with respect to t_1 gives a one-dimensional spectrum of full intensity centerband peaks, whatever the value of a.

In its simplest form, our method does not make full use of the available signal energy. Indeed, a spectrum $S(\omega_1,t_2=0)$ is identical to the *integral* over ω_2 of the two-dimensional spectrum $S(\omega_1,\omega_2)$. The integration adds up unwanted noise in addition to the signal energy which is concentrated in the sidebands at (known) equidistant frequencies in ω_2. More efficient use of the signal energy could in principle be made by sampling all rotary echoes in t_2 and co-adding the signals so obtained.

Experiments were performed on powdered magnesium pyrophosphate, $Mg_2P_2O_7$, which features two isotropic ^{31}P shifts separated by 750 Hz at 121.5 MHz on our Bruker MSL 300 spectrometer. Owing to the high values of the two different ratios a (for $\omega_r/2\pi$ = 2 kHz), a conventional TOSS spectrum (Figure 2b) shows severe intensity losses. In contrast, the spectrum acquired using the new method (but with a 90° excitation pulse instead of cross-polarization) has two equal intensity lines, as expected for a method which quantitatively reflects the stoichiometry of the sites (Figure 2c). A similar spectrum could be obtained by the PASS technique, albeit in a more cumbersome manner.[16]

Our new experiment is more powerful than TOSS since it not only suppresses the sidebands completely but also transfers the intensity of each sideband family into the corresponding centerband line. Moreover, in contrast to TOSS, this method is applicable to samples with an anisotropic distribution of crystallites, since the t_1 evolution does not depend on their orientation.[12] We use the acronym TIPSY (*t*otally *i*sotro*p*ic *s*pectroscop*y*) for experiments which incorporate this scheme for effecting evolution under the isotropic shifts alone.

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A One-Step Synthesis of the Ciclamycin Trisaccharide

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We have been investigating a glycosylation method that involves the use of anomeric phenyl sulfoxides activated with triflic anhydride[1] or catalytic triflic acid.[2,3] We now report that by using the sulfoxide method we are able to construct two glycosidic linkages sequentially in a single reaction. This has allowed us to synthesize the ciclamycin 0 trisaccharide stereoselectively from the component monosaccharides in one step.

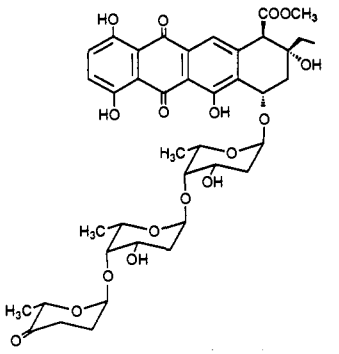
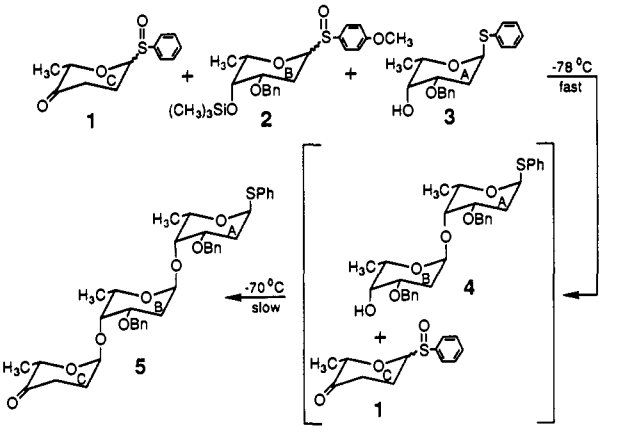


Figure 1. Ciclamycin 0.

Scheme I[a]



[a] Conditions: Premixed **1** (3.0 equiv), **2** (2.0 equiv), and **3** (1.0 equiv), Et_2O–CH_2Cl_2 (1:1), $HC{\equiv}CCOOCH_3$ (20.0 equiv), TfOH (0.05 equiv), −78 to −70 °C, 45 min, then quenched with saturated $NaHCO_3$ solution.

This synthetic approach grew out of mechanistic studies on the sulfoxide glycosylation reaction. We have found that the rate-limiting step in the reaction is triflation of the sulfoxide; therefore, the reactivity of the glycosyl donor can be influenced by manipulating the substituent in the para position of the phenyl ring (reactivity order: OMe > H > NO_2).[4,5] For perbenzylated glucose sulfoxides, the difference in reactivity is large enough that the *p*-methoxyphenyl sulfoxide can be selectively activated in the presence of an equimolar amount of the corresponding unsubstituted phenyl sulfoxide, *as long as only one-half of an equivalent of activating agent is present*. Both sulfoxides react, presumably,

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sequentially, when a full equivalent of activating agent is added. In addition, while silyl ethers are stable to Tf_2O/base activation of anomeric sulfoxides, they are good glycosyl acceptors when catalytic triflic acid is the activating agent; however, they react more slowly than unprotected alcohols because they must be unmasked to couple. The ability to manipulate the reactivity of both the glycosyl donors and the glycosyl acceptors suggested the novel strategy of synthesizing a complicated trisaccharide in one step.

We chose the ciclamycin 0 trisaccharide as a target for two reasons. First, we are interested in the mode of action of ciclamycin 0 (Figure 1) and it is difficult to obtain from natural sources.[6] Second, and more germane to the point here, Danishefsky has published an impressive stepwise synthesis of this trisaccharide using the best available methods for 2-deoxy oligosaccharide synthesis. The Danishefsky synthesis therefore sets a high standard to evaluate the efficacy of our one-step approach.[7,8]

The ciclamycin 0 trisaccharide was synthesized stereospecifically from the readily available monosaccharides **1**, **2**, and **3** as shown in Scheme I.[9-12] The major product, isolated in 25% yield after flash chromatography on silica gel (20% ethyl acetate/petroleum ether), was the desired trisaccharide **5**. No other trisaccharides were produced, and the only other significant coupled product of the reaction was disaccharide **4** (Scheme I, 15% yield), the precursor to the trisaccharide. The yield of trisaccharide **5** in the reaction is limited *not* by any undesired cross-coupling[13] but by the instability of the glycosyl donors, particularly keto sulfoxide **1** which decomposes readily at room temperature even in the absence of activating agent.

The products of the reaction indicate that glycosylation takes place in a sequential manner as hoped, with *p*-methoxyphenyl sulfoxide **2** activating faster than phenyl sulfoxide **1** and C-4 alcohol **3** reacting faster than C-4 silyl ether **2**. Consistent with this, if the reaction is quenched at −100 °C, *only* the silyl ether of disaccharide **4** can be isolated (60%). We have thus manipulated the reactivity of both the glycosyl donors and the glycosyl acceptors to control the order in which glycosylation takes place.

By way of comparison, the Danishefsky synthesis of the ciclamycin trisaccharide, which makes elegant use of glycal chemistry,[14] requires 14 steps starting from the 3 glycal precursors and produces the trisaccharide in an overall yield of 9%.[7] Several steps are needed simply to modulate the reactivity of the donor/acceptor pairs (glycals) to achieve coupling specificity. Although the glycal method remains a very effective method for the construction of 2-deoxy oligosaccharides, the sulfoxide method has allowed us to achieve coupling specificity and construct the ciclamycin trisaccharide stereospecifically in a single step. This has resulted in a dramatic savings in time and labor (less than 3 h from monosaccharides to purified trisaccharide).

Finally, it should be noted that the trisaccharide (**5**) produced in the one-step reaction has an anomeric phenyl sulfide on the A ring. Anomeric phenyl sulfides are stable ("disarmed") to the conditions that activate anomeric phenyl sulfoxides for glycosylation, but they can be readily oxidized under mild conditions.[5,15] Thus, the sulfoxide glycosylation reaction also lends itself well to an iterative strategy for oligosaccharide synthesis.[5,14c,d,15,16] The ciclamycin trisaccharide **5** was oxidized to the corresponding sulfoxide in 80% yield (1.2 equiv of *m*-CPBA, CH_2Cl_2, −78 to −50 °C, 2 h) and is ready for coupling to the ciclamycin chromophore.

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Supplementary Material Available: MS (FAB) and ^1H and ^{13}C NMR spectra for compound **5** and ^1H NMR spectra for compounds **1**-**4** (16 pages). Ordering information is given on any current masthead page.

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Regio- and Stereoselective Formation and Isomerization of 1,3-Cyclohexadienes Catalyzed by Titanium Aryloxide Compounds†

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One of the conceptually simplest strategies for the synthesis of the 1,3-cyclohexadiene nucleus involves the selective (2 + 2 + 2) cycloaddition of 2 equiv of an alkyne with an olefin.[1] The overall formation of three new carbon–carbon bonds during this reaction offers the potential for controlling both the regio- and the stereochemistry of the products.[2] This communication reports our observations concerning the ability of titanium aryloxide compounds to catalyze this reaction as well as some mechanistic

† Dedicated to Professor Bob Squires on the occasion of his 40th birthday.

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