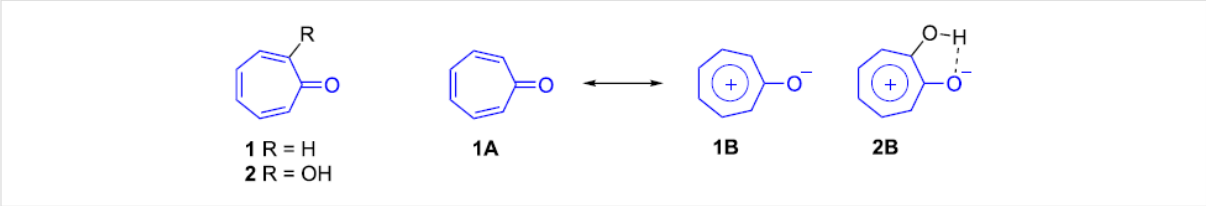
Tropone and Azulene ImiD Analogs

By: Robert B. Login rloginconsulting.com

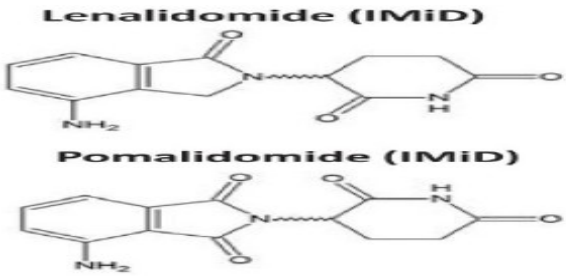
"Immunomodulatory imide drugs (**IMiDs**) are a class of immunomodulatory drugs (drugs that adjust immune responses) containing an imide group. The **ImiD** class includes thalidomide and its analogues (lenalidomide, pomalidomide, and apremilast)". Wikipedia

Tropone and tropolone are nonbenzenoid aromatic cyclic seven membered compounds.

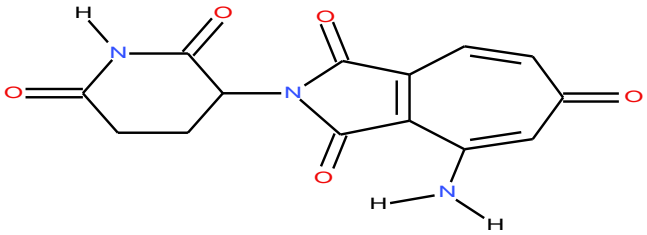


Scheme 1: Tropone (**1**), tropolone (**2**) and their resonance structures.

Thinking about ImiD's anti-cancer drugs such as lenalidomide and pomalidomide that have the following structures:



It struck me that the following analog could be possible.

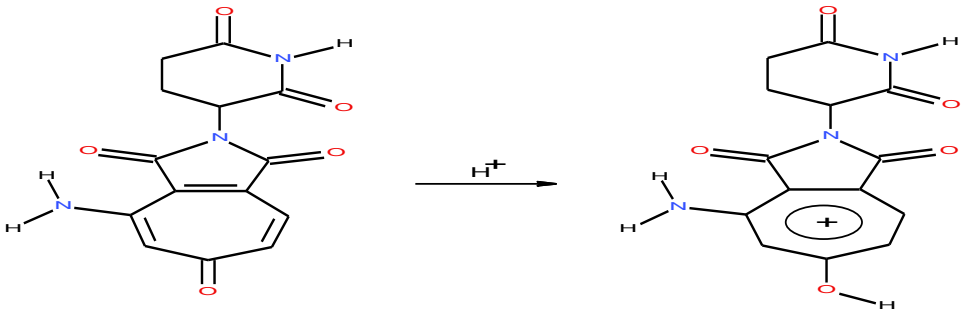


4-amino-2-(2,6-dioxo-3-piperidyl)cyclohepta[c]pyrrole-1,3,6-trione

Of course I have no idea if this compound would be of value in treating multiple myeloma or for anything else but what attracts me to this type of compound is the remarkable utility of tropone derivatives in a variety of important natural product medicinals. The placement of the amine, if it's even required, can be, if needed, at other locations on the tropone ring.

Considering the resonance structures, I would think that the positive ionic aromatic

structure would prevail in the acidic cancer cell environment. If the amine also protonates then two positive charges would occur which is not favorable and if the amine donates its pair of electrons then the aromaticity would be gone, hence the amine might be free and hence a completely different ImiD effect might be observed.



Scheme 1: Is the oxygen more basic or is the amine? Since aromaticity is a powerful driving force and with the positive charge, I don't believe the amine would be very basic.

Synthesis:

The literature concerning Tropone chemistry is quite extensive. There are several reviews (see rloginconsulting.com for brief review):

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

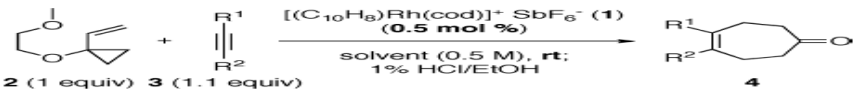
Pietra, F. (1973). Seven-membered conjugated carbo-and heterocyclic compounds and their homo-conjugated analogs and metal complexes. Synthesis, bio-synthesis, structure, and reactivity. *Chemical Reviews*, *73*(4), 293-364.

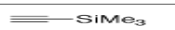
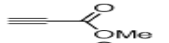
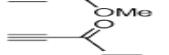
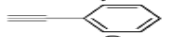
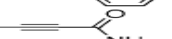
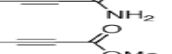
Ylijoki, K. E., & Stryker, J. M. (2012). [5+ 2] Cycloaddition reactions in organic and natural product synthesis. *Chemical reviews*, *113*(3), 2244-2266.

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

Pellissier, H. (2018). Recent Developments in the [5+ 2] Cycloaddition. *Advanced Synthesis & Catalysis*, *360*(8), 1551-1583.

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

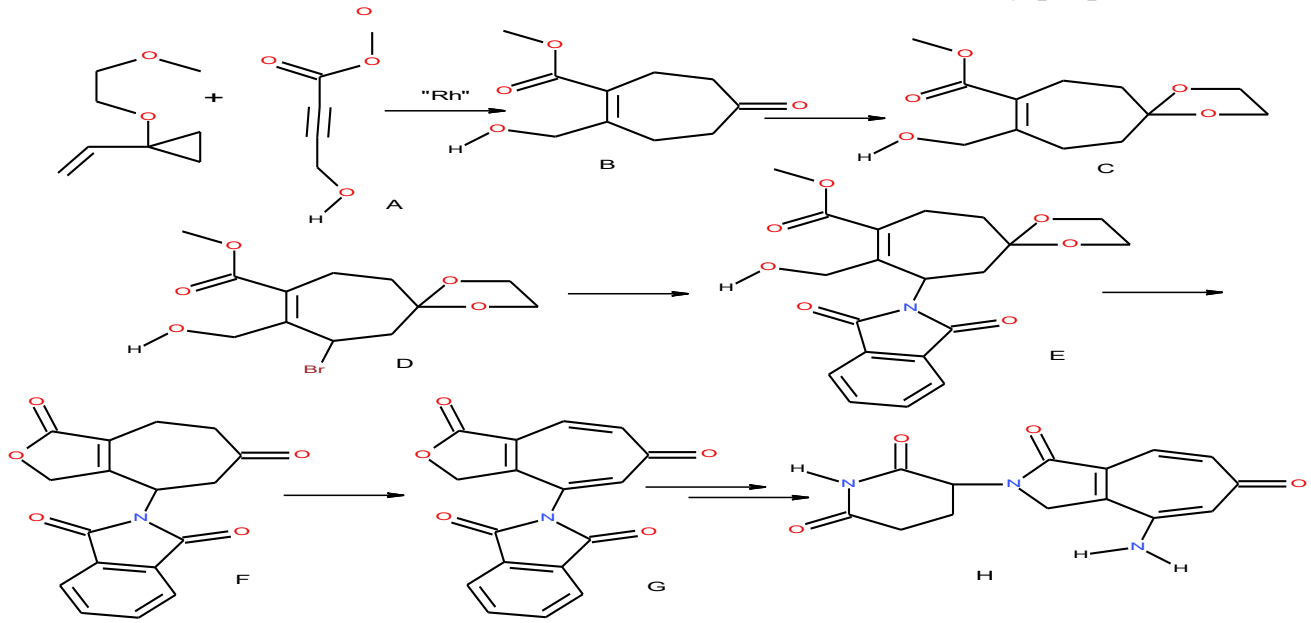


entry		alkyne	solvent[a]	product	time (min)	yield[b]
1	**3a**		DCE	**4a**	5	96%
2[c]	**3a**		DCE	**4a**	60	93%
3	**3b**		DCE:TFE	**4b**	5	94%
4	**3c**		DCE:TFE	**4c**	150	94%
5	**3d**		DCE:TFE	**4d**	10	97%
6	**3e**		DCE:TFE	**4e**	5	97%
7	**3f**		DCE	**4f**	5	92%
8[d]	**3g**		DCE:TFE[d]	**4g**	24 h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

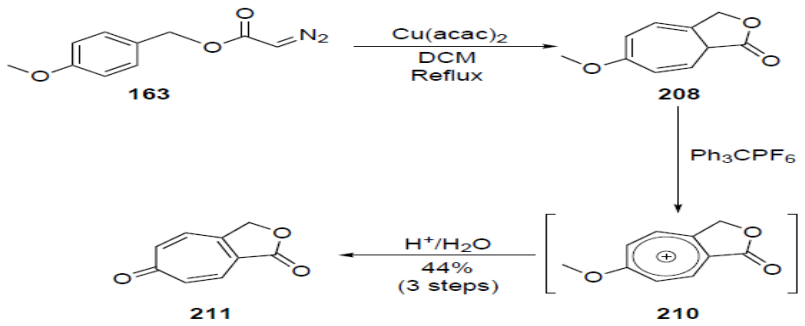
Wender, P. A., Sirois, L. E., Stemmler, R. T., & Williams, T. J. (2010). Highly Efficient, Facile, Room Temperature Intermolecular [5+ 2] Cycloadditions Catalyzed by Cationic Rhodium (I): One Step to Cycloheptenes and Their Libraries. *Organic letters*, *12*(7), 1604-1607.

Of all the references the above one seems to be the most useful to my proposals.



Scheme 2: My idea for a synthesis of the lenalidomide analog. Intermediate A, the alcohol group probably needs to be protected since none of Wender's examples have a free alcohol. The bromine derivative D is at the allylic position and should be doable

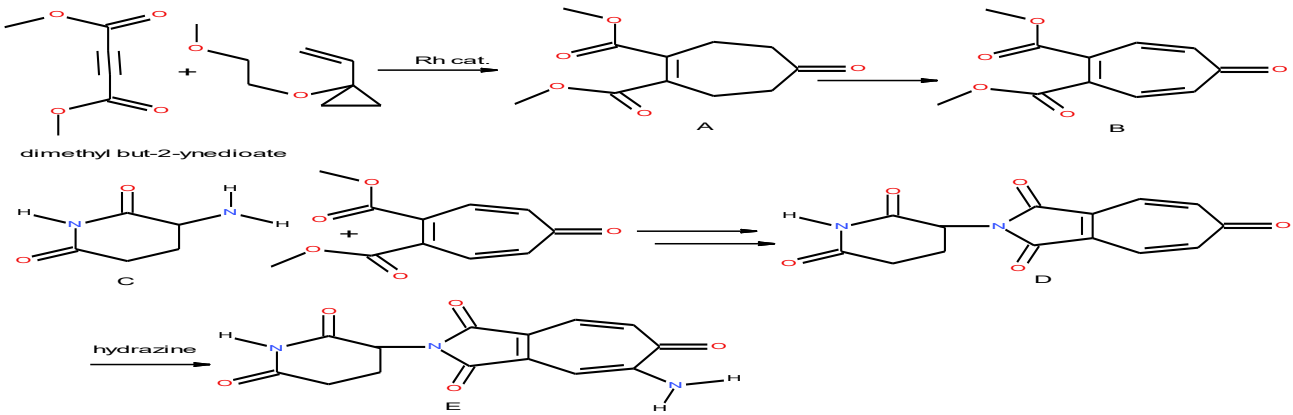
with ammonia. But D to E might also do a Michael on the double bond? Other amine protective groups might be better?



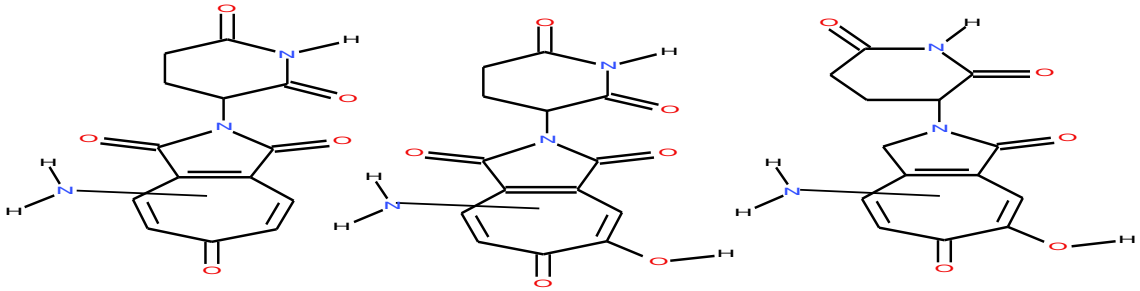
Scheme 1: Buchner ring expansion followed by oxidation via hydride abstraction to produce tropone **211**

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

The Wells' thesis shows a method to synthesize a starting compounds that can be readily converted to a ImiD with 3-Aminoglutarimide.



Scheme 3: My idea for the synthesis of a pomalidomide type analog. Note it was simpler to use the known reaction of hydrazine to put the amine on the 2 position. I'm just guessing at what position the amine should be located. It is conceivable that D without the amine, a thalidomide analog, may also be worth evaluating against multiple myeloma.

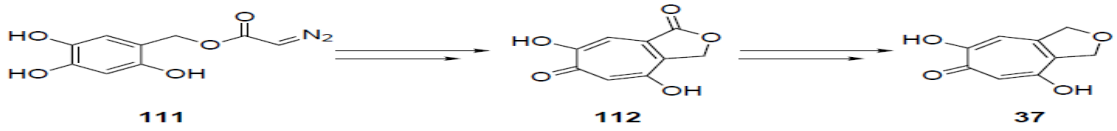


Scheme 4: Are the amines necessary and if so where to attach them? I also want to include tropolones as additional possibilities. The following reference details how tropolones can potentially act against multiple myeloma!

Novel tropones induce the unfolded protein response pathway and apoptosis in multple myeloma cells

"Tropolones are small organic compounds with metal-directing moieties. Tropolones inhibit the proliferation of cancer cell lines, possibly through their effects on metalloenzymes such as select histone deacetylases (HDACs). Pan-HDAC inhibitors are therapeutically beneficial in the treatment of multiple myeloma, however there is interest in the use of more selective HDAC inhibitor therapy to minimize adverse side effects. We hypothesized that tropolones might have anti-myeloma activities. To this end, a series of novel α-substituted tropolones"

Haney, S. L., Allen, C., Varney, M. L., Dykstra, K. M., Falcone, E. R., Colligan, S. H., ... & Holstein, S. A. (2017). Novel tropolones induce the unfolded protein response pathway and apoptosis in multiple myeloma cells. *Oncotarget*, *8*(44), 76085.

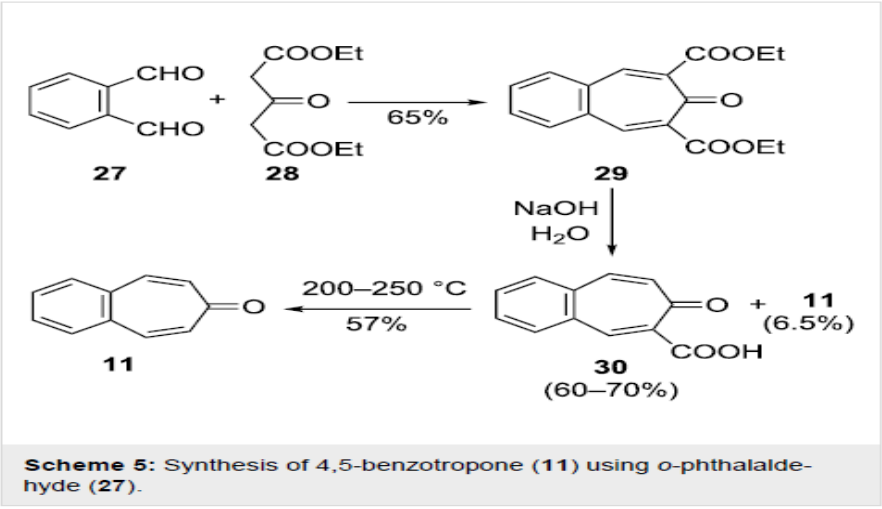


Scheme 1.28: Buchner ring expansion with diazoester **111** would produce lactone **112** which would need to be removed to produce cordytropolone **37**

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

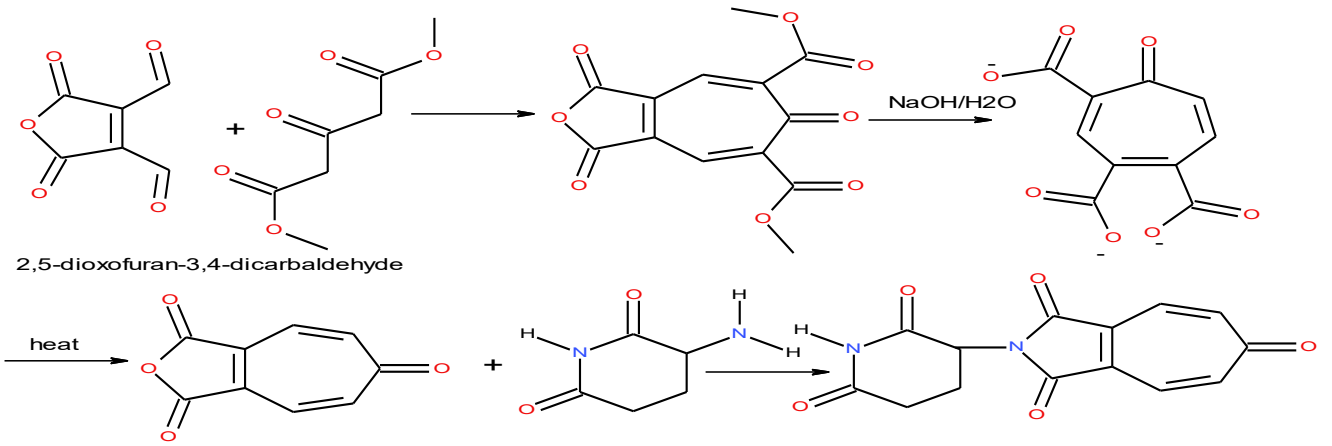
Obviously it would be straight forward to convert this lactone(112) to the ImiD.

What follows is my idea, that synthesis can follow known procedures but with a maleic ahydride substituted for the benzene in the following examples. For example:

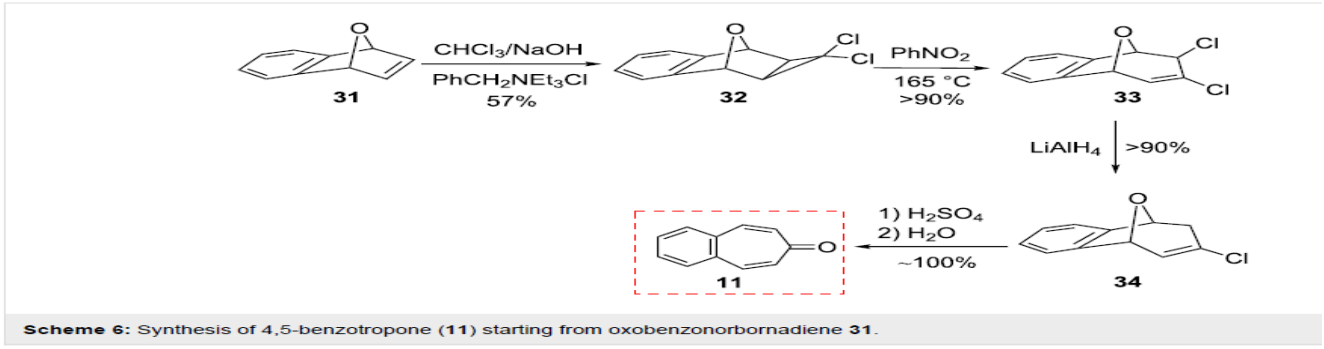


Scheme 5: Synthesis of 4,5-benzotropone (**11**) using *o*-phthalaldehyde (**27**).

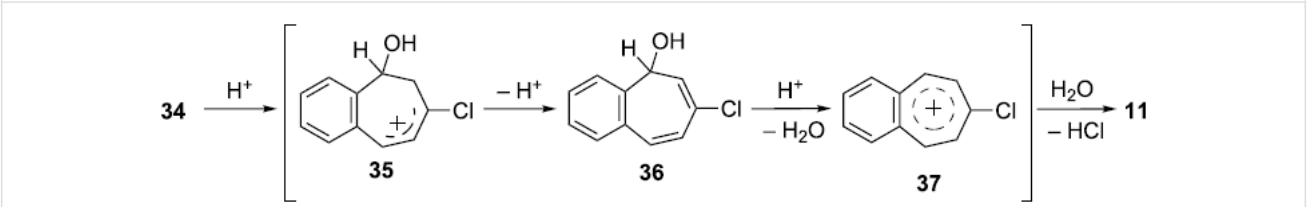
Dastan, A., Kilic, H., & Saracoglu, N. (2018). One hundred years of benzotropone chemistry. *Beilstein journal of organic chemistry*, *14*(1), 1120-1180. The above and following are from this reference.



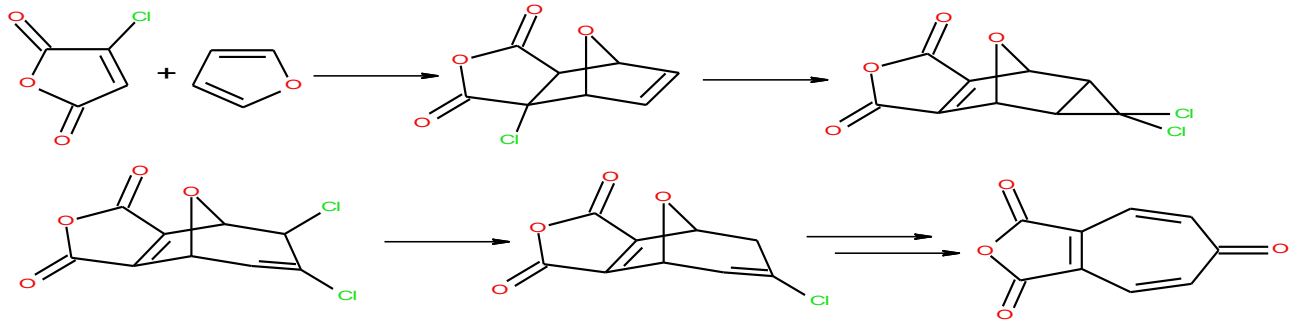
Scheme 5: I have not found a reference to the dialdehyde starting material but this is still a possible approach. Note, the step to the anhydride requires an acidic azeotropic environment.



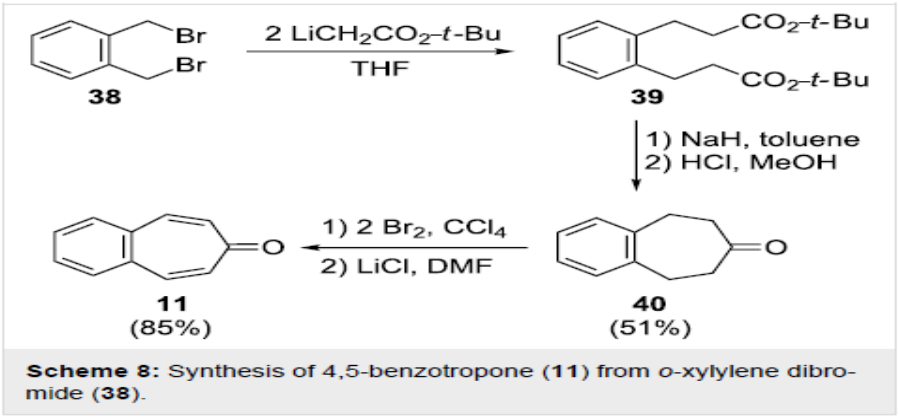
Scheme 6: Synthesis of 4,5-benzotropone (**11**) starting from oxobenzonorbornadiene **31**.



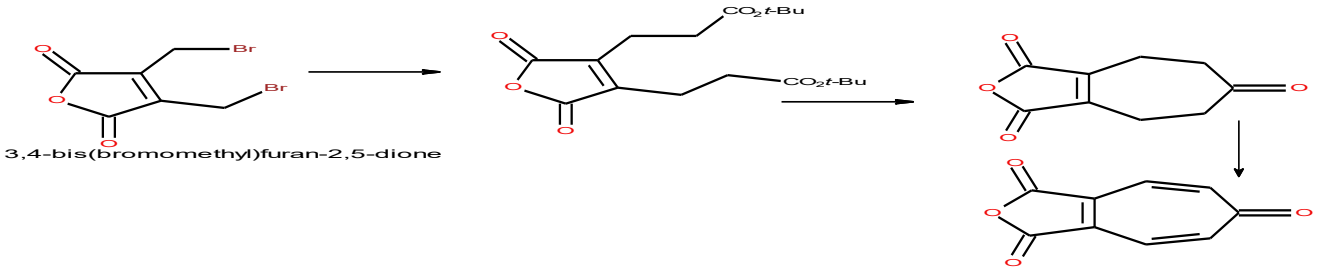
Scheme 7: Acid-catalyzed cleavage of oxo-bridge of **34**.



Scheme 6: My proposal.



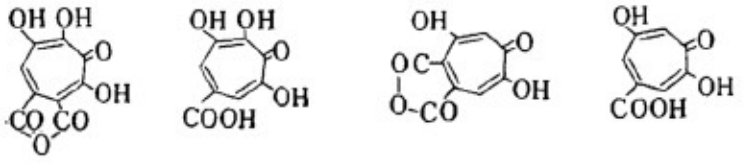
Scheme 8: Synthesis of 4,5-benzotropone (**11**) from *o*-xylylene dibromide (**38**).



Scheme 7: In this case the starting dibromo compound is known. All of the above can be amine derivatised but I have left that out but it is understood. The anhydride can be converted to the desired ImiD product.

After an extensive search I found references to the following maleic anhydride derivatives.

acid[6,7] (II). As other mould tropolones, stipitatonic acid[8] (III) and stipitatic acid[9] (IV) have been isolated from culture of *P. stipitatum* Thom. Of the above four mould tropolones, puberulic acid[10] (II) and stipitatic acid[11,12] (IV) have already been synthesized by Johnson and his collaborators from 1, 2, 4-trimethoxybenzene and diazoacetate.



I II III IV

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

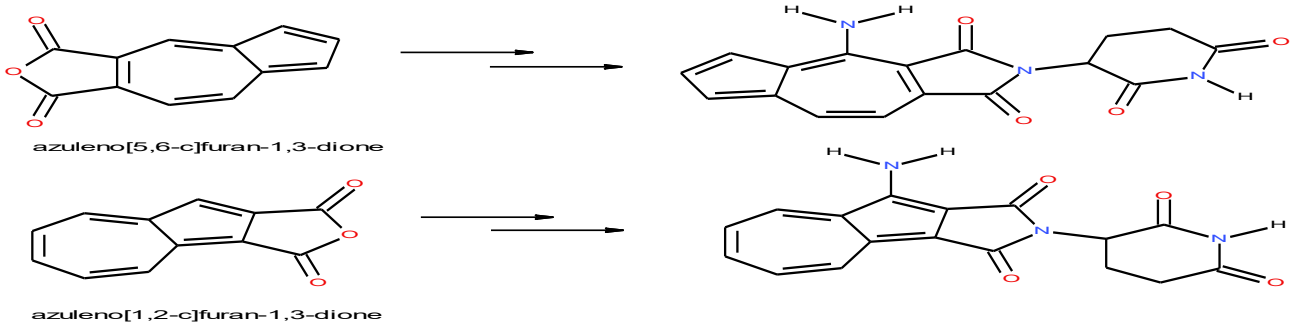
Most of the additional synthesis references for the above are from the 1950's and were not available to me. I mention this reference because it shows the biological – medical

potential for these 7-membered maleic anhydride derivatives and in analogy with my proposals for ImiD structures.

Azulene

As additional proposals, the above ideas can be applied to other non-benzenoid aromatics. Please look at my review of azulene synthesis literature also on rloginconsulting.com. I will just show the basic idea and then some synthesis possibilities. For example:

(The pomalidomide analog version is not shown but assumed.)



Scheme 8: I'm guessing if the amine is needed and if so, where to attach it? The azulene literature is extensive and goes back to the 1800's. Here are excerpts that I found interesting.

Azulene, $C_{10}H_8$, an aromatic bicyclic isomer of naphthalene, is a nonalternant and nonbenzenoid hydrocarbon. Azulene was named in 1863 by Piesse and has attracted wide interest since it was discovered.[1] In its simplest form (Figure 1), resonance

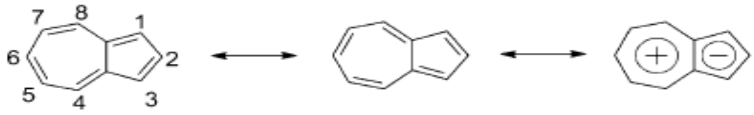


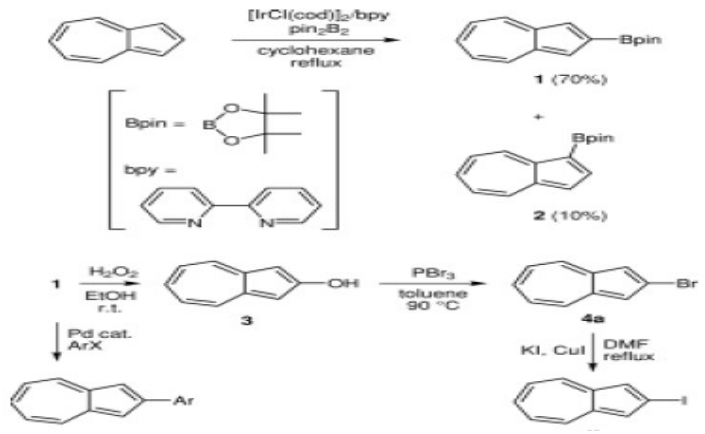
Figure 1. The numbering legend of azulene and its polarized resonance structure.

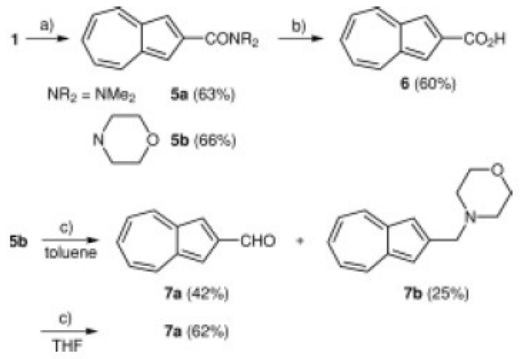
delocalization of azulene affords an electron-deficient seven-membered ring and an electron-rich five-membered ring to gain Hückel aromatic stabilization, bringing about an inherent dipole moment of about 1.08 D.[2] Azulene exhibits a small

Xin, H., & Gao, X. (2017). Application of azulene in constructing organic optoelectronic materials: new tricks for an old dog. *ChemPlusChem*,*82*(7), 945-956.

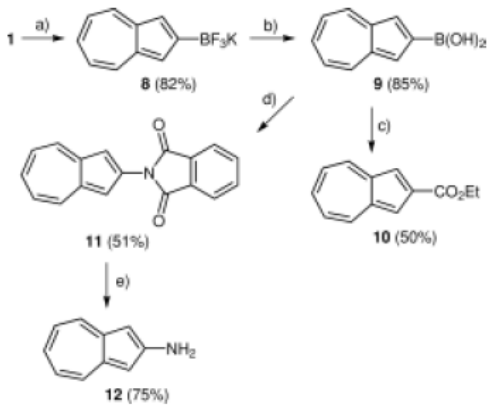
Azulene synthesis literature is quite extensive but the following reference has a excellent review.

Johansson, NG (2014). Preparation of multi-substituted azulene derivatives focusing on positions 1, 2 and 6.





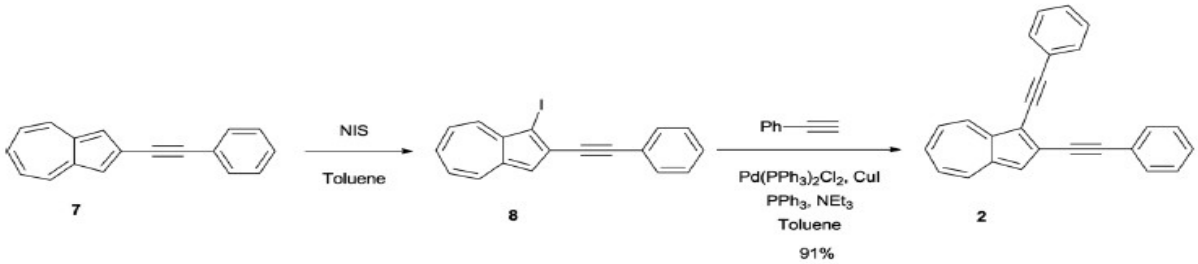
Scheme 2 **Reagents and conditions**: *a) $PdCl_2(PPh_3)_2$, $ClCONR_2$, CsF, THF, reflux; b) KOH (excess),* **5a**, *EtOH-H_2O, reflux; c) DIBAL-H,* **5b**, *-78 °C.*



Scheme 3 **Reagents and conditions:** *a) KHF_2, MeOH, r.t.; b) Na_2CO_3, MeCN-H_2O, r.t.; c) $Pd(PPh_3)_4$, $K_3PO_4 \cdot nH_2O$, $ClCO_2Et$, toluene, 90 °C; d) $Cu(OAc)_2$, phthalimide, pyridine, H_2O, DMF, r.t.; e) NH_2NH_2, THF, r.t.*

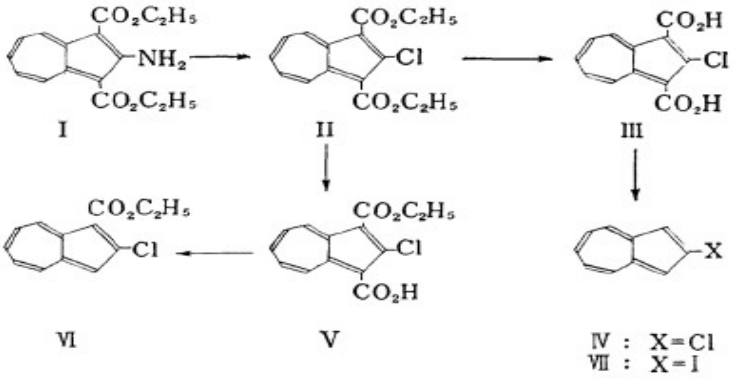
Fujinaga, M., Suetake, K., Gyoji, K., Murafuji, T., Kurotobi, K., & Sugihara, Y. (2008). An Easy Access to 2-Substituted Azulenes from Azulene-2-boronic Acid Pinacol Ester. *Synthesis*, *2008*(23), 3745-3748.

I show these synthesis procedures because compounds 6 or 10(2-carboxyazulene) might be useful for subsequent synthesis ideas.



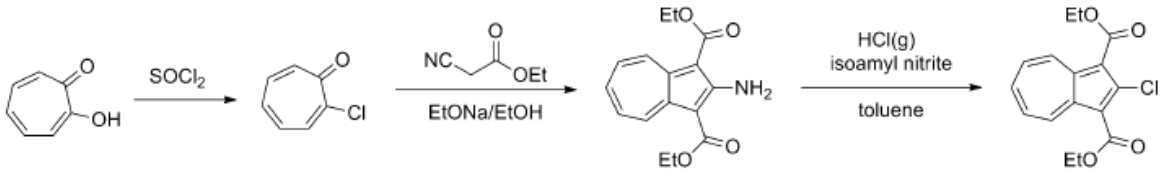
Koch, M., Blacque, O., & Venkatesan, K. (2013). Impact of 2, 6-connectivity in azulene: optical properties and stimuli responsive behavior. *Journal of Materials Chemistry C*, *1*(44), 7400-7408.

This reference shows that both the 1 and 2 positions can be derivatised without involving the 3 position.



Nozoe, T., Seto, S., & Matsumura, S. (1962). Synthesis of 2-substituted azulenes by nucleophilic substitution reactions of 2-haloazulene derivatives. *Bulletin of the Chemical Society of Japan*, *35*(12), 1990-1998.

I am interested in compound VI because I think it can be a useful intermediate.



Xin, H., & Gao, X. (2017). Application of azulene in constructing organic optoelectronic materials: new tricks for an old dog. *ChemPlusChem*, *82*(7), 945-956.

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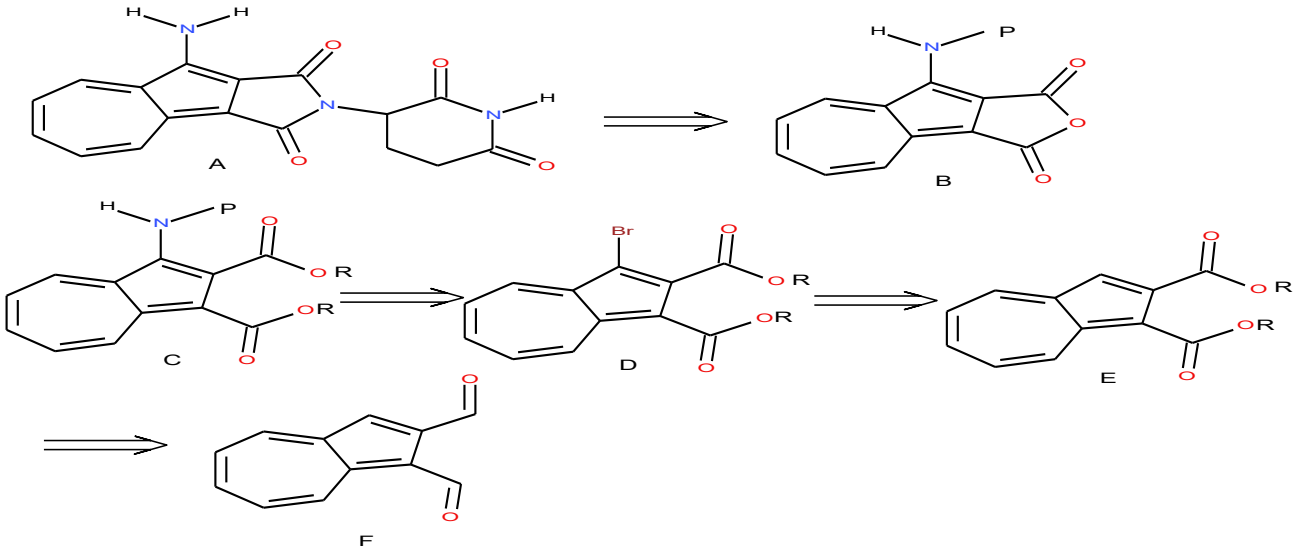
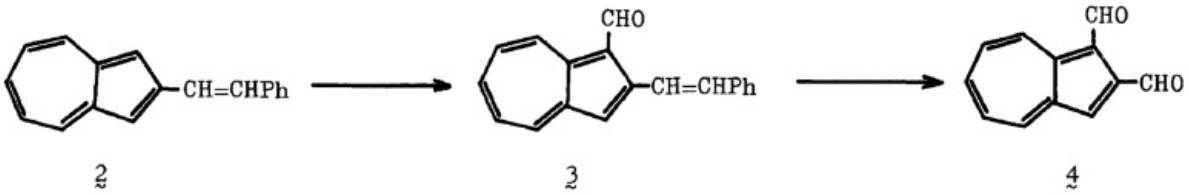


Scheme 9: F is available and I would think, can be oxidized to the di-ester.



Saito, M., Morita, T., & Takase, K. (1974). THE SYNTHESIS AND SOME PROPERTIES OF 3 H-CYCLOHEPT [a] AZULEN-3-ONE. *Chemistry Letters*, *3*(9), 955-958.

Saito, M., Morita, T., & Takase, K. (1980). Synthesis of 2-Formylazulene and Its Derivatives by Oxidative Cleavage of 2-Styrylazulenes. *Bulletin of the Chemical Society of Japan*, *53*(12), 3696-3700.

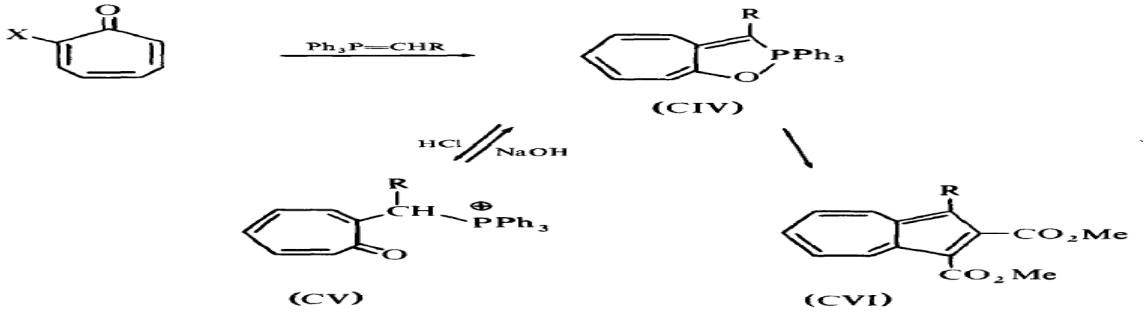
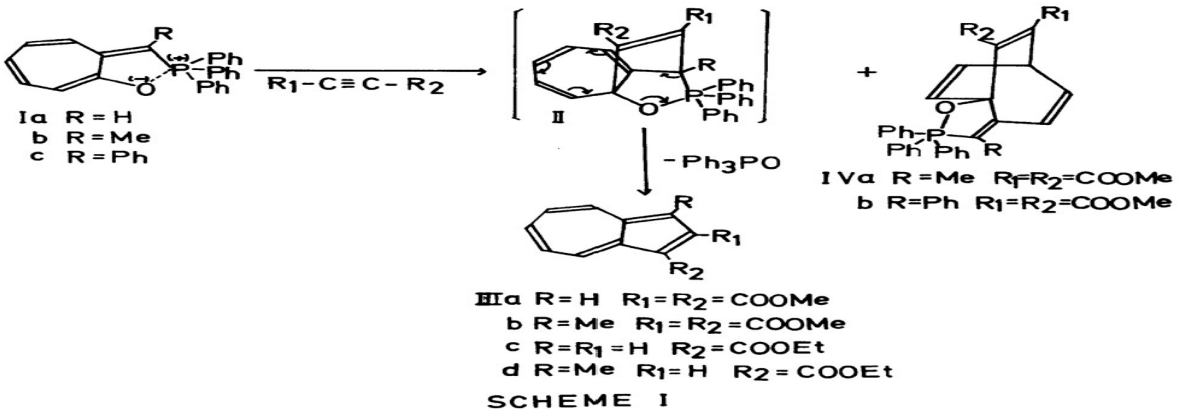


Figure 12. Reaction with phosphonium ylide.

Reaction of tropone with phosphonium ylide ($Ph_3P{=}CHR$) provides a 2-substituted tropone (CII) and a rearranged product (CIII)[46]. 2-Halo- and 2-methoxy-tropone afford phosphorus-containing oxa-azulanone-type compounds (CIV). The latter compounds undergo ring cleavage and recyclization with acid and alkali, and (CIV) affords azulene derivatives (CVI) with acetylenedicarboxylate (*Figure 12*).

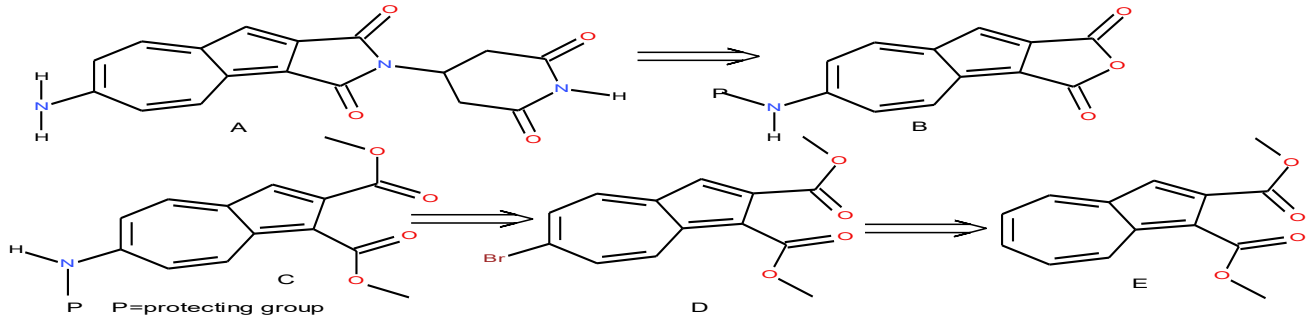
Nozoe, T. (1971). Recent advances in the chemistry of troponoids and related compounds in Japan. *Pure and Applied Chemistry*,*28*(2-3), 239-280.



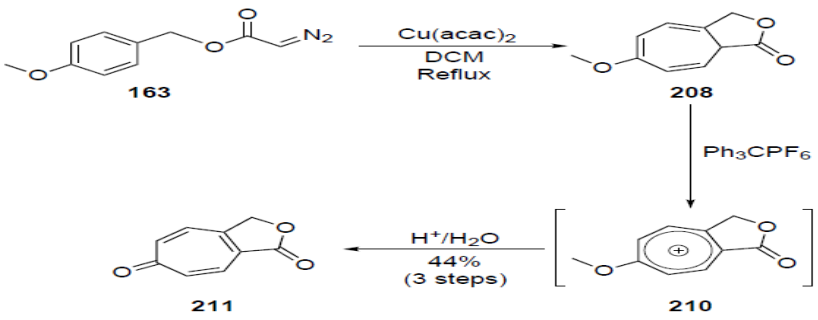
SCHEME I

III and/or Diels-Alder adducts IV. For example, on refluxing (2-troponyl)-methylenetriphenylphosphorane (Ia) with dimethyl acetylenedicarboxylate in dioxane for 8 hours, only dimethyl 1,2-azulenedicarboxylate (IIIa)[2] was produced. The crude IIIa chromatographed on a silica gel column to give dark violet needles of mp 45°C in 44% yield [$C_{14}H_{12}O_4$ (based on mass spectrum and analytical data);

Kawamoto, I., Sugimura, Y., Soma, N., & Kishida, Y. (1972). (2-TROPONYL) METHYLENETRIPHENYLPHOSPHORANES. III. NOVEL SYNTHESES OF AZULENES VIA CYCLOADDITION REACTIONS. *Chemistry Letters*, *1*(10), 931-934.

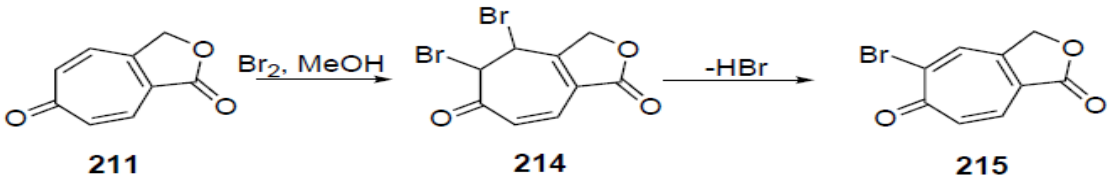


Scheme 10: Much simpler if amine can be at the 6 position. Is the amine required for Imid activity? Without it these would be thalidomide analogs.

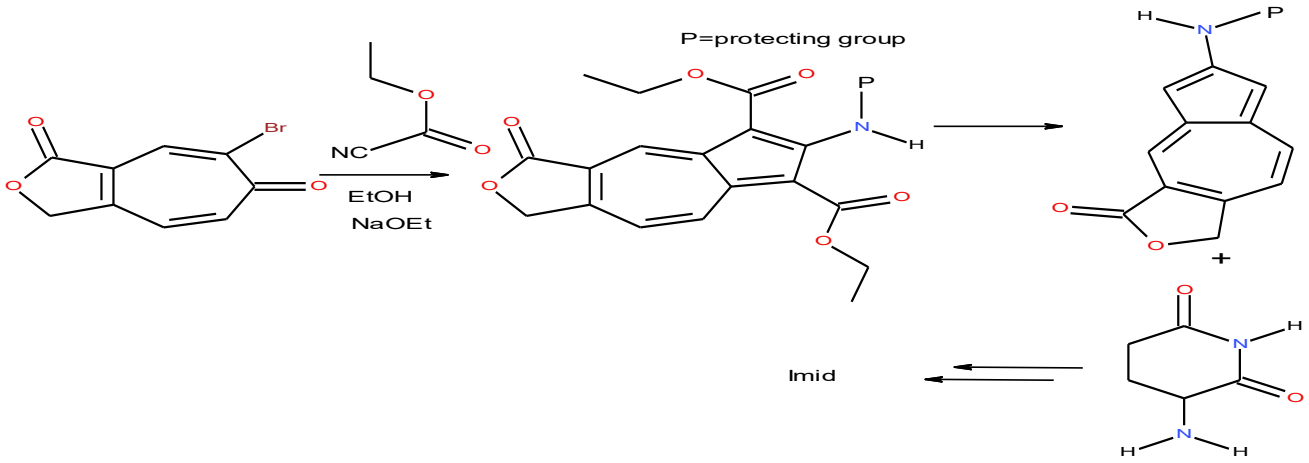


Scheme 1: Buchner ring expansion followed by oxidation via hydride abstraction to produce tropone **211**

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



Scheme 3.21: Product formed as a result of attempted substitution of **211**



Scheme 11: Using "Wells new route" to produce the indicated ImiD. I would hope the lactone would stand-up to the indicated reaction?

Thank you for reading these proposals!
Dr. Robert B. Login rloginconsulting.com