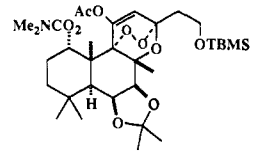
7,8-β epoxidation with 2.5 equiv of *tert*-butyl hydroperoxide and 0.05 equiv of $Mo(CO)_6$ in C_6H_6 at 68 °C for 1 h;[9] (3) elimination of H from C(9) and O from C(8) using 4 equiv of KOH in CH_3OH at 23 °C for 10 min (86% yield for two steps); and (4) ketalization with excess 2,2-dimethoxypropane–acetone with tosic acid as catalyst at 23 °C for 90 min (99% yield).

The highly reactive lactone carbonyl of **8** was readily ethynylated by slow addition of 2.8 equiv of $LiC{\equiv}CCH_2CH_2OTBMS$ (TBMS = *tert*-butyldimethylsilyl) to **8** in THF at 0 °C (80%), and the resulting 1-hydroxy ketone was carbamoylated by reaction with 10 equiv each of dimethylcarbamoyl chloride, 2,6-lutidine, and silver triflate in CH_2Cl_2 (0.06 M) at 23 °C (addition of the silver salt to the other two reactants) to give **9** (60%). Ynone **9** was converted to enol acetate **10** (60% overall)[10] by the following steps: (1) conjugate addition of hydroxyl to C≡C (10 equiv of 0.3 M K_2CO_3 in 1:1 THF–ethylene glycol at 23 °C for 2 h followed by exposure to 1:1 2 N aqueous oxalic acid and acetone at 60 °C for 7 h); (2) resilylation (10 equiv of TBMSCl, 30 equiv of imidazole in DMF at 23 °C for 30 min; 73% overall); and (3) acetylation of the resulting β-hydroxy enone by reaction first with thallous ethoxide at 23 °C for 30 min and then acetyl chloride (−78 °C to −45 °C over 1 h; 82%).

Irradiation of **10** (GE sunlamp) in the presence of 2% of methylene blue in O_2-saturated $CHCl_3$ at 10 °C for 4–5 h resulted in photocyclization to a pyran and subsequent 4 + 2 addition of $^1\Delta_gO_2$ to form endoperoxide **11** in 55–63% yield. This key step



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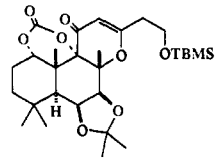

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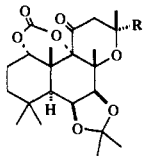
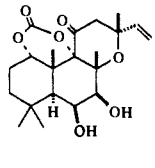


13 R = CH_2CH_2OTBMS
14 R = $CH{=}CH_2$



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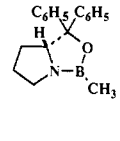

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to form the C ring of the forskolin system was completely stereoselective.[11] Enone **12** was obtained from endoperoxide **11** by the following sequence: (1) β-elimination–hydroperoxide reduction using sodium ethoxide (0.05 M, 2.2 equiv)–tributylphosphine (10 equiv) in ethanol at 0 °C for 2.5 h (80%) and (2) cyclic carbonate formation by reaction with 10:1 acetic acid–acetic anhydride at 100–105 °C (sealed tube) for 23 h. β-Face stereospecific conjugate addition of methyl to enone **12** was effected by reaction with excess $MeCuPBu_3$ and $BF_3{\cdot}Et_2O$ (each 0.2 M) in ether at −78 °C for 4 h and −50 °C for 15 min to provide keto carbonate **13** in 85% yield. Conversion of **13** to vinyl ketone **14** was carried out in >90% yield by (1) desilylation using 2% HF in 50:1 acetonitrile–water at 0 °C for 15 min, (2) reaction with *o*-nitrophenylselenocyanide[12] and tri-*n*-butylphosphine (each 0.02 M) in THF at 0 °C for 2 h, and (3) treatment with 10 equiv of 30% aqueous hydrogen peroxide in THF (0.16 M) at 23 °C for 4 h. Deketalization of **14** (2:1 acetic acid–water, 10 equiv of semicarbazide, 70 °C, 4 h) gave carbonate **15** (>95%). Reaction of **15** with 0.14 M LiOH in 4:2:1 THF–H_2O–*i*-PrOH at 23 °C for 5 min produced (±)-desacetyl forskolin (>95%) which upon treatment with excess Ac_2O–pyridine at 0 °C for 4 h gave (±)-forskolin (**1**) in 90% yield. Synthetic (±)-forskolin thus obtained was identical with an authentic sample of forskolin[13] by 500 MHz ^1H NMR, infrared, and high resolution mass spectral comparison as well as by thin layer chromatography by using several different solvent systems.

Reduction of the ketone corresponding to **2** by 0.6 equiv of borane in the presence of 10 mol% of the (*R*)-oxazaborolidine **16** as catalyst[14,15] in THF solution proceeded with 95/5 enantioselectivity to afford the (*S*)-enantiomer of **2** (as shown), the form required for enantioselective synthesis of the natural form of forskolin, and this alcohol has been converted to the chiral lactone **4**. Thus the synthetic approach reported herein can provide the natural form of forskolin as well as the racemate.

A number of the steps of this synthesis are noteworthy or novel including (1) the enantioselective synthesis of **2**, (2) the facile one-step synthesis of **4** from **2** and **3** at room temperature, (3) the functional group transformation in the conversion **4** → **5**, **5** → **7**, **9** → **11**, and **11** → **12**. The stereospecificity of the C-ring annulation **10** → **12** and the conjugate methylation **12** → **13** also stand out.[16]

Supplementary Material Available: Spectroscopic data for compounds **1–15** and other reaction intermediates mentioned herein (4 pages). Ordering information is given on any current masthead page.

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(10) The ^1H NMR spectrum of **10** indicates rapid interconversion of the two position isomeric β-acetoxyenones (acetyl migration) at 23 °C which becomes slow on the NMR time scale at 227 K.

(11) For related photocyclizations, see: (a) Büchi, G.; Yang, N. C. *Helv. Chim. Acta* **1955**, *38*, 1338–1341. (b) Cerfontain, H.; van Noort, P. C. M.; Geenevasen, J. A. J. *J. Chem. Soc., Perkin Trans. II* **1980**, 1057–1062. (c) Barker, A. J.; Begley, M. J.; Mellor, M.; Otieno, D. A.; Pattenden, G. *J. Chem. Soc., Perkin Trans. I* **1983**, 1893–1900.

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(13) We thank Drs. R. H. Rupp, W. Bartmann, and J. Knolle of the Hoechst Co. for a generous supply of plant-derived forskolin.

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(15) We are indebted to Dr. Tetsuya Mohri of these laboratories for carrying out the enantioselective synthesis of **2** which will be reported separately.

(16) We are grateful to the National Institutes of Health for support of this research and to Dr. Keith Kyler for experimental contributions to an early stage of our program.

Hexagonal Lattice Hosts for Urea. A New Series of Designed Heterocyclic Receptors

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Beginning with crown ethers,[1] the field of host–guest,[2] or supramolecular,[3] chemistry focused initially on complexation of cations.[4] Although hydrogen bonds between neutral molecules are generally weaker than charge/dipole attraction and polar hydrogen bonds,[5] several recent reports indicate that networks of hydrogen bonds may be used to form neutral complexes that

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(2) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1039–1057, and references therein.

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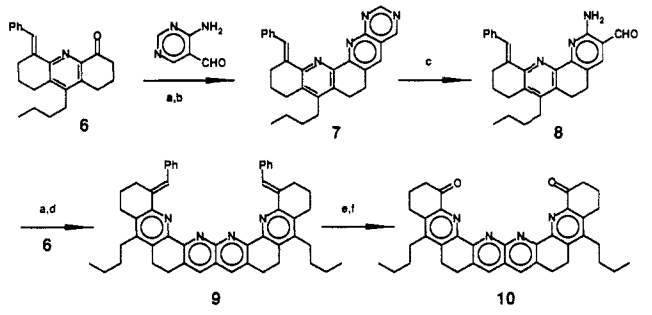
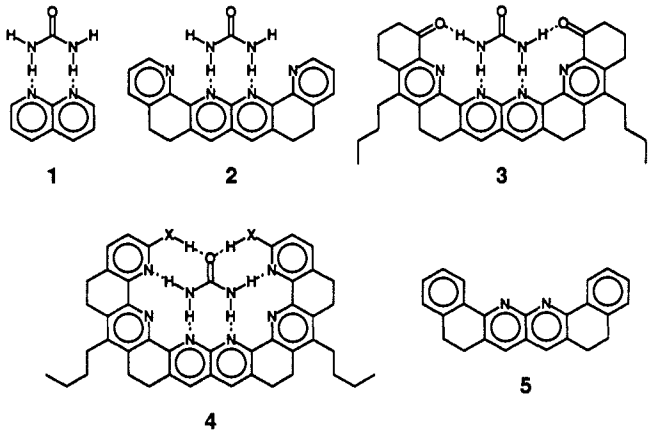
Scheme I. Synthesis of Receptor **10**[a]



[a] (a) KOH, CH_3OH, reflux; (b) 75%; (c) 2 N HCl, reflux (100%); (d) 79%; (e) O_3, CH_3OH, CH_2Cl_2, −78 °C; (f) Me_2S (87%).

are stable in solution.[6] We have developed a relatively rigid molecular framework that organizes hydrogen bonding sites for effective complexation of urea.

Urea is a good target guest because it is small, it has a well-defined geometry, and it can form at least six hydrogen bonds; moreover, urea-selective hosts may be applied to the sequestration and analysis[7] of urea in solutions. With the assistance of CPK molecular models, we have designed a series of urea complexes **1–4** that have a backbone of fused carbocyclic and heterocyclic



rings. Their "hexagonal lattice" architecture is similar to that of ion-binding torands[8] and also to the uric acid receptor of Kelly and Maguire.[6g] Complexes **1–4** represent a graded series containing 2, 4, or 6 hydrogen bonds to pyridine or ketone groups, which are effective hydrogen bond acceptors (β = 0.6–0.8 and 0.5, respectively).[9] In hosts **2–4** two pyridine rings serve as structural spacers and stabilize the complexes, since the negative ends of their group dipoles converge upon the positive end of the urea dipole (4.58 D).[10] A CPK model of complex **4** (X = RNH or OH) reveals a nearly ideal fit between host and guest, implying that receptors having this structure may complex urea specifically.

Our initial studies tested the proposed formation of an eight-membered chelate ring between urea and 1,8-naphthyridine[11] (complex **1**). NMR titration experiments indicated that 1,8-naphthyridine does form a complex with 1,3-dimethylurea that is more stable than the 1,3-dimethylurea dimer in $CDCl_3$. We have also obtained urea complexes **1**[12] and **2**[13] by recrystallization from acetone and ethanol, respectively. In naphthyridine derivative **5**[13,14] two benzene rings hinder the binding site, and a urea complex is not formed under similar conditions. Our synthesis of the diketone host in complex **3** relied on a general sequence for preparation of 1,8-naphthyridines from ketones[13-15] and is shown in Scheme I.[16]

Receptor **10**[17] has the unusual ability to dissolve urea in relatively nonpolar organic solvents. When crystals of urea are added to a solution of **10** in $CDCl_3$, the NH resonances of complex **3** are observed in the NMR spectrum as a broad peak at approximately 6.3–6.7 ppm, and new absorptions are observed in the NH and C=O stretching regions of the infrared spectrum. Urea may be extracted from the complex by washing a chloroform solution of **3** with water. The stability constant (K_s) of complex **3** is readily calculated by using the assumption that the free urea concentration is equal to its solubility in the absence of a receptor. We have used gravimetric and colorimetric[7b] methods for analysis of urea to determine that the solubility of urea in pure chloroform is approximately 5×10^{-4} M, and the ratio of **3** to **10** is greater than 19 when a chloroform solution of **10** (10^{-2} M) attains equilibrium with solid urea at room temperature. Hence, the calculated K_s for complex **3** is at least 4×10^4 L/mol.

The new urea complex **3** is at least 10 times more stable than that of a crown ether receptor that also solubilizes solid urea in chloroform.[6a,18] This stability is remarkable because **3** can have, at most, four hydrogen bonds between host and guest, whereas the latter complex contains five hydrogen bonds. Moreover, receptor **3** does not contain a strong hydrogen bond donor, such as the benzoic acid group that forms a hydrogen bond to the urea carbonyl oxygen in Reinhoudt's complex. We conclude that the molecular architecture of **10** effectively preorganizes hydrogen bonding sites for complexing urea. Current efforts are directed toward the development of hexagonal lattice hosts for selective sequestration and analysis of urea in biological fluids and in the environment.

Acknowledgment. The National Institutes of Health is gratefully thanked for partial support of this research (PHS Grant GM 32937).

Supplementary Material Available: Chemical shift curves used to measure the stability constant of the 1,3-dimethylurea/1,8-naphthyridine complex and ^{1}H NMR spectra of diketone urea receptor and its urea complex (2 pages). Ordering information is given on any current masthead page.

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(12) Mp 147–148 °C. Satisfactory CHN microanalytical data were obtained, proving the 1:1 stoichiometry of the complex.

(13) Mp 278–280 °C. The proton NMR spectrum demonstrated approximately 1:1 stoichiometry of the complex, and the infrared spectrum showed NH absorptions not present in spectra of pure urea or a 1:1 admixture of the solid components. The receptor was synthesized by methods similar to those described by the following: Thummel, R. P.; Lefoulon, F.; Williamson, D.; Chavan, M. *Inorg. Chem.* **1986**, *25*, 1675–1679.

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(16) Spectroscopic properties of all intermediates were in agreement with the assigned structures.

(17) Mp 296–300 °C dec; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 7.92 (s, 2 H), 3.09 (m, 8 H), 3.02 (t, J = 6 Hz, 4 H), 2.76 (m, 8 H), 2.20 (m, 4 H), 1.47 (m, 8 H), 0.98 (t, J = 7 Hz, 6 H); IR (KBr) 1695 cm^{-1} (C = 0); UV ($CHCl_3$) λ_{max} nm (log ϵ) 316 sh (4.1), 360 (4.4), 377 (4.5); MS, m/z 584 (M^+).

(18) From the data reported in ref 6a the stability constant may be estimated as 2×10^3 L/mol.