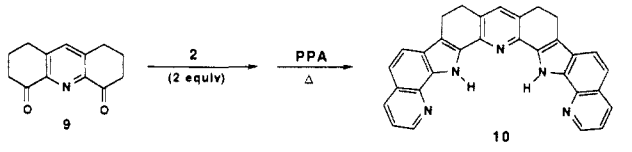
The 3,3'-tetramethylene bridge of **7** causes an estimated twist of about 65° about the 2,2'-bond so that the two pyridoindole subunits do not really form a cavity as indicated in the structure drawing. Each of these subunits can undergo a cyclometallation reaction with palladium 2,4-pentanedionate,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

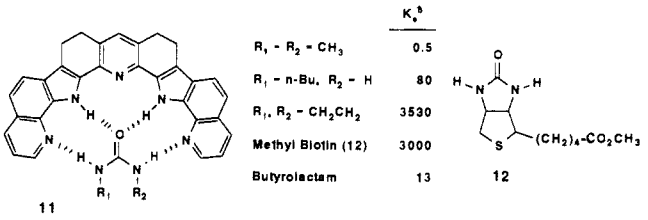
When the pyridyl diketone **9** is treated with 2 equiv of **2**, a bis(hydrazone) is formed, which after treatment with PPA provided the cavity-shaped molecule **10** in 77% yield. This system



9 10

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 CD_2Cl_2–$CDCl_3$ 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.



11 12

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.

Acknowledgment. Financial support from the Robert A. Welch Foundation and the National Science Foundation (CHE-8607935) is gratefully acknowledged. The NMR spectrometer was also partially funded by the NSF (CHE-866352). We also thank Prof. Craig Wilcox and Prof. Paul Street for helpful discussions.

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** ($R_1 = R_2$ = Me), 126664-18-4; **11** (R_1 = Bu; R_2 = H), 126664-19-5; **11** (R_1, $R_2 = CH_2CH_2$), 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; MeNHCONHMe, 96-31-1; $BuNHcONH_2$, 592-31-4; $Pd(acac\text{-}F_6)_2$, 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.

(5) The results of these complexation studies will be published separately.

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

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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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Received December 11, 1989

Over the last six years, it has been clearly established that α,β-unsaturated Fischer carbene complexes[1] 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.

(1) For recent reviews on the chemistry of carbene complexes, see: (a) Dötz, K. H.; Fischer, H.; Hofmann, P.; Kreissel, F. R.; Schubert, U.; Weiss, K. *Transition Metal Carbene Complexes*; Verlag Chemie: Deerfield Beach, FL, 1984. (b) Wulff, W. D. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press Inc.: Greenwich, CT, 1989; Vol. 1.

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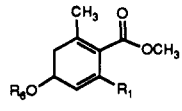
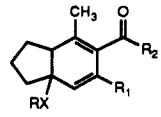
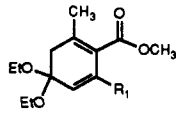
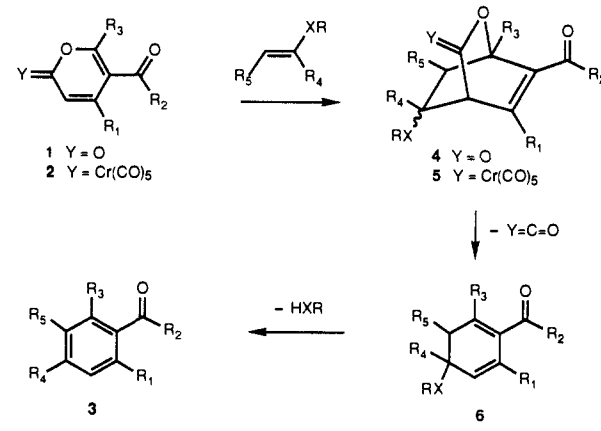
Table I. Dihydrobenzenes via Inverse-Electron-Demand Diels–Alder Reactions of Pyranylidene Complexes

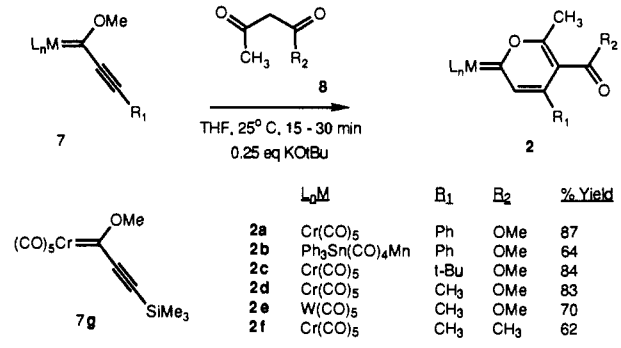
entry	pyranylidene complex **2**	cycloaddition method [a]	dihydrobenzene **6**	% yield **6**
				
			R_6 = Et	
1	**2a**	A 25 °C, 4.5 h	**6a** R_1 = Ph	93 [b]
2	**2b**	A 25 °C, 22 h	**6a** R_1 = Ph	88
3	**2c**	A 25 °C, 69 h	**6b** R_1 = t-Bu	97
4	**2d**	A 25 °C, 40 h	**6c** R_1 = CH_3	96
5	**2e**	A 25 °C, 48 h	**6c** R_1 = CH_3	88 [b]
			R_6 = Me_2t-BuSi	
6	**2d**	A 80 C, 14 h	**6d** R_1 = CH_3	78
				
			RX = morpholino	
7	**2a**	B 25 °C, 19 h	**6e** R_1 = Ph, R_2 = OMe	95
8	**2d**	B 25 °C, 9.5 h	**6f** R_1 = Me, R_2 = OMe	84
9	**2f**	B 25 °C, 24 h	**6g** R_1, R_2 = Me	80
			RX = methoxyl	
10	**2d**	A 80 °C, 5 d	**6h**	88 [c]
				
11	**2d**	B [d] 25 °C, 24 h	**6i** R_1 = CH_3	98 [e]
12	**2a**	B 25 °C, 19 h	**6j** R_1 = Ph	85 [e]

[a] Method A: 0.05 M in neat olefin. Method B: 0.05 M in CH_2Cl_2 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.

pyranylidene 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-pyrones **1**[3] 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.

Pyranylidene 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 pyranylidene complexes. The preparation of a variety of pyranylidene complexes of this type (**2**) can be accomplished in excellent yields by exposure of a THF solution of an alkynyl carbene complex **7**[5] 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.





	L_nM	R_1	R_2	% Yield
2a	$Cr(CO)_5$	Ph	OMe	87
2b	$Ph_3Sn(CO)_4Mn$	Ph	OMe	64
2c	$Cr(CO)_5$	t-Bu	OMe	84
2d	$Cr(CO)_5$	CH_3	OMe	83
2e	$W(CO)_5$	CH_3	OMe	70
2f	$Cr(CO)_5$	CH_3	CH_3	62

Pyranylidene 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 **2b**[7] (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

(3) For inverse-electron-demand Diels–Alder reactions of α-pyrones, see: (a) Posner, G. H.; Haces, A.; Harrison, W.; Kinter, C. M. *J. Org. Chem.* **1987**, *52*, 4836. (b) Jung, M. E.; Hagenah, J. A. *Heterocycles* **1987**, *25*, 117. (c) Jung, M. E.; Hagenah, J. A. *J. Org. Chem.* **1987**, *52*, 1889. (d) Posner, G. H.; Wettlaufer, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 7373. (e) Himbert, G.; Brunn, W. *Liebigs Ann. Chem.* **1986**, 1067. (f) Ziegler, T.; Layh, M.; Effenberger, F. *Chem. Ber.* **1987**, *120*, 1347. (g) Jung, M. E.; Street, L. J.; Usui, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6810. (h) Posner, G. H.; Wettlaufer, D. G. *Tetrahedron Lett.* **1986**, *27*, 667. (i) Posner, G. H.; Harrison, W. *J. Chem. Soc., Chem. Commun.* **1985**, 1786. (j) Martin, P.; Steiner, E.; Streith, J.; Winkler, T.; Bellus, D. *Tetrahedron* **1985**, *41*, 4057. (k) Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1984**, *49*, 4050. (l) Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1984**, *49*, 4045. (m) Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1984**, *49*, 4033. (n) Gingrich, H. L.; Roush, D. M.; Van Saun, A. *J. Org. Chem.* **1983**, *48*, 4869. (o) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988. (p) Boger, D. L.; Patel, M.; Mullican, M. D. *Tetrahedron Lett.* **1982**, *23*, 4559. (q) Boger, D. L.; Mullican, M. D. *Tetrahedron Lett.* **1982**, *23*, 4555. (r) Boger, D. L.; Mullican, M. D. *Tetrahedron Lett.* **1982**, *23*, 4551. (s) Bryson, T. A.; Donelson, D. M. *J. Org. Chem.* **1977**, *42*, 2930. (t) Corey, E. J.; Watt, D. S. *J. Am. Chem. Soc.* **1973**, *95*, 2303. (u) Märkl, G.; Fuchs, R. *Tetrahedron Lett.* **1972**, 4695. (v) Behringer, H.; Heckmaier, P. *Chem. Ber.* **1969**, *102*, 2835.

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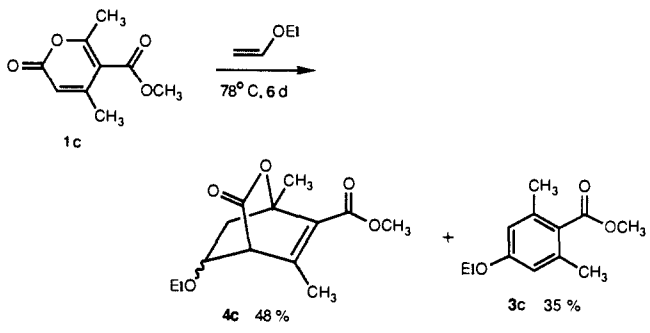
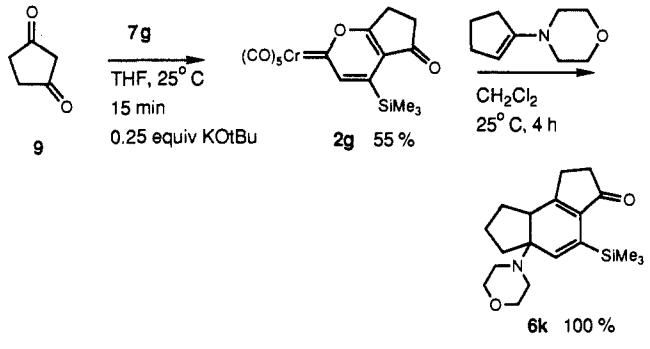
(5) (a) Fischer, E. O.; Kreissl, F. R. *J. Organomet. Chem.* **1972**, *35*, C47. (b) Chan, K. S.; Wulff, W. D. *J. Am. Chem. Soc.* **1986**, *108*, 5229.

(6) A Diels–Alder reaction of a pyranylidene complex with benzyne has been reported.[4a]

(7) Complex **7b** (*cis* isomer) was prepared in 30% yield from lithium phenylacetylide and $(CO)_5MnSnPh_3$ 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 pyranylidene 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 pyranylidene 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 pyranylidene complexes offer a clean method for their generation.[3m,8]

The inverse-electron-demand Diels–Alder reactions of pyranylidene 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.

(8) (a) Atkinson, R. S.; Gawad, N. A. *J. Chem. Soc., Perkin Trans. 1* **1985**, 825. (b) Atkinson, R. S.; Fawcett, J.; Gawad, J.; Nagwa, A.; Russell, D. R.; Sherry, L. J. S. *J. Chem. Soc. Chem. Commun.* **1984**, 1072. (c) Russell, R. A.; Evans, D. A. C.; Warrener, R. N. *Aust. J. Chem.* **1984**, *37*, 1699. (d) Kurosawa, K.; Takamura, T.; Ueno, Y.; McOmie, J. F.; Pearson, N. D. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1914. (e) Spangler, L. A.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 1800. (f) Chenard, B. L.; Dolson, M. G.; Sercel, A. D.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 318. (g) Kikuchi, Y.; Hasegawa, Y.; Matsumoto, M. *J. Chem. Soc., Chem. Commun.* **1982**, 878. (h) Chenard, B. L.; Anderson, D. K.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1980**, 932.

Total Synthesis of (+)-Breynolide

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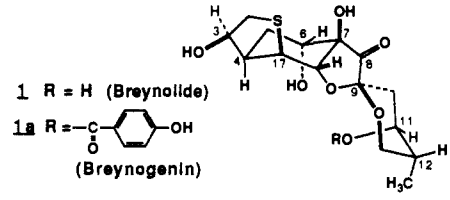
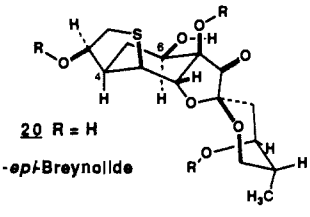
Received December 21, 1989

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** ($C_6 \rightarrow C_8$) 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 C_7–C_{13} of breynolide (**1**) allowed masking of the C_9 ketone by internal participation of the C_{13} 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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