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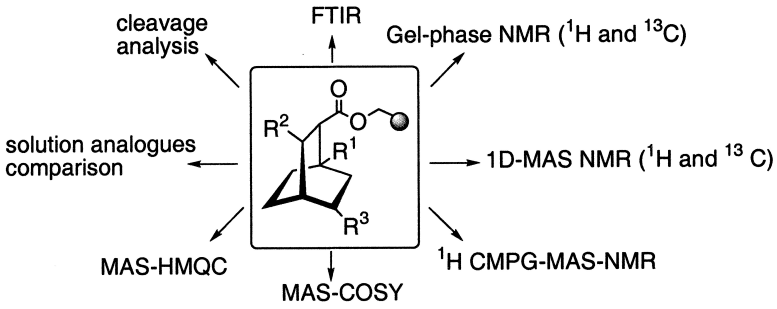


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# Combined Application of Analytical Techniques for the Characterization of Polymer Supported Species

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The combined application of a diverse range of analytical techniques is described for the complete analysis of polymer supported molecules. These techniques permit complete description of the FTIR, $^{1}$H NMR, and $^{13}$C NMR spectra. The comparison of supported bicyclo[2.2.2]octane derivatives with analogous species prepared using polymer supported reagents is made.

Polymer supported species have proved to be of great value in the preparation of libraries as part of combinatorial chemistry programs.[1] Analysis of reaction species during the optimization of the chemistry used for the library generation is a key part of assessing the success or failure of each reaction, especially without using destructive cleavage methods. This optimization process is slow and often the most frustrating element of the synthesis. The best available analytical methods should therefore be at the heart of the development stage of any library synthesis. However, it is likely that the analysis of each product of each step of a library synthesis using polymer supported substrates will remain an impracticality given the number of compounds being generated.

The necessity for the analysis of polymer supported species during a library synthesis can be eliminated altogether by the use of polymer supported reagents rather than substrates.[2] In this strategy, the analysis of supported species would be necessary only for those involved in the design and synthesis of the reagent since the rest of the analysis will be conducted in solution in the normal way.

A number of reports concerning analytical methodology suitable for the nondestructive characterization of supported species have appeared. The techniques described include the following: (1) IR spectroscopy (KBr disk,[3] diffuse reflectance,[4] single bead IR/optical microscopy,[5] and flattened bead techniques[6]); (2) NMR spectroscopy (gel-phase, especially $^{13}$C,[7] magic angle spinning (MAS) spectroscopy,[8] 2D MAS pulse sequences[9] and heteronuclear NMR—$^{19}$F, $^{31}$P, $^{15}$N and $^{13}$C enriched samples[10−13]); (3) ESR spectroscopy.[14]

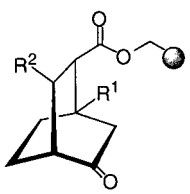
Each of the methods described allows unique data to be obtained. The analysis is generally performed by experts in that particular analytical method and frequently is not adopted by chemists at other institutions. It is important that the various techniques be used together and so produce detailed data that might not otherwise be obtained.

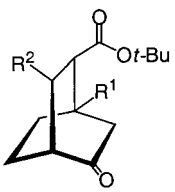
We wish to describe our recent experiences with analytical methodology in the context of supported substrate synthesis. The system to be described involves a polymer supported synthesis of an array of bicyclo[2.2.2]octane derivatives.[15] The analysis of the polymer supported intermediates will be used to illustrate the range of data that can be obtained for supported substrates and may go someway to defining what constitutes full characterization of polymer supported organic molecules. A set of similar molecules were prepared using polymer supported reagents but on a much reduced time scale thanks to the ease of handling of these reagents and the simple optimization of the reactions involved.[16] The spectra of corresponding supported and solution-phase species were compared and demonstrate a very close similarity. Measurement of diastereomeric excesses on a support in tandem with the ratios observed following various cleavage conditions, along with the ratios obtained in solution, permits the influence of the support to be quantified.

All the techniques described have also proved valuable in the identification of problematic synthetic steps in other syntheses and have provided a useful guide to overcoming these problems. Furthermore, good analytical methods such as those described have been essential parts of our polymer supported reagent development program.

## Results and Discussion

We have reported the preparation of bicyclo[2.2.2]-octanones **1**−**7** using both a solid supported substrate[15] and a solid supported reagent synthesis.[16] The key step in both syntheses is a tandem double Michael addition reaction. The *endo* to *exo* ratio obtained after this step is a key aspect of the synthesis as it governs the ratio of isomers ultimately




**1a** $R^1$ = OEt; $R^2$ = Me **1b** $R^1$ = OEt; $R^2$ = Me
**2a** $R^1$ = OEt; $R^2$ = 3'-Fu **2b** $R^1$ = OEt; $R^2$ = 3'-Fu
**3a** $R^1$ = Me; $R^2$ = 3'-Fu **3b** $R^1$ = Me; $R^2$ = 3'-Fu
**4a** $R^1$ = OEt; $R^2$ = Ph **4b** $R^1$ = OEt; $R^2$ = Ph
**5a** $R^1$ = Me; $R^2$ = Ph **5b** $R^1$ = Me; $R^2$ = Ph
**6a** $R^1$ = OEt; $R^2$ = 3'-Th **6b** $R^1$ = OEt; $R^2$ = 3'-Th
**7a** $R^1$ = Me; $R^2$ = 3'-Th **7b** $R^1$ = Me; $R^2$ = 3'-Th

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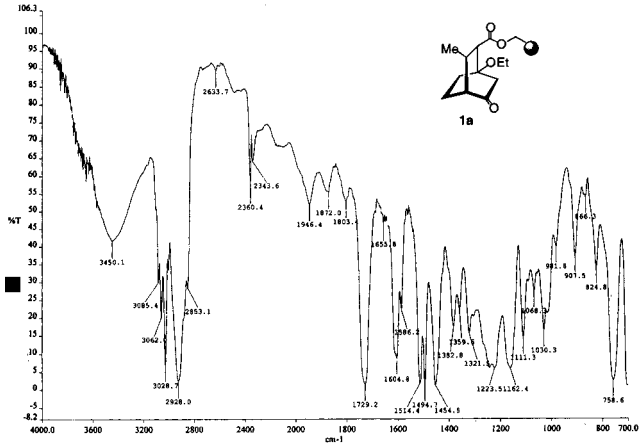



**Figure 1.** Single flattened bead FTIR spectrum.

obtained after cleavage (only the *endo* isomers are represented for **1**−**7**).

During our original supported substrate synthesis, analysis of the supported species was limited, consisting of gel-phase $^{13}C$ NMR spectroscopy, KBr disk IR, and MALDI-TOF mass spectroscopy in tandem with trifluoroacetic acid (TFA) cleavage of the substrate from the resin. Recently, the supported intermediates from this synthesis have been reinvestigated employing many of the improved analytical techniques now available. The library of analogous intermediates prepared in solution, using a supported reagent approach, has allowed us to make an assessment of these techniques, and we feel that the level of analysis undertaken should assist in *defining the standard* that should be expected in the characterization of supported intermediates. Of particular interest is the ability to assess diastereomeric excesses on the support. This enables the measurement of the ratio of isomers produced in each step and the identification of any steps which lead to a change in this ratio.

Each polymer supported sample **1a**−**7a** was analyzed by single flattened bead FTIR spectroscopy, $^1H$ CPMG-MAS-NMR, and MAS-COSY and compared with the corresponding *tert*-butyl esters **1b**−**7b**. A selected set of samples was also characterized by $^{13}C$ MAS-NMR and MAS-HMQC (see also Supporting Information).

The single bead FTIR spectrum of **1a** shown in Figure 1 demonstrates the high quality that can be achieved with such techniques.[17] The utility of IR spectroscopy is fundamentally limited by the lack of quantitative information that may be obtained from the spectra, but it does provide an excellent means for the detection of reaction completion for reactions that involve the transformation of functional groups with distinctive IR properties. The particular system under study in the synthesis demonstrates the limit of the technique. Frequently, several carbonyl stretches can be discerned, but in all of the bicyclo[2.2.2]octane derivatives studied, the ester and ketone stretches (∼1730 $cm^{-1}$) were unresolved. However, the complete consumption of starting polymer supported acrylate ester during the double Michael addition reaction could be detected by the disappearance of the absorption at ∼1654 $cm^{-1}$ corresponding to the alkene.

The supporting matrix for compounds **1a**−**7a** was a Wang resin based on 1−2% cross-linked polystyrene, and

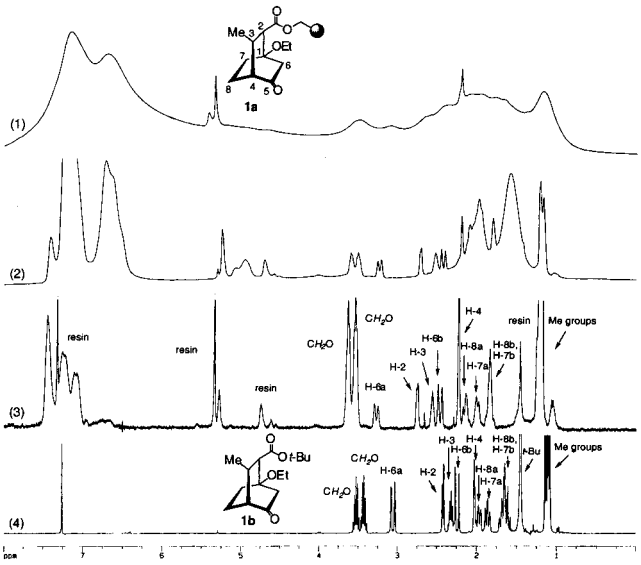



**Figure 2.** (1) Gel-phase $^1H$ NMR spectrum of **1a** (solvent: $CD_2Cl_2$); (2) $^1H$ MAS-NMR spectrum of **1a**; (3) $^1H$ CPMG-MAS-NMR spectrum of **1a**; (4) $^1H$ NMR spectrum of **1b** (solvent: $CDCl_3$).

although reports concerning the analysis of simple polystyrene based species by MAS-NMR have appeared,[1c,f,k,l] the technique appears only to have been routinely adopted for the analysis of PS-PEG graft resin supported molecules. We found that high quality $^1H$ spectra were obtained after less than 2 min acquisition time and CPMG spectra in less than 4 min. CPMG spectroscopy is known in solution-phase work for the reduction in intensity of peaks which are broadened by virtue of having a short $T_2$ such as those due to NH exchangeable protons.[18] Its application in tandem with MAS yields spectra with greatly sharpened peaks as effected by spinning at the magic angle (which averages dipole−dipole interactions and chemical shift anisotropy) and with any broad peaks, notably those due to the polymer backbone, greatly reduced in magnitude. This leads to spectra with a high signal-to-noise ratio which ensures that smaller peaks such as those due to minor products can be seen and identified. The spectra thus acquired will usually provide sufficient information to detect reaction success or failure and often allow the degree of such success or failure to be quantified. Figure 2 illustrates graphically the evolution of $^1H$ NMR techniques for the analysis of polymer supported species. Spectrum 1 is the gel-phase $^1H$ spectrum of **1a** which is composed of very broad peaks and from which no useful details can be discerned.[19] Spectrum 2 is the $^1H$ MAS spectrum[20] of the same compound and consists of reasonably well separated peaks, many of which can be assigned in a straightforward manner. Broad peaks due to the resin backbone persist that prevent the identification of all of the signals corresponding to the supported framework. Spectrum 3 on the other hand is the CPMG spectrum of **1a**[21] in which these peaks are much reduced and the $^1H$ spectrum of the supported molecule is seen with sharp signals due to each $^1H$ environment although small couplings are not resolved. Finally, spectrum 4 is the $^1H$ spectrum for the analogous *tert*-butyl ester **1b** prepared in solution. This spectrum shows a remarkable resemblance to that of its supported equivalent. All peaks in the spectrum of the supported species are shifted

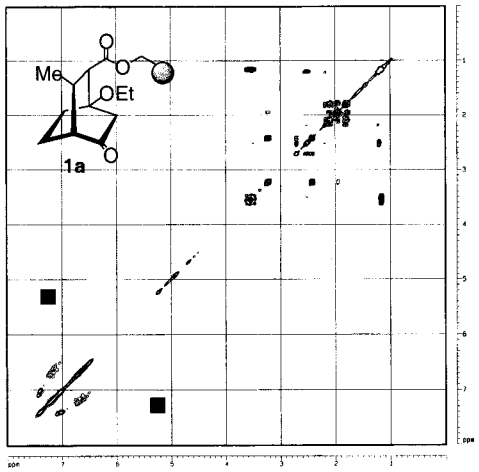



**Figure 3.** MAS-COSY spectrum.

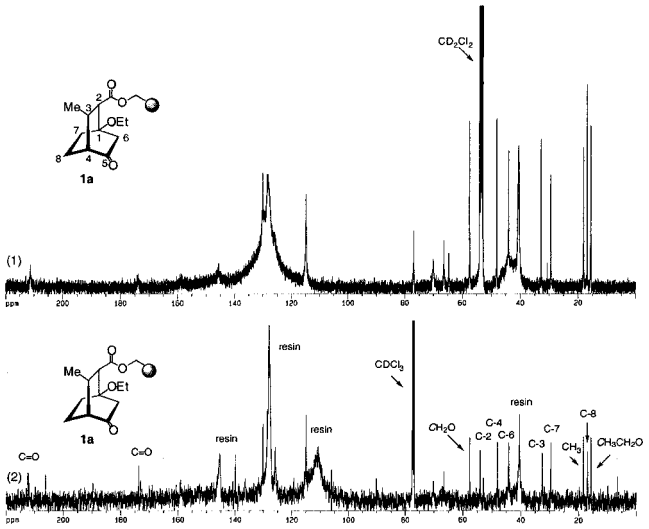



**Figure 4.** (1) Gel-phase $^{13}C$ NMR spectrum (solvent $CD_2Cl_2$); (2) $^{13}C$ MAS-NMR spectrum.

downfield slightly due to the high density of aromatic rings within the polymer matrix. However, there is a high degree of homology between the two spectra, and this similarity provides one method for assigning the spectrum of the supported molecules. The high degree of correspondence between spectra of supported structures and their solution-phase equivalents is maintained across all of the molecules studied (see also Supporting Information).

The assignment of spectra of polymer supported species need not rely on the preparation of solution-phase analogues. Application of more complex NMR spectroscopic methods provides further high quality data for the species on support. For instance, the 2D-COSY spectrum of **1a**[22] shown in Figure 3 permits each of the $^1H$ resonances to be assigned based on the coupling patterns and connectivities deduced. The COSY spectrum obtained for the *tert*-butyl ester **1b** in solution shows a very close resemblance.

The techniques described so far should usually permit identification of all the expected $^1H$ peaks. It would clearly be desirable to use similar techniques to obtain high quality $^{13}C$ data. Spectrum 1 in Figure 4 shows that reasonable $^{13}C$ spectra[19] can be obtained from gel-phase samples and most of the expected signals can be seen. However, the peaks are all rather broad, and the carbonyl peaks at 174 and 212 ppm

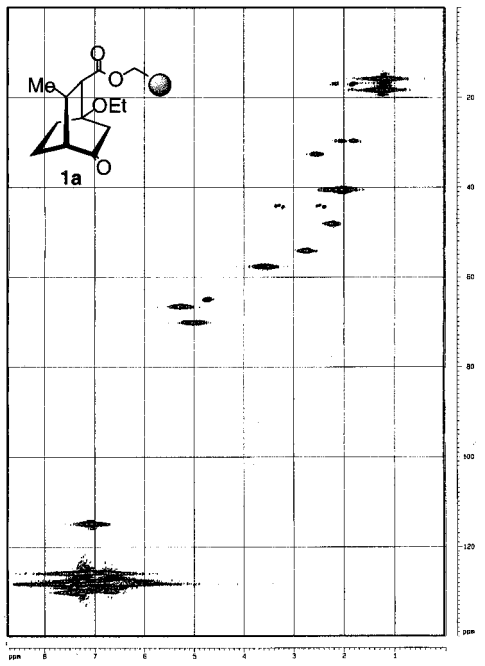



**Figure 5.** MAS-HMQC spectrum.

are far from clear. Spectrum 2 is the corresponding $^{13}C$ MAS-NMR spectrum[20] and demonstrates that some improvement may be expected in terms of reducing the peak widths.

Heteronuclear correlation experiments such as HMQC or HMBC also work well with MAS. The application of the techniques described earlier should allow assignment of the $^1H$ spectra. This information, in tandem with HMQC and HMBC data, should allow rapid identification and assignment of all of the $^{13}C$ signals. These data may take several hours to acquire but may not always be an essential part of the analysis as reaction success or failure will often be clear from IR or 1D-NMR data but may provide crucial confirmation of a product's identity. Figure 5 shows the HMQC spectrum of **1a** and provides sufficient data to assign all of the nonquaternary carbons. The two carbonyl carbons could be identified from the MAS-$^{13}C$ thus, the $^{13}C$ chemical shift for all but *C*-1 could be identified.

Two steps in the supported substrate synthesis may lead to the production of a mixture of isomers. The tandem double Michael addition reaction leads to a mixture of *exo* and *endo* isomers, and the reductive amination may involve reduction from either the *si* or *re* face of the intermediate imine. CPMG spectroscopy has permitted the assessment of the ratio of isomers produced in each of these steps by integration of peaks due to chemically similar protons. Spectrum 1 in Figure 6 is the CPMG spectrum of **2a** and shows two of the furyl signals clearly resolved due to the *endo* and the *exo* isomers. The identity of these peaks was ascertained by comparison with the $^1H$ NMR spectrum of **2b** and by MAS-COSY. Integration of these two peaks allowed a measurement of the ratio of isomers to be made.

Similarly, Figure 7 shows the CPMG spectrum of the product of reductive amination **8a**. The signals due to *H*-5 in the *endo* and *exo* isomers are clearly resolved and are readily integrated to obtain a value for the selectivity of the reduction.

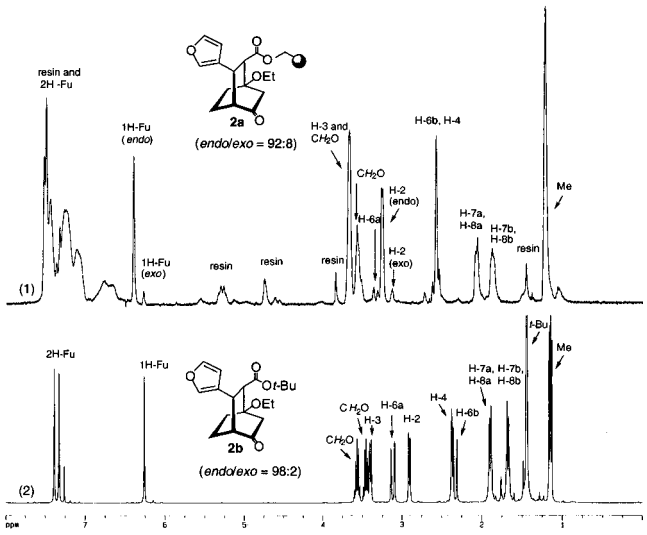



**Figure 6.** (1) $^1$H CPMG-MAS-NMR spectrum of **2a**; (2) $^1$H NMR spectrum of **2b** (solvent: $CDCl_3$).

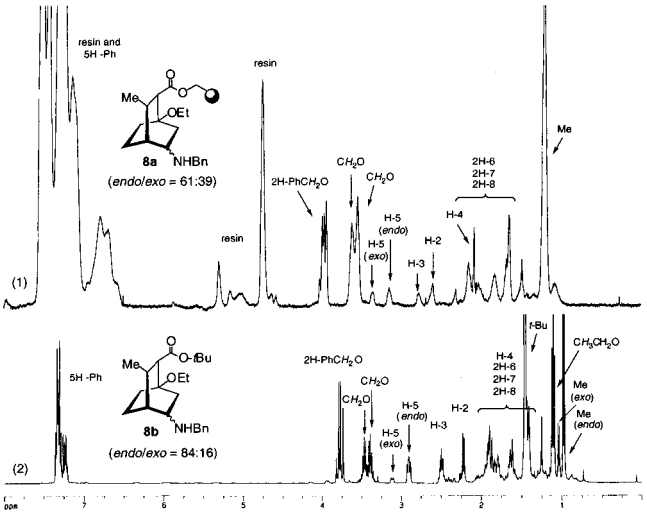



**Figure 7.** (1) $^1$H CPMG-MAS-NMR spectrum of **8a**; (2) $^1$H NMR spectrum of **8b** (solvent: $CDCl_3$).

Although the CPMG procedure of itself may cause problems with integration, we felt it reasonable that chemically similar protons would have similar $T_2$ values and hence be affected almost identically by the pulse sequence. The integrals of these signals could be compared without serious error. This is indeed borne out by the measurement of diastereomeric ratios which correlate well with those observed on reductive cleavage (Table 1). This type of measurement is only possible if the spectra can be properly assigned.

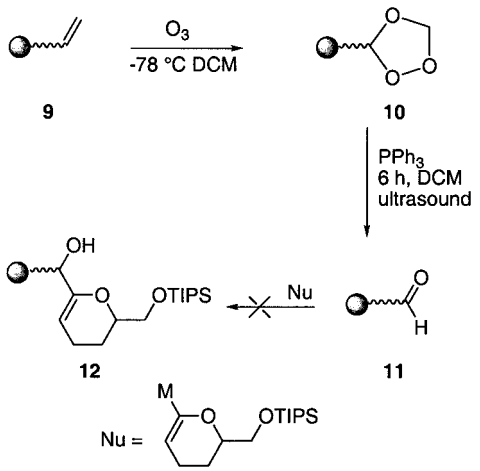
Although application of the spectroscopic techniques described has merit for confirming the identity of reaction products, it is perhaps more valuable in a routine sense for the identification of reaction failures. A synthesis recently undertaken to prepare spiroketals benefited from this high quality analysis. Ozonolysis conditions for a supported olefin **9** were optimized, and the resulting aldehyde **11** was characterized fully by the techniques described (see Supporting Information). The addition of a dihydropyranyl nucleophile into this aldehyde to give **12** was a key coupling step for the synthesis (Scheme 1). The analytical techniques

**Table 1.** Summary of Observed Diastereomeric Ratios

| entry | $R^1$ | $R^2$ | *endo/exo* ratio, after cleavage[a] | *endo/exo* ratio, NMR analysis[b] | *endo/exo* ratio, solution[c] |
|---|---|---|---|---|---|
| 1 | OEt | Me | 100:0 | 100:0 | 100:0 |
| 2 | OEt | 3′-Fu | 91:9 | 92:8 | 98:2 |
| 3 | Me | 3′-Fu | 94:6 | 89:11 | 100:0 |
| 4 | OEt | Ph | 86:14 | 85:15 | 97:3 |
| 5 | Me | Ph | 95:5 | *d* | 99:1 |
| 6 | OEt | 3′-Th | 74:26 | 68:32 | 100:0 |
| 7 | Me | 3′-Th | 90:10 | 89:11 | 100:0 |

[a] The ratio was determined after reductive cleavage of **1a**−**7a** from the solid support.[15] [b] The ratio was determined by integration of characteristic signals in the $^1$H CPMG-MAS-NMR spectra of the corresponding polymer bound bicyclo[2.2.2]octanones **1a**−**7a** (see also Supporting Information). [c] The ratio was determined by GC analysis of the corresponding *tert*-butyl ester derivatives **1b**−**7b** prepared in solution.[16] [d] Not observable by integration.

**Scheme 1**




described allowed us to know that all of the conditions attempted to bring about this reaction failed. Without high quality analysis, the following three steps may have been undertaken. The negative results obtained on cleavage would then have been difficult to explain correctly.

All of the techniques described along with those such as $^{31}$P and $^{77}$Se NMR are also key components of our polymer supported reagent development program.

In conclusion, the application of a range of analytical techniques similar to those that might be used to characterize a solution-phase molecule can be used to confirm the structure of polymer supported molecules. The techniques described allow high quality IR, $^1$H, and $^{13}$C NMR spectra to be obtained without any cleavage of the supported molecules from their support. This characterization should form a key part in reporting syntheses carried out on polymer supports but more critically should be adopted on a more routine basis during the optimization phase of such a synthesis for the quantification of reaction success or failure.

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**Supporting Information Available.** Single flattened bead FTIR and $^1$H CPMG-MAS-NMR spectra for **1a**−**8a** and **11**; a selected set of MAS-COSY, $^{13}$C MAS-NMR, and MAS-HMQC spectra for **1a**−**8a** and **11**; and $^1$H NMR spectra for **1b**−**8b**. This material is available free of charge via the Internet at http://pubs.acs.org.

## References and Notes


(1) See, for instance: (a) Obrecht, D.; Villalgordo, J. M. *Solid-supported combinatorial and parallel synthesis of small-molecular-weight compound libraries*, 1st ed.; Pergamon: New York, 1998; Vol. 17. (b) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555.

(2) (a) Hinzen, B.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1. (b) Haunert, F.; Bolli, M. H.; Hinzen, B.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2235. (c) Ley, S. V.; Bolli, M. H.; Hinzen, B.; Gervois, A.-G.; Hall, B. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2239. (d) Bolli, M. H.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2243. (e) Habermann, J.; Ley, S. V.; Scott, J. S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3127. (f) Caldarelli, M.; Habermann, J.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 107. (g) Ley, S. V.; Thomas, A. W.; Finch, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 669. (h) Ley, S. V.; Schucht, O.; Thomas, A. W.; Murray, P. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1251. (i) Habermann, J.; Ley, S. V.; Scott, J. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1253. (j) Caldarelli, M.; Habermann, J.; Ley, S. V. *J. Bioorg. Med. Chem. Lett.* **1999**, *9*, 2049. (k) Habermann, J.; Ley, S. V.; Smits, R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2421. (l) Habermann, J.; Ley, S. V.; Scicinski, J. J.; Scott, J. S.; Smits, R.; Thomas, A. W.; *J. Chem. Soc., Perkin Trans. 1* **1999**, 2425. (m) Parlow, J. J.; Devraj, R. V.; South, M. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 320. (n) Dewry, D. H.; Coe, D. M.; Poon, S. *Med. Res. Rev.* **1999**, *19*, 97.

(3) Frechet, J. M. J.; Schuerch, C. *J. Am. Chem. Soc.* **1971**, *93*, 492.

(4) Chan, T. Y.; Chen, R.; Sofia, M. J.; Smith, B. C.; Glennon, D. *Tetrahedron Lett.* **1997**, *38*, 2821.

(5) Yan, B.; Kumaravel, G.; Anjaria, H.; Wu, A. Y.; Petter, R. C.; Jewell, C. F.; Wareing, J. R. *J. Org. Chem.* **1995**, *60*, 5736.

(6) Yan, B.; Kumaravel, G. *Tetrahedron* **1996**, *52*, 843.

(7) (a) Giralt, E.; Rizo, J.; Pedroso, E. *Tetrahedron* **1984**, *40*, 4141. (b) Look, G. C.; Holmes, C. P.; Chinn, J. P.; Gallop, M. A. *J. Org. Chem.* **1994**, *59*, 7588. (c) Lorge′, F.; Wagner, A.; Mioskowski, C. *J. Comb. Chem.* **1999**, *1*, 25.

(8) (a) Shea, K. J.; Sasaki, D. Y. *J. Am. Chem. Soc.* **1991**, *113*, 4109. (b) Fitch, W. L.; Detre, G.; Holmes, C. P.; Shoolery, J. N.; Keifer, P. A. *J. Org. Chem.* **1994**, *59*, 7955. (c) Anderson, R. C.; Stokes, J. P.; Shapiro, M. J. *Tetrahedron Lett.* **1995**, *36*, 5311. (d) Wehler, T.; Westman, J. *Tetrahedron Lett.* **1996**, *37*, 4771. (e) Garigipati, R. S.; Adams, B.; Adams, J. L.; Sarkar, S. K. *J. Org. Chem.* **1996**, *61*, 2911. (f) Sarkar, S. K.; Garigipati, R. S.; Adams, J. L.; Keifer, P. A. *J. Am. Chem. Soc.* **1996**, *118*, 2305. (g) Keifer, P. A. *J. Org. Chem.* **1996**, *61*, 1558. (h) Pursch, M.; Schlotterbeck, G.; Tseng, L. H.; Albert, K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2867. (i) Meissner, A.; Bloch, P.; Humpfer, E.; Spraul, M.; Sorensen, O. W. *J. Am. Chem. Soc.* **1997**, *119*, 1787. (j) Dhalluin, C.; Boutillon, C.; Tartar, A.; Lippens, G. *J. Am. Chem. Soc.* **1997**, *119*, 10494. (k) Shapiro, M. J.; Chin, J.; Marti, R. E.; Jaroninski, M. A. *Tetrahedron Lett.* **1997**, *38*, 1333. (l) Chin, J.; Fell, B.; Pochapsky, S.; Shapiro, M. J.; Wareing, J. R. *J. Org. Chem.* **1998**, *63*, 1309.

(9) (a) Sanders, J. K. M.; Hunter, B. K. *Modern NMR spectroscopy: a guide for chemists*, 2nd ed.; Oxford University Press: Oxford, 1993. (b) Anderson, R. C.; Jarema, M. A.; Shapiro, M. J.; Stokes, J. P.; Ziliox, M. *J. Org. Chem.* **1995**, *60*, 2650.

(10) (a) Manatt, S. L.; Amsden, C. F.; Bettison, C. A.; Frazer, W. T.; Gudman, J. T.; Lenk, B. E.; Lubetich, J. F.; McNelly, E. A.; Smith, S. C.; Templeton, D. J.; Pinnell, R. P. *Tetrahedron Lett.* **1980**, *21*, 1397. (b) Shapiro, M. J.; Kumaravel, G.; Petter, R. C.; Beveridge, R. *Tetrahedron Lett.* **1996**, *37*, 4671. (c) Svensson, A.; Fex, T.; Kihlberg, J. *Tetrahedron Lett.* **1996**, *37*, 7649.

(11) Johnson, C. R.; Zhang, B. R. *Tetrahedron Lett.* **1995**, *36*, 9253.

(12) Swayze, E. E. *Tetrahedron Lett.* **1997**, *38*, 8643.

(13) Kanemitsu, T.; Kanie, O.; Wong, C. H. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3415.

(14) (a) Bauld, N. L.; Bellville, D. J.; Gardner, S. A.; Migron, Y.; Cogswell, G. *Tetrahedron Lett.* **1982**, *23*, 825. (b) Katritzky, A. R.; Belyakov, S. A.; Strah, S.; Cage, B.; Dalal, N. S. *Tetrahedron Lett.* **1999**, *40*, 407.

(15) Ley, S. V.; Mynett, D. M.; Koot, W. J. *Synlett* **1995**, 1017.

(16) Ley, S. V.; Massi, A. *J. Comb. Chem.* **2000**, *2*, 104−107.

(17) IR spectra were obtained on a Perkin-Elmer Spectrum 1000 IR spectrometer in conjunction with a Perkin-Elmer Autoimage IR/visible microscope. Beads were flattened in a Specac diamond compression cell.

(18) Freeman, R. *A Handbook of Nuclear Magnetic Resonance*, 2nd ed.; Longman: Harlow, 1997; p 268−270.

(19) Gel-phase spectra were recorded in $CD_2Cl_2$ on a Bruker DPX400 equipped with a 5 mm $^1$H/$^{13}$C DUAL probe. Samples were spinning at 20 Hz, and the temperature was set to 300 K. Peak positions were referenced to external residual $CHCl_3$ in $CDCl_3$ at 7.26 ppm ($^1$H) or to the central line of $CDCl_3$ (internal) taken as 77.0 ppm.

(20) HR-MAS spectra were recorded on a Bruker DRX400 equipped with a 4 mm HR-MAS probe with gradients. Samples were swollen in $CDCl_3$ and used inserts to give an approximately spherical sample of ∼12 $\mu$L volume. The $^{13}$C spectrum illustrated was run with this sample volume and thus has a poorer signal/noise ratio than the gel-phase spectrum recorded using ∼600 $\mu$L sample volume. HR-MAS $^{13}$C may also be recorded without inserts to give a sample volume of ∼60 $\mu$L.

(21) CPMG spectra were obtained using the standard Bruker pulse program. The loop counter was set to between 16 or 128 depending on the level of suppression required.

(22) DQF-COSY spectra were obtained using the standard Bruker pulse program.


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