4-alkoxypyrylium salt, followed by O-3 desilylation to give the desired oxidopyrylium intermediate. Of the several alkylating agents screened to test this possibility, methyl trifluoromethanesulfonate (MeOTf) proved to be the reagent of choice. When **6c** in CH_2Cl_2 was treated with MeOTf at 20 °C for 8 h, O-4 alkylation occurred readily to give pyrylium salt **12c** (Scheme III).[14] Gratifyingly, when this salt[15] in CH_2Cl_2/DMF was exposed to anhydrous cesium fluoride, cycloaddition proceeded smoothly *at room temperature* to give cycloadducts **4a/b** (3.8:1 mixture) in 84% yield. A variant of this protocol allowed for the direct use of hydroxypyrones. Thus, when **6b** in CH_2Cl_2 was treated with MeOTf for 11 h, the pyrylium salt **12b**[14] was produced. Upon reaction with the nonnucleophilic base 2,2,6,6-tetramethylpiperidine, **12b**[15] gave at 20 °C cycloadducts **4a/b** (3.8:1, respectively, 82% yield, 94% based on recovered **6b**).

The novel protocols developed for the cyclization of substrates **6b** and **6c** were also applicable to pyrones **8a** and **8c** (Scheme II). The respective cycloadducts **9a** and **9c** were obtained again at room temperature in 83% and 88% yield as single isomers. The differences in stereoselectivity observed in the cycloadditions of substrates **8** and **6** are potentially a reflection of the relative energy differences between pro-axial and pro-equatorial C-11 substituents on the developing C rings in the cyclization transition states (cyclohexanyl for **8** and cyclohexenyl for **6**).[6a,c]

In summary, a new method has been developed for the synthesis of complex seven-membered rings based on the novel generation and cycloaddition of 4-methoxy-3-oxidopyrylium intermediates. The mild conditions involved with the method create new opportunities for its use with thermally unstable functionalities, as required in the synthesis of phorbol derivatives and other highly functionalized seven-membered carbocycles. In the present case, this process delivers cycloadducts incorporating C ring unsaturation directly amenable to elaboration into diterpenoid promoters, including those bearing oxidation at the C-11 group. Further studies on the scope and limitations of this methodology are in progress.

Acknowledgment. Support of this research by the National Cancer Institute through grant CA31841 is gratefully acknowledged.

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(14) ^1H and ^{13}C NMR spectra indicate that the pyrylium salt is the major product in the crude reaction mixture (>80%).

(15) In order to obtain a efficient cycloaddition, complete elimination of the excess MeOTf (under vacuum at room temperature) from the crude pyrylium salt is required.

Dipolar Cycloaddition of Cyclic Rhodium Carbenoids to Aromatic Heterocycles

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Summary: Cyclic diazo 1,3-dicarbonyl compounds are decomposed by rhodium carboxylate salts in the presence of furans, dihydrofurans, pyrroles, and indoles to generate 7-oxatricyclo[6.4.0.0^{2,6}]dodecane derivatives.

Rhodium-mediated decomposition of diazo carbonyl compounds has become an important methodology in organic synthesis.[1] The reactions in which the putative intermediate metal–carbene participates include ylide formation,[2] O–H and C–H insertion,[3] cyclopropanation,[4] and dipolar cycloaddition.[5] Acyclic diazo ketones and diazo β-keto esters[6] have been widely used for these processes. In reactions of carbenoids derived from these compounds with furans, the products are (*Z*)-α,β,γ,δ-dienals or dienones.[7] It has been postulated that they are produced via initial cyclopropanation followed by electrocyclic ring opening (eq 1). Much less study has been made of the reactions of cyclic metal carbenoids. In this paper we report that cyclic diazo β-diketones preferentially yield dipolar cycloaddition products in rhodium-mediated reactions with aromatic heterocycles such as furan. The

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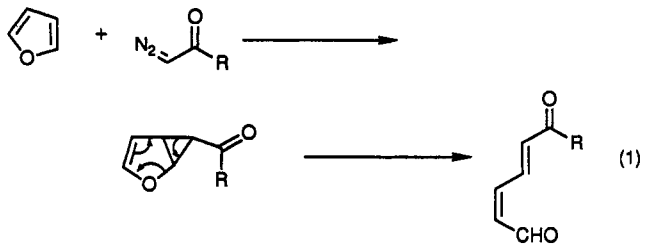
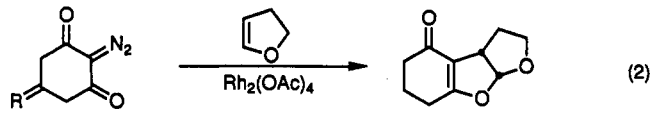


(1)

reaction provides a concise synthetic entry into desirable polyheterocyclic targets.

Diazo compounds used in this study include 2-diazo-1,3-cyclohexanedione (1) and diazodimedone (2).[8] Reactions with dihydrofuran were first examined. When treated with 1 (neat, reflux, 2 h or 25 °C, 4 h, 2 mol % $Rh_2(OAc)_4$), dipolar cycloadduct 3 is obtained (>80%). The cycloadduct is also produced in solvents containing 2 equiv of heterocycle (25 °C, 24 h). There is a strong solvent dependence, with the best yield being obtained in fluorobenzene (70%). Other solvents studied include THF (61%), benzene (48%), dichloroethane (43%), and acetonitrile (20% + 18% of oxazole[9]). We have been unable to conduct any reactions of 1 or 2 in methylene chloride; the major product is always derived from carbene insertion into adventitious water. $Rh_2(OAc)_4$ is the superior catalyst[10] for reaction 2.



(2)

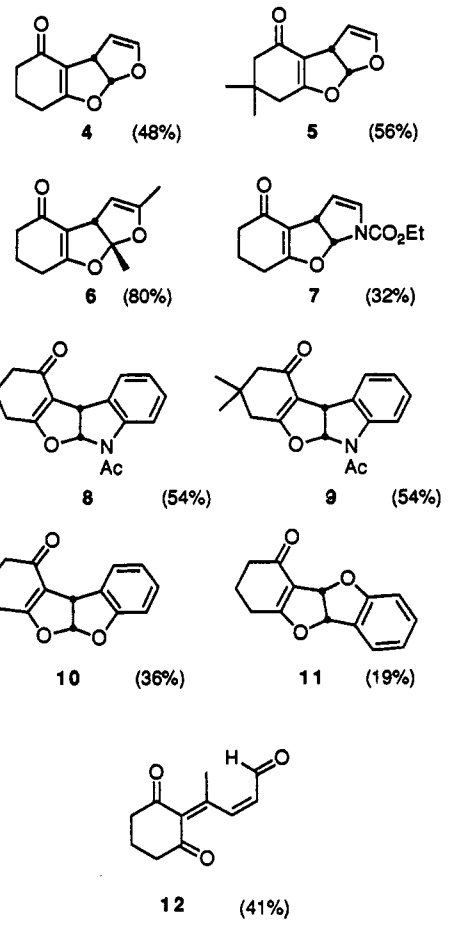
1 R = H, H
2 R=Me, Me

3 (84%)

These cyclic metal carbenoids show a startling departure from the reactivity previously observed with furans: dipolar cycloadducts rather than dienals are produced. The yields of 4 and 5 are 48 and 56%, respectively (furan solvent, room temperature, $Rh_2(OAc)_4$, 24 h, flash chromatography) (Chart I). An even higher yielding reaction occurs with 2,5-dimethylfuran. Similarly, with substituted pyrroles, cycloadducts 7–9 are produced. Because of its aminal and enamine substructures, 7 is somewhat unstable, leading to the modest yield. Attempts to achieve cycloaddition to acetylimidazole lead to recovery of diazo compound. Control experiments demonstrate that acetylimidazole (3 mol %) completely inhibits the addition of 1 to dihydrofuran. With benzofuran, two regioisomeric cycloadducts, 10 and 11, are obtained in 36 and 19% yields, respectively. A non-acetal product similar to 11 is exclusively produced in the reaction of benzofuran and ethyl diazopyruvate, another diazo compound that strongly favors dipolar cycloaddition.[5c] Uniquely, 2-methylfuran provides dienal product 12 (41%).[11]

These cycloadducts can be elaborated toward interesting polycyclic systems. For example, 7 can be selectively hydrogenated (88%) and treated with methylamine hydrochloride (EtOH, Δ, 12 h) to produce 3-acylpyrrole 13 (72%), and subjecting compound 4 to a second cycloaddition produces the interesting bis-adduct 14 (54%). An

Chart I



4 (48%) 5 (56%)

6 (80%) 7 (32%)

8 (54%) 9 (54%)

10 (36%) 11 (19%)

12 (41%)

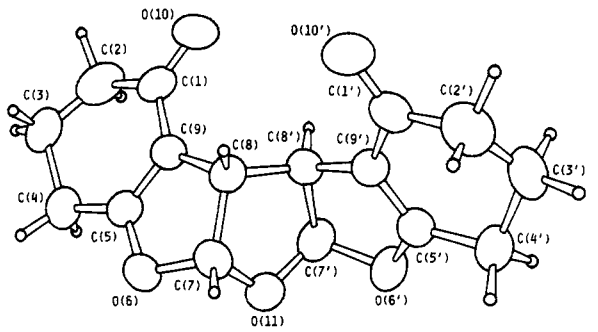


Figure 1. ORTEP diagram showing the crystallographic atom numbering scheme for the major (60%) solid-state conformer of 14; small circles represent hydrogen atoms.

ORTEP plot derived from a crystal structure determination[12] (Figure 1) shows 14 to be the sterically favored C_2-symmetric isomer.[13]

Mechanistic details on dipolar cycloadditions of diazo carbonyls are sparse.[5] Some evidence is available concerning the addition of diazo carbonyls to acetylenes to produce furans. In this work,[5a] initially formed acylcyclopropenes were shown to convert to furans under

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(10) OAc, 90%; OCO-adamantane, 82%; OCO-*t*-Bu, 79%; $OCOCF_3$, 71%; $OCSCH_3$, 0% (rt, 24 h).
(11) With diazo-2,4-pentanedione, dipolar adducts can be obtained from vinyl ethers in ~40% yield. Attempted cycloadditions of diazocyclooctane-1,3-dione and diazocyclopentane-1,3-dione with dihydrofuran (Rh_2OAc_4) give transannular C–H insertion and no decomposition of diazo compound, respectively.

(12) Crystal data for 14: $C_{16}H_{16}O_5$, M = 288.30, tetragonal, space group $P4_32_12$, $a = b$ = 8.813 (1) Å, c = 17.583 (2) Å, v = 1365.7 (5) Å^3, Z = 4, d_{calcd} = 1.402 g cm^{-3}, μ(Cu K$_\alpha$ radiation) = 8.3 cm^{-1}. The crystal structure was solved by direct methods. Full-matrix least-squares refinement of atomic parameters converged at R = 0.033 (R_w = 0.049, GOF = 1.21) over 682 reflections with $I > 3.0\sigma(I)$ recorded on an Enraf-Nonius CAD-4 diffractometer (Cu K$_\alpha$ radiation, λ = 1.5418 Å; graphite monochromator; ω–$2T\sigma$ scans). The cyclohexenone ring of 14 is disordered in the solid state where it occurs as each of the alternative envelope (half-boat) conformations (60:40) in which C(3) is the out-of-plane atom. Further details are provided as supplementary material.
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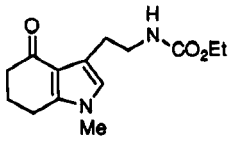
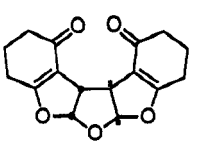


13 (72%)



14 (54%)

rhodium catalysis. The existing postulate that diazo compounds initially cyclopropanate furans and the production of both types of products from 1 suggest a unified mechanism for these reactions involving the acylcyclopropane. An explanation for the favored conversion of this adduct to the dihydrofuran product rather than a dienal is then required (eq 3). Ring opening to the zwitterion with cyclic dicarbonyls could be aided by "spiroactivation".[14] NMR experiments aimed at identifying intermediates in the cycloadditions to give 3 or 6 have thus far given no evidence for such cyclopropanes. An alternative mechanism that has been proposed previously for dipolar addition involves direct generation of the zwitterion.[1] This is difficult to reconcile with the known preference of furan for electrophilic attack at the 2-position.

(3)

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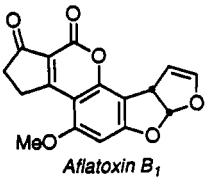
In summary, the dipolar cycloaddition of cyclic diazo 1,3-diketones provides a rapid entry into polyheterocyclic systems. The influence of ring size and breadth of application of this reaction will be established in the future. It is already apparent, however, that the method provides an expeditious synthetic route toward such natural heterocycles as aflatoxin.[15]



Aflatoxin B_1

Acknowledgment. The support of NIH grant GM-38226 and the Johnson Matthey Metals Loan Program is gratefully acknowledged.

Supplementary Material Available: Experimental procedures and spectral data, ORTEP diagrams and tables of crystallographic data, atomic positional and thermal parameters, and bond lengths and angles for 14 (12 pages); listing of observed and calculated structure amplitudes (5 pages). Ordering information is given on any current masthead page.

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Articles

Smenochromenes, Unusual Macrocyclic Sesquiterpene Hydroquinone Derivatives from a Seychelles Sponge of the Genus *Smenospongia*

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Smenochromenes A–D (2–5) are four unusual macrocyclic chromenes that can be derived by cyclization of farnesyl hydroquinone. The structure of smenochromene A (2) was determined by X-ray analysis and the structures of the remaining compounds were elucidated by interpretation of spectral data. The unusual geometry of smenochromene A gives rise to some unexpected spectral data. The sponge *Smenospongia* sp. also contains smenodiol (6), which is related to compounds previously found in this genus.

Compounds of mixed biogenesis that are based on the farnesyl hydroquinone skeleton are commonly found in Dictyoceratid sponges[2] and occasionally in brown algae of the genus Dictyopteris.[3] Some compounds in this series such as avarol (1) from *Dysidea avara*[4] have been extensively studied due to their pharmacological properties.[5] Although a wide variety of carbon skeletons derived by

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(2) There are at least 24 papers reporting this class of compounds. For reviews, see: Faulkner, D. J. *Tetrahedron* **1977**, *33*, 1421. Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 551; **1986**, *3*, 1; **1987**, *4*, 539; **1988**, *5*, 613; **1990**, *7*, 269; **1991**, *8*, 97.

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