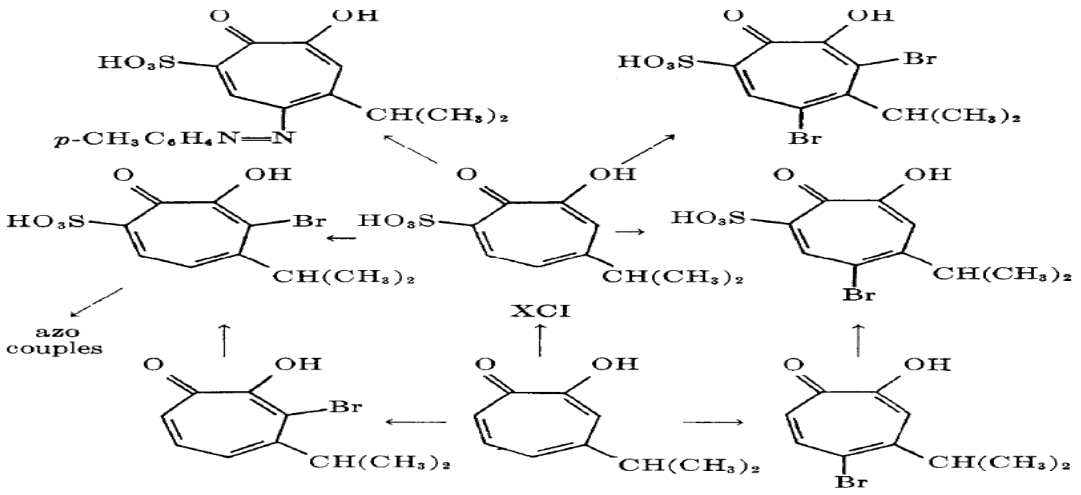


Chart I. Interrelation and orientation of 5-substituted tropolones



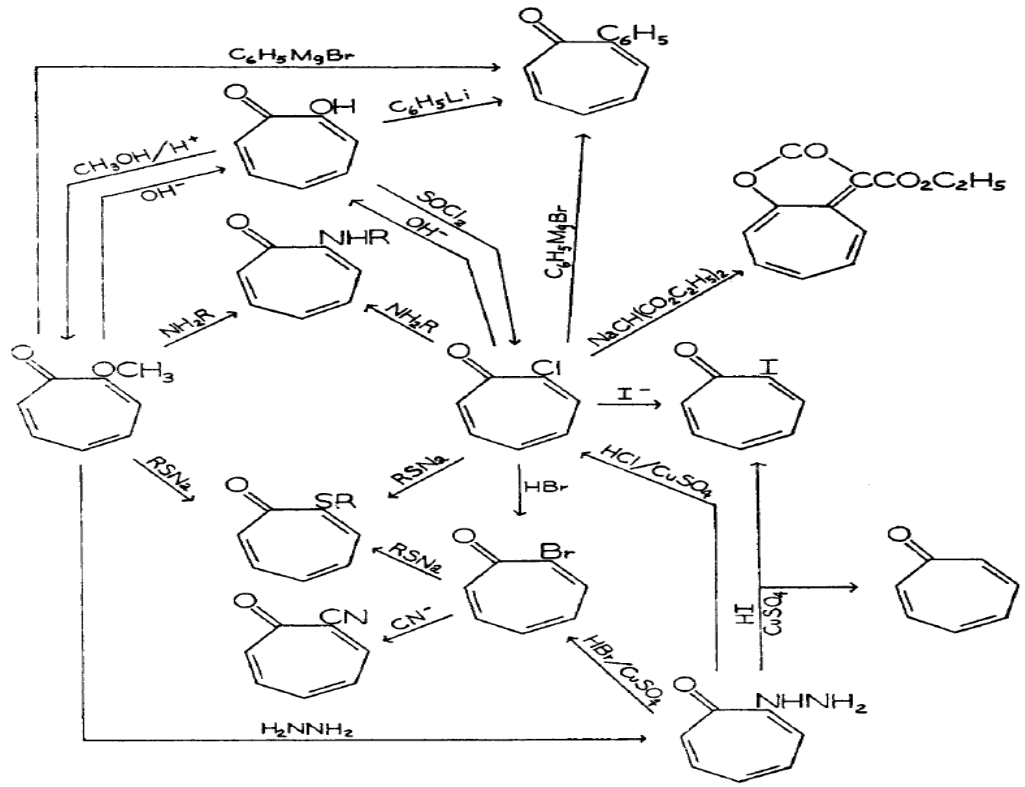
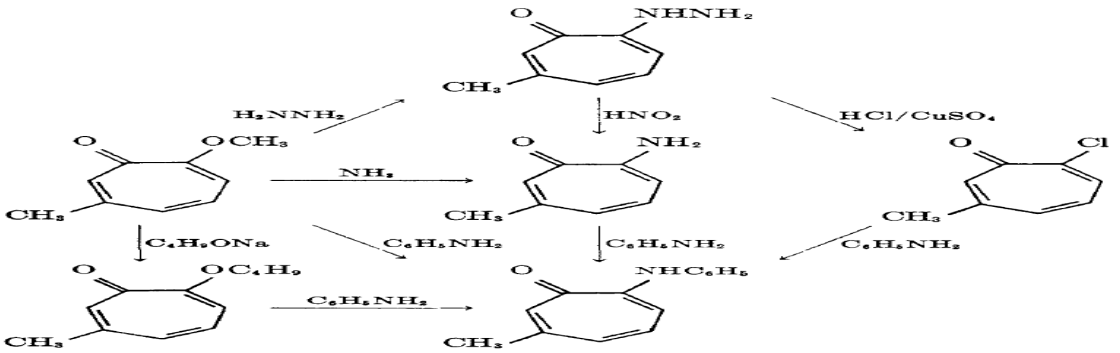


Chart II. Interconversion of 2-substituted tropones



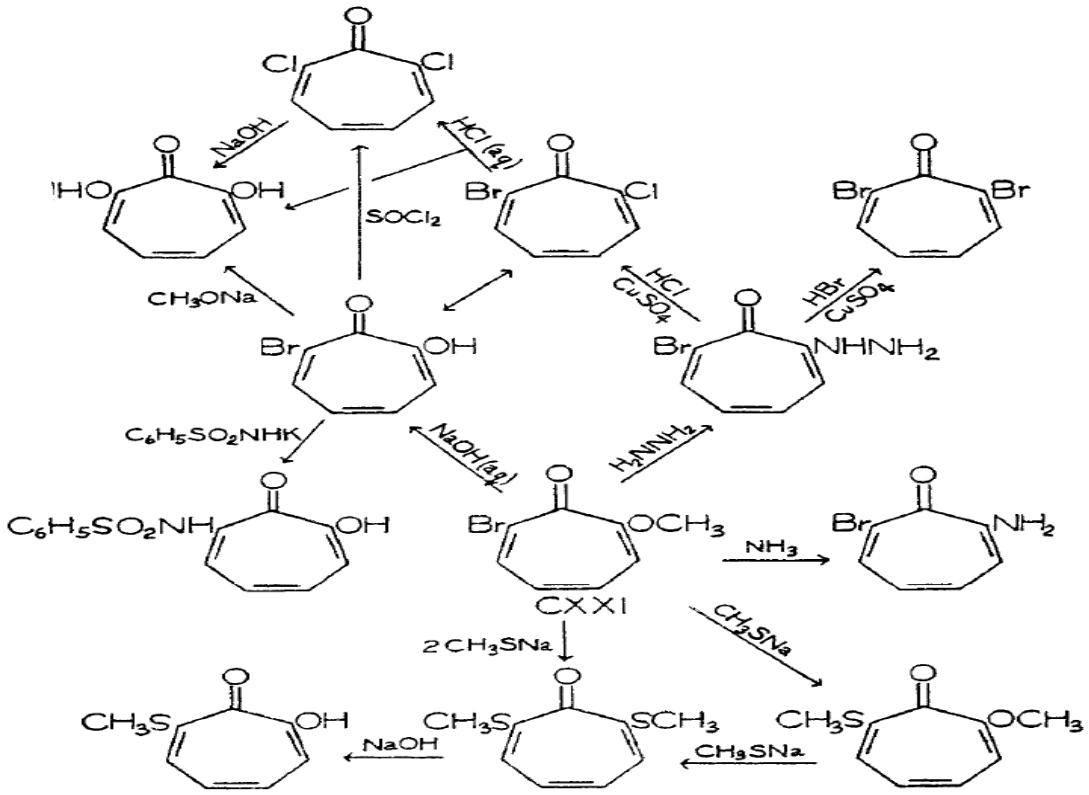


Chart IIIA. Reactions of 2-bromo-7-methoxytropone

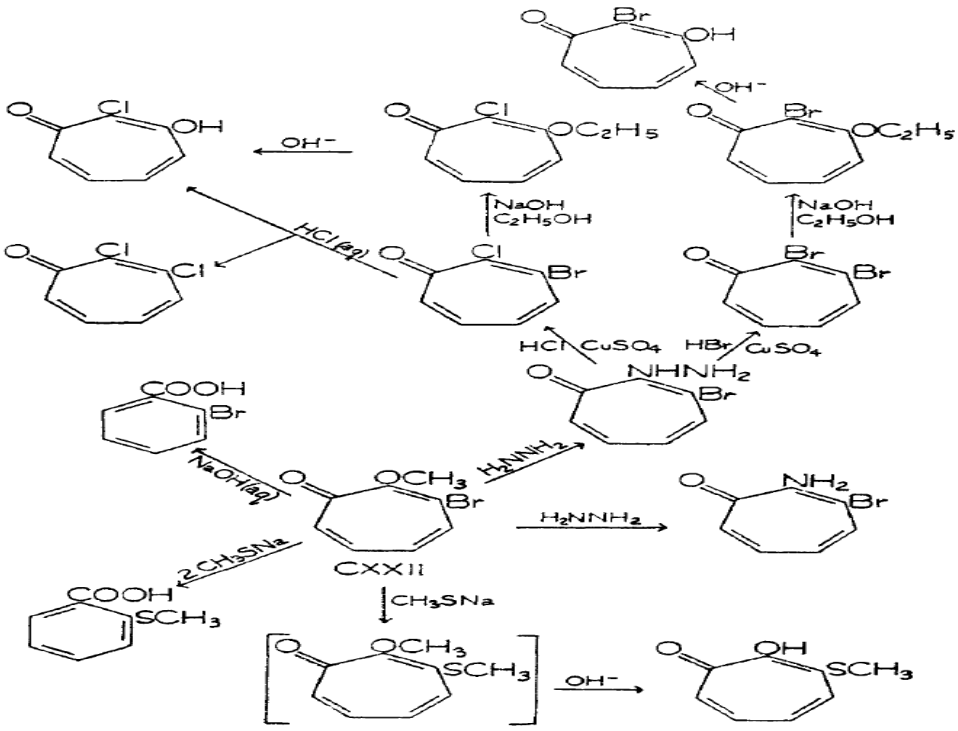


Chart IIIB. Reactions of 3-bromo-2-methoxytropone

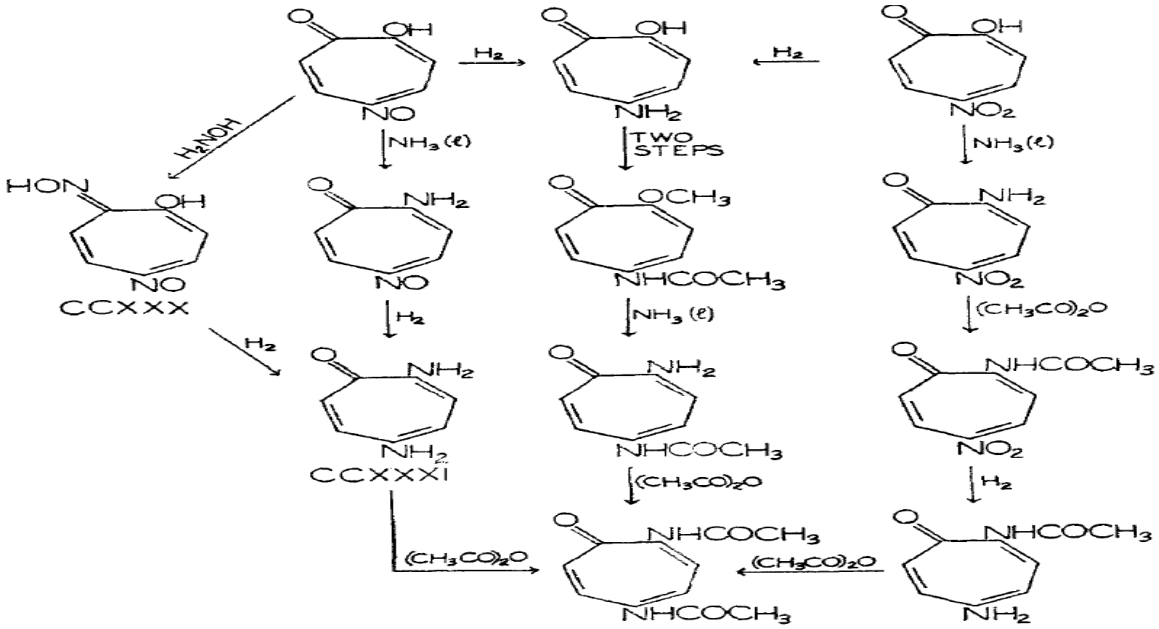


Chart IV. Reactions relating 2,5-diaminotropone to 5-substituted tropolones

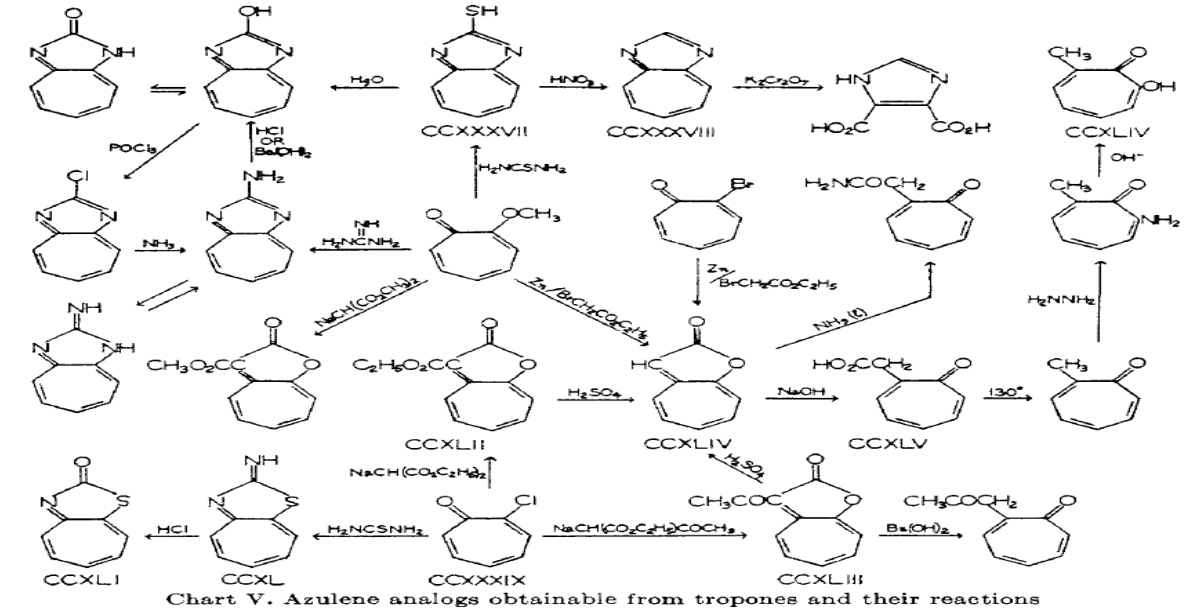
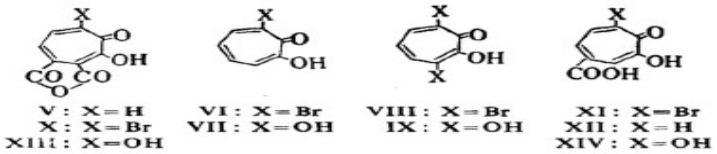


Chart V. Azulene analogs obtainable from tropones and their reactions

These charts give you an idea of the detail in this review but there's much more worth reading. Its also amazing how much activity there was before 1954!

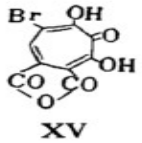


V : X=H
X : X=Br
XIII : X=OH

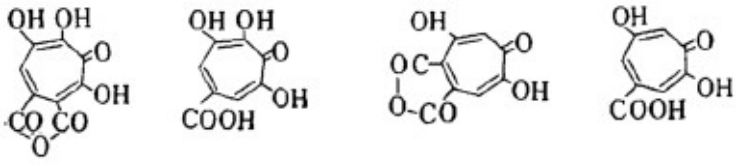
VI : X=Br
VII : X=OH

VIII : X=Br
IX : X=OH

XI : X=Br
XII : X=H
XIV : X=OH



XV



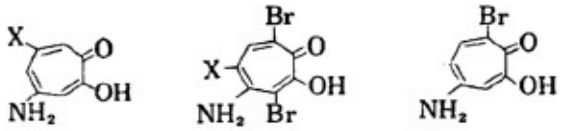
I II III IV

The present authors have been able to synthesize puberulonic acid (I), the details of which will be reported in this communication.

Nozoe, T., Doi, K., & Hashimoto, T. (1960). Synthesis of puberulonic acid. *Bulletin of the Chemical Society of Japan*, *33*(8), 1071-1074.

Prof. Nozoe was the leading authority concerning tropone and tropolone chemistry. His papers although complete in every respect need to be carefully read as they do not contain summary figures. Compounds V-XV are the reagents but you have to read the article to know how they are used.

The following reference is another example where summary schemes are not shown. An excerpt shows how the reactions are described.



I: X=H
II: X=Me

III: X=Br
V: X=H

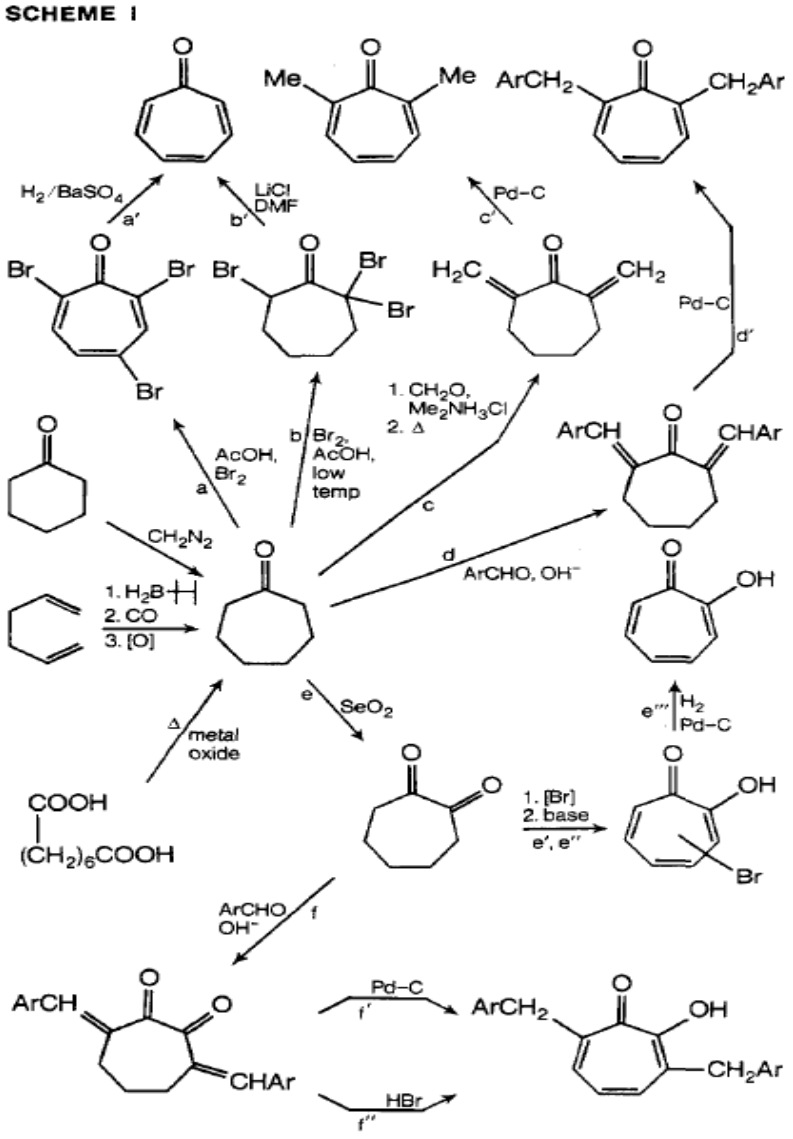
IV

On bromination the aminotropolone (I) has been found to give nuclear substitution products in the same manner as many other tropolones. For example, in the presence of sodium acetate as a hydrogen bromide acceptor, I consumes three molar equivalents of bromine to afford in a good yield the tribromotropolone (III). On the other hand, in the absence of any hydrogen bromide acceptor, I reacts with one molar equivalent of bromine to give not only a monobromo derivative, IV, which was identified with that obtained from an application of the Schmidt reaction to the known 6-acetyl-3-bromotropolone[2], but also a dibromo compound, V, whose respective yield is better in the latter than the former. Such a preferential formation of dibromo compound by one molar equivalent of bromine has also been observed in the case of tropolone itself[5].

Doi, K. (1961). Some Electrophilic Substitution Reactions of 4-Aminotropolone. *Bulletin of the Chemical Society of Japan*, *34*(10), 1410-1414.

The following review is by Prof. Nozoe from 1971 and it reviews Japaneese chemists contributions to this chemistry. There are numerous examples and I suggest if interested you read it as it is too unwiedly to go into.. Prof. Nozoe was by far one of the experts concerning this chemistry.

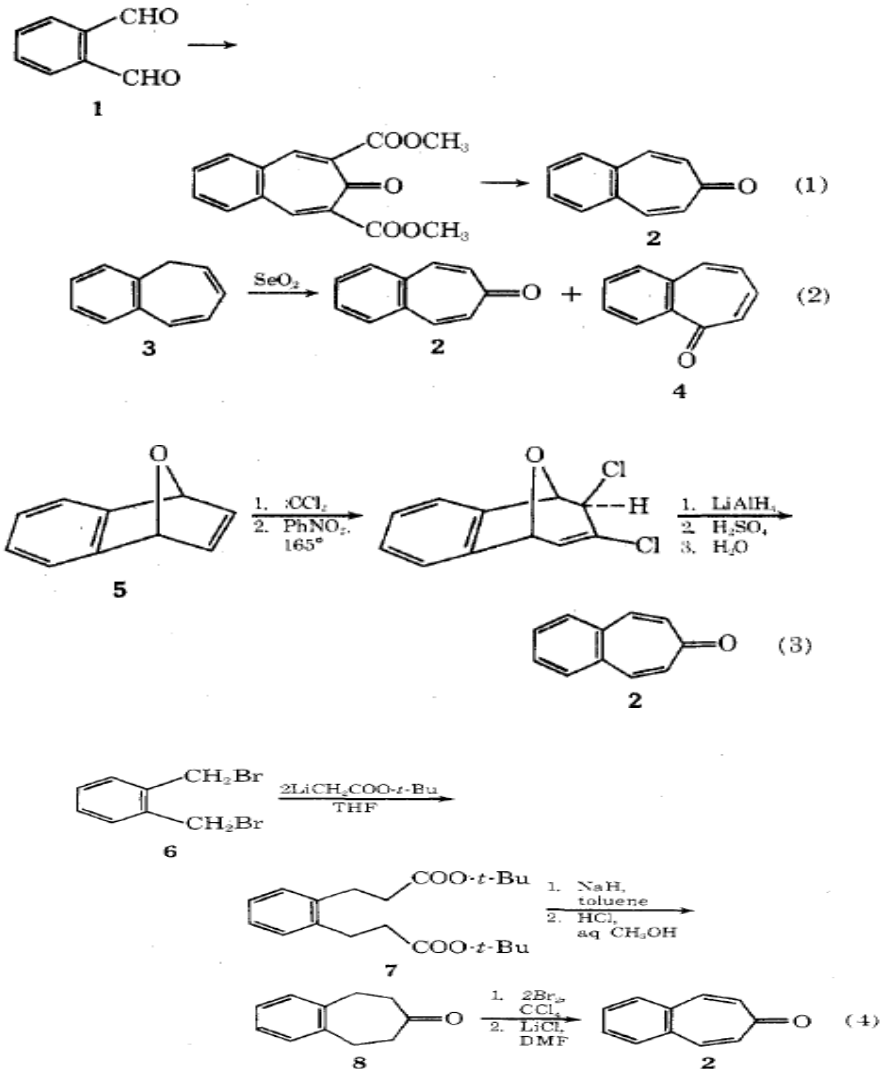
Nozoe, T. (1971). Recent advances in the chemistry of troponoids and related compounds in Japan. *Pure and Applied Chemistry*, *28*(2-3), 239-280.



Pietra, F. (1973). Seven-membered conjugated carbo-and heterocyclic compounds and their homoconjugated analogs and metal complexes. Synthesis, biosynthesis, structure, and reactivity. *Chemical Reviews*, *73*(4), 293-364.

The above is just a sample of what is in this review! Prof. Pietra affords a masterful review with over 600 references through 1973. This is a 72 page review of everything in

this time frame. This review is very well done!



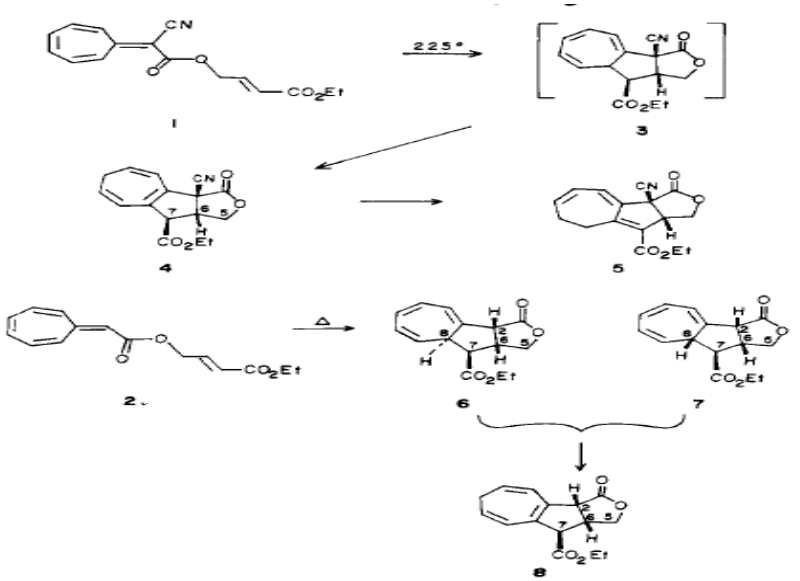
Ewing, G. D., & Paquette, L. A. (1975). Efficient synthesis of 4, 5-benzotropone from o-xylylene dibromide. *The Journal of Organic Chemistry*, *40*(20), 2965-2966.

1a : X=*p*-CH_3
1b : X=H
1c : X=*p*-CH_3O
1d : X=*p*-Cl
1e : X=*o*-CH_3
1f : X=*o*-CH_3O

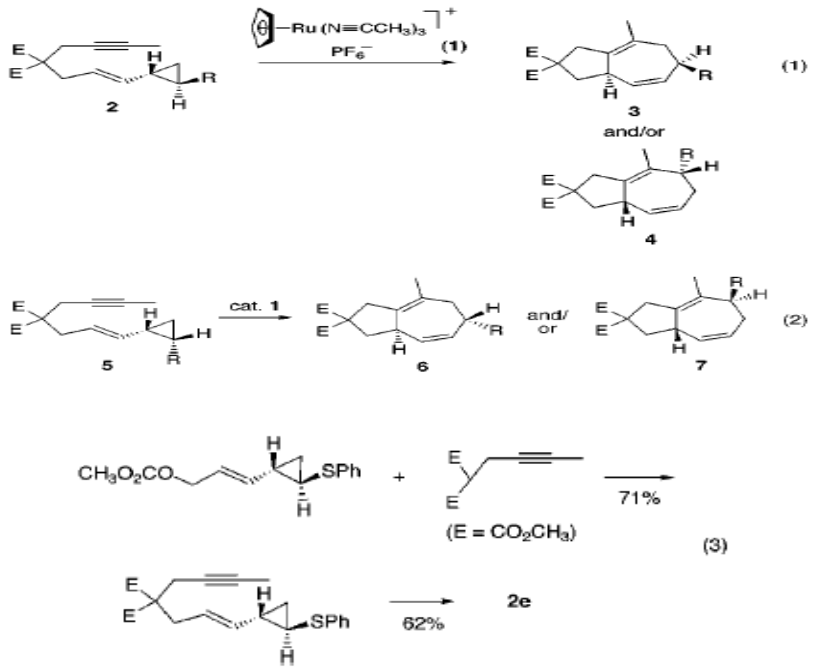
2a : X=*p*-CH_3
2b : X=H
2c : X=*p*-CH_3O
2d : X=*p*-Cl

When tropone was treated in a closed vessel with a solution of copper(II) acetate and *p*-toluidine in methanol at room temperature for several days, 2-*p*-toluidinotropone (**1a**) and 1-(*p*-toluidino)-7-(*p*-tolylimino)-1,3,5-cycloheptatriene (**2a**)[4] were obtained in about 39 and 17% yields respectively. That the reaction

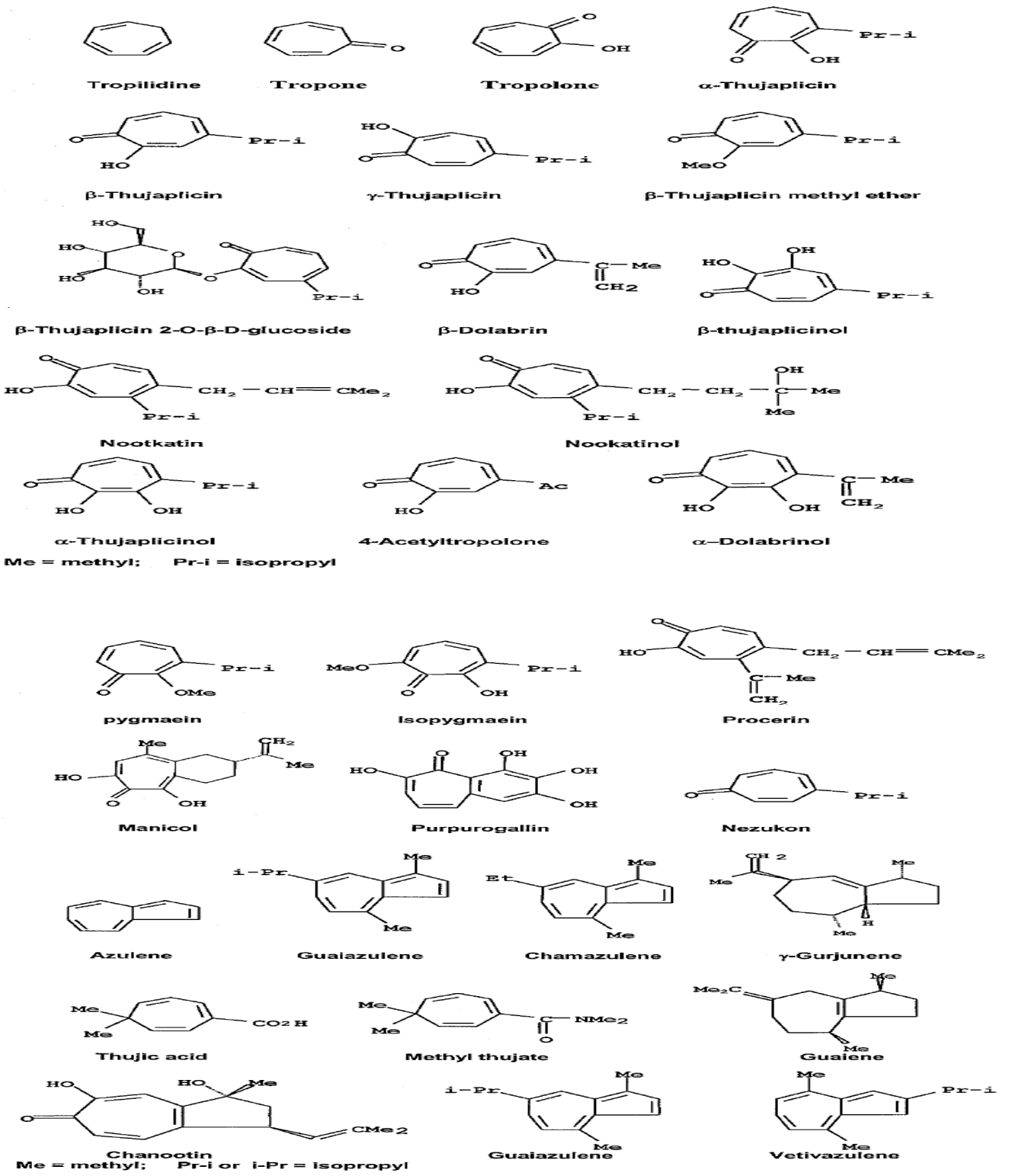
Kikuchi, K., Maki, Y., & Sato, K. (1978). The Oxidative Animation of Tropone and Tropolone. *Bulletin of the Chemical Society of Japan*, *51*(8), 2338-2341.



Liu, C. Y., Mareda, J., Houk, K. N., & Fronczek, F. R. (1983). Intramolecular [8+ 2] cycloadditions of alkenylheptafulvenes. *Journal of the American Chemical Society*, *105*(22), 6714-6715.



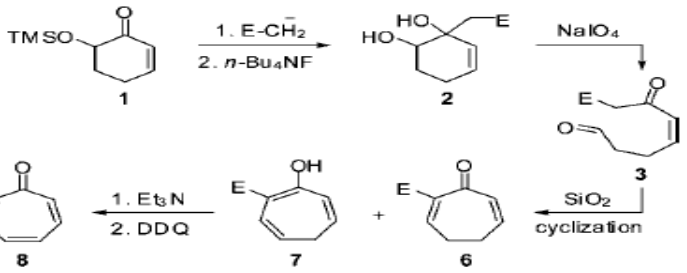
Trost, B. M., & Shen, H. C. (2000). On the Regioselectivity of the Ru-Catalyzed Intramolecular [5+ 2] Cycloaddition. *Organic letters*, *2*(16), 2523-2525.



ig. (2). A. Basic seven-membered ring structures and natural plant troponoids. B. Plant troponoids and azulene compounds.

Zhao, J. (2007). Plant troponoids: chemistry, biological activity, and biosynthesis. *Current medicinal chemistry*, *14*(24), 2597-2621.

SCHEME 2. Reaction Sequence for Dihydrotropone Synthesis by the Ring-Expansion Strategy[a]



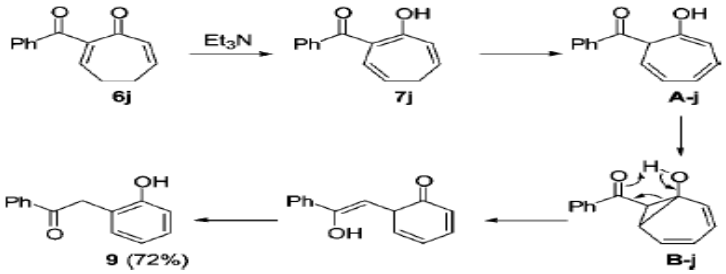
[a] See Table 2 for yields and conditions.

TABLE 2. Yields of Diols 2, Dihydrotropones 6/Cycloheptatrienols 7, and Tropones 8 in Scheme 2

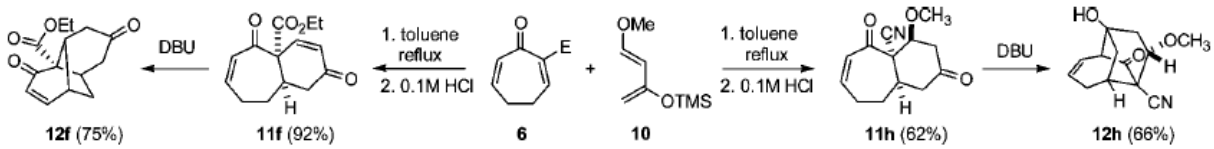
entry	compd	E	2 (%)[a,b]	6/7 (%)[a]	8 (%)[a]
1	f	CO_2Et	85 (6:1)	62/31	95
2	g	$C(O)CH_3$	63 (2.7:1)	70/ 9	96
3	h	CN	94 (1.3:1)	100/0	76
4	i	$C(O)CH_2CO_2Et$	65 (2.3:1)	73/0[c]	*d*
5	j	C(O)Ph	60 (10:1)	56/8	50[e]
6	k	$C(O)NMe_2$	85 (5:1)	63/0[f]	64[g]
7	l	SO_2Ph	95 (2:1)	58/19	86[h]

[a] Isolated yields after purification by SiO_2 flash column chromatography. [b] Diastereomeric ratios in parenthesis. [c] Crude yield. [d] Decomposition of **6i** presumably due to oligomerization. [e] Oxidation was carried out by DDQ in refluxing toluene without Et_3N. [f] $Pb(OAc)_4$ was used instead of $NaIO_4$ to induce oxidative ring-opening reaction. [g] DBU was used instead of Et_3N for tautomerization. [h] Cyclohepta-2,4,6-trienone (**8l**) was obtained by dehydrosulfonation.

SCHEME 3. Ring Contraction of Dihydrotropone 6j

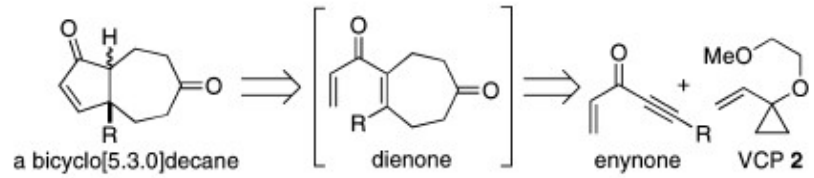


SCHEME 4. Diels–Alder Reaction of Dihydrotropones 6 To Produce Polycyclic Compounds



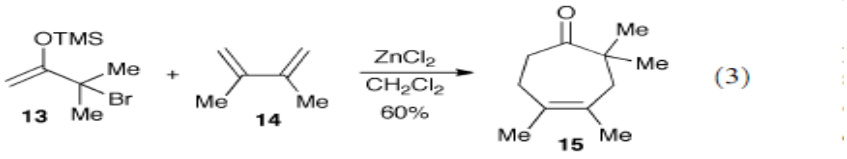
Do, Y. S., Sun, R., Kim, H. J., Yeo, J. E., Bae, S. H., & Koo, S. (2008). Ring-Expansion Protocol: Preparation of Synthetically Versatile Dihydrotropones. *The Journal of organic chemistry*, *74*(2), 917-920.

Scheme 1. [5+2] Cycloaddition/Nazarov Cyclization Sequence



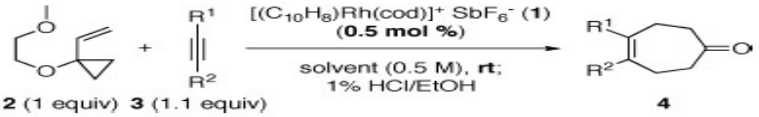
Wender, P. A., Stemmler, R. T., & Sirois, L. E. (2010). A metal-catalyzed intermolecular [5+ 2] cycloaddition/Nazarov cyclization sequence and cascade. *Journal of the American Chemical Society*, *132*(8), 2532-2533.

Fig. 1 Generic (4 + 3)-cycloaddition reaction.



Harmata, M. (2010). The (4+ 3)-cycloaddition reaction: simple allylic cations as dienophiles. *Chemical Communications*, *46*(47), 8886-8903.

Table 1. Intermolecular [5 + 2] Cycloadditions Catalyzed by Complex 1



entry		alkyne	solvent[a]	product	time (min)	yield[b]
1			DCE		5	96%
2[c]	**3a**	$SiMe_3$	DCE	**4a**	60	93%
3	**3b**	OMe	DCE:TFE	**4b**	5	94%
4	**3c**	NHTs	DCE:TFE	**4c**	150	94%
5	**3d**	O, OMe	DCE:TFE	**4d**	10	97%
6	**3e**	O	DCE:TFE	**4e**	5	97%
7	**3f**		DCE	**4f**	5	92%
8[d]	**3g**	O, NH_2	DCE:TFE[d]	**4g**	24 h	92%
9	**3h**	O, OMe	DCE	**4h**	5	95%
10	**3i**		DCE	**4i**	10	91%
11	**3j**	MeO, OMe	DCE:TFE	**4j**	15	91%

[a] 1,2-Dichloroethane:2,2,2-trifluoroethanol (90:10, v:v). [b] Isolated yield. [c] 0.2 mol % of catalyst **1**. [d] 60 °C, 0.4 M, DCE:TFE (80:20).

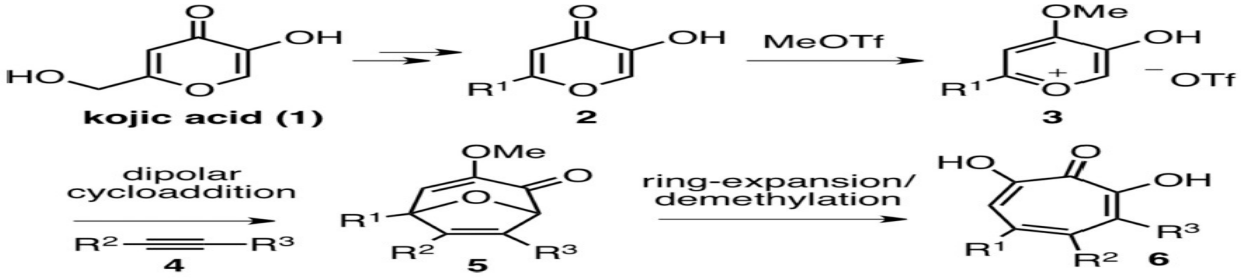
Wender, P. A., Sirois, L. E., Stemmler, R. T., & Williams, T. J. (2010). Highly Efficient, Facile, Room Temperature Intermolecular [5+ 2] Cycloadditions Catalyzed by Cationic Rhodium (I): One Step to Cycloheptenes and Their Libraries. *Organic letters*, *12*(7), 1604-1607.

The following is a detailed review of this reaction;

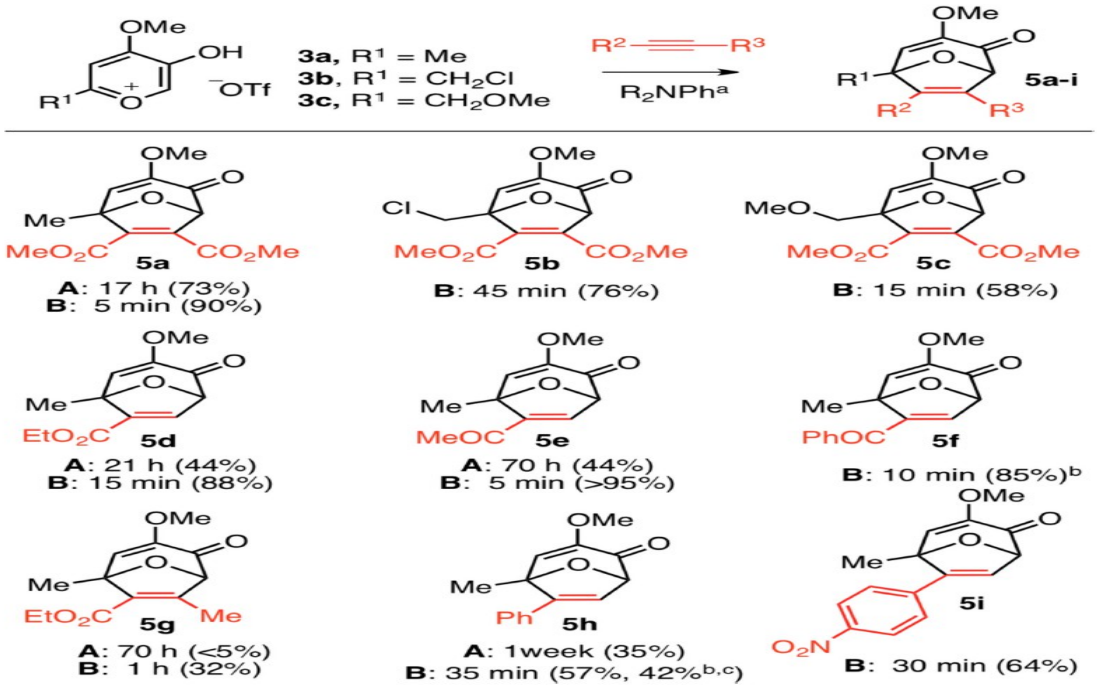
Ylijoki, K. E., & Stryker, J. M. (2012). [5+ 2] Cycloaddition reactions in organic and natural product synthesis. *Chemical reviews*, *113*(3), 2244-2266.

Inaddition the following reference covers many other derivatives of this 5+2 reaction.

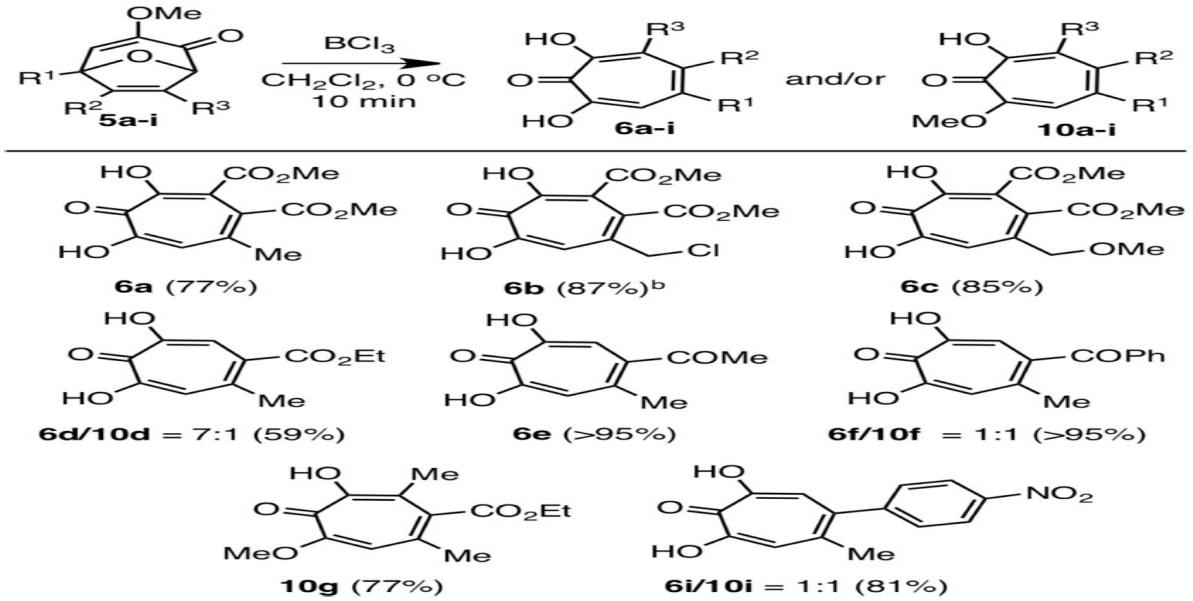
Shu, X. Z., Li, X., Shu, D., Huang, S., Schienebeck, C. M., Zhou, X., ... & Tang, W. (2012). Rhodium-catalyzed intra-and intermolecular [5+ 2] cycloaddition of 3-acyloxy-1, 4-enyne and alkyne with concomitant 1, 2-acyloxy migration. *Journal of the American Chemical Society*, *134*(11), 5211-5221.



Scheme 1.
General route toward polysubstituted α-hydroxytropolones from commercially available kojic acid



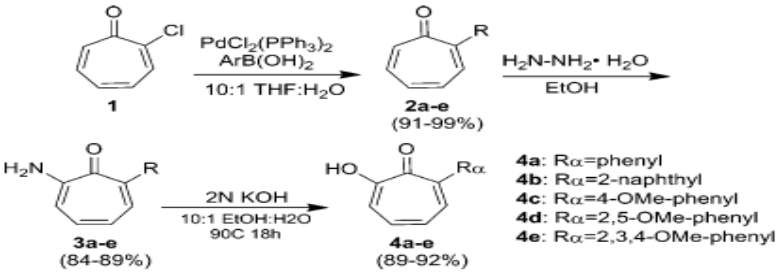
Scheme 3.
Substrate studies for oxidopyrylium cyclization
[a] **Condition A**: 2 equiv of N,N-dimethylaniline, CH_2Cl_2, rt.
Condition B: 1.2 equiv of N,N-diisopropylaniline, $CHCl_3$, 100 °C, μwave. Unless otherwise indicated, 20 equiv of alkyne were used.
[b] 5 equiv of alkyne were used. [c] Reaction run without solvent.



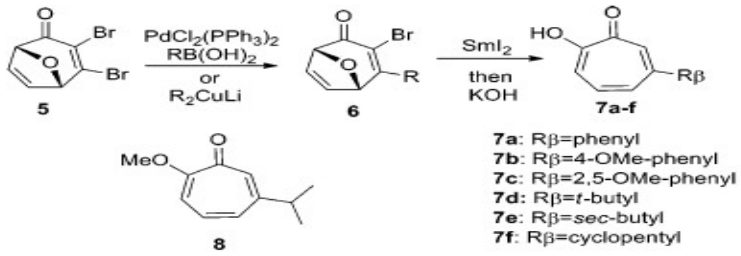
Scheme 5.
Ring-expansion substrate scopea
[a] Reactions were run with 7 equiv of BCl_3 unless otherwise noted. Reaction yields are reported following aqueous workup with ratios of **6a–i** to **10a–i** being calculated by 1H NMR integration.
[b] 15 equiv of BCl_3 were used.

Meck, C., Mohd, N., & Murelli, R. P. (2012). An oxidopyrylium cyclization/ring-opening route to polysubstituted α-hydroxytropolones. *Organic letters*, *14*(23), 5988-5991.

Scheme 1. Synthesis of α-Tropolones

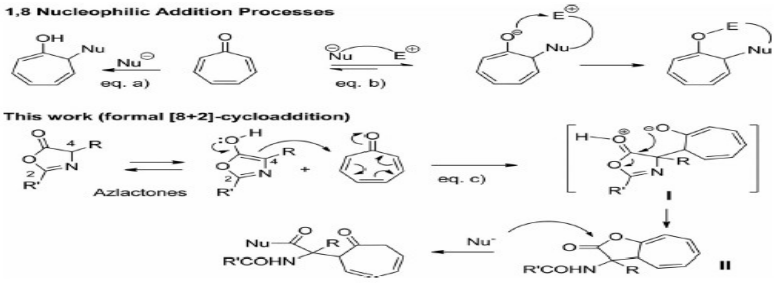


Scheme 2. Synthesis of β-Tropolones



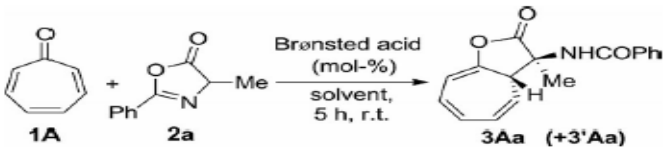
Ononye, S. N., VanHeyst, M. D., Oblak, E. Z., Zhou, W., Ammar, M., Anderson, A. C., & Wright, D. L. (2013). Tropolones as lead-like natural products: the development of potent and selective histone deacetylase inhibitors.

ACS medicinal chemistry letters,*4*(8), 757-761.



Schema 1. Different reactivities of tropone derivatives

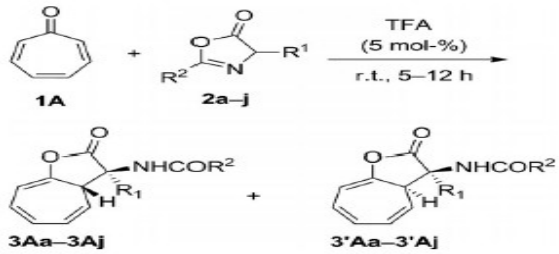
Table 1. Screening results for the addition of **2a** to tropone **1A**.[a]



Entry	Catalyst (mol-%)	Solvent	*dr*[b]	Conversion [%]
1	dpp (5)	CH_2Cl_2	70:30	100
2	BzOH (5)	CH_2Cl_2	70:30	83
3	TsOH (5)	CH_2Cl_2	76:24	65
4	CSA[c] (5)	CH_2Cl_2	73:27[d]	98
5	TFA (5)	CH_2Cl_2	77:23	100
6	TFA (5)	THF	65:35	86
7	TFA (5)	$HCCl_3$	71:29	90
8	TFA (5)	toluene	85:15	100
9	TFA (5)	*p*-xylene	93:7	100 (95)[e]
10	TFA (1)	*p*-xylene	90:10	85[f]
11	TFA (5)	CH_2Cl_2	81:19	25[g, h]

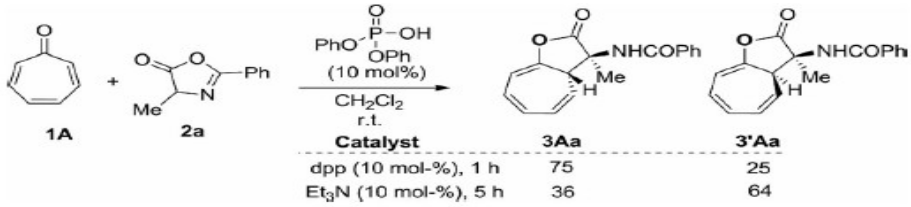
[a] All reactions were performed with **1A** (0.1 mmol), **2a** (0.12 mmol), and solvent (0.3 mL). [b] Diastereomeric ratio determined by ^{1}H NMR spectroscopy. [c] Camphorsulfonic acid. [d] Compound **3Aa** was nearly racemic. [e] Combined isolated yield. [f] Conversion after 24 h. [g] Reaction was performed at 0 °C. [h] Conversion after 48 h.

Table 2. Scope of the 1,8-nucleophilic addition of different azlactones **2a**–**2j** to the tropone **1A**.[a]



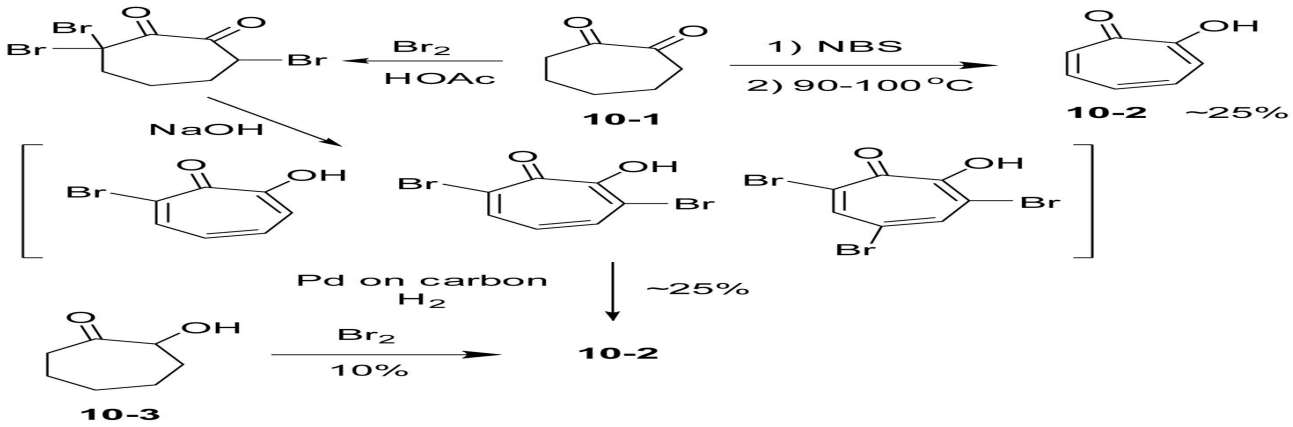
Entry	Azlactone (R^1, R^2)	*dr*[b] (3/3′)	Compound[c] (yield [%])
1	**2a** (Me, Ph)	93:7	**3Aa** (95)
2	**2b** (*n*Pr, Ph)	93:7	**3Ab** (95)
3	**2c** ($PhCH_2CH_2$, Ph)	88:12	**3Ac** (95)
4	**2d** (CH_3SCH_2, Ph)	87:13	**3Ad** (98)
5	**2e** ($PhCH_2$, Ph)	88:12	**3Ae** (89)
6	**2f** ($CyCH_2$, Ph)	81:19	**3Af** (76)
7	**2g** (*i*PrCH_2, Ph)	86:14	**3Ag** (91)
8	**2h** (*i*Pr, Ph)	94:6	**3Ah** (70)
9	**2i** (Ph, Ph)	62:38	**3Ai** (92)
10	**2j** (Me, Me)	85:15	**3Aj** (32)

[a] All reactions were performed with **1A** (0.1 mmol) and **2** (0.12 mmol) in xylene (0.3 mL). [b] Diastereomeric ratio determined by ^{1}H NMR spectroscopy. [c] Combined isolated yield.

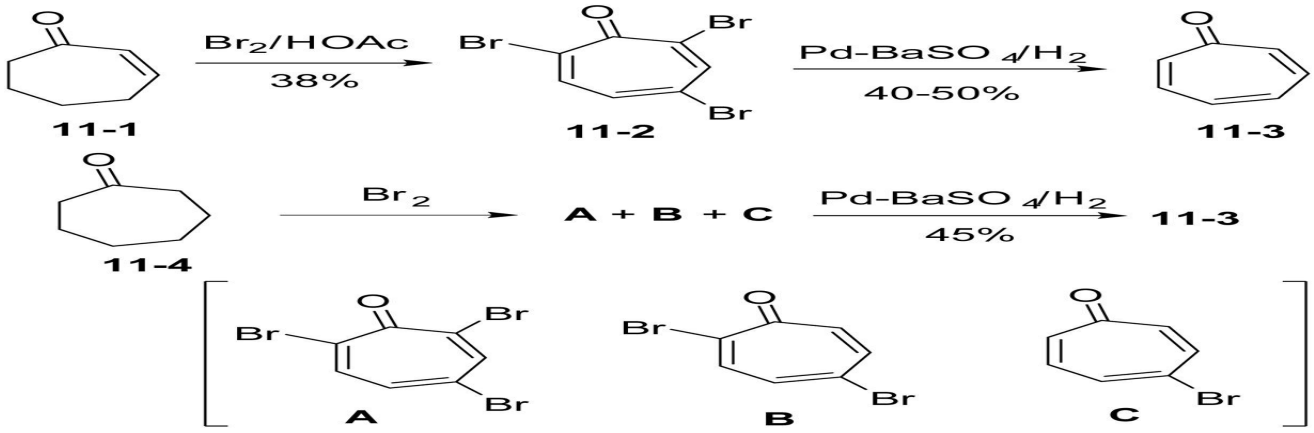


Scheme 2. Reaction of the tropone **1A** with the azlactone **2a** under different conditions.

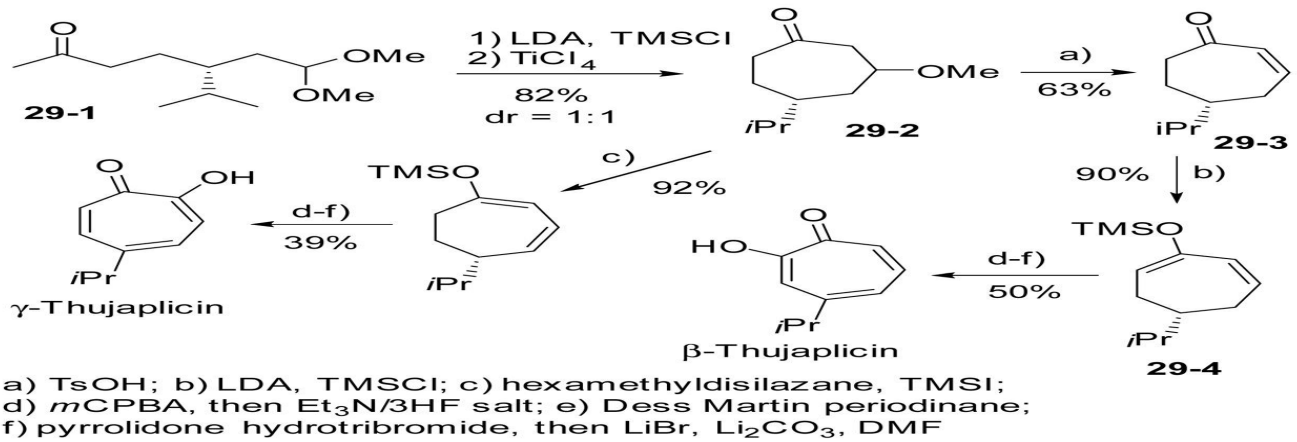
Esteban, F., Alfaro, R., Yuste, F., Parra, A., Ruano, J. L. G., & Aleman, J. (2014). [8+ 2] Formal Cycloaddition Reactions of Tropones with Azlactones under Brønsted Acid Catalysis and Synthesis of α-(2-Tropyl), α-Alkyl α-Amino Acids. *European Journal of Organic Chemistry*, *2014*(7), 1395-1400.



Scheme 10. Oxidation of 1,2-cycloheptanedione and 2-hydroxycycloheptanone by bromine and NBS



Scheme 11.
Oxidation of cycloheptanone to tropone by Br2

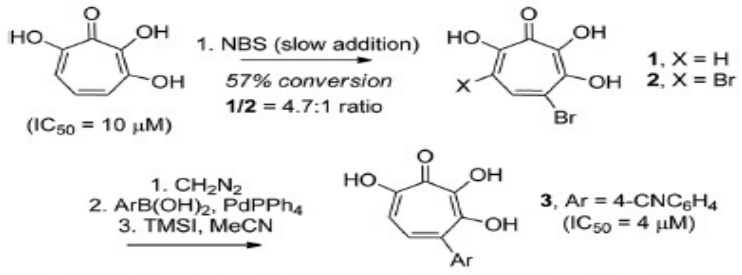


Scheme 29.

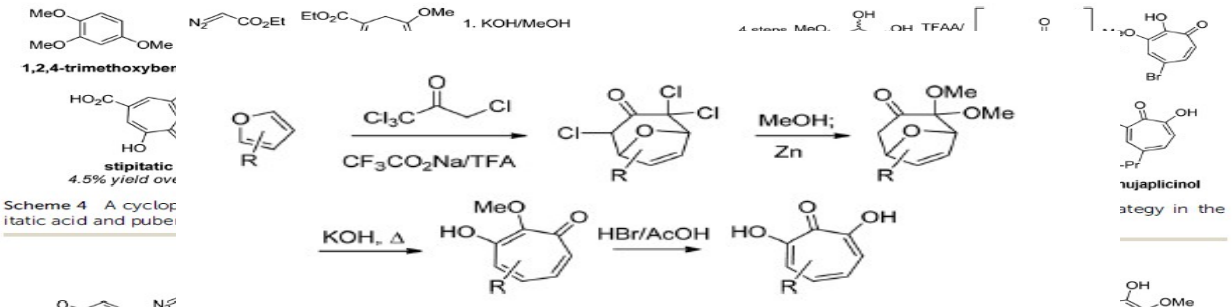
Divergent regioselective synthesis of thujaplicins

This very detailed review has 75 schemes illustrating the synthesis of Naturally Occurring Tropones and Tropolones and the above are just examples to give you an idea of its value.

Liu, N., Song, W., Schienebeck, C. M., Zhang, M., & Tang, W. (2014). Synthesis of naturally occurring tropones and tropolones. *Tetrahedron*, *70*(49), 9281.



Scheme 2 Method for functionalizing 3,7-dihydroxytropolone, and inhibitory activity against inositol monophosphatase.



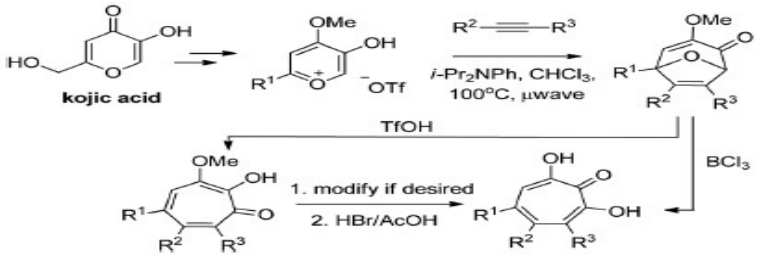
Scheme 4 A cyclop... itatic acid and pube...

...ategy in the

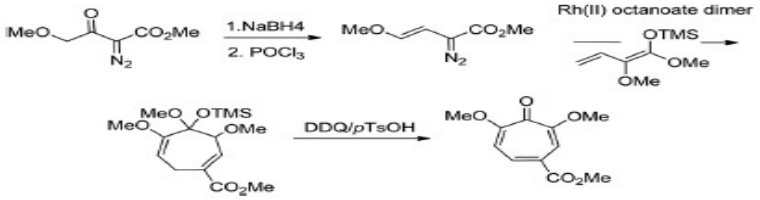
Scheme 8 [4 + 3] Cycloaddition approach to α-hydroxytropolones leveraging the ring-opening of 8-oxabicyclo[3.2.1]octenes.

Scheme 5 Singlet oxygen oxidation/cobalt-mediated rearrangement to form αHTs from cyclopropanation-generated cyclohexatrienes.

Scheme 7 A cyclopropanation/Grob fragmentation strategy in the synthesis of puberulic acid.



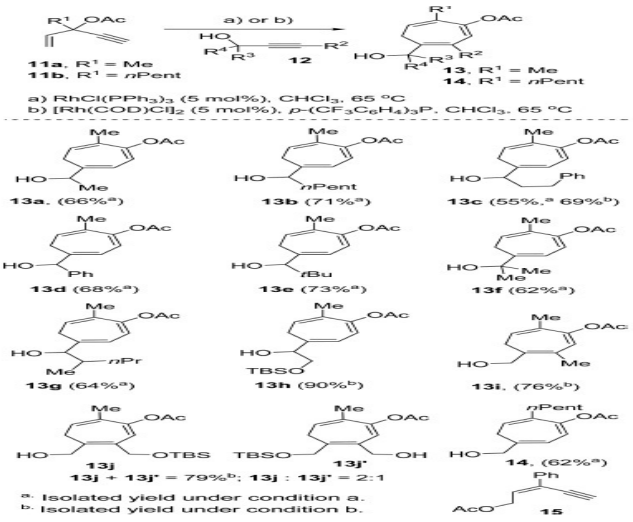
Scheme 9 An oxidopyrylium cycloaddition/ring-opening route to α-hydroxytropolones. The ring-opening can be conducted with either triflic acid or boron trichloride, the latter of which will often lead directly to the α-hydroxytropolone.



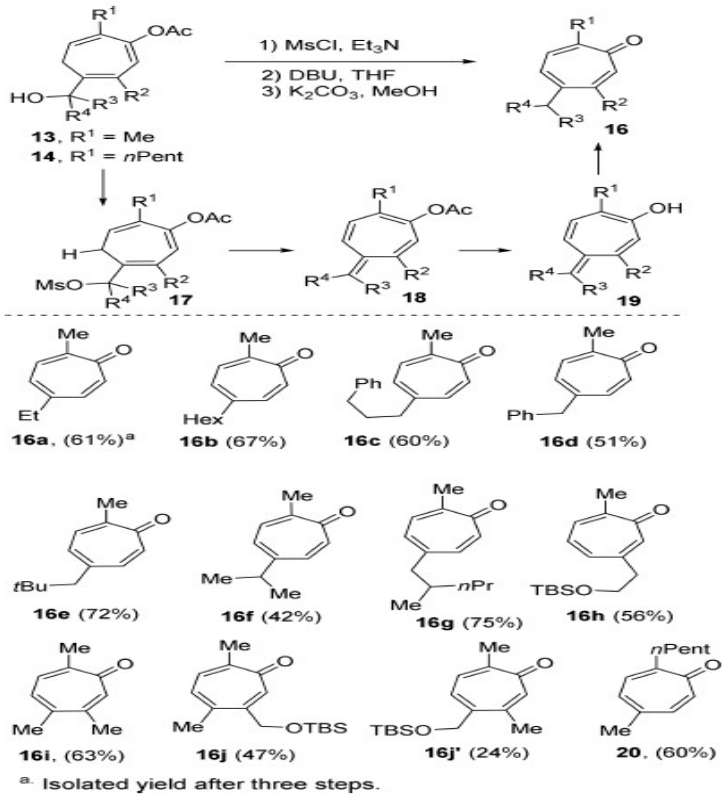
Scheme 10 A cyclopropanation/Cope rearrangement strategy to highly oxidized tropones.

Meck, C., D'Erasmo, M. P., Hirsch, D. R., & Murelli, R. P. (2014). The biology and synthesis of α-hydroxytropolones. *MedChemComm*, *5*(7), 842-852.

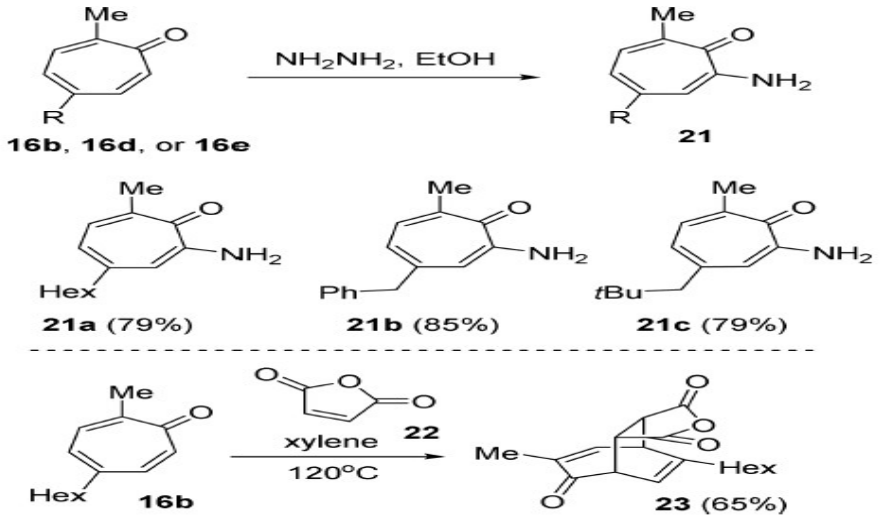
This reference is of great value. Although it revolves around natural derivatives, the reactions can be applied to tropolones in general.



Scheme 3.
Synthesis of substituted cyclohepatrienes

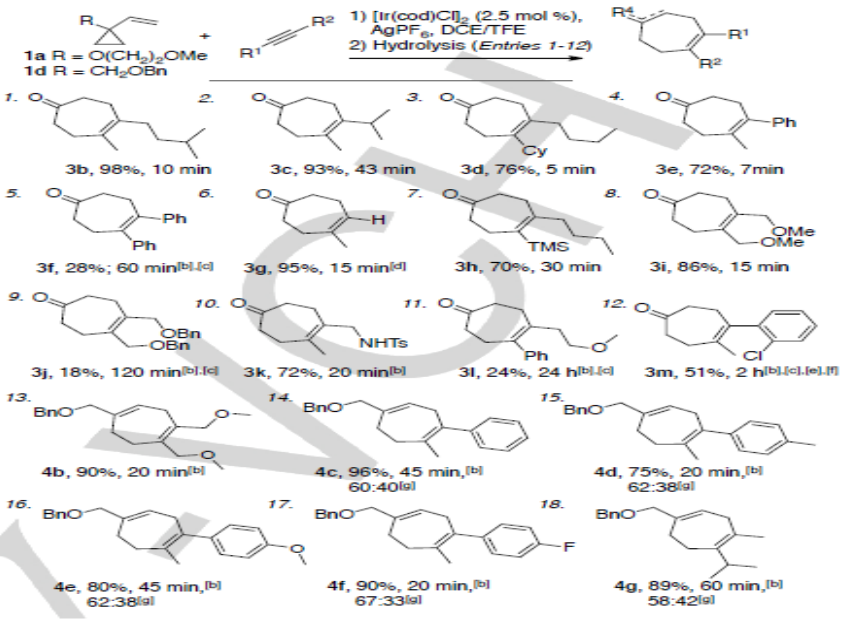


Scheme 4.
Synthesis of substituted tropones



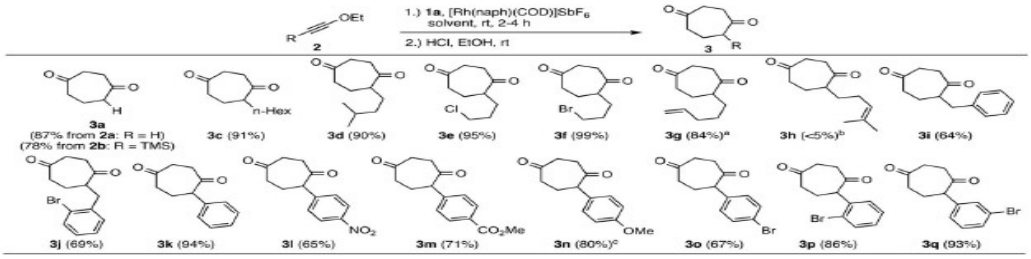
Scheme 5.
Amination and cycloaddition of substituted tropones

Song, W., Xi, B. M., Yang, K., & Tang, W. (2015). Synthesis of substituted tropones by sequential Rh-catalyzed [5+2] cycloaddition and elimination. *Tetrahedron*, *71*(35), 5979-5984.



[a] Isolated yields are given unless otherwise stated. [b] $[Ir(dbcot)Cl]_2$ was used. [c] 5.0 mol % pre-catalyst used. [d] 1-Trimethylsilylpropyne was used as the alkyne component. [e] Yield determined by ^1H NMR spectroscopy of the reaction crude using 1-methoxynaphtalene as internal standard. [f] HFIP was used. [g] Ratio of regioisomers measured by ^1H NMR spectroscopy of the reaction crude. Major regioisomer is shown.

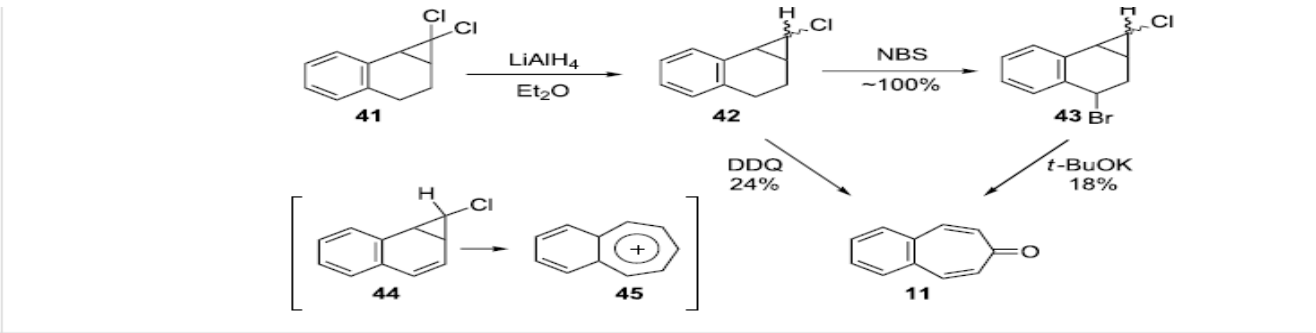
Melcher, M. C., von Wachenfeldt, H., Sundin, A., & Strand, D. (2015). Iridium Catalyzed Carbocyclizations: Efficient (5+ 2) Cycloadditions of Vinylcyclopropanes and Alkynes. *Chemistry–A European Journal*, *21*(2), 531-535.



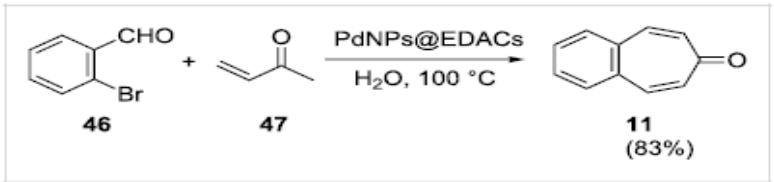
Scheme 2. Substrate Scope[d]

[a]Additional 12% of double bond migration byproduct were isolated. [b]Complex product mixture was formed. [c]**2n** was added over 4 h. [d]Reaction conditions: 5 mol % catalyst, 1.0 equiv VCP, 1.1 equiv ynol ether added dropwise over 2 h. Solvent: TFE (**3a–3h**), TFE/DCE 1:1 (**3i–3q**). For aryl substituted ynol ether (**3k–3q**), the reaction mixture was stirred for additional 2 h.

Wender, P. A., Ebner, C., Fennell, B. D., Inagaki, F., & Schröder, B. (2017). Ynol Ethers as Ketene Equivalents in Rhodium-Catalyzed Intermolecular [5+ 2] Cycloaddition Reactions. *Organic letters*, *19*(21), 5810-5813.

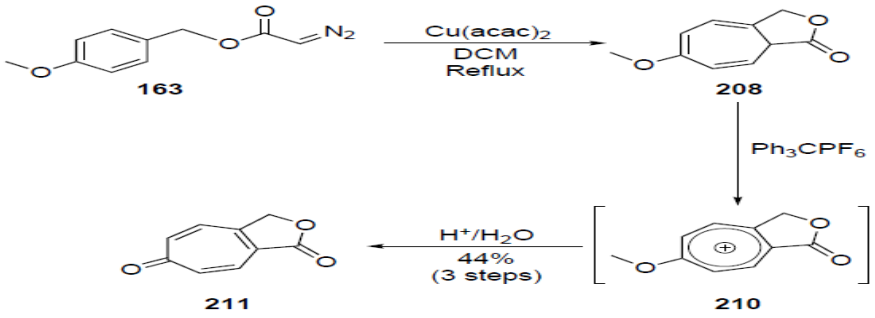


Scheme 9: Synthesis of 4,5-benzotropone (**11**) via the carbene adduct **41**.

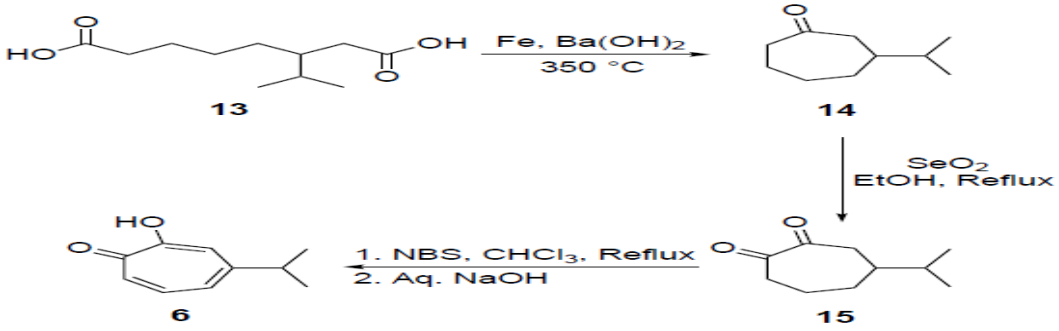


Scheme 10: Heck coupling strategy for the synthesis of **11**.

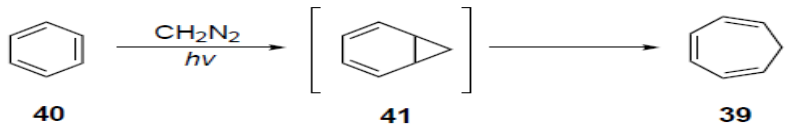
Dastan, A., Kilic, H., & Saracoglu, N. (2018). One hundred years of benzotropone chemistry. *Beilstein journal of organic chemistry*, *14*(1), 1120-1180.



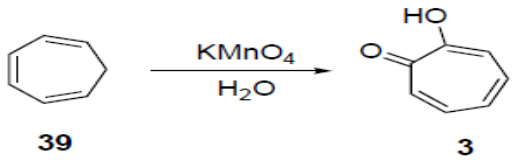
Scheme 1: Buchner ring expansion followed by oxidation via hydride abstraction to produce tropone **211**



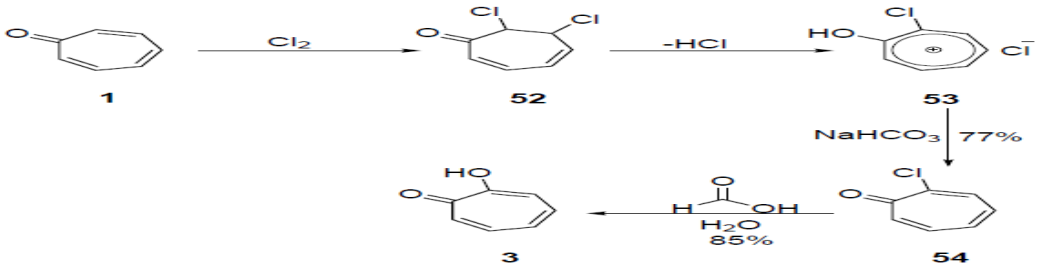
Scheme 1.1: Nozoe's synthesis of β-thujaplcin



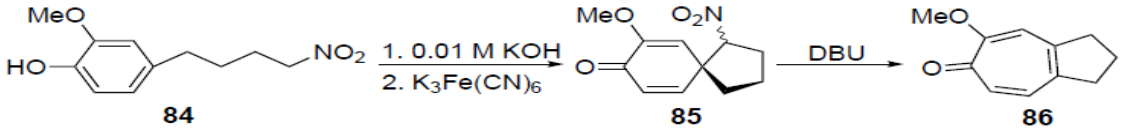
Scheme 1.3: Cycloheptatriene **39** was synthesised from benzene **40** by carbene addition of diazomethane



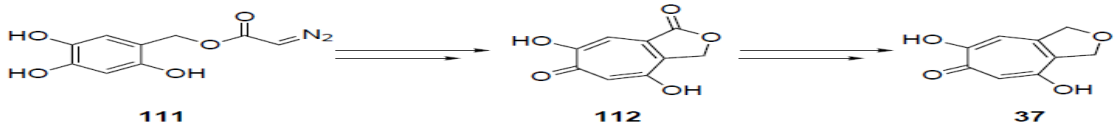
Scheme 1.4: Cycloheptatriene **39** was oxidised to tropolone using permanganate



Scheme 1.10: Chlorination of tropone **1** to give tropolone **3**



Scheme 1.19: Intramolecular reaction of a phenolic nitro alkane to produce a tropolone



Scheme 1.28: Buchner ring expansion with diazoester **111** would produce lactone **112** which would need to be removed to produce cordytropolone **37**

Wells, J. M. (2018). *New Routes to Troponoid Natural Products* (Doctoral dissertation, Curtin University).

Dr. Wells thesis is well worth looking at!

I hope this of value!

Dr. Robert B. Login rloginconsulting.com