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A Convenient Enantiospecific Route towards Bioactive Merosesquiterpenes by Cationic-Resin-Promoted Friedel–Crafts Alkylation with α,β-Enones

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An enantiospecific route towards bioactive merosesquiterpenes, based on the cationic-resin-promoted Friedel–Crafts alkylation of alkoxyarenes with an α,β-unsaturated ketone, is reported. Reaction of ketone **11** with 3,4-methylenedioxyphenol afforded the corresponding chromene. Treatment of **11** with protected phenol **20** gave aryl nordrimane ketone **21**, a suitable intermediate in the synthesis of bioactive merosesquiterpenes and their 8-epi derivatives. By utilizing this methodology, a formal synthesis of (+)-puupehenone and other related metabolites, via triflate **25**, is described.

Introduction

Merosesquiterpenes are natural products of mixed biosynthetic origin (polyketide–terpenoid) containing a sesquiterpene unit joined to a phenolic or quinone moiety. The most important metabolites of this family of compounds, mainly due to their relevant, potent biological activities, are those bearing a bicyclic terpene (drimane) moiety. Examples of drimenyl quinones are the antitumour tauranin (**1**),[1] which also inhibits cholesterol biosynthesis, the anti-HIV (+)-hyatellaquinone (**2**)[2] or the most recently reported sphingosine kinase inhibitor (–)-F-12509 A (**3**).[3] Another important group of compounds belonging to this family of terpenoids is that of the marine puupehenones, which possess a tetracyclic structure, including a pyran ring. Examples of the latter are puupehenone (**4**),[4] 15-cyanopuupehenone (**5**),[5a] halopuupehenones **6** and **7**,[5b,5c] puupehedione (**8a**),[5a] 15-oxopuupehenol (**9**)[4] and 15-cyanopuupehenol (**10**) (Figure 1).[6] Although a wide variety of relevant biological properties, including antitumour, antiviral, antibiotic, antituberculosis, antimalarial, antioxidant, insecticidal and antifungal activities, have been reported for these compounds in the last twenty years,[7] the most recent studies have revealed that some of them inhibit lipoxygenase[8a] and angiogenesis,[8b] further heightening the interest in this class of compounds.

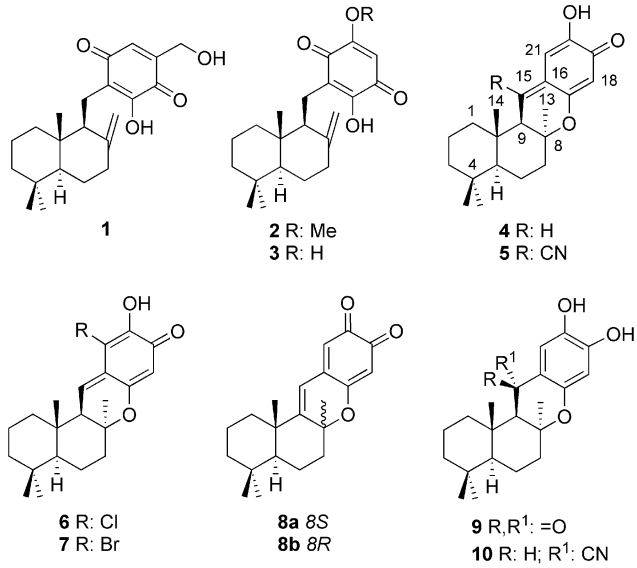

Figure 1. Some representative merosesquiterpenes.

The important biological properties and the natural scarcity of these metabolites have motivated chemists to study their synthesis. In general, two main strategies have been utilized to create the merosesquiterpene skeleton: (a) the biomimetic cyclization of farnesylphenols, as first used by Trammell[9a] in a racemic synthesis of **4** and more recently by Yamamoto et al.[9b] in an asymmetric synthesis of **8b** and other related compounds; (b) a two-synthon strategy, involving in most cases the reaction of a drimane electro-

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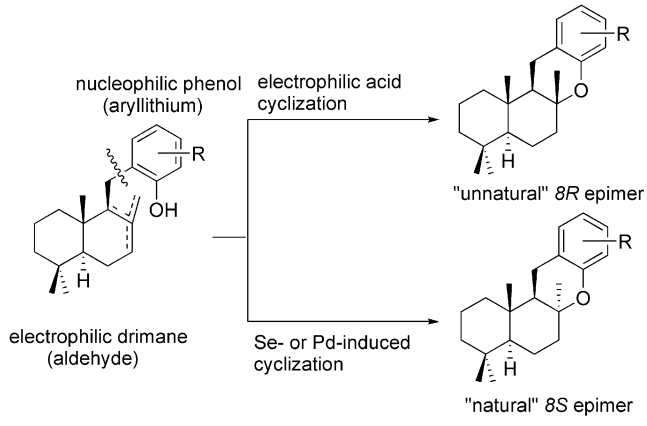
phile with a nucleophilic phenol derivative,[10] usually an aryllithium compound. An 8-oxygenated aldehyde,[10a,10d,10g] an 8,9-epoxyaldehyde[10e] or an unsaturated aldehyde,[10b,10c,10i] possessing the correct chirality for three of the four stereogenic centres, that is, C-5, C-9 and C-10, have been utilized as the drimane synthon. Banerjee et al.[10f] reported an alternative two-synthon strategy to create the carbon skeleton of compounds **8a**,**b**, which lack the chirality at C-9, which involves the reaction of a nordrimane anion with a protected polyhydroxybenzaldehyde. In another version of this synthetic strategy, Akita synthesized (+)-zonarol, an exocyclic drimenyl hydroquinone, by 1,4-addition of an arylcuprate on nordrimane α,β-enone **11**.[10k] An interesting strategy for the elaboration of a tetracyclic skeleton, based on a [4+2] cycloaddition of 1,3,3-trimethyl-2-vinylcyclohexene with 3-cyanochromone derivatives, has been reported; the main drawbacks of this procedure lie with the low yield and the unfavourable stereoselectivity of the process.[11] Very recently, Wallace et al. described rapid stereoselective access to the tetracyclic core of this type of compound by utilizing metal-free radical cyclizations.[12]

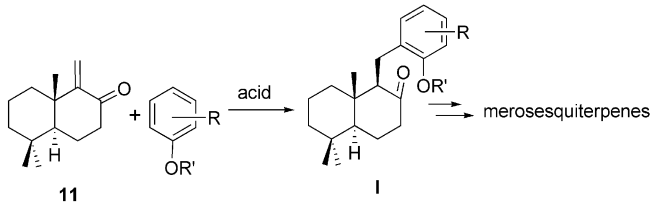
The synthesis of tetracyclic merosesquiterpenes, such as puupehenone-related metabolites **4**–**10**, requires the construction of the C pyran ring in a second phase of the synthetic sequence, when the two synthon (drimane electrophile–nucleophile phenol) strategy is utilized. The stereoselectivity of this process determines the stereochemistry at C-8, affording the natural (C8α-Me) compounds or their epimers. Various methodologies have been utilized to elaborate the pyran ring. Electrophilic acid cyclization of drimenylphenols leads to, as the major diastereoisomer, the "unnatural" (C8β-Me) compounds.[9a,10b,10d] The obtention of natural 8-epimers, such as (+)-puupehenone (**4**) and related compounds, starting from drimenylphenol, was first accomplished by the present authors through β-attack of the phenol hydroxy group on an α-selene-[10a] or α-oxacyclopropane[10d] generated from the carbon–carbon double bond; more recently, a palladium-promoted cyclization was utilized in the synthesis of the antitumour 15-oxopuupehenol (**9**) by our group.[10i] Quideau et al. synthesized **4** by starting from an 8-hydroxydrimane with a suitable configuration at C-8, by attack onto an oxidatively activated 1,2-dihydroxyphenyl unit.[10g] Very recently, an alternative strategy was utilized by the present authors in the synthesis of the potent angiogenesis inhibitor 8-epipuupehedione (**8b**), involving the Diels–Alder cycloaddition of a C_{19} dienol ether, derived from sclareol oxide, with a suitable dienophile.[10j] Scheme 1 summarizes the most commonly utilized synthetic strategies towards puupehenone-related metabolites.



Scheme 1. The previous two-synthon strategy with subsequent pyran ring construction.

Results and Discussion

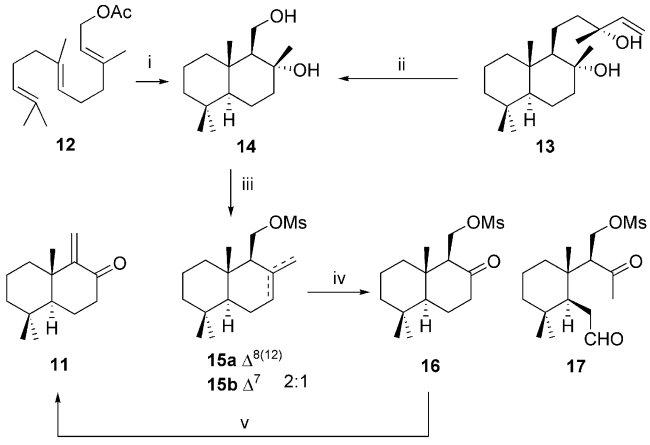
Continuing our investigation into the synthesis of bioactive merosesquiterpenes, we are interested in developing new methodologies, utilizing easily accessible synthons and convenient reaction conditions, which at the same time enable control of the C-8 stereochemistry of the final compound. An alternative to the usual two-synthon strategy, which involves the addition of the inconvenient aryllithium or arylcuprate to the drimane aldehyde or nordrimane α,β-enone **11**, could be the Friedel–Crafts alkylation of a suitable aromatic synthon with α,β-unsaturated ketone **11** (Scheme 2). Adduct **I** could be easily transformed into the corresponding merosesquiterpene after regenerating the exocyclic double bond or after introducing a methyl group into the ketone carbonyl. Only a few examples of this type of reaction have been reported. Bunce et al. reported the Amberlyst-15 catalyzed addition of different phenols to some acyclic α,β-unsaturated ketones;[13] in most cases, the corresponding *p*-substituted phenols were obtained in moderate yields. Alkylation of indole derivatives with β,γ-unsaturated α-keto esters[14] and cyclization of aryl derivatives of diethyl malonate,[15] catalyzed by Lewis acids, were recently described. The reaction of dicyclohexylammonium acrylate with hydroxyarenes is another recent example.[16]



Scheme 2. Planned synthetic strategy via nordrimane α,β-enone **11**.

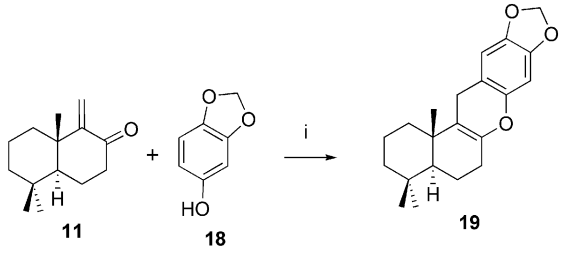
α,β-Enone **11** is a common nordrimane synthon utilized in the synthesis of diverse terpenoids, and different procedures have been reported for its preparation. These include a total synthesis after acid cyclization of methyl geranyl acetoacetate;[17a] pure enantiomers of ketone **11** were obtained through enzymatic functionalization[10k] or optical resolution.[17b] An enantiospecific synthesis starting from a natural drimane was also reported.[17c] We developed a very efficient synthesis of compound **11**, starting from diol **14** (Scheme 3). Enantiomerically pure drimane diol **14** was obtained by lipase-catalyzed kinetic resolution after acid cyclization of farnesyl acetate (**12**) (two steps, 8% overall yield),[18] or after a three-step sequence starting from commercial (–)-sclareol (**13**) (70% overall yield), previously re-

ported by our group.[19] Mesylation of diol **14** gave an unresolvable 2:1 mixture of mesylate regioisomers **15a/b**, which after ozonolysis led to ketone **16** and ketoaldehyde **17**. Further treatment of compound **16** with DBU afforded enone **11**.[20]



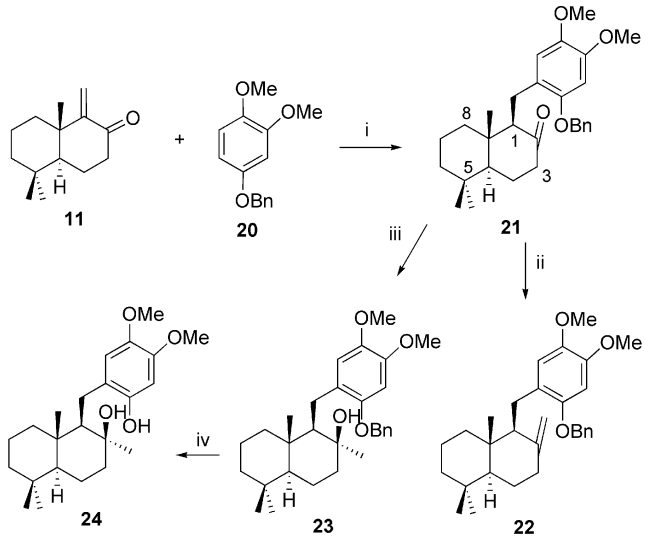
Scheme 3. Synthesis of α,β-enone **11** from diol **14**. Reagents and conditions: (i) Ref.[16] (ii) Ref.[17] (iii) MsCl, pyridine, room temp., 15 h, 80%. (iv) O_3, CH_2Cl_2, –78 °C, 30 min; PPh_3, 4 h, **16** (58%), **17** (34%). (v) DBU, benzene, room temp., 1 h, 95%.

Following this, we investigated the cationic-resin-promoted Friedel–Crafts alkylation of hydroxyarenes with enone **11**, as postulated in Scheme 2. An initial, exciting outcome was obtained when compound **11** was treated with sesamol (**18**) (Scheme 4) and cationic-resin Amberlyst A-15, in benzene under reflux; namely, the formation of chromene **19** in high yield. Besides being a new, mild procedure to synthesize xanthene derivatives, this finding could be exploited to develop a rapid synthesis of merosesquiterpenes; unfortunately, the pyran ring opening of compound **19**, under the conditions reported in the literature, which involves the treatment with methylmagnesium bromide in the presence of low-valent nickel species,[21] was unsuccessful.



Scheme 4. Reaction of sesamol (**18**) with the nordrimane α,β-enone **11**. Reagents and conditions: (i) Amberlyst A-15, 4 Å molecular sieves, benzene, reflux, 1 h 50 min, 99%.

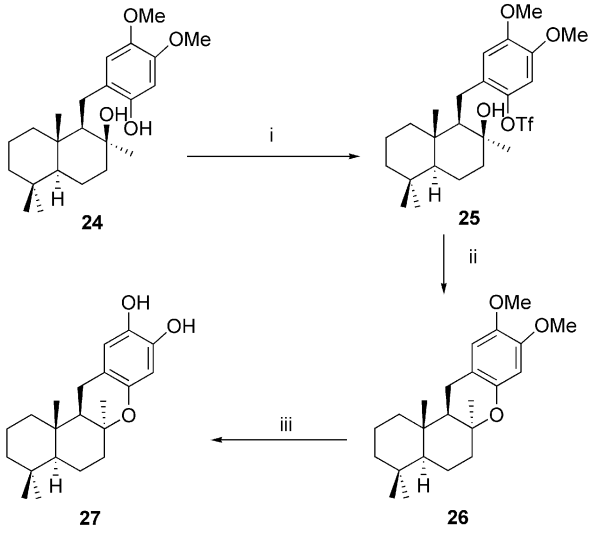
In order to prevent the formation of the pyran ring, a protected phenol was utilized (Scheme 5). At this point, it should be noted that the behaviour of aryl ethers is quite different from that previously reported for phenols. Thus, we have observed that the reaction on α,β-unsaturated ketone **11**, mediated by cationic resin, only occurs when the attack position of the aryl ether is sufficiently activated; in this way, we confirmed that the anisol did not react and neither did the catechol dimethyl ether. However, treatment of compound **20**[22] with enone **11**, under the above conditions, afforded ketone **21** in high yield and with complete diastereoselectivity, as the NOE experiments revealed; thus, the ^1H NMR CH_2-C_1 signals (doublet of doublets at δ = 2.67 and 2.73 ppm) increased after irradiating the angular methyl protons (s, δ = 0.73 ppm). Exocyclic drimane alkene **22** was then obtained after Wittig condensation. Compound **22** is a suitable intermediate in the synthesis of pupehenone-related metabolites, through acid-mediated cyclization or selenium- or palladium-promoted cyclization. Obviously, this resin-promoted Friedel–Crafts alkylation will also allow the synthesis of merosesquiterpenes bearing an exocyclic carbon–carbon double bond, such as compounds **1**–**3**, by utilizing a suitable aromatic synthon. Alternatively, treatment of ketone **21** with MeMgBr and further deprotection of the benzyl ether gave drimane phenol **24**, which is a suitable intermediate for synthesizing pupehenone-related metabolites and "unnatural" 8-epi derivatives. Its cyclization under acidic conditions will provide the corresponding (8*R*)-tetracyclic compound, as was unequivocally established.[10i]



Scheme 5. Synthesis of drimenyl phenol **23**. Reagents and conditions: (i) Amberlyst A-15, 4 Å molecular sieves, CH_2Cl_2, reflux, 12 h, 94%. (ii) $Ph_3P{=}CH_2$, THF, room temp., 4 h, 74%. (iii) MeMgBr, OEt_2, 0 °C, 30 min, 94%. (iv) H_2, Pd–C, MeOH, room temp., 1 h, 93%.

Hydroxyphenol **24**, which possesses the correct stereochemistry at C-8 to achieve natural metabolites, has been transformed into puupehenol (**27**), whose transformation into puupehenone-related metabolites, such as **4**, **5**, **9** and **10**, we had previously reported[10i] (Scheme 6). Cyclization of triflate **25** with $Pd(OAc)_2$ (10 mol-%), 1,1′-bis(diphenylphosphanyl)ferrocene (DPPF; 15 mol-%) and sodium *tert*-butoxide in toluene at 100 °C gave tetracyclic compound **26**, which was easily converted into diphenol **27**. The complete

sequence constitutes a formal synthesis of puupehenone (**4**) and related metabolites, from (–)-sclareol (**13**), based on the resin-promoted Friedel–Crafts alkylation.



Scheme 6. Synthesis of puupehenol (**27**) from hydroxyphenol **24**. Reagents and conditions: (i) $(TfO)_2O$, CH_2Cl_2, *i*PrNEt$_2$, 0 °C, 5 min, 83%. (ii) cat. $Pd(OAc)_2$, cat. DPPF, NaO*t*Bu, toluene, 100 °C, 14 h, 76%. (iii) BBr_3, CH_2Cl_2, 0 °C, 1 h 20 min, 82%.

Conclusions

In summary, a cationic-resin-promoted Friedel–Crafts alkylation of polyphenol ethers with an α,β-unsaturated ketone is utilized for the first time to synthesize bioactive merosesquiterpenes. The reaction of sesamol (**18**) with enone **11** afforded compound **19** in high yield; this process constitutes a new, convenient procedure for synthesizing xanthene derivatives. The reaction of protected phenol **20** with ketone **11** gave aryl nordrimane ketone **21**, which was easily transformed into merosesquiterpene **22**. Alternatively, hydroxyphenol **24**, also obtained from ketone **21**, was converted into puupehenol (**27**), the precursor of puupehenone-related metabolites, utilizing a new method involving C–O coupling catalyzed by palladium. Compound **24** is also a suitable intermediate in the synthesis of the 8-epi derivatives, such as the angiogenesis inhibitor 8-epipuupehedione (**8b**), through acid-mediated cyclization.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data and NMR spectra for all the new compounds.

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