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Homo Diels–Alder chemistry in the synthesis of portulal: construction of the functionalized hydroazulene core

Bin Ma and John K. Snyder*

Department of Chemistry, Boston University, 590 Commonwealth Ave., Boston, MA 02215, USA

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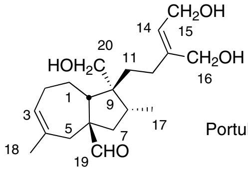
Abstract—A highly stereoselective synthesis of the functionalized hydroazulene skeleton of portulal (**1**), has been achieved using the newly developed cobalt catalyzed [4+2+2] homo Diels–Alder chemistry.

Portulal (**1**) is a diterpene plant growth regulator reported in 1965 following its isolation from *Portulacca grandiflora* leaves.[1,2] It has shown concentration-dependent adventitious root growth stimulation depending upon the phase of rooting,[3] and since then, several related natural products have also been reported from *P. grandiflora*, though their biological activities have not been evaluated.[4] The structure of **1** was secured by X-ray crystallography.[2]



Portulal (**1**)

To date, there has been one published synthesis of portulal, which followed a 40-step pathway.[5–7] Difficulties were particularly notable in this synthesis in the construction of a properly functionalized hydroazulene core. An efficient approach to the portulal hydroazulene core has also been reported by Marino employing cyclopropyl phosphonium reagents to annulate the cyclopentane ring onto a cycloheptanone.[8,9]

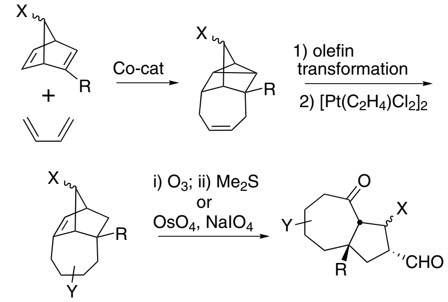


Figure 1. General strategy to hydroazulenes.

For the past several years, we have been investigating the cobalt-catalyzed [4+2+2] homo Diels–Alder reactions of norbornadienes and related homoconjugated bicyclic dienes with butadienes, and their subsequent opening to synthetically desirable polycyclic systems.[10–15] We have reported a particularly effective cobalt catalyst for accomplishing the [4+2+2] chemistry,[16] and the use of Zeise's dimer to open the cycloadduct to the tricycloundecenes after olefin transformation, followed by ozonolysis, to give hydroazulenes in four key steps (Fig. 1). We now report the application of this chemistry to a hydroazulene system suitably functionalized for conversion into **1**.

In our approach to portulal (**1**), the goal was to generate a hydroazulene core, such as **2**, which would allow for facile attachment of the C11–C16 side chain, as well as for the replacement of this side chain with various structural analogues (Fig. 2). The nitrile in **2** thus serves as both a hydroxymethyl equivalent as found in **1** and also allows for α-alkylation for attachment of the side chain.[17–19]

Keywords: Homo Diels–Alder; Portulal; Hydroazulene.

* Corresponding author. Tel.: +1 617/353 2621; fax: +1 617/353 6466; e-mail: jsnyder@chem.bu.edu

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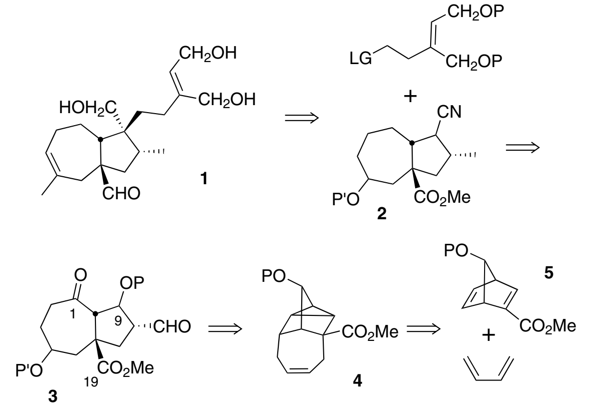
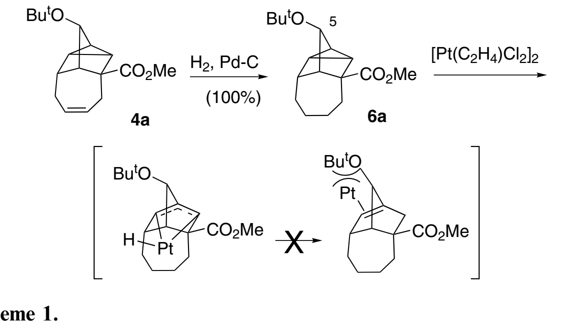


Figure 2. Retrosynthesis of portulal (**1**).

Hydroazulene **2** can be derived from ketoaldehyde **3**, with the C9 protected alcohol (portulal numbering) being the precursor to the C9 quaternary center in **1**; **3** in turn comes from homo Diels–Alder cycloadduct **4**. The angular C19 aldehyde of portulal thus derives from the C2 ester substituent of protected methyl *anti*-7-hydroxynorbornadiene-2-carboxylate (**5**), while portulal's C17 methyl group originates from aldehyde reduction in hydroazulene **3** following the opening of the cycloadduct **4**. We now report the successful preparation of **2** ($P' =$ TBDPS).

The cobalt-catalyzed [4+2+2] cycloaddition of methyl *anti*-7-*tert*-butoxynorbornadiene-2-carboxylate (**5a**, P = Bu^t) with butadiene produced **4a** in excellent yield as previously reported (86%),[16] with hydrogenation then giving **6a** quantitatively. Concern arose about the suitability of Zeise's dimer opening of cycloadducts such as **6a** with the bulky *tert*-butoxy group at C5 potentially blocking the top face of the adduct to which the platinum must migrate subsequent to insertion into the cyclopropane (Scheme 1).

However, the stereochemical alternative *syn*-7-*tert*-butoxynorbornadiene-2-carboxylate was shown not to be a viable diene for the catalyzed homo Diels–Alder cycloaddition due to the chelation of the cobalt, which apparently sequesters the catalyst away from complexation with the diene bottom face required for the success of the homo Diels–Alder chemistry (Fig. 3).[16] Indeed, hydrogenation of **4a** followed by attempted Zeise's dimer opening led only to recovered **6a**.



Scheme 1.

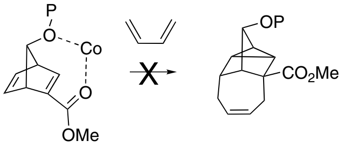
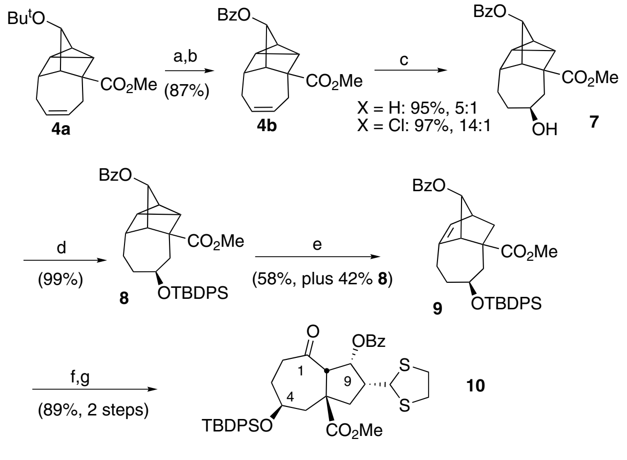


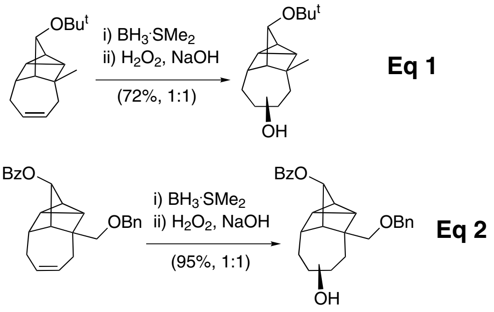
Figure 3. Catalyst chelation preventing the homo Diels–Alder reaction.

Previously we had noted that a benzoyl group at C5 of homo Diels–Alder cycloadducts does allow for Zeise's dimer opening with platinum migration *syn* to the C5 benzoyloxy substituent.[14] Applying this strategy to the problem at hand, the *tert*-butyl group of **4a** was replaced by benzoyl protection (**4b**, Scheme 2). Regioselective hydroboration with $BH_2Cl{\cdot}SMe_2$ directed by the C1 ester group gave alcohol **7**, (97%, optimal 14:1 regioisomers, both *exo*, inseparable mixture), which was subsequently protected as the TBDPS ether **8**. The regioisomers of the alcohols were readily assigned by oxidation to the corresponding ketones (which were separable) upon examination of the coupling patterns of the methylene protons α—to the ketone carbonyl group. Treatment of **8** with Zeise's dimer gave tricycloundecene **9** in 58% yield, along with 42% starting **8**, which was recovered following the subsequent ozonolysis and recycled (unreacted **8** and **9** were difficult to separate). Ozonolysis of tricycloundecene **9** and immediate dithioacetal protection of the aldehyde produced **10** in 89% yield for the two steps. Only monoacetal formation at the aldehyde was detected in all experiments; the C1 ketone carbonyl was retained.

Metal catalyzed directed hydroborations are well established,[20–24] and there are a few examples of intramolecular hydroborations[25–27] to control regioselectivity. Other, isolated examples of substrate-directed, nonmetal catalyzed hydroborations have also appeared in the literature,[28–33] and in 1973 House reported an ester directed hydroboration.[34] The role of the C1 ester in directing the hydroboration of **4b** was briefly probed.



Scheme 2. Reagents and conditions: (a) $ZnCl_2$, CH_2Cl_2; (b) BzCl, Et_3N, CH_2Cl_2; (c) (i) $BH_2X{\cdot}SMe_2$, Et_2O; (ii) H_2O_2, NaOH; (d) TBDPSCl, Im, DMAP, CH_2Cl_2; (e) $[Pt(C_2H_4)Cl_2]_2$, PhMe; (f) O_3, CH_2Cl_2; SMe_2; (g) $HSCH_2CH_2SH$, $Zn(OTf)_2$, CH_2Cl_2.

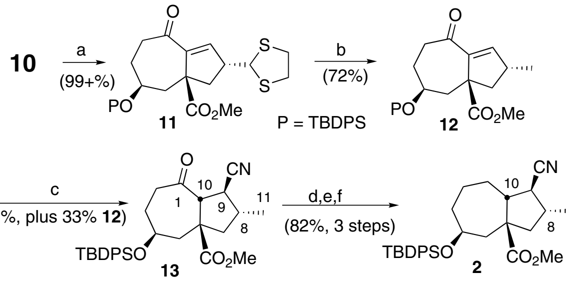


Scheme 3.

Use of the less Lewis acidic $BH_3 \cdot SMe_2$ in the hydroboration resulted in only 5:1 regioselectivity in favor of **7**, presumably due to the less effective coordination with the ester carbonyl oxygen. Other models showed no directing effect by either a C1 methyl group (Eq. 1, Scheme 3) or a C1 protected alcohol (Eq. 2, Scheme 3).

The benzoate ester in **10** and its precursor aldehyde proved to be very sensitive to elimination, readily producing the α,β-unsaturated ketone **11** upon silica gel chromatography or exposure to base (Scheme 4). Indeed, it proved most efficient to proceed from **9** to **11** without purification of intermediate **10**. Desulfurization with Raney nickel then produced the C17 methyl group (72%) as found in portulal. Conjugate addition of cyanide[35] to the desulfurized derivative **12** led to the *cis* fused cyanoketone **13** as the only isomer in 57% isolated yield, along with 33% recovered **12**. In contrast, conjugate addition of cyanide to **11** produced a mixture of *cis* and *trans* fused stereoisomers in favor of the latter. The relative stereochemistry of **13** was confirmed by NOE observations between H10 and H8, as well as H9 and H11. Consequently, the ketone oxygen in **13** was removed by a three-step sequence using Barton-McCombie deoxygenation[36] to give the target hydroazulene **2**. No epimerization was observed during this process and the stereochemistry in **2** was confirmed by an NOE between H10 and H8.

In conclusion, racemic hydroazulene **2**, a key core structure suitably functionalized for conversion into the plant growth regulator portulal (**1**), was efficiently prepared using [4+2+2] homo Diels–Alder methodology. Three of the four stereogenic centers as found in **1** were correctly established, with the fourth at C9 poised for alkylation from the convex β-face to complete the stereoselective synthesis. Enantiopure synthesis of **2** is also underway beginning with homochiral norbornadiene **5a**, which was obtained following a lipase resolution of endo-7-*tert*-butoxynorborn-2-en-5-ol.[37]



Scheme 4. Reagents and conditions: (a) Et_3N, CH_2Cl_2; (b) Ra-Ni, CH_2Cl_2, EtOH; (c) KCN, NH_4Cl, H_2O, DMF; (d) $NaBH_4$, THF–MeOH (4:1); (e) CS_2, NaH, THF, MeI; (f) Bu_3SnH, AIBN, PhMe.

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Supplementary data

Full experimental details for all reactions and compound characterizations. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.11.104.

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