metric methods and by ab initio calculations. The initial structure of the protonated dimers seems to be that of a proton-bridged conformation, in which the proton and the two carbonyl oxygen atom lone pairs form a "three-center bond". The symmetric dimers, in which the proton is equidistant from both oxygen atoms, are more stable toward dissociation to reactants than the asymmetric protonated dimers, in which the proton is further from one of the oxygen atoms forming a weaker O-H bond. The tendency of the neutral reactants to participate in the formation of protonated dimers was related to their proton affinity. Thus, in order for the acidic fluorides to form asymmetric protonated dimers with formaldehyde, a large excess of the former is needed. Electron deformation density maps were calculated. These also indicate that the three-center bond is strongest in the symmetric protonated dimers, while in the asymmetric ones, especially in $(H_2CO\text{-}F_2CO)H^+$, there is a tendency toward dissociation to protonated formaldehyde and a neutral fluoride molecule. Finally, the reactions rates were correlated with the exothermicities of the association reactions.

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Supplementary Material Available: Schematic conformations and the STO-4G charges (condensed to atoms) of protonated formaldehyde dimers (Figure S1), the electronic difference density map of a square planar protonated formaldehyde dimer in the molecular plane (Figure S2), the charge distribution, condensed to atoms, in proton-bridged dimers, calculated with the 4-31G basis set (Figure S3), the electronic difference density map of the proton-bridged asymmetric dimer $(H_2CO\text{-}HFCO)H^+$ in the molecular plane (Figure S4), the electronic difference map of a protonated formyl fluoride in the molecular plane (Figure S5), and the electronic difference density map of the protonated asymmetric dimer $(H_2CO\text{-}F_2CO)H^+$ in the molecular plane (Figure S6) (6 pages). Ordering information is given on any current masthead page.

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Communications to the Editor

A General Methodology for Pseudoguaiane Synthesis: Total Synthesis of (±)-Damsinic Acid and (±)-Confertin[1]

Sir:

The facile synthesis and further elaboration of functionalized bicyclo[5.3.0]decanes constitute an objective of considerable dimension in synthesis as suggested, in part, by the number and complexity of natural product families characterized by this subunit (e.g., pseudoguaiane, guaiane, daphnane, tigliane, ingenane, asebotoxin).[2] The significance of this objective is further amplified by the potent and varied biological activity and, in particular, significant antitumor[3] or cocarcinogenic activity[4] exhibited by various constituents of this series. In connection with these considerations, we describe herein an efficient synthesis of (±)-damsinic acid (**1**) and (±)-confertin (**2**)[5] which embodies a general methodology of potentially broad applicability to the synthesis of the above skeleta.

With respect to synthesis design, a convergent route to the previously noted families was expected to be derivable from methodology which would allow for the annelation of a seven-membered ring onto a preformed five-membered ring. Our studies on the development of such methodology in the specific context of pseudoguaiane synthesis were guided by two considerations which bear on the generality of an approach to this family. Specifically, the A-ring functionality of most pseudoguaianes is characterized by or could be derived from a C-4 carbonyl and the stereochemistry of those pseudoguaianes characterized by α-oriented hydrogens at B-ring stereocenters could be efficiently established by a single-step hydrogenation of unsaturated intermediates[6] such as **5** or **6** derivable from a common precursor such as dienone **7**. With respect to these considerations, we previously described a method for the preparation of divinylcyclopropanes which can be utilized to efficiently effect the requisite annelation (e.g., Scheme I: **8** + **9a** (and/or **10a**) → **11a** (and/or **12a**) → **13a**, 72% overall).[7,8] However the simple but crucial extension of

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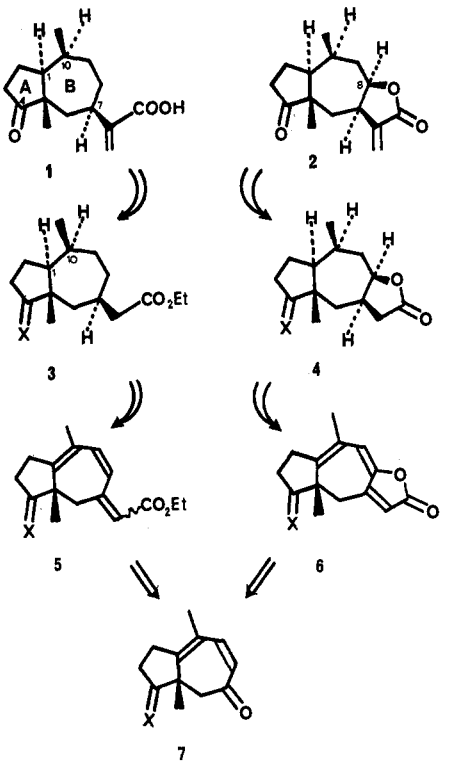
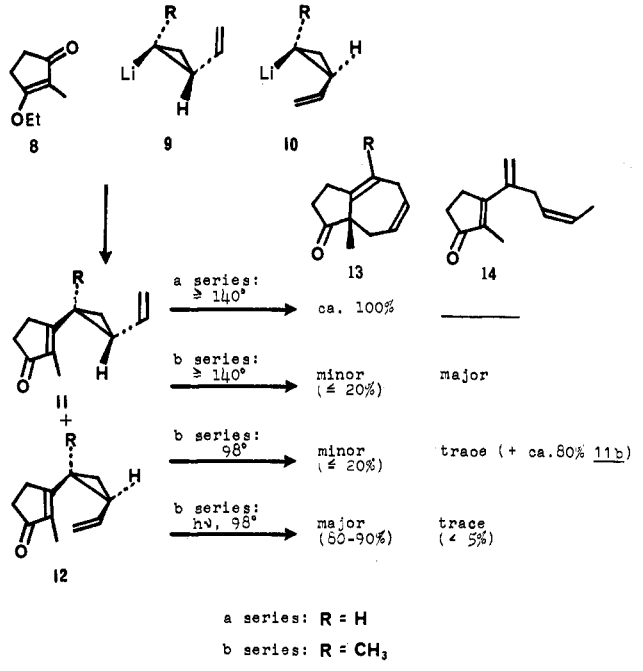
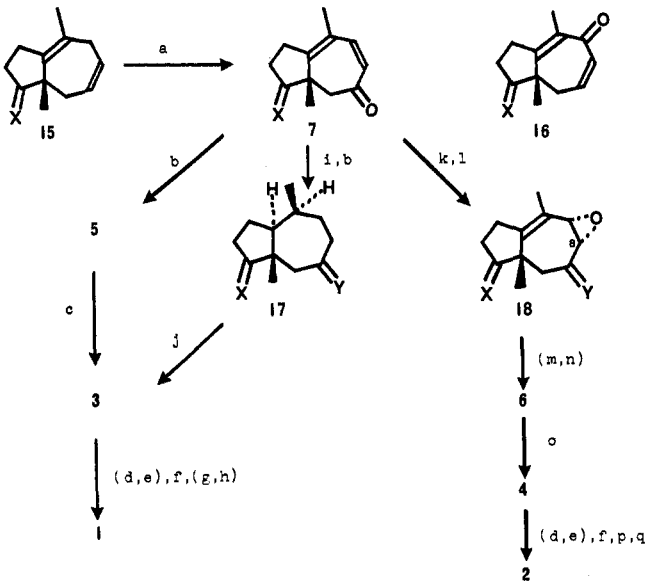


this chemistry in the methyl series (R = CH_3)[9] was frustrated by the formation of triene **14** along with only minor amounts of desired product (**13b**) when ketones **11b** and **12b** were pyrolyzed under a variety of conditions. The amount of **13b** formed in these pyrolyses was approximately equivalent to the amount of *cis*-divinylcyclopropane starting material (**12b**).[9,10] Thus, while both **11a** and **12a** lead to annelated product (**13a**), a process implicating thermal epimerization of **11a** to **12a**, the corresponding epimerization of **11b** to **12b** is precluded by the more facile rearrangement of **11b** to **14** involving a homo [1,5]-sigmatropic hydrogen shift.[11] The stereospecific preparation of **12b** would circumvent this problem; however, we have found that it can be more conveniently resolved by photoepimerization of **11b**. Thus, irradiation (>290 nm) of the **11b–12b** mixture (4:1, respectively) provided a mixture enriched in **12b** which upon selective pyrolysis (98 °C) gave **13b** and unreacted **11b**. Repetition of this sequence or simultaneous irradiation and thermolysis (98 °C) of the **11b–12b** mixture gave **13b** in 80–90% yield.

Scheme I



Scheme II[a]



[a] (a) PCC, CH_2Cl_2; (b) $LiMe_3SiCHCO_2Et$; (c) H_2, PtO_2, EtOH; (d) LDA; (e) $Me_2NCH_2^+I^-$, THF; (f) MeI, MeOH; (g) 10% aqueous NaOH–MeOH (1:1), room temperature; (h) 2 N HCl; (i) H_2, 5% Pd/alumina, PhH; (j) H_2, PtO_2, EtOH, NaOAc; (k) H_2O_2, NaOH; (l) $Na(EtO)_2POCHCO_2Et$, PhH; (m) 10% aqueous H_2SO_4, MeCOMe, room temperature; (n) 30% aqueous NaOH, THF; (o) H_2, Pd/C, EtOH; (p) $NaHCO_3$, H_2O; (q) 10% aqueous H_2SO_4, MeCOMe, 50 °C.

In order to allow for the selective introduction of B-ring appendages (Scheme II), ketone **13b** was converted into ketal **15** which upon treatment with pyridinium chlorochromate (PCC)[12,13] gave dienones **7** and **16** (70%) in the ratio of 9:1, respectively. The complementary selectivity (**7**/**16** = 1/3, ~65%) was obtained using $CrO_3 \cdot Py_2$ or *tert*-butyl chromate as oxidants. The chemoselectivity of PCC is noteworthy in that, unlike other chromium-based oxidants, PCC does not effect oxidation of isolated double bonds[12] or, as we have found in our studies, more reactive systems such as diphenylmethane and allylbenzene.

For the synthesis of damsinic acid, dienone **7**, available in >40% overall yield from **8**, was first converted[14] into triene ester **5** (81%) which upon hydrogenation afforded the expected hexahydro product (**3**, 37%, mp 33–34 °C), in accord with the previously discussed rationale, along with a tetrahydro derivative with a C-1,C-10 double bond (55%). Since the latter could not be stereospecifically converted into **3** under these or other hydrogenation conditions, thereby suggesting that these products arise from competitive modes of reduction, an alternative approach to ester **3** was investigated. To this end, reduction of dienone **7** was found to give with >92% stereoselectivity ketone **17** (Y = O, mp 75.5–76.5 °C)[15] which was converted into ester **17** (Y = $CHCO_2Et$). Hydrogenation of this ester afforded ester **3** with 90% stereoselectivity, thereby providing for its efficient (~70%) elaboration from dienone **7**. The stereochemistry assigned to ester **3** was established by its conversion[16] into (±)-damsinic acid (**1**, mp 99–100 °C).[17]

In the extension of this general strategy to the synthesis of confertin (**2**), introduction of the *pro* C-8 oxygen was accomplished by reaction of dienone **7** with basic hydrogen peroxide

which afforded a single epoxy ketone **18** (Y = O, 80%, mp 84.5–85.5 °C (α), mp 122–123 °C (β)). Olefination of this ketone in ethanol gave the *E*- and *Z*-unsaturated esters **18** (Y = $CHCO_2Et$) in a ratio of 3:1, respectively, whereas in benzene the *Z* isomer was obtained with >95% stereoselectivity, a result which, if similar approach control occurs in both solvents, would be consistent with a more facile collapse of *erythro*- and *threo*-alkoxyphosphonates to starting materials relative to products in going from a polar protic to nonpolar aprotic solvent.[18] On exposure to acid, this *Z* isomer (**18**, Y = $CHCO_2Et$) gave a mixture of hydroxylactones[19] which when treated with base provided triene lactone **6** (mp 111–113 °C). Hydrogenation[15] of this lactone (**6**) afforded lactone **4** (mp 100–102 °C; 57% overall from **18**, Y = O) with >80% stereoselectivity (i.e., 95% stereoselectivity per center). This stereochemical assignment was subsequently confirmed by conversion[16] of lactone **4** into (±)-confertin (**2**, mp 112–113.8 °C).[20]

In summary, the above strategy allows for the stereoselective synthesis of (±)-damsinic acid (**1**) and (±)-confertin (**2**) in ~20% (11 steps) and 5–10% (12 steps) overall yield, respectively, via a readily available and potentially general pseudoguaiane precursor, dienone **7**. Moreover, the methodology used in this approach should be readily adaptable to other objectives in the previously noted families. Further studies are in progress.

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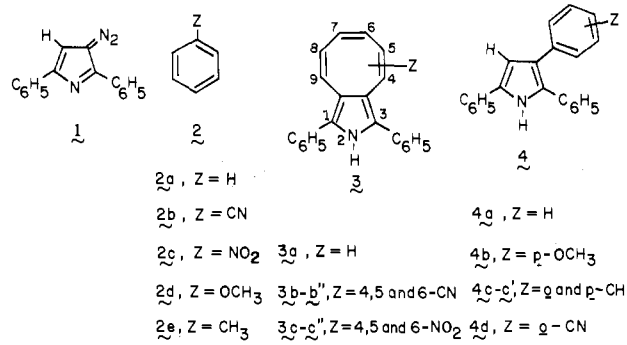
Unusual Substituent and Multiplicity Effects in Carbenic Ring Expansion and Substitution Reactions of Benzenes with 3-Diazo-2,5-diphenylpyrrole

Sir:

Reactions of carbenes with benzenoid derivatives have had limited study.[1] We now report that (1) thermolysis and photolysis of 3-diazo-2,5-diphenylpyrrole (**1**) result in ring expansion of benzene (**2a**) and benzenes **2b,c** containing electron-withdrawing substituents to give 1,3-diphenyl-2*H*-cycloocta[*c*]pyrroles **3a–c″**, a new heterocyclic system, whereas benzenes **2d,e** containing electron-donor groups undergo directed substitution to yield 2,3,5-triarylpyrroles **4a–c′** and (2) photosensitization of **1** in **2a** and **2b** leads to aromatic substitution (**4a,d**) rather than ring expansion. The unusual substituent and multiplicity effects in ring expansion and substitution of **2** by **1** contribute to the theory and the synthetic applicability of reactions of carbenes with aromatic substrates.[1]



Thermolysis (175 °C) or photolysis[2] of **1** in benzene (**2a**, 560 equiv) yields 1,3-diphenyl-2*H*-cycloocta[*c*]pyrrole (**3a**, 69%, mp 196.5–197.5 °C, yellow). Similarly, **1** ring expands benzonitrile (**2b**) to 4-, 5-, and 6-cyano-1,3-diphenyl-2*H*-cycloocta[*c*]pyrroles **3b–b″** (47 and 36%).[3] Aromatic substitution of **2b** is not detectable. Further, **1** converts nitrobenzene (**2c**) at 170 °C to 4-, 5-, and 6-nitro-1,3-diphenyl-2*H*-cycloocta[*c*]pyrroles **3c–c″** (32%).[3,4] Pyrroles **3a, 3b–b″**, and **3c–c″** are assigned from elemental analyses, mass and IR spectra,

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