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The development of more efficient syntheses of polycyclic diterpenes through intramolecular cyclopropanation of aryl rings in diazomethyl ketones

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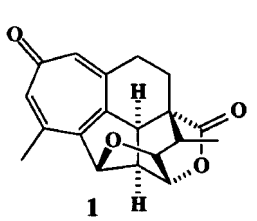
Abstract - Several approaches to the total synthesis of the troponoid diterpene lactone **1** have been undertaken. The most successful approach to date has afforded secoharringtonolide **26**. The intramolecular cyclopropanation reaction of an aryl ring by means of the transition metal catalysed reaction of a diazoacetyl function was used to assemble the 5/7 ring system and to provide a cycloheptatrienyl precursor to the tropone moiety. In a cognate study, the intramolecular cyclopropanation reactions of the aromatic ring in a wide range of tetralin 2-diazomethyl ketones afforded norcaradiene products which, because of geometric constraints, were energetically more favoured than the tautomeric cycloheptatrienes. The [4+2] cycloaddition of selected dienophiles to some of these products, *e.g.* the vinyl analogue **34**, allowed the rapid stereocontrolled assembly of advanced intermediates for the synthesis of diterpenoids **2** and **3**.

INTRODUCTION

Benzenoid synthons afford a rich and diverse array of options for the synthesis of polycyclic structures (1). Reductive processes, especially the Birch reduction (2), have proven to be extremely useful, but the more powerful protocols have involved carbon-carbon bond formation at substituted positions on the aryl ring with concomitant dearomatisation. The photo-initiated intramolecular 1,3-cycloadditions of alkenes to benzene derivatives developed by Wender, for example, have been especially effective in allowing remarkably short syntheses of complex target molecules (3), while the intramolecular *ipso* alkylations of benzenoid moieties in methoxytetralin diazomethyl ketones were a key element in the total synthesis of gibberellins carried out in our laboratories (4).



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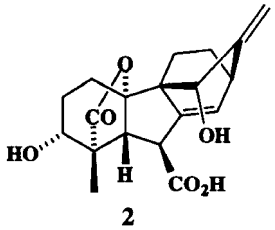

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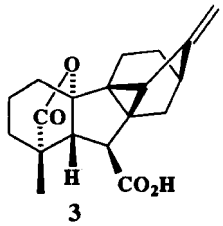

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In a continuing quest for greater efficiency in the synthesis of complex polycyclic structures, we have examined further ways of utilising benzenoid synthons for this purpose and now describe recent studies on the intramolecular cyclopropanation reactions of the aromatic ring in hydrophenanthryl and tetralin diazomethyl ketones initiated by transition metal catalysts. These studies have been undertaken within the context of the total synthesis, *inter alia*, of the unusual troponoid diterpene lactone, harringtonolide **1** (5)

(which shows promising anticancer and antiviral properties) as well as a more direct synthesis of the fern antheridiogen, antheridic acid **2** (6), and its likely biosynthetic precursor, cyclogibberellin **3** (7). During the passage of this work, it became apparent that **3** is representative of a new family of gibberellins isolated from fern gametophytes and apple seeds (8).

APPROACHES TO THE TOTAL SYNTHESIS OF HARRINGTONOLIDE

Synthetic Plan

An arene cyclopropanation process leading to a cycloheptatriene system was envisaged as the pivotal step in the synthesis of harringtonolide **1**, *i.e.* ring expansion of a benzenoid ring to afford **7**, from which the preparation of the tropone moiety should be readily achieved. Provided that such a process could be achieved efficiently as outlined in Fig. 1, the proposed synthesis is broadly simplified to one of preparing a suitably substituted phenanthrene derivative **4**. The synthesis of molecules like **4** appeared to be readily achievable through the adaptation of our well established methodology based on the Birch reductive alkylation of aromatic acids (9) and on the controlled C-acylation of preformed enolates with alkyl cyanoformates (10).

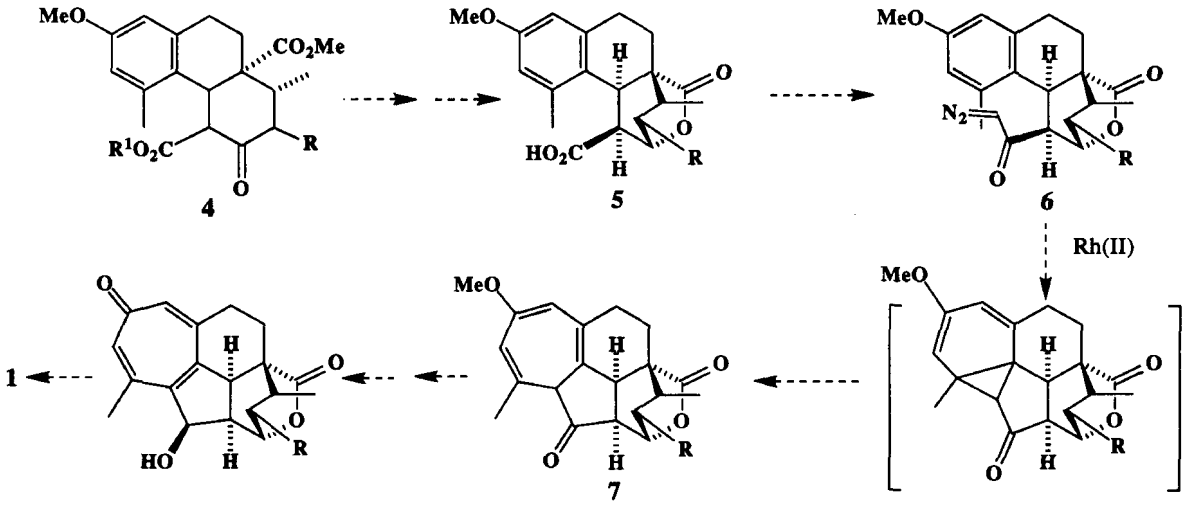


Fig. 1. Synthetic strategy for the total synthesis of harringtonolide **3**

Athough there were excellent precedents for the cyclopropanation process from McKervey's research (11), it was very difficult to gauge the likely outcome in the proposed sequence, especially in view of the steric crowding of the aryl ring and the possibility of a competing CH insertion. Indeed, a model study on the reaction of tetralin diazoketone **8** with rhodium acetate afforded only 13% of the desired product **9** (Fig. 2). However, one of the alternative catalysts developed by Doyle and Padwa, namely the rhodium caprolactam complex [$Rh_2(capr)_4$], afforded a 75% yield of **9** (12).

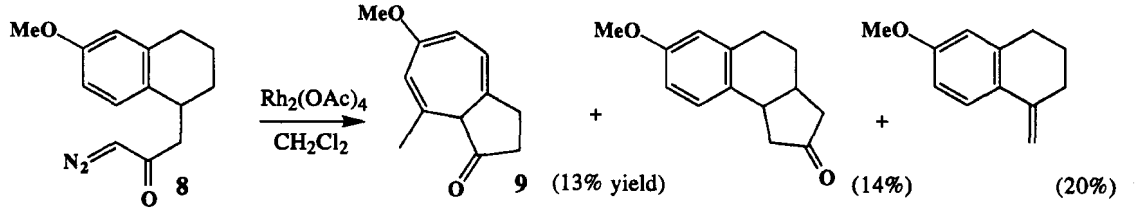


Fig. 2 Model studies on cyclopropanation processes for application to the synthesis of harringtonolide.

The formation of the alkene was totally unexpected, but leads us to the conclusion that, instead of the normally concerted 3-membered transition state assumed for CH insertion (13) in which hydride transfer to the carbenoid complex occurs somewhat in advance of C-C bond formation, hydride transfer might occur independently of C-C bond formation when sufficient stabilisation of the incipient cationic centre was available. In the present case, fragmentation with loss of ketene would then lead to the observed alkene as outlined in Fig. 3. In the examples of other tetralin diazoketones studied later (*vive infra*), evidence for the probable formation of ketene was shown by distilling the solvent (CH_2Cl_2) from one reaction mixture into a sample of *p*-toluidine, resulting in the formation of the acetamide derivative.

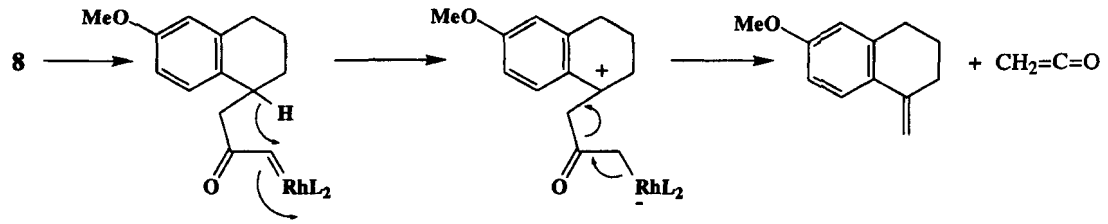


Fig. 3. Proposed mechanism for alkene formation.

Preparation of Hydrophenanthrene Intermediates

The assembly of tricyclic intermediates proceeded smoothly as outlined in Fig. 4, readily affording **12**, but we were unable to obtain the 5β-epimer of this intermediate (*cf.* **5**). While the 5β-stereochemistry corresponds to that of harringtonolide, it is not necessarily required to be established at this stage, since a subsequent epimerisation at this centre was feasible. Rather, the 5β-stereochemistry is essential to achieve the geometry required for the subsequent cyclopropanation. We also examined the preparation of a precursor to **5** (R = OMOM) by trapping the adduct of cuprate addition to **10** as the enol ether **13** and treating this product with a variety of oxidising reagents. The resulting α-ketol **14** was then converted into **15**, with a view to preparing a suitable analogue of **5** possessing an additional functional group suitable for ether ring formation, but **18** could not be C-acylated.

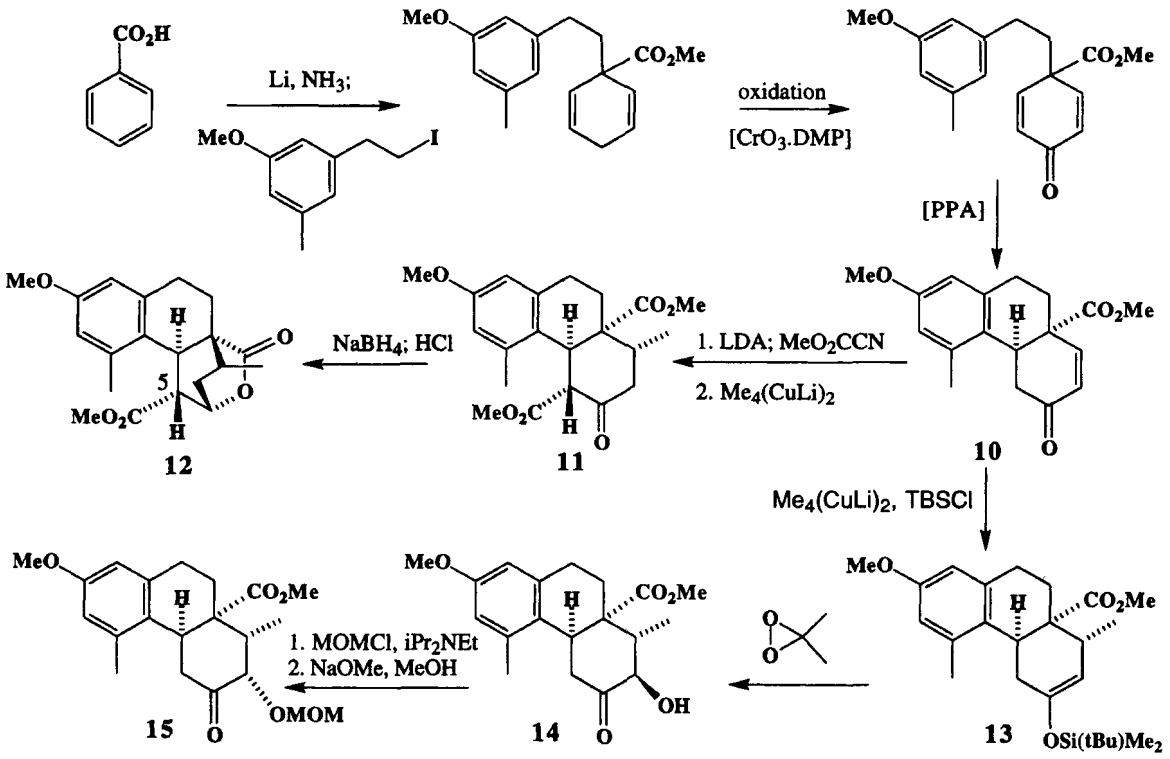


Fig. 4. Initial phase of synthetic approaches to harringtonolide.

Aldol Approach to the Synthesis of Harringtonolide

Given the difficulties in preparing an intact phenanthrene derivative with the correct stereochemistry at C-5, an alternative approach was devised whereby the desired stereochemistry might be established by means of an intramolecular aldol reaction, as outlined in Fig. 5.

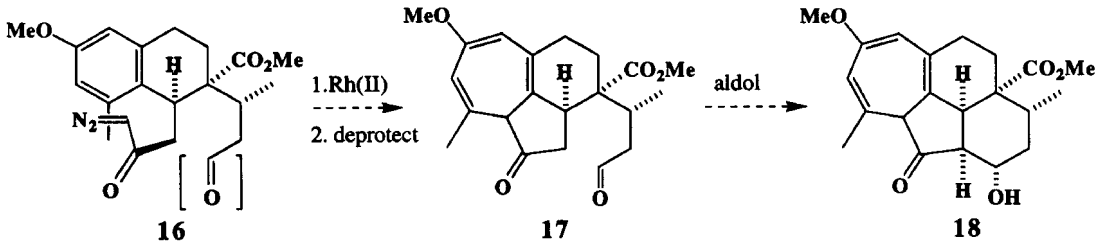


Fig. 5. Aldol strategy for the synthesis of harringtonolide.

This new strategy was rendered to practice as summarised in Fig. 6. Thus, ketol **14** was oxidatively cleaved by $Pb(OAc)_4$-MeOH and then transformed into the dimethyl acetal analogue of **16** by means of a Wittig reaction. After further elaboration, cyclopropanation proceeded in excellent yield and the very labile adduct (corresponding to **17**) stabilised by conjugation (treatment with DBU) to afford **22**. After selective hydrolysis of the acetal function, the aldol reaction proceeded smoothly to **23**, as confirmed by NMR spectroscopy and single crystal X-ray analysis (14).

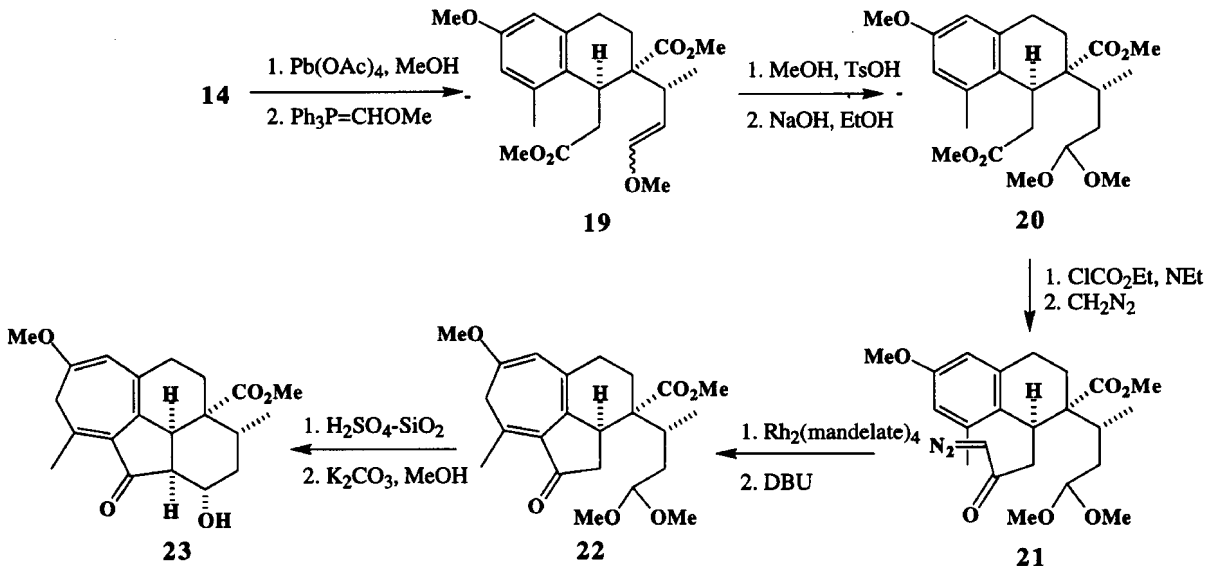
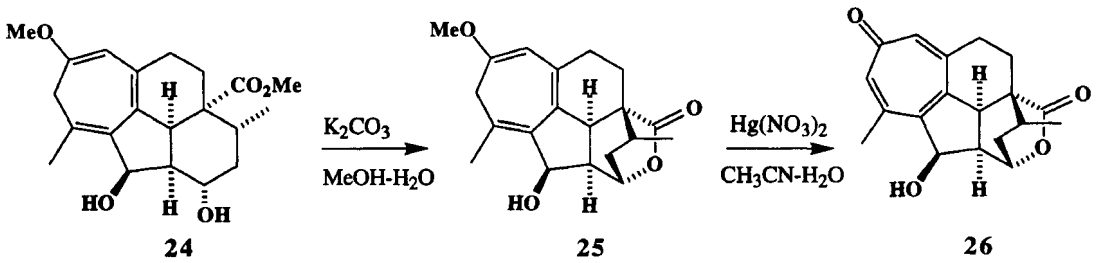


Fig. 6. Aldol approach to harringtonolide.

Synthesis of Secoharringtonolide

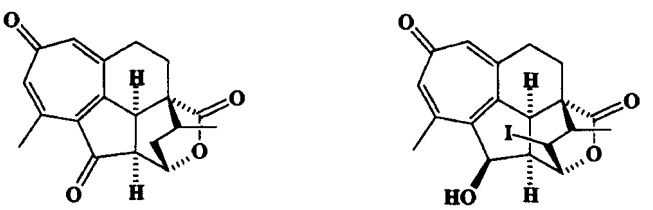
The preparation of **23** by this approach had apparently established the general feasibilty of preparing the harringtonolide system, while enol ether **19** affords the opportunity to introduce further functionality to allow ultimately for the completion of the ether ring. Before addressing this last point, however, we elected to investigate formation of the lactone and tropone functionalities. Thus, ketone **23** was reduced by sodium borohydride, the convexity of the lower face ensuring formation of the desired β-epimer **24**. This product was converted into lactone **25** by K_2CO_3 in aqueous methanol and then the tropone functionality established in a single step by treatment with mercuric nitrate to afford secoharringtonolide **26** (Fig. 7).



24 25 26

Fig. 7. Preparation of secoharringtonolide.

Although this sequence was regarded mainly as a model system to establish the necessary methodology for the preparation of harringtonolide **1**, there appeared to be a reasonable prospect of converting **26** into **1** through transannular oxidation. Under most standards conditions (*e.g.* $Pb(OAc)_4$, I_2), however, **26** was converted into ketone **27**. Treatment of **26** with N-iodosuccinimide with irradiation did afford a small amount of the unstable iodide **27**, but this had the incorrect stereochemistry for direct ether formation by nucleophilic displacement and all attempts to utilise this intermediate were unsuccessful. Continuing research is directed at preparing a suitable variant of **7** which will make ether formation more secure. In one very promising approach we have demonstrated in a model system the very efficient construction of a five-membered ether ring by means of intramolecular nucleophilic attack on a suitably located cyclopropyl ring with concomitant opening to form an adjacent methyl group.



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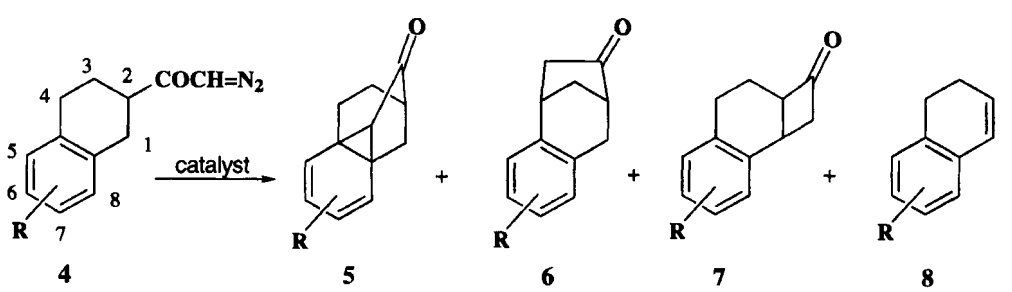
APPROACHES TO THE TOTAL SYNTHESIS OF ANTHERIDIOGENS

Cycopropanation Studies on Tetralin Diazomethyl Ketones

In the case of tetralin 2-diazomethyl ketones, it was expected that stable norcaradiene products would be obtained, since geometric constraints were expected to make these products energetically more favourable than the tautomeric cycloheptatrienes, the expected products with simpler substrates (15). Thus, the reaction of diazomethylketone **29** (6-OMe) (16) with rhodium acetate afforded an excellent yield (75%) of the norcaradiene **30** (6-OMe) accompanied by the CH-insertion product, cyclopentanone **31** (6-OMe) (14% yield) (Fig. 8). Trace amounts of the cyclobutanone **32** (6-OMe) derived from CH-insertion into the alternative benzylic position and the dihydronaphthalene **33** (6-OMe) were also obtained.



4 5 6 7 8

Fig. 8. Transition metal catalysed reactions of tetralin diazomethyl ketones.

Evidence for structure **30** (6-OMe) was readily apparent from ^{1}H NMR spectra which, in addition to the expected olefinic resonances, displayed a doublet (J=1.6 Hz) at δ 0.68, consistent with the cyclopropyl ketone moiety. A range of further tetrahydronaphthalene substrates and a selection of rhodium(II) and copper(II) catalysts were then used to establish the scope and limitations of this type of conversion. The results, summarised in Table 1, proved to be extremely variable when rhodium complexes were employed, the desired norcaradiene products being formed in yields ranging from 20-75%, depending on the substitution pattern of the substrate **29** and the choice of catalyst. When lower yields of cyclopropanated products **30** were obtained, such outcomes appeared to be primarily due to the formation of greater amounts of cyclopentanones **31**. This was especially noticeable for the 7- and 8-methoxy derivatives (entries 11, 16). In the case of the latter, significant quantities of cyclobutanone **32** (up to 15%) were obtained.

TABLE 1. Products from the reactions of tetrahydronaphthyl diazoketones with selected catalysts.

29[a]	**30**[b]	**31**[b]	entry
R = H			
$Rh_2(OAc)_4$, CH_2Cl_2	41 (39)	46 (41)	1
$Cu(acac)_2$, $ClCH_2CH_2Cl$	55 (56)	(6)	2
R = 5-OMe			
$Rh_2(OAc)_4$, CH_2Cl_2	41 (34)	45(41)	3
$Cu(acac)_2$, $ClCH_2CH_2Cl$	55 (56)	(12)	4
R = 6-OMe			
$Rh_2(OAc)_4$, CH_2Cl_2	76 (71)	16 (14)	5
$Rh_2(mandelate)_4$, CH_2Cl_2	50	33.5	6
$Rh_2(cap)_4$, CH_2Cl_2	55	29	7
$Rh_2(pfb)_4$, CH_2Cl_2	17	51	8
$Rh_2(TPA)_4$, CH_2Cl_2	52 (51)	45 (38)	9
$Cu(acac)_2$, $ClCH_2CH_2Cl$	65 (61)	(17)	10
R = 7-OMe			
$Rh_2(OAc)_4$, CH_2Cl_2	51 (46)	49 (44)	11
$Rh_2(mandelate)_4$, CH_2Cl_2	44	51	12
$Rh_2(cap)_4$, CH_2Cl_2	21	76	13
$Rh_2(TPA)_4$, CH_2Cl_2	10 (5)	89 (81)	14
$Cu(acac)_2$, $ClCH_2CH_2Cl$	65 (64)	(3)	15
R = 8-OMe			
$Rh_2(OAc)_4$, CH_2Cl_2	24 (21)	56 (57)	16
$Rh_2(mandelate)_4$, CH_2Cl_2	21	38	17
$Rh_2(TPA)_4$, CH_2Cl_2	0	75 (70)	18
$Cu(acac)_2$, $ClCH_2CH_2Cl$	(65)	(6)	19

[a]All reactions carried out with 2 mol% of catalyst at reflux unless otherwise indicated.
[b]Yields are based on NMR spectra of total reaction mixtures; yields in parenthesis are of isolated compounds.

Attempts to steer the reaction towards higher levels of cyclopropanation were not productive. Competitive intramolecular experiments by Padwa, Doyle and coworkers (12) have shown that the use of dirhodium perfluorobutyrate [$Rh_2(pfb)_4$] favoured aromatic cyclopropanation over CH-insertion in diazoacetamides, but conversely, only CH-insertion was observed with alkene substituted diazoketones. With amide based catalysts, however, complementary outcomes were obtained, *e.g.* with rhodium(II) caprolactam dimer [$Rh_2(cap)_4$], CH-insertion was preferred over aromatic cyclopropanation in aryl diazoamides, but only cyclopropanation occurred with the alkene substituted diazoketones. There was no direct precedent for our type of substrate, but in the event, both $Rh_2(cap)_4$ and $Rh_2(pfb)_4$ afforded lower yields of norcaradienes in all cases (entries 7, 8, 13). As might have been expected, dirhodium(II) tetrakistriphenylacetate

$[Rh_2(TPA)_4]$ (17) (entries 9, 14, 18) also favoured higher levels of CH-insertion with enhanced yields of cyclopentanones **31**. Rhodium mandelate, which has been reported (18) to afford better yields than the acetate with similar substrates, was less satisfactory in the present study (entries 6,12,17). In contrast to the results obtained with rhodium complexes, copper catalysts gave consistent yields of the cyclopropyl ketones which were largely independent of substrate and fell into the 50-65% range. Of the catalysts that were examined, $Cu(II)(acac)_2$ gave the best results (entries 2, 4, 10, 15, 19).

Yields of the norcaradienes generally appear to be enhanced by higher electron densities associated with methoxy-substitution, except in the case of the 8-methoxy derivative of **29**. In this case the low yield is possibly due to eclipsing of the *peri* substituent with one of the neighbouring benzylic hydrogens in the transition state leading to cyclopropanation. However, methoxy substituents could also be expected to promote CH-insertion at benzylic positions, since it is believed that a concerted 3-membered transition state (13) in which hydride transfer to the carbenoid complex occurs somewhat in advance of C-C bond formation is involved. Insertion could be expected to become a more dominant pathway when such electronic factors coincided with the formation of a 5-membered ring, as in the case of the 7-methoxy derivative. The impact of benzylic activation is also apparent with the formation of a relatively greater amounts of cyclobutanone from the 8-methoxy derivative. The formation of alkenes from similar substrates has been discussed earlier (*vide supra*).

Advanced Intermediates for the Synthesis of Polycyclic Diterpenoids

Having established the practicality of preparing norcaradiene derivatives **30**, we proceeded to develop a method for the addition of a suitably substituted A-ring to these products, thereby allowing the rapid assembly of advanced intermediates for the synthesis of tetra- and pentacyclic diterpenes such as **2** and **3**. We were especially concerned that the desired stereochemical relationship be established between the D-ring and the A/B-ring fusion, *i.e.* H(5) should be *syn* to C(15). One feasible route appeared to be a Diels Alder reaction with an appropriate dienophile, *e.g.* methyl acrylate, to the vinylnorcaradiene **34** (this intermediate was formed in 70% yield from the appropriate diazoketone, which was readily obtained in only 5 steps from 1,6-dimethoxynaphthalene). The [4+2] cycloaddition could reasonably be expected to lead to **35** as the preferred adduct, assuming that (a) the more exposed vinylcyclohexene moiety would function as the operational diene, (b) the preferred regiochemistry would afford an "*ortho* adduct", (c) *endo* adducts would be kinetically preferred over the *exo* isomers, and (d) the upper face of the triene would be effectively shielded by the pro-15 hydrogen atom attached to the cyclopropyl ring (Fig. 9).

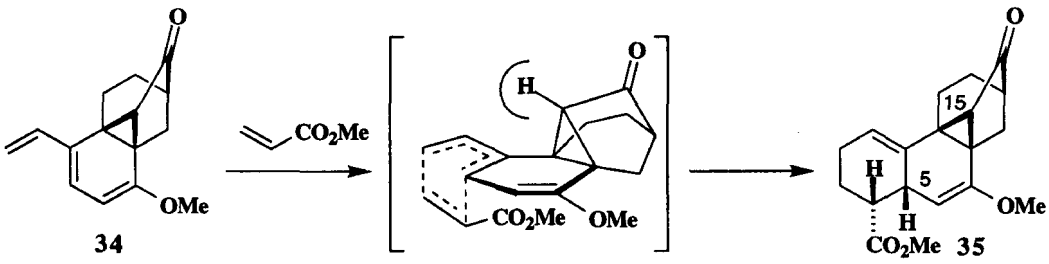


Fig. 9. [4+2] Cycloaddition of a vinyl norcaradiene intermediate with methyl acrylate.

In the event, **35** was formed in 70% yield and, *inter alia*, could serve as an intermediate for the synthesis of the diterpenoid toxin, atractyligenin, but we were more concerned with gaining access to **2** and **3**. There are good precedents for indicating that C-methylation of **35** should establish the correct C(4) configuration of the kaurenoid diterpenes (20). However, provided that a suitable dienophile could be harnessed, [4+2] cycloaddition had the potential to provide a more direct and efficient synthesis of such compounds. Methyl methacrylate, not surprisingly, failed to react with **34**, but citraconic anhydride afforded a 90% yield of adduct **36**, the stereochemistry of which was established from psNOESY spectra. The potential of this intermediate for the synthesis of derivatives of **3** (and thence **2**) is indicated in Fig. 10.

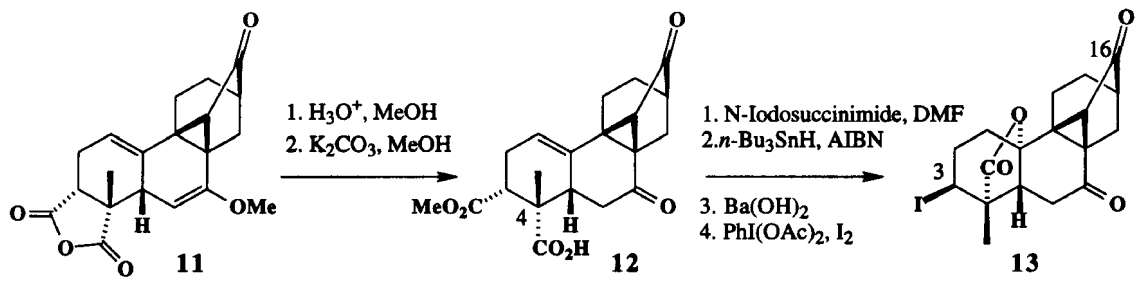


Fig. 10 Preparation of an advanced intermediate for antheridiogen synthesis

Thus, lactone **38** is readily prepared in a very efficient sequence and the 3β-iodo function may be replaced by hydrogen, hydroxyl or eliminated by an E2 process to allow for a wide range of functionality in the A-ring. Only a simple ring contraction (21) followed by methylenation of the C(16) carbonyl group is required to complete the synthesis of **2**. Alternatively, the full kaurenoid skeleton may be completed via intramolecular cyclopropanation as described by us previously for similar molecules (22).

ACKNOWLEDGEMENT

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