at room temperature for 20 h, and then taken up in water and extracted with ether. The organic phase was washed with 5% HCl, dried, and evaporated to give a dark solid residue (2.2 g). This was taken up in 175 mL of refluxing methanol, treated with decolorizing charcoal, and hot filtered. The resulting yellow solution was boiled down to ca. 45 mL and seeded with material obtained by evaporation of a drop of the solution. Crystals formed slowly on standing at room temperature; after several hours, filtration gave 799 mg (55%) of bright yellow **7**, mp 182-184 °C. The mother liquor was reduced to ca. 20 mL and placed in a freezer after standing at room temperature overnight to give a second crop of **7**, 107 mg, (7%).

A portion was recrystallized (methanol) to give analytically pure **7** as bright yellow needles, mp 184-185 °C: ^{1}H NMR δ 0.43 (s, 9 H), 0.55 (s, 9 H), 6.81 (m, 2 H), 7.24 (m, 1 H), 7.39 (m, 3 H), 7.55 (d, 1 H, J = 8 Hz), 7.72 (d, 1 H, J = 8 Hz), 7.89 (d, 1 H, J = 8 Hz), 7.95 (d, 1 H, J = 8 Hz), 8.38 (s, 1 H), 8.59 (s, 1 H); MS, m/z (relative intensity) 438 (18), 366 (15.2), 323 (14.5), 322 (47.5), 73 (100); MS, calcd for $C_{28}H_{30}OSi_2$ 438.1835, found 438.1845. Anal Calcd: C, 76.66; H, 6.89. Found: C, 76.44;, H, 6.89.

Pentaphene (9): (a) The TFA-LiAlH$_4$ Route. Compound **7** (109 mg, 0.249 mmol) was dissolved in 5 mL of CH_2Cl_2, in a flask equipped with a stir bar and rubber stopper, under N_2. The flask was cooled in an ice bath, and 2.1 mL of a 0.622 M solution of TFA in CH_2Cl_2 (1.31 mmol) was added dropwise. Precipitation was observed after a few minutes; stirring was maintained at room temperature for 3.5 h, and then the volatiles were removed by vacuum evaporation to give a yellow solid. A portion of this crude product (68 mg, 0.230 mmol of assumed **8**) was dissolved in 5 mL of THF and added dropwise to an ice-cooled, stirred solution of 52 mg (1.36 mmol) of $LiAlH_4$ in 5 mL of THF. A bright orange color developed. After 20 min, the excess hydride was decomposed by careful addition of 5% HCl, followed by 3 mL of concentrated HCl, with 15 min of additional stirring. The mixture was added to water, extracted with CH_2Cl_2, dried, and evaporated to afford a solid residue (80 mg). This material was chromatographed twice, first with neat CH_2Cl_2 to give 23 mg (36%) of slightly discolored pentaphene (essentially pure by NMR) and then with 40% CH_2Cl_2/hexanes, which gave a high recovery of rapidly eluted pure pentaphene **9** as yellow plates, mp 264-265 °C (lit.[6] mp 257 °C): ^{1}H NMR δ 7.57 (symmetrical m, 4 H), 7.65 (s, 2 H), 8.03 (m, 2 H), 8.15 (m, 2 H, mirror image of preceding absorption), 8.26 (s, 2 H), 9.25 (s, 2 H); the 60-MHz NMR spectrum was identical with that depicted by Martin et al.;[9] MS, m/z (relative intensity) 280 (2.7), 279 (23.8), 278 (P, 100), 277 (4.2), 276 (13.7), 275 (1.5), 274 (4.3), 139.5 (4.4), 139 (18.6), 138.5 (2.4), 138 (8.6), 137 (4.2),125 (3.6).

(b) The Zn/HOAc Method. To a 50-mL round-bottom flask equipped with a stir bar and reflux condenser were added 340 mg (0.775 mmol) of **7**, 2.0 g (31 mmol) of Zn dust, and 10 mL of glacial HOAc. The mixture was refluxed (under N_2) for 4 h and then allowed to stand at room temperature overnight (yellow crystals were observed). The mixture was then taken up in 50 mL of CH_2Cl_2 and filtered into a separatory funnel, with washings of the residual Zn and other solids. The organic phase was washed twice with water and three times with 10% KOH solution. Drying and evaporation gave 162 mg (75%) of yellow solid pentaphene (**9**), essentially pure by NMR, mp 259-260 °C. Recrystallization from HOAc returned 128 mg of golden plates, mp 263-264 °C.

The course of this reaction could not be followed by TLC because of the very similar behavior of **7** and **9**. It may be possible to improve the yield by increasing the reaction time and amount of solvent, and more thorough extraction of the solid residue (the Zn dust had coagulated into brittle pellets prior to workup).

5-Deuteriopentaphene (10). A solution of **7** (162 mg, 0.370 mmol) in 5 mL of CH_2Cl_2 was treated with 1.24 mmol of TFA in 2 mL of CH_2Cl_2. After the mixture was stirred for 15 h, the volatiles were removed in vacuo to give 110 mg of yellow solid (100% based on the formula of **8**). The ^{1}H NMR spectrum taken in THF-d_8 exhibited a small singlet at 4.98 ppm attributed to ketone **8** (estimated to account for no more than 20% of the material), a complex aromatic proton pattern (7.3-8.6 ppm), and singlets at 8.95 and 9.35 ppm. On standing (3 days) in the capped NMR tube, decomposition occurred (oxidation ?), leading to new signals in the aromatic region but no increase in the peak attributed to **8**.

A solution of 57 mg (1.36 mmol) of $LiAlD_4$ (98% D) in 15 mL of THF was treated with 97 mg of the yellow solid from the TFA reaction (dissolved in 5 mL of THF), with stirring of the bright orange solution for 4.5 h prior to workup as described above. Chromatography gave 12 mg (13%) of deuterated pentaphene **10**, mp 264-265 °C. The ^{1}H NMR of this material was identical with that of **9**, except for diminution of the singlet at 8.26 ppm to an integrated value of one H in **10**: MS, m/z (relative intensity) 281 (5.9), 280 (34.3), 279 (P, 100), 278 (5.9), 277 (13.4), 276 (3.2), 275 (4.0); the relatively high intensity of the 280 peak suggests that some dideuterated material may have been formed, although the mechanism to accomplish this is unclear.

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Registry No. **1**, 75802-19-6; **2**, 96913-93-8; **3**, 101517-29-7; **4**, 4888-02-2; **5**, 4985-70-0; **7**, 101493-04-3; **8**, 101493-05-4; **9**, 222-93-5; **10**, 101493-06-5; o-$Cl_2C_6H_4$, 95-50-1.

(9) Martin, R. H.; Defay, N.; Geerts-Evrard, F.; Delavarenne, S. Tetrahedron **1964**, *20*, 1073.

Crystal Structure of 1-(Phenoxycarbonyl)-2-(*p*-chlorophenyl)-4,5-dimethyl-1,2-dihydropyridine. Insight into the Facial Selectivity of 1,2-Dihydropyridine Diels-Alder Cycloadditions

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Recently, there has been considerable interest in 2-substituted-*N*-(alkoxycarbonyl)-1,2-dihydropyridines (**1**), especially as diene components in Diels-Alder reactions.[1-8] A useful stereochemical feature of such cycloadditions is

(1) For recent reviews of 1,2-dihydropyridines, see: (a) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223-243. (b) Eisner, U.; Kuthan, J. *Ibid.* **1972**, 72, 1-42.

(2) (a) Comins, D. L.; Abdullah, A. H. *Tetrahedron Lett.* **1985**, 43-46. (b) Comins, D. L.; Abdullah, A. H.; Mantlo, N. B. *Ibid.* **1984**, 4867-4870. (c) Comins, D. L., Abdullah, A. H.; Smith, R. K. *Ibid.* 1983, 2711-2714. (d) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315-4319.

(3) (a) Natsume, M.; Utsunomiya, I.; Yamaguchi, K.; Sakai, S. I. *Tetrahedron*, **1985**, 41, 2115-2123, and references therein. (b) Natsume, M.; Ogawa, M. *Chem. Pharm. Bull.* **1982**, *30*, 3442-3445.

(4) Courtois, G.; Al-Arnaout, A.; Miginiac, L. *Tetrahedron Lett.* **1985**, 1027-1030.

(5) (a) Yamaguchi, R.; Moriyasu, M.; Yoshioka, M.; Kawanisi, M. *J. Org. Chem.* **1985**, *50*, 287-288. (b) Yamaguchi, R.; Nakazono, Y.; Kawanisi, M. *Tetradron Lett.* **1983**, 1801-1804. (c) Nakazono, Y.; Yamaguchi, R.; Kawanisi, M. *Chem. Lett.* **1984**, 1129-1132.

(6) Whitney, R. A.; Boyle, J. M. *Heterocycles* **1985**, *23*, 57-60.

(7) (a) Dubey, S. K.; Knaus, E. E. *J. Org. Chem.* **1985**, *50*, 2080-2086. (b) Knaus, E. E.; Avasthi, K.; Giam, C. S. *Can. J. Chem.* **1980**, *58*, 2447-2451. (c) Knaus, E. E.; Pasutto, R. M.; Giam, C. S.; Swinyard, E. A. *J. Heterocycl. Chem.* **1976**, 13, 481-490.

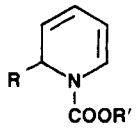
(8) (a) Krow, G. R.; Lee, Y. B.; Szczepanski, S. W.; Raghavachari, R.; Baker, A. D. *Tetrahedron Lett.* **1985**, 2617-2618. (b) Krow, G. R.; Carey, J. T.; Cannon, K. C.; Henz, K. J. *Ibid.* **1982**, 2527-2528. (c) Krow, G. R.; Carey, J. T.; Zacharias, D. E.; Knaus, E. E. *J. Org. Chem.* **1982**, *47*, 1989-1993.

0022-3263/86/1951-1916$01.50/0

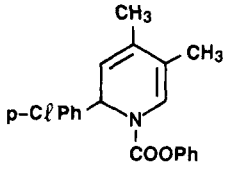
Table I. Crystal Data

molecular formula	$C_{20}H_{18}N_1O_2Cl_1$
molecular weight	339.82
crystal color	colorless
crystal shape	block
crystal dimensions	0.20 × 0.20 × 0.15 mm
space group	$P2_1$, monoclinic No. 4
absences	$0k0, k = 2n + 1$
temperature	293 K
cell constants	a = 10.077 (2) Å
	b = 9.228 (3) Å
	c = 10.177 (1) Å
	β = 113.06 (1)°
volume	870.7 Å^3
Z	2
ρ(calcd)	1.296 g·cm^{-3}
μ	2.272 cm^{-1}
F(000)	178

the observation that, for all intermolecular dienophiles studied,[3,7,8] attack upon 1 occurs only from the face of the



1



2

diene anti to the 2-substituent. By way of comparison, addition of *N*-phenylmaleimide to 5-methylcyclopentadiene does not result in a syn/anti preference for the 7-methyl substituent of the cycloadduct.[9] In order to gain further insight into this phenomenon of high selectivity we have performed an X-ray crystallographic analysis[10] of 1-(phenoxycarbonyl)-2-(*p*-chlorophenyl)-4,5-dimethyl-1,2-dihydropyridine (**2**).[13]

An ORTEP diagram[14] of a single molecule of **2** showing the labeling scheme is presented in Figure 1. It crystallizes in the space group $P2_1$ with only one molecule in the asymmetric unit. Crystal data are presented in Table I. The diene in **2** is characterized by the short C8–C9 (1.339 (8) Å) and C10–C11 (1.315 (7) Å) distances contrasting with the single bond orders between C9–C10 (1.456 (7) Å) and C7–C8 (1.496 (7) Å). The C9–C10 bond of **2** is slightly longer than observed in crystal structures (1.446 (10) Å,[11] 1.407 (8) Å,[12] 1.426 (13) Å[11]) of the chromium(0) complexes referred to in note 10. The torsion angles about the diene carbons (C8–C9–C10–C11, 8.5°; C8–C9–C10–C13, −174.9°; C12–C9–C10–C11, −171.8°; C12–C9–C10–C13, 4.8°), reveal only minor distortions of diene planarity. These distortions can be compared to the torsion angle rotation of one ethylene relative to the other about the C3–C4 single bond in cyclohexa-1,3-diene. This has been determined to be

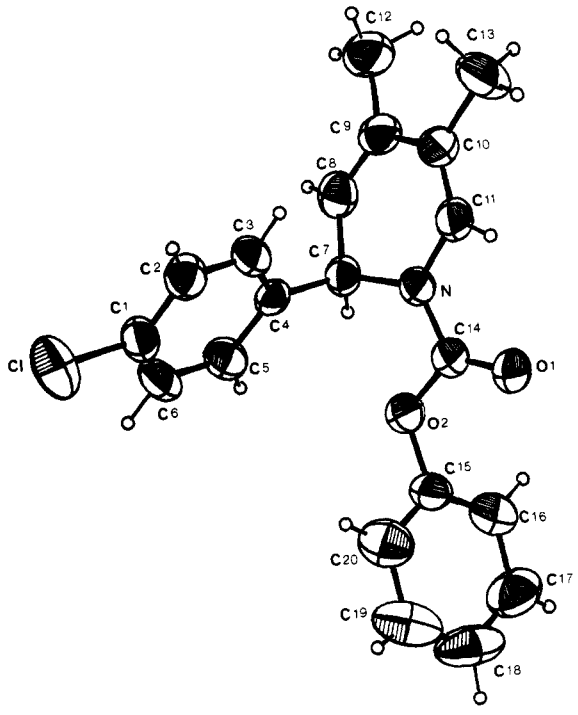


Figure 1. ORTEP diagram showing the labeling scheme for **2**.

17.5 ± 2° by microwave spectroscopy[15] and 17° and 18.34° by diffraction techniques.[16,17]

Other evidence against a bis-methyl buttressing effect as a cause of skewing of the diene in **2** is provided by the 4-H–5-methyl analogue. Work in progress shows it to be isomorphous and isostructural to **2** with only minor geometrical distortions about the diene moiety.[18]

The spatial orientations of the substituents on **2** are revealed by calculations of selected least-squares planes. N and C7 lie on opposite sides of the best calculated plane for the diene (C8–C9–C10–C11) at distances of 0.125 (4) Å and 0.192 (4) Å, respectively. C4 lies 1.578 (4) Å from this calculated plane on the same side as C7, while HC7 and C14 lie syn and oppositely disposed to the plane at nearly the same distances of 0.48 (4) Å and 0.477 (4) Å, respectively.

An important feature is the plane of the *p*-chlorophenyl substituent (C1–C2–C3–C4–C5–C6), which is approximately orthogonal to the plane of the diene (92.8° dihedral angle). The skewed conformational disposition of the C7 substituent with respect to the heterocycle is further described by the torsion angles C3–C4–C7–C8, −60.4°, and C3–C4–C7–N, 63.9°. It is clear from the crystal structure of **2** that the face of the diene near the C7 substituent is the more sterically hindered one.

It was once suggested from Dreiding model inspections that acyl groups on the nitrogen atom of a 1,2-dihydropyridine (**1**) might exert a steric effect upon approach of a dienophile greater than the effect of the substituent group at the 2-position. Although the original basis for such a suggestion, i.e., a presumed exo orientation of the 2-substituent in a Diels–Alder transition state, has been found to be in error, the present work indicates why the preference for attack from the face opposite the 2-substituent is greatly favored.[19] It is also apparent that the

(9) Anh, N. T. *Tetrahedron* **1973**, *29*, 3227–3232. McLean, S.; Hayes, P. *Ibid.* **1965**, *21*, 2313–2327.

(10) Although no X-ray crystal structure determinations of *N*-acyl-1,2-dihydropyridines (**1**) have been reported, the structures of (3-ethyl-*N*-methyl-1,2-dihydropyridine,[11] 4,*N*-dimethyl-1,2-dihydropyridine,[12] and 5-ethyl-*N*-methyl-1,2-dihydropyridine)tricarbonylchromium(0)[11] have been determined. In these molecules the $Cr(CO)_3$ fragment is bonded to five atoms of the 1,2-dihydropyridine ligand. All ligand atoms are nearly coplanar; however, the methylene group is bent out of the plane in the direction opposite the metal.

(11) Bear, C. A.; Trotter, J. *J. Chem. Soc., Dalton Trans.* **1973**, 2285–2288.

(12) Huttner, G.; Mills, O. S. *Chem. Ber.* **1972**, *105*, 3942–3935.

(13) Lyle, R. E.; Comins, D. L. *J. Org. Chem.* **1976**, *41*, 3250–3252.

(14) Johnson, C. K. "ORTEP" *A Fortran Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations*, Oak Ridge National Laboratory: Oak Ridge, TN; Report ORNL-3794.

(15) Butcher, S. S. *J. Chem. Phys.* **1965**, *42*, 1830–1832.

(16) Oberhammer, H.; Bauer, S. H. *J. Am. Chem.* **1969**, *91*, 10–16.

(17) Dallinga, G.; Toneman, L. H. *J. Mol. Struct.* **1967**, *1*, 11–23.

(18) $C_{19}H_{16}NO_2Cl$, M = 325.80, a = 9.672 (2) Å, b = 9.225 (2) Å), c = 10.261 (2) Å, β = 116.08°, v = 822.3 Å^3, space group $P2_1$, monoclinic No. 4, Z = 2.

(19) See ref 8c for further discussion.

preference for a pseudo-axial orientation of the C7 substituent is a result of avoidance of in-plane steric interference between the *p*-chlorophenyl and phenoxycarbonyl substituents. This crystal picture of 1,2-dihydropyridine (**2**) is consistent with the high stereoselectivity observed for dienophilic attack upon other 1,2-dihydropyridines (**1**) in solution.[3,7,8]

Experimental Section

1-(Phenoxycarbonyl)-2-(*p*-chlorophenyl)-4,5-dimethyl-1,2-dihydropyridine (**2**) was prepared by the established procedure.[13] Recrystallization from 2-propanol afforded white crystals, mp 113–114 °C (lit, 111–114 °C), circular dichroism (1.6 mg in 10 mL of absolute ethanol) $[\theta]_{300nm} = 8700$, $\Delta\epsilon = 2.636$. Crystals of **2** suitable for X-ray analysis were obtained by slow evaporation from methylene chloride. A suitable single crystal was mounted with epoxy on a glass fiber for diffraction work. Table I details the crystal data. Intensity data were collected at 293 K with an Enraf-Nonius CAD4 diffractometer using graphite single-crystal monochromated Mo Kα radiation ($\lambda = 0.71073$ Å; takeoff angle = 2.8°). A variable scan speed ω–2θ scan technique ($d\omega/d\theta = 2.0$), as suggested by peak shape analysis, was employed to collect 1728 unique intensity measurements in the range $2° \leq 2\theta \leq 50°$ ($^{+}h,^{+}k,^{+}l$). The minimum and maximum scan speeds (in ω) were 2.5° and 6.7° min^{-1}, respectively. Background measurements were obtained at each end of the scan range using a moving crystal–moving counter technique (scan time/background time = 2.0). Three standard reflections were measured every 3 h of X-ray exposure time. A plot of these standard intensities indicated no crystal decay during data collection. The data were corrected for Lorentz-polarization effects but not for absorption effects.

After rejection of systematically absent reflections and averaging of equivalent observations, 1628 measured intensities remained. Of these 1036 were deemed observed ($I \geq 3\sigma(I)$) and were used in the final least-squares treatments.

The structure was solved by direct methods using the program MULTAN.[20] Data were converted to normalized structure factor amplitudes and 216 E values ($E_{min} = 1.437$) were used for determining phases of reflections for the structural model development. An E-map calculated from the phase set with the highest combined figure of merit gave starting positions for all non-hydrogen atoms. Refinement of these positions along with isotropic thermal parameters afforded the values of the standard agreement factors: $R = \sum||F_o| - |F_c||/\sum|F_o| = 11.4\%$; $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w(F_o)^2]^{1/2} = 11.1\%$, where the weights were initially defined as unity (isotropic refinement) and were eventually defined as $\omega = 1/\sigma(F_o)^2$ with $\sigma(F_o)^2 = [\sigma(I)^2 + (pF_o)^2]^{1/2}$ and $p = 0.05$ (final refinement). All least squares treatments were full matrix on F; the function minimized was $\omega(|F_o| - |F_c|)^2$. After refinement of all non-hydrogen atoms with anisotropic librational parameters a difference Fourier calculation next revealed positions for all hydrogen atoms. The hydrogen atoms were assigned isotropic thermal parameters (5.0, as suggested by a Wilson plot) and only their positions were allowed to vary in the final cycles of the refinement. The model used in the final cycle contained 24 atoms (anisotropic), 18 hydrogens, 270 variables and 1036 observations. Refinement converged to $R = 0.037$ and $R_w = 0.045$ with no non-hydrogen atom parameter shifting by more than 0.03 times its estimated standard deviation. The maximum corresponding shift for hydrogen atoms was 0.08 times it esd except H3C12 which shifted 0.18 times its esd in the final cycle. The goodness of fit was 1.157. An extinction coefficient was not refined. A final difference Fourier synthesis was featureless with no peaks of height greater than one-third of the height of a hydrogen atom. A plot of the function minimized vs. $(\sin\theta)\lambda^{-1}$ showed no significant trends. Values of the neutral atom scattering factors were taken from ref 21 as were the values of F' and F'' for anomalous dispersion, the effects of which were included in the refinement. Hydrogen atom scattering factors used were those of Stewart, Davidson, and Simpson.[22]

There are no unusually short intermolecular interactions; the intermolecular distances correspond to van der Waals interactions. The two phenyl systems are planar and show no unusual bonding features.

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Supplementary Material Available: Complete tables of bond distances, bond angles, torsional angles, calculated least squares planes, a figure showing packing of the molecules in the unit cell, additional tables listing all atomic positional and thermal parameters, root mean square amplitudes of thermal vibration, intermolecular distances and angles, and values of F_o and F_c (31 pages). Ordering information is given on any current masthead page.

(20) Germain, G.; Main, P.; Wolfson M. M. *Acta Crystallog.* **1971**, *A27*, 368–376. All computer programs used for structure solution and refinement are from the Enraf-Nonius Structure Determination Package with local modifications.

(21) *International Tables for X-ray Crystallography*, Kynoch Press: Birmingham, England, 1973; Vol. IV: (a) p 99; (b) p 149.

(22) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175–3187.

Artificial Receptor Recognizing Hydrophobic Carbonyl Compounds

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Hydrophobic recognition by cyclodextrin cavities in an aqueous solution is most effective for hydrophobic guests of appropriate sizes and shapes.[1] The large "recognition free energy change" ($-\Delta G$) associated with the best van der Waals contact and with maximum elimination of structured water along the guest surface,[2] is mainly responsible for this moderately sharp substrate specificity. An additional recognition element such as metal coordination enhances total $-\Delta G$ where the component recognition free energies (hydrophobic and metal coordination) are nearly additive (eq 1).[3] Therefore "artificial receptor" molecules

$$(-\Delta G)_T = (-\Delta G)_{\text{hydrophobic}} + (-\Delta G)_{\text{coordination}} \quad (1)$$

with a sophisticated capacity to recognize particular selected guests may be conveniently designed on the basis of the concept of multiple recognition.[4] This type of approach may lead to *artificial affinity column chromatography* based on appropriate molecular design. Prostaglandins like other transmitters and/or modulators, are known to bind to their corresponding native receptors via multiple recognition and therefore seem to be appropriate target substrates to be bound to a designed artificial receptor via multiple recognition.

We now wish to report that hydrophobic carbonyl compounds are selectively bound to the artificial receptor, *prim,prim*-bis((2-aminoethyl)sulfenyl)-β-cyclodextrin immobilized on polymer beads, via double recognition: hydrophobic binding by the cyclodextrin cavity and carbonyl binding via reversible amino alcohol formation.

The host compound **2** was prepared via A,D-cap **1** as shown in Scheme I. The host compound was then attached to acrylonitrile–methyl acrylate copolymer **3** (average

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