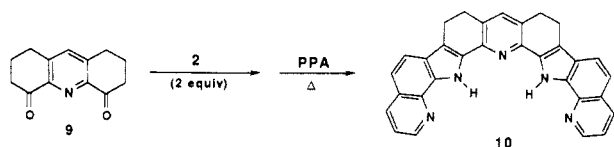


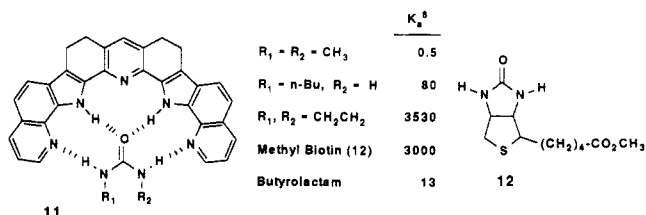
The 3,3'-tetramethylene bridge of **7** causes an estimated twist of about 65° about the 2,2'-bond so that the two pyridindole subunits do not really form a cavity as indicated in the structure drawing. Each of these subunits can undergo a cyclometallation reaction with palladium 2,4-pentanedionate, resulting in the formation of a binuclear complex.⁵

When the pyridyl diketone **9** is treated with 2 equiv of **2**, a bis(hydrazone) is formed, which after treatment with PPA provided the cavity-shaped molecule **10** in 77% yield. This system



is interesting in that the interior of the cavity contains five nitrogens arranged in a 1,4-relation to one another. The three pyridine ring nitrogens are electron-pair donors while the pyrrole ring NH's are potential electron-pair acceptors in a hydrogen-bonding fashion. Inspection of a molecular model indicates that this system should be a good host for urea derivatives. A variety of related donor-acceptor-type hosts have recently been described.⁶

We find that **10** not only solubilizes urea in chloroform but also forms complexes with a variety of substituted ureas. When incremental amounts of the guest were added to a 0.005 M solution of **10** in 1:1 CD₂Cl₂-CDCl₃ at 18 °C, the chemical shift of the NH of **10** moved downfield over a 2 ppm range. The NMR titration data were analyzed by using a linear least-squares fitting procedure similar to that described by Wilcox and Cowart,⁷ and the calculated association constants are given with structure **11**. We were unable to measure urea and some of its simpler derivatives due to their insolubility in our solvent system.



The K_a values are consistent with the binding model depicted in structure **11**. The weakest binder is dimethylurea, whose most favorable binding conformation is hindered by its two *N*-methyl groups. This steric problem is somewhat alleviated for *n*-butylurea, which binds 160× better while bridging the two nitrogens as in imidazolidone provides an excellent host-guest fit. To test the generality of this binding, we employed methyl biotin (**12**) as the guest and again observed strong binding. Butyrolactam is a simple amide analogue of imidazolidone. Although it is only capable of forming three H bonds, it still associates reasonably well.

These results are significant in that the receptor contains a relatively rigid, well-defined cavity, allowing predictions to be made

regarding binding interactions with a suitable guest. Systems with greater conformational mobility do not enjoy this advantage.⁹ Other receptors for urea-type molecules have been reported but they bind primarily through the NH's such that the carbonyl group is pointed away from the binding site.¹⁰ The receptor **10**, however, binds urea with its carbonyl group pointed inward, permitting the potential incorporation of a wide variety of substituted derivatives. It is particularly interesting that a cavity-shaped receptor allows greater latitude as a host than cyclic species which have more stringent size requirements.

Future efforts will be aimed at defining the scope of the binding interaction by structural variations in both the host and the guest. Predictive computations will also be employed in this regard.

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Registry No. **1**, 56826-69-8; **2**, 14148-42-6; **3**, 126664-10-6; **4**, 126664-11-7; **5**, 126664-12-8; **7**, 126664-13-9; **8**, 126664-14-0; **9**, 63371-62-0; **10**, 126664-15-1; **11** ($R_1 = R_2 = \text{Me}$), 126664-18-4; **11** ($R_1 = \text{Bu}, R_2 = \text{H}$), 126664-19-5; **11** ($R_1, R_2 = \text{CH}_2\text{CH}_3$), 126664-20-8; **11-12**, 126783-78-6; **11**-butyrolactam, 126664-21-9; **12**, 608-16-2; VH-157, 126664-16-2; VH-189, 126664-17-3; VH-226, 126664-22-0; MeN-HCONHMe, 96-31-1; BuNHCONH₂, 592-31-4; Pd(acac-F₆)₂, 64916-48-9; 1,2-cyclooctanedione, 3008-37-5; 8-aminoquinoline, 578-66-5; imidazolidin-2-one, 120-93-4; butyrolactam, 616-45-5.

Supplementary Material Available: Experimental details for the preparation of several compounds including **2-5**, **7**, and **10** and the measurement of association constants (5 pages). Ordering information is given on any current masthead page.

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Inverse-Electron-Demand Diels-Alder Reactions of Fischer Carbene Complexes: A New and Efficient Dihydrobenzene Synthesis via a Retrocycloaddition of Chromium Hexacarbonyl†

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Over the last six years, it has been clearly established that α,β -unsaturated Fischer carbene complexes¹ are potent dienophiles in their Diels-Alder reactions with 1,3-dienes.² We report here the first examples of an inverse-electron-demand Diels-Alder reaction of Fischer carbene complexes involving the reactions of

† Dedicated to Professor Wolfgang Kirmse on the occasion of his 60th birthday.

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(8) The association constant, K_a , for each host-guest complex was calculated with an accuracy of $\pm 15\%$ by following the method of Horman and Dreux.⁷

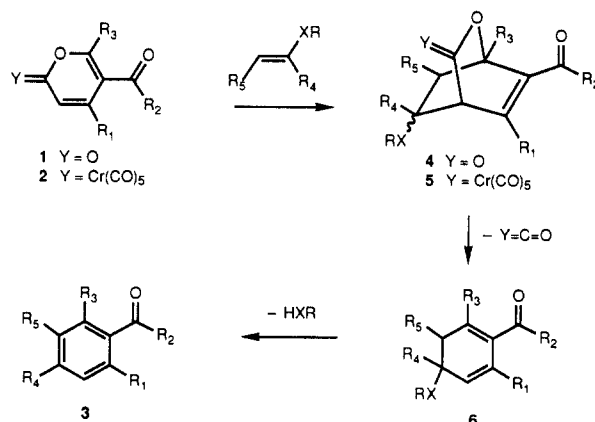
Table I. Dihydrobenzenes via Inverse-Electron-Demand Diels–Alder Reactions of Pyranilidene Complexes

entry	pyranilidene complex 2	cycloaddition method ^a	dihydrobenzene 6	% yield 6
1	2a	A 25 °C, 4.5 h		93 ^b
2	2b	A 25 °C, 22 h		88
3	2c	A 25 °C, 69 h		97
4	2d	A 25 °C, 40 h		96
5	2e	A 25 °C, 48 h		88 ^b
6	2d	A 80 °C, 14 h		78
7	2a	B 25 °C, 19 h		95
8	2d	B 25 °C, 9.5 h		84
9	2f	B 25 °C, 24 h		80
10	2d	A 80 °C, 5 d		88 ^c
11	2d	B ^d 25 °C, 24 h		98 ^e
12	2a	B 25 °C, 19 h		85 ^e

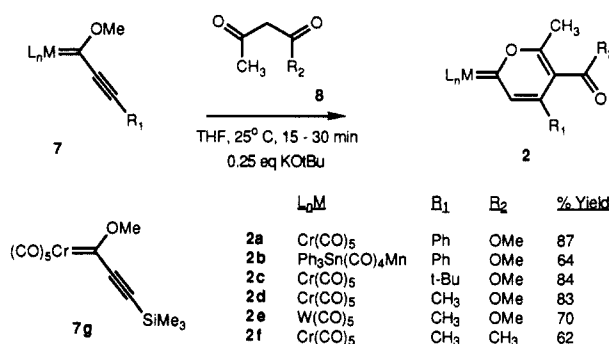
^a Method A: 0.05 M in neat olefin. Method B: 0.05 M in CH₂Cl₂ with 2.5–4.5 equiv of olefin. ^b Reaction carried out on ethyl ester. ^c Aromatized product 3h obtained in 8% yield. ^d Concentration 0.1 M in benzene with 3 equiv of olefin. ^e Isolated yield of the aromatized product.

pyranilidene complexes of the type 2 with electron-rich olefins. These reactions have the anticipated advantage of increased rate enhancements^{1b,2} compared to the reactions of α -pyrones¹³ and have the unexpected advantage that dihydrobenzenes 6 can be typically isolated from these reactions rather than the aromatized products 3 typically produced from the corresponding reactions of α -pyrones. This is a consequence of the fact that the retro-Diels–Alder reaction producing 6 is more facile for the extrusion of a metal carbonyl than for the extrusion of carbon dioxide.

Pyranilidene pentacarbonyl complexes of the group 6 metals have been reported before; however, the methods for their preparation are not suitable for synthetic development due to low yields and lack of generality.⁴ The most successful inverse-electron-



demand Diels–Alder reactions of α -pyrones are those that are activated with carbalkoxy groups in either the 3- and 5-position on the pyrone,³ and it was anticipated that this would also be the case for pyranilidene complexes. The preparation of a variety of pyranilidene complexes of this type (2) can be accomplished in excellent yields by exposure of a THF solution of an alkynyl carbene complex 7⁵ and a β -dicarbonyl compound to a catalytic amount of potassium *tert*-butoxide (or sodium hydride) for a few minutes at room temperature.^{3b} It is important that a substoichiometric amount of base be employed; otherwise a complex mixture of products is generated.



Pyranilidene complexes of the type 2 were found to undergo facile inverse-electron-demand Diels–Alder reactions with electron-rich olefins including alkoxy and silyl enol ethers, enamines, and ketene acetals.⁶ With the exception of entry 10 (Table I), where a small amount of the aromatized product was also isolated, dihydrobenzenes were the exclusive products of the cycloaddition. In none of the examples could the initial chromium Diels–Alder adduct 5 be observed, and this was found to be true for tungsten complex 2e (entry 5) and manganese complex 2b⁷ (entry 2). Apparently the retro-Diels–Alder reaction involving extrusion of a metal carbonyl is rapid from the initial adduct 5 even at room temperature. This is in contrast to the inverse-electron-demand Diels–Alder reactions of α -pyrones where dihydrobenzenes have been isolated only on rare occasions.^{3m,n,t} This is illustrated in the recently reported reaction of the coumalate ester 1c with ethyl vinyl ether, which produces only the initial cycloadduct 4c and the aromatized product 3c.^{3b,c} Decomposition of the cycloadduct

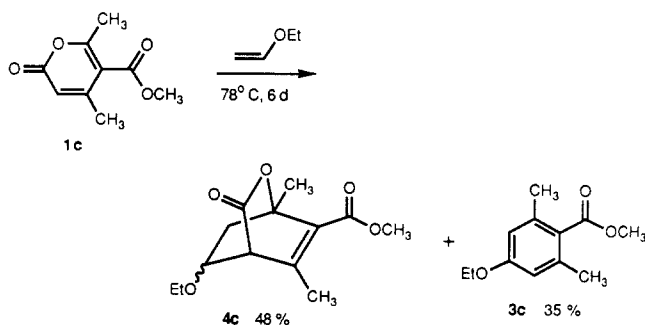
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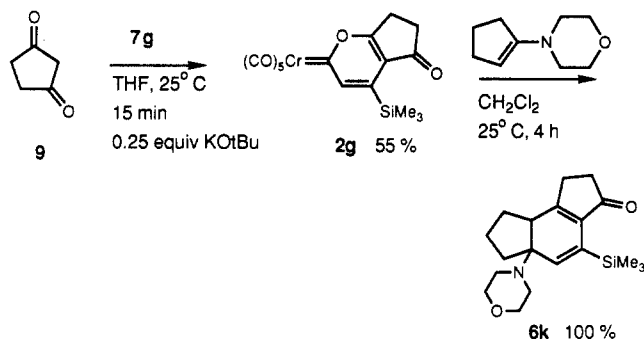
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(6) A Diels–Alder reaction of a pyranilidene complex with benzyne has been reported.^{4a}

(7) Complex 7b (*cis* isomer) was prepared in 30% yield from lithium phenylacetylide and (CO)₅MnSnPh₃ according to a procedure described for related rhenium complexes: Filippou, A. C.; Fischer, E. O.; Müller, G.; Alt, H. G. *J. Organomet. Chem.* **1987**, *329*, 223.



4c resulted only in the formation of the aromatized product **3c**. Also illustrated in this example is the expected rate enhancement^{1b,2} of the pyranilidene complexes. Complex **2d** reacts with ethyl vinyl ether at room temperature (entry 4), whereas the α -pyrone **1c** requires an elevated temperature (78 °C) over a longer period of time. As indicated by the preparation of **6k**, these



reactions can be extended to pyranilidene complexes prepared from cyclic dicarbonyl compounds. The ketene acetal derived products **6i** and **6j** are produced in high yields and can be obtained relatively pure as crude products since the chromium carbonyl side product can be removed under vacuum. Although these products can be characterized in this form, any attempts to purify them by silica gel chromatography or distillation result in aromatization. Phenol acetals of this type have been reported in only a few limited occasions, and pyranilidene complexes offer a clean method for their generation.^{3m,8}

The inverse-electron-demand Diels–Alder reactions of pyranilidene complexes give dihydrobenzene products and complement the reactions of α -pyrones where aromatic products are typically produced, and accordingly, synthetic applications of these reactions are to be expected.

Acknowledgment. This work was supported by a grant from the National Institutes of Health (PHS-GM 33589). Some of the mass spectral data were obtained at the Midwest Center for Mass Spectrometry, an NSF Regional Instrument Facility (CHE-8211164). The NMR instruments used were funded in part by the NSF Chemical Instrumentation Program and by the NCI via the University of Chicago Cancer Research Center (CA-14599).

Supplementary Material Available: Spectral data for all new compounds (6 pages). Ordering information is given on any current masthead page.

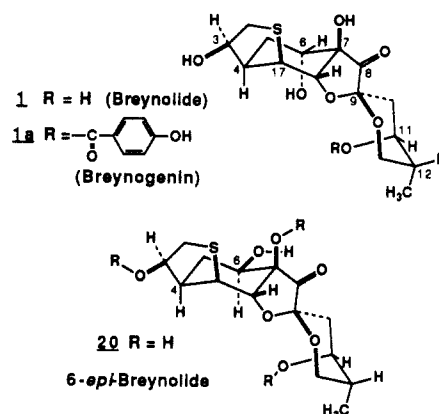
Total Synthesis of (+)-Breynolide

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Breynin A and B are novel sulfur-containing glycosides isolated from *Breynia officinalis* Hemsl,¹ which have displayed remarkable hypocholesterolemic activity in rats at daily oral doses of 0.005 mg/kg and 0.025 mg/kg, respectively. Investigators at the Bristol-Banyu Research Institute have characterized (+)-breynogenin (**1a**) and (+)-breynolide (**1**) as the aglycon hydrolysis products of these antibiotic disaccharides. Stereochemical features and the absolute configuration of (+)-breynolide (**1**) have been unambiguously determined by X-ray crystallography,² revealing a unique perhydrobenzothiophene as part of a highly oxygenated polycyclic nucleus. The 1,6-dioxaspiro[5.4]ketal is structurally similar to that component as found in (+)-phyllanthocin, the aglycon of a family of potent antineoplastic agents.³ Herein we report the first total synthesis of optically active (+)-breynolide.



From the onset of our investigations, we had sought to develop an efficient convergent strategy that would introduce the thioether (position 1 of breynolide) after the necessary oxygenations of a carbon framework. All of these hydroxy and alkoxy substituents are disposed as axial or pseudoaxial within their respective ring systems. Secondly, the presence of the β -hydroxy ketone of **1** (C₆ \rightarrow C₈) suggested that an aldol condensation could be adopted for construction of the cyclohexane ring in the final stages. Thus, the 1,6-dioxaspiro[5.4]decanone could be assembled from a highly oxygenated acyclic backbone with completion of the natural product via closure of the only carbocyclic ring of the molecule.⁴

An aldehydic subunit representing C₇–C₁₃ of breynolide (**1**) allowed masking of the C₉ ketone by internal participation of the C₁₃ alcohol as a mixed ketal **2**. This material was prepared as shown in Scheme I, starting with monoprotected 4(*S*)-methyl-2-pentene-1,5-diol **3**, which was readily supplied via modifications of literature procedures from (–)-methyl 3-hydroxy-2(*R*)-methylpropionate.⁶ Mosher esters of allylic alcohol **3** showed

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(5) Footnote deleted on revision.