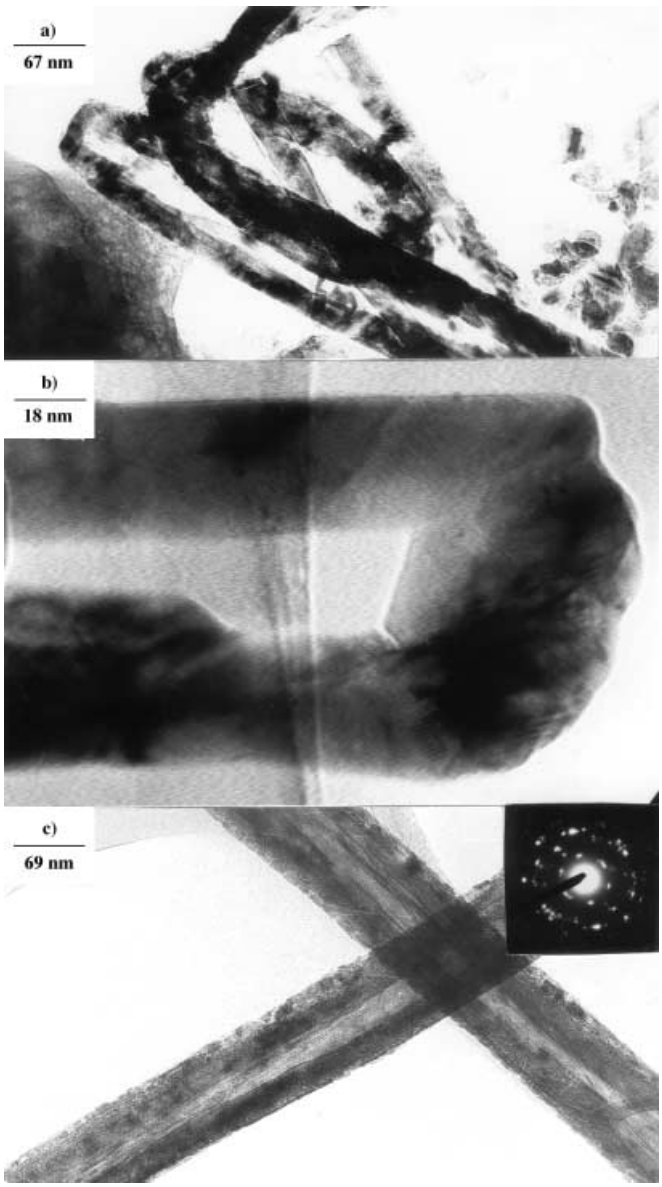

Figure 4. Low-resolution TEM images of the ZrS_2 nanotubes. The tubes in images (b) and (c) show rectangular tips. The inset in (c) shows a typical ED pattern.

In conclusion, nanotubes of the disulfides of the three Group 4 metals, Hf, Zr, and Ti have been successfully prepared by the decomposition of the corresponding trisulfides in a reducing atmosphere.

Experimental Section

The trisulfides were synthesized in a sealed-tube reaction by the direct combination of the elements.[5,6] In a typical synthesis Hf and S powders were mixed in a stoichiometric ratio and the mixture sealed in a quartz ampoule under vacuum. The ampoule was placed in a furnace, which was raised slowly to 560 °C and maintained at that temperature for 36 h. HfS_3 formed as a bright orange solid.

The trisulfides were decomposed in a stream of Ar and H_2 around 900 °C to obtain the disulfide nanotubes. The HfS_3 powder was placed in the central zone of a horizontal furnace, the temperature of which was slowly raised to 900 °C (heating rate of 10 °C min^{-1}), and a steady flow of a mixture of Ar (285 standard cubic centimeters (sccm)) and H_2 (15 sccm) was maintained. The decomposition was carried out for 40 min, after which the temperature of the furnace was reduced. A dark brown powder containing HfS_2 nanostructures were obtained.

Powder X-ray diffraction patterns were obtained using a Seifert diffractometer. SEM images and EDX analysis was carried out using a Leica S440I instrument equipped with ISIS Link software. TEM images were obtained by using a JEOL JEM-3010 transmission electron microscope operating at 300 kV. The HfS_2 and ZrS_2 nanotubes were quite beam-stable, unlike the TiS_2 nanotubes. Photoluminescence studies were performed with a Perkin Elmer LS 55 luminescence spectrometer. Raman measurements were performed with a solid-state Nd-YAG laser and an excitation of 532 nm.

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A Straightforward NMR-Spectroscopy-Based Method for Rapid Library Screening**

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A variety of NMR-based methods have been devised to facilitate the screening of compound mixtures for components that bind protein drug targets.[1–6] The majority of these approaches have been developed in recent years, hand in hand with methods for generating libraries of compounds by combinatorial chemistry.[7] The ability to screen such libraries rapidly and simply to identify potential leads is an important

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requirement of the drug discovery process, hence the considerable activity seen in developing such methods. Although NMR-based screening methods are less sensitive than other alternatives, they are less prone to give artifacts and can be considered comparatively robust. In one class of NMR-based approach, the binding of a molecule to the target macromolecule is monitored by observing changes in the characteristic ^{15}N, ^{13}C, or ^{1}H NMR spectroscopy protein chemical shifts upon ligand-binding.[2,8] In the other class of NMR-based screening methods, low molecular-weight molecules are detected *directly*, by making use of differential relaxation, diffusion, transferred NOEs, or saturation transfer effects of free and bound molecules.[9–16] Direct methods require that the molecule to be detected be in fast chemical exchange between bound and free states, as only then can the easily detected signals display average properties that reflect the bound state. Generally speaking, in the bound state, a small ligand will behave as a macromolecule and exhibit the attendant broad peaks, negative NOEs, and small diffusion coefficients, whereas in the free state molecules will continue to manifest their characteristic narrow linewidths, small and positive NOEs, and large diffusion coefficients. Despite numerous examples of successful applications, methods based on transferred NOEs, relaxation, or diffusion techniques have a shortcoming in that they cannot be used for monitoring high-affinity ligands, which will undergo only slow chemical exchange.

We present herein a 1D ^{1}H NMR screening method that exploits the well-known phenomenon of competitive binding.[17] A known *low-affinity* ligand for a targeted receptor—a "probe"—is included as a component in the mixture of compounds to be screened. In the event that a molecule in the library under scrutiny happens to be a ligand, it competes with the "probe" for binding sites on the target receptor. There ensues a change in the NMR parameters which, at equilibrium, reflects the binding affinity of any new ligand.[18] Here the approach is experimentally demonstrated by using the plant lectin, concanavalin A (Con A),[19] as a model receptor and a handful of designed libraries, consisting of commercially available compounds—essentially mono—and disaccharides. Con A is a $\approx$120 kD homotetrameric carbohydrate-binding protein (lectin) that has been the subject of extensive structural and binding studies.[20,21] Interactions of lectins with their respective saccharide ligands is increasingly identified as crucial in a wide variety of biologically important processes.[20] The possibility that oligosaccharides or mimetics thereof might have promise as drugs has motivated the synthesis of oligosaccharide libraries intended to uncover tight-binding ligands of this particular class of protein.[21]

That the method is fundamentally sound was established by a series of straightforward experiments. Thus, Con A (0.1 mM) was mixed with α-D-(+)-methylglucopyranoside (**1**; 0.05 mM) and D-(+)-galactose (**4**; 0.1 mM) in D_2O and a 500 MHz 1D ^{1}H NMR spectrum of the solution recorded (Figure 1a). As **4** does not bind to Con A, signals from this sugar can conveniently serve as an internal reference to aid in monitoring changes in spectral intensity or linewidth. Based on the reported binding constant data for Con A (Table 1), approximately 25% of **1** in this sample is expected to be bound. The resonance signals corresponding to **1** remain

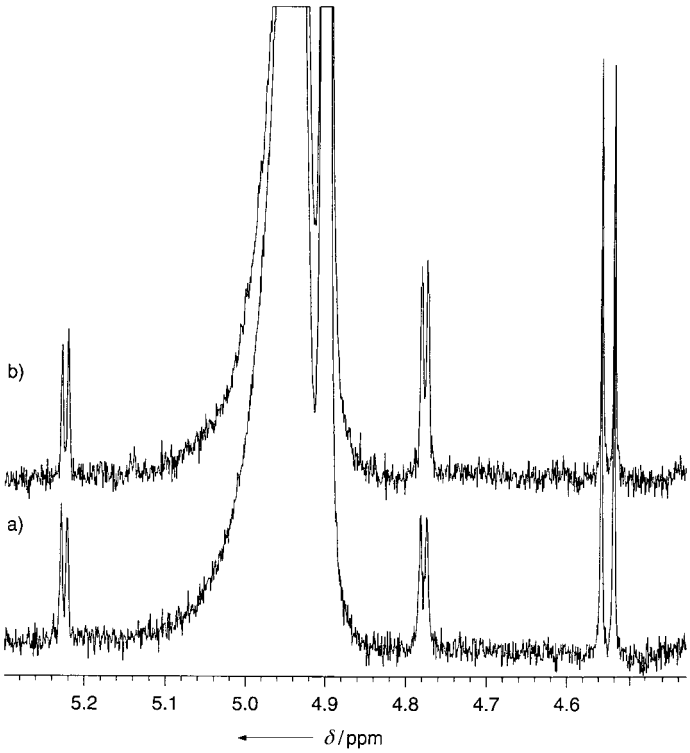

Figure 1. Portion of 1D proton spectra acquired of Con A (0.1 mM) in D_2O: a) in the presence of 0.05 mM compound **1** and 0.1 mM compound **4**, b) upon addition of a 20 mM solution of compound **3** to the mixture. The final concentration of compound **3** is 0.12 mM. The signal at $\delta = 4.78$ ppm is from H-1 of compound **1**. Signals at $\delta = 4.55$ and 5.22 ppm are from H-1 of α and β-anomers, respectively, of compound **4**. Spectra were acquired at 10 °C with spectral width 6000 Hz, 1.5 s acquisition time, 1.5 s recycle delay, and 360 scans.

Table 1. Components of the library and their binding constants[a] to concanavalin A.

	Compound	$K_D \times 10^{-4}$
Active compounds[b]		
1	methyl-α-D-glucopyranoside	3.2
2	methyl-α-D-mannopyranoside	0.91
3	methyl 3,6-di-*O*-(α-D-mannopyranosyl)-α-D-mannopyranoside (trimannoside)	0.03
Inactive compounds[b]		
4	D(+)-galactose	
5	L(−)-fucose	
6	6-deoxy-L-mannose (rhamnose)	
7	L-threonine	
8	6-*O*-α-D-galactopyranosyl-D-glucose (melibiose)	
9	4-*O*-β-D-galactopyranosyl-D-glucose (lactose)	
10	L-histidine	

[a] Data taken from ref. [20a]. [b] Con A and all compounds are commercially available

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sharp (Figure 1a) and are derived from the fraction of this molecule that remains free in solution (slow exchange), as resonance signals of the bound fraction would be too broad to be observable. The change in intensity of the proton signal at $\delta = 4.78$ ppm (H-1 of the probe) is proportional to the amount unbound **1**. Addition of a large molar excess of trimannoside **3** to the sample results in an increase in the relative intensity of signals corresponding to **1** in the ^{1}H NMR spectrum (Figure 1b). Ligand **3** binds considerably more tightly to Con A than does **1** (Table 1) which results in a greater proportion of bound **1** displaced into the bulk solution. The observed increase in the integrated intensity of the anomeric proton of probe **1** upon addition of **3** is $\approx 30\,\%$, and is consistent with the increase expected from reported binding constant values (Table 1).

The scope of this method for identifying potential ligands from a pool of unknowns is demonstrated by using three designed compound libraries. The libraries are each composed of five compounds, all present in concentrations of 0.1 mM. Library I is composed of components **5**–**10** (none of which are ligands of Con A). Library II is identical to library I, except that compound **10** is replaced by compound **2** (a known ligand of Con A). Library III is also essentially identical to library I, except that in Library III, compound **10** is exchanged for compound **3** (also known to bind Con A). To each of these libraries is added a cocktail comprising Con A (0.1 mM), compound **1** (0.1 mM)—the "probe"—and compound **4** (0.2 mM)—the reference. The 500 MHz 1D ^{1}H NMR spectrum of each mixture was recorded and are shown, in part, in Figure 2. It is immediately apparent that variation in the probe signal intensities correctly reflect the presence, *or not*, of active compounds in the designed libraries. Moreover, the observed difference in signal intensity of the "probe" in the spectra of libraries II (Figure 2d) and III (Figure 2c) suggests that the ligand identified in library III is of a higher affinity than that present in library II. When only one active compound is present in a given mixture (true for the libraries under consideration here), a lower limit of K_D (dissociation constant) for that compound can be estimated from the relative changes in "probe" signal, provided that the binding constant of the latter is known. Further, classical titration experiments allow binding strengths of any "hit" to be assessed semi-quantitatively.[17b] The K_D values of the active compounds in libraries II and III, estimated in this way (data not shown), are in agreement with values obtained by independent methods (listed in Table 1).

The method described here is operationally very simple, requiring only that one 1D ^{1}H NMR spectrum be recorded per library under scrutiny. No isotope labeling is required, either of the probe or the target protein nor is the protein required to be pure. The only prerequisite is that at least one molecule be available capable of binding weakly to this macromolecule, and thus, of serving as the all-important probe. All the active ligands, including those displaying either very fast or very slow exchange behavior, are equally susceptible to detection. Moreover, the method is opaque to non-specific association of compounds to the target protein, which includes any binding to secondary sites, minimizing potential sources of false positives. Furthermore, the ratio of protein to probe may

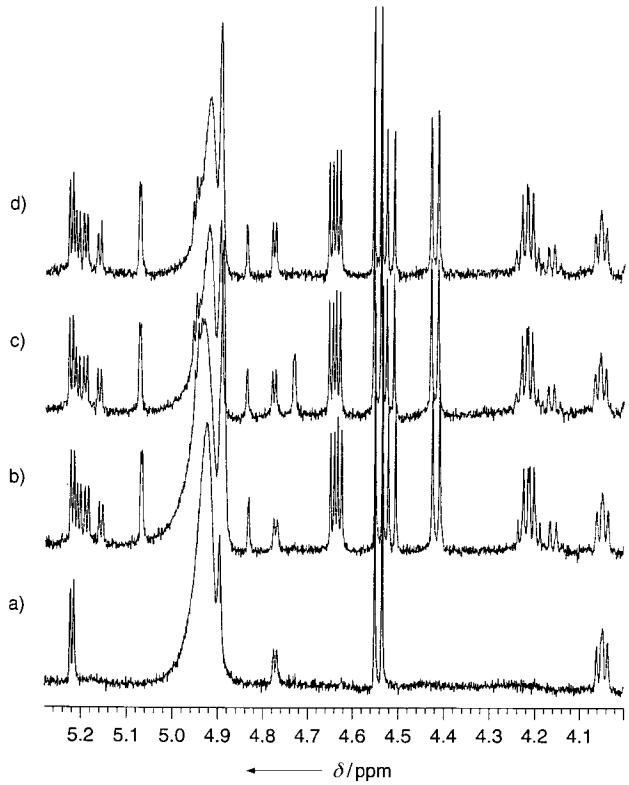

Figure 2. Portions of 1D proton spectra acquired on compound mixtures: a) stock solution, Con A (0.1 mM) with compound **1** (0.05 mM), and compound **4** (0.2 mM), b) compounds **5**–**10** (0.1 mM) with stock solution, c) compound **2** (0.1 mM) and compound **5**–**9** with stock solution (Library II), d) Compound **3** (0.1 mM) and compound **5**–**9** with stock solution (Library III). The signal at $\delta = 4.78$ ppm is from H-1 of compound **1**—the probe molecule. Spectra were acquired at 10 °C with spectral width 6000 Hz, 1.5 s acquisition time, 1.5 s recycle delay and 240 scans. Water suppression is achieved by presaturation.

be tuned so as to limit selection of ligands to those of a chosen binding strength or greater. For example, the binding constant of compound **2** is only about three times greater than that of the probe (compound **1**), but was nevertheless identified in Library II. The sensitivity of this approach compares well with other NMR-based screening methods. In the model experiments described here, 100 μM Con A was used per sample, with constituents of the libraries each present in concentrations of 100 μM. Under these conditions each screen took less than 15 minutes to perform using a 500 MHz NMR spectrometer. However, a significant reduction in amounts of required ligand would result if ligands displaying K_D values in the nM range were being screened. Resonance intensity has been exploited in this study to monitor the percentage of free probe, but other parameters—including line broadening or transferred NOEs (in the case of a probe in rapid exchange)—might also be taken advantage of to achieve this end.[18] No structural information can be gleaned and in the event of an active molecule being detected, its identity would have to be elucidated with recourse to more sophisticated NMR spectroscopic techniques. If resonances derived from the probe were to overlap with others arising from the library, editing techniques such as the diffusion-filter method would be expected to allow selective monitoring of the probe signals. Alternatively, use of an isotopically labeled probe would

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effectively render "invisible" signals other than those of the probe and, if the label could be easily incorporated, lead to a further simplification of the screening method.

The approach demonstrated here provides a general and rapid means for detecting active molecules, especially when these are constituents of a combinatorially generated library. The method could conceivably be automated, and thereby transformed into a routine, high-throughput technique of even greater potential in the process of drug discovery.[22]

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Highly Enantioselective Rh-Catalyzed Intramolecular Alder–Ene Reactions for the Syntheses of Chiral Tetrahydrofurans**

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Dedicated to Professor Robert H. Grubbs on the occasion of his 60th birthday

Alder–ene reactions are a powerful way to construct carbon–carbon bonds. The intramolecular version of these reactions can provide efficient routes to produce a variety of heterocyclic and carbocyclic compounds.[1] Since the thermal Alder–ene reaction requires high temperature, it has found limited applications in organic syntheses. In contrast, transition-metal-catalyzed Alder–ene reactions can be performed under mild conditions and therefore are widely applied to organic syntheses.[2] However, the enantioselective processes of metal-catalyzed Alder–ene reactions are relatively unexplored and the development of highly efficient catalysts still remains a great challenge.[3] Recently, we have developed Rh-catalyzed intramolecular Alder–ene reactions of enynes using a $[\{Rh(diphos)Cl\}_2]$ precursor.[4] Enantioselectivities between 65–98 % *ee* were obtained by using 1,2-bis(phospholano)benzene (Duphos), (2*R*,2′*R*)-bis(diphenylphosphanyl)-(1*R*,1′*R*)-dicyclopentane (BICP), or the related (2*R*,2′*R*)-bis(diphenylphosphinite)-(1*R*,1′*R*)-dicyclopentane (BICPO) as chiral ligands.[4a] Herein, we report a significant improvement of the catalytic system for these reactions. The new catalysts are prepared in situ by simply mixing a commercially available metal precursor and a ligand. Over 99 % *ee* has been achieved for a number of substrates.

To achieve high enantioselectivities for Rh-catalyzed Alder–ene reactions, we have screened a number of chiral phosphane ligands. The enyne **1a** was chosen as a standard substrate to optimize the reaction conditions and the results are given in Table 1. In the absence of phosphane ligand, $[\{Rh(cod)Cl\}_2]$ was an ineffective catalytic precursor at either room temperature or 65 °C (Table 1, entries 1 and 2). However, $[\{Rh(nbd)Cl\}_2]$ (nbd = norbornadiene) can be used as a catalyst precursor at 65 °C (Table 1, entry 6). Using the C_n-Tunaphos ligands developed by our group,[5] high efficiency was observed. When *rac*-C_4-Tunaphos was used as the ligand in the presence of $[\{Rh(cod)Cl\}_2]$ and $AgSbF_6$, high conversion (100 %) and a high yield (98 %) were obtained at room temperature within 20 min (Table 1, entry 9). Control experiments indicated that there were big differences between this new catalytic system and the earlier protocol developed by us using $[\{Rh(diphosphane)Cl\}_2]$ as catalytic precursor. We previously reported that $[\{Rh(BINAP)Cl\}_2]$ (BINAP = 2,2′-

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