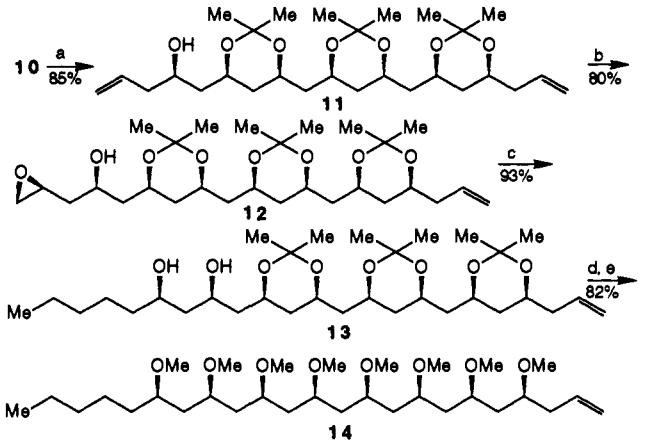
Scheme III[a]



[a](a) DEAD, Ph_3P, $PhCO_2H$, THF, then NaOH; (b) $VO(Oi\text{-}Pr)_3$ (catalytic), *t*-BuOOH, CH_2Cl_2; (c) $(n\text{-}Bu)_2CuLi$, Et_2O, −20 °C; (d) MeOH, *p*-TsOH (catalytic); (e) KH, MeI, THF.

the ketoester functionalities to give **4**. Simultaneous chelation controlled reduction[11] of both of the hydroxy ketone moieties in **4** afforded the *all-syn*-pentaol derivative with a 12:1 syn/anti ratio,[9] which was silylated to provide **5**. Subsequent reduction/oxidation provided *meso*-dialdehyde **6**.

We chose a reaction with the Brown reagents,[12] (+)- or (−)-diisopinylcampheyl allyl borane (Ipc_2BAll) to convert the C_s symmetric **6** into either antipode of the enlongated product (Scheme II). As we expected, dialdehyde **6** underwent additions with (+)-Ipc_2BAll or (−)-Ipc_2BAll to provide either **7** ($[a]_D^{25}$ +22.8, *c* 3.3, $CHCl_3$) or **8** ($[a]_D^{25}$ −23.0, *c* 3.4, $CHCl_3$), respectively, with high diastereoselectivity (>15:1).[9] The enantiomeric excess **7** and **8** were determined to be >98% based upon ^1H NMR analysis of their corresponding Mosher ester derivatives.[13] It is remarkable that a single enantiomeric reagent introduced two new stereocenters and determined the absolute stereochemistry at five preexisting stereocenters. Inspired by the chemistry of "ancillary stereocontrol"[14] and "diastereoselective resolution"[2i,15] involving acetonide groups as messengers to deliver stereochemical information in 1,3-diol systems, we examined a diastereotopic group selective acetonide formation as a means of terminal differentiation present in **7** and **8**. Desilylation of **7** or **8** and treatment with a catalytic amount of camphorsulfonic acid in acetone resulted in selective formation of tris(acetonide) **9** or **10** engaging the six *syn*-hydroxyl groups.[16] The excellent diastereotopic group selectivity (15:1)[9] in this transformation can be rationalized by the thermodynamic preference for a *syn*-1,3-acetonide over an *anti*-1,3-acetonide due to 1,3-diaxial interaction of methyl groups encountered in the latter.

For synthetic application of this strategy, we chose a novel isotactic polymethoxy-1-alkene **14**, isolated from the tolytoxin-producing blue-green algae *Tolypothrix conglutinata var. colorata* Ghose[17] and *Scytonema burmanicum*[18] (Scheme III). Mitsunobu inversion[19] of **10** provided **11**. Subjecting **11** to the V^{5+} catalyzed epoxidation conditions[8] resulted in a 5:1 diastereomeric mixture of epoxides with the desired compound **12** as the predominant product. Separation of **12** from its diastereomer by HPLC and subsequent *n*-butylcuprate opening of the epoxide afforded **13** with all of the required stereocenters. Finally, deprotection and methylation accomplished the synthesis of octamethoxy-1-tricosene **14**.

In conclusion, we have demonstrated an enantiodivergent synthesis of *syn*-1,3-polyols from a meso precursor via a exclusively reagent-controlled diastereofacial selective allylation reaction.[20] The diastereotopic group selective reactions can provide a solution to the problem of terminus differentiation. Studies toward synthesis of *anti*-1,3-polyols are underway and will be reported in the future.

Acknowledgment. We are grateful to Professor S. L. Schreiber and Dr. M. T. Goulet for helpful discussions on this subject. We thank Drs. M. Bernstein and L. A. Trimble for NMR measurement and Ms. C. Li for mass spectra on several intermediates. We also thank Dr. D. Dubé for his critical reading of this manuscript.

Supplementary Material Available: Spectral data for **2-6**, **8**, **10**, and **14** (3 pages). Ordering information is given on any current masthead page.

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Cryptoclastic Diastereotopism: NMR Evidence for the Chirotopicity of the Methyl Group in (α-Deuterio-*o*-chlorotoluene)chromium Tricarbonyl

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On the basis of symmetry arguments, the hydrogens of a chirotopic methylene group CH_2XY* reside in diastereotopic environments.[2] This chirotopicity commonly manifests itself as an AB pattern in the ^1H NMR spectrum of the molecule.[3] However, except for α-deuterio-1,2-dimethylpiperidine (**1**),[4] no such AB pattern has been observed when X or Y is deuterium.[5] In **1**, the diastereotopicity is enhanced by "a strong conformational (rotomeric) preference as well as the existence of widely different magnetic environments at the sites occupied by the methylene protons".[4]

The rotational preference in **1** stems from an orbital interaction between the lone pair on N and the σ* orbital of the α-CH bond and from the propensity for D to occupy the strongest binding site.[8] The ability of arene-bound metals to accelerate the solvolysis of α-halo aromatics and the increased acidity of alkyl protons α to a metal–arene system point to a significant interaction between the orbitals of the metal and those of the α carbon.[9] If the

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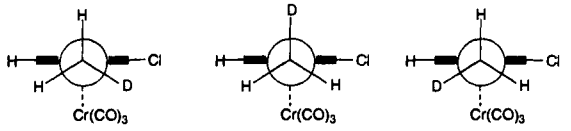


Figure 1. Newman projections down the C(a)-C(aromatic) bond of the three different conformations of the methyl group.

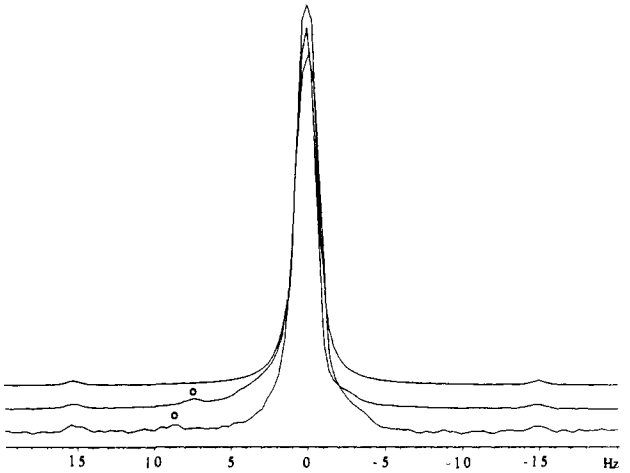
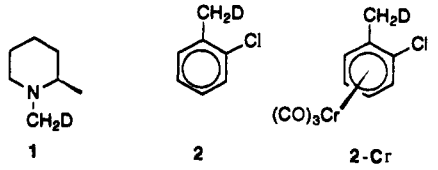


Figure 2. Deuterium-coupled ^{1}H NMR spectra of the CH_2D AB pattern in **2-Cr-d_1**. Top: Simulated spectrum fit to the 500-MHz spectrum (J = 14.7 Hz, $\Delta\nu$ = 4 Hz, w = 1 Hz). Middle: 500-MHz spectrum. Bottom: 600-MHz spectrum. o = Trace of unlabeled **2-Cr**.

hypothesis for the magnitude of the diastereotopicity in **1** is correct, then it should be possible to detect the chirotopicity of a methyl group in a compound like (α-deuterio-*o*-chlorotoluene)chromium tricarbonyl (**2-Cr**) (Figure 1).



1 **2** **2-Cr**

Reduction of α-bromo-*o*-chlorotoluene with lithium aluminum deuteride in tetrahydrofuran yields α-deuterio-*o*-chlorotoluene (**2**).[10] Treatment of **2** with chromium hexacarbonyl in refluxing diglyme affords **2-Cr**.[11,12]

A cursory glance at the ^{1}H NMR spectrum of **2-Cr** at 500 MHz in benzene-d_6 shows the expected aromatic signals (7.0-8.0 ppm) and a 1:1:1 triplet for the methylene protons (2.5 ppm, $J_{H,D}$ = 2.2 Hz). A closer look betrays two additional triplets, one to either side of the central peak but of minuscule (1-2%) intensity. Deuterium decoupling collapses the central peaks into a singlet, and the wing signals follow suit (Figure 2). The spectrum at 600 MHz shows a similar behavior, whereas spectra at 360 or 300 MHz shows no wings at all. The spectra at 500 and 600 MHz are invariant to changes in spinning rate and are reproduced in samples of different concentrations and synthetic batches.

Under conditions where the ratio of the AB coupling constant to the chemical shift difference between sites A and B, $\Delta\nu$(AB), is large, a second-order three-line AB pattern can appear.[13] There is a specific relationship between the differences of the chemical shifts of the signals and the relative intensities of the lines in the spectrum. From one set plus the coupling constant one can obtain the other. The expected range of $\Delta\nu$(AB) in order to observe a three-line pattern with $J_{H,H}$ ca. 15 Hz lies between 2 and 5 Hz; the intensity of the wings compared to the central peak ranges between 1 and 3%.

The spectrum of **2-Cr** shows these general features. From the deuterium-coupled spectra were derive the value for the geminal H,H coupilng ($J_{H,D}$ = 2.2 Hz, $J_{H,H}$ = 14.7 Hz). With this coupling and the measured $\Delta\nu$ between the wings (30.0 Hz), we can simulate the spectrum for various $\Delta\nu$(AB). Figure 2 shows the best fit to the spectrum at 500 MHz, $\Delta\nu$(AB) = ca. 4.0 Hz. To our knowledge, **2-Cr** is the first example of a second-order AB pattern resulting from isotopic substitution at a chirotopic methyl group.

This study demonstrates the power of NMR spectroscopy to elucidate even subtle aspects of molecular symmetry. It also opens up the possibility of designing new reagents for determining the configuration at stereogenic methyl groups (a la Anet et al.[14]) by direct NMR observations.

Acknowledgment. We thank the National Science Foundation Presidential Young Investigator Award Program (CHE-8857812), the American Cancer Society Junior Faculty Fellowship Program (C-58024), and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. We greatly appreciate additional support of our program from the Exxon Educational Fund, Hofman-La Roche, Rohm+Haas, Monsanto, Eli Lilly, Zambon (Italia), and Sterling Drug. The 500-MHz NMR spectrometer was purchased with funds from NIH (RR04733) and NSF (CHE-8814866). We thank Dan Iverson (Varian) for the 600-MHz spectra.

(10) Spectral data for **2**: bp 158-159 °C (ca. 95% yield); ^{1}H NMR ($CDCl_3$) δ 2.36 (t, 2 H, J_{HD} = 2.1 Hz), 7.18 (m, 2 H), 7.28 (dd, 1 H, J = 6.83 Hz, J = 1.9 Hz), 7.40 (dd, 1 H, J = 6.82 Hz, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 19.7 (t), 126.6 (d), 127.1 (d), 129.0 (d), 130.8 (d), 134.3 (s), 135.9 (s).

(11) Spectral data for **2-Cr**: mp 99-101 °C (lit. mp 101-102 °C) (ca. 38% yield); ^{1}H NMR ($CDCl_3$) δ 2.32 (t, 2 H, J_{HD} = 2.1 Hz), 5.10 (td, 1 H, J = 6.23 Hz, J = 1.1 Hz), 5.22 (td, 1 H, J = 6.23 Hz, J = 1.1 Hz), 5.32 (dd, 1 H, J = 6.23 Hz, J = 1.1 Hz), 5.55 (dd, 1 H, J = 6.23 Hz, J = 1.1 Hz); ^{13}C NMR ($CDCl_3$) δ 19.1 (t), 90.3 (d), 90.8 (d), 93.1 (d), 93.6 (d), 106.1 (s), 111.7 (s), 231.9 (s).

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The Rigidity of Sucrose: Just an Illusion?

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Received September 16, 1991

The conformation of sucrose in solution has been under scrutiny by NMR spectroscopic and theoretical studies for over ten years.[1] Early NMR and HSEA modeling studies concluded that the molecule exists in solution in a single conformation similar to its crystal structure.[2] These findings were supported by detailed ^{13}C relaxation measurements.[3a-d] However, a recent NOE study[1] and molecular mechanics calculations[4a,b] indicate that sucrose in solution is flexible.

Up to now, the solution conformation of sucrose was determined on the basis of just one[2] or two[1] interglycosidic NOE contacts. We sought to extend this data base by conducting more detailed NMR experiments on sucrose in aqueous solution. Table I lists interglycosidic NOE contacts obtained for sucrose in D_2O and

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