

An *o*-Iminothioquinone: Its Cycloaddition To Produce an Indologlycoside and Its Self-Dimerization To Form a Dithio-Diazocyclooctane, the Structure Assignment of Which Is Based on the DFT Prediction of Its IR Spectrum

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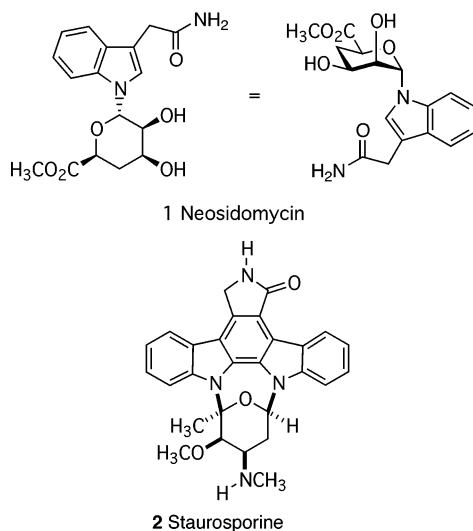
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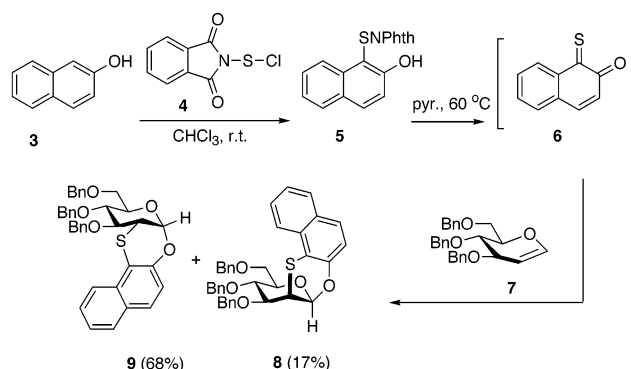
Abstract: An unusual heterodiene, an indolothiono quinone, undergoes cycloaddition with a glycal to form an indole-*N*-glycoside. A novel dimer of the indolothionoquinone is assigned its structure on the basis of a match between its predicted and observed IR spectrum.

Neosidomycin (**1**) was the first example of a naturally occurring glycoside with an indole-*N*-aglycone. It was isolated from the fermentation broth of a strain of *Streptomyces hygroscopicus*, and it possessed weak activity against Gram-negative bacteria.¹ A limited number of other examples of this structural type have been reported.²



There is a related class of *N*-glycosides, namely, the carbazoles where there are described both mono- and bisglycosides. Staurosporine (**2**) is perhaps the most well-known.³ Both classes of hetaryl-*N*-glycosides have been

SCHEME 1. Typical Example of [4 + 2] Cycloaddition of an *o*-Thioquinone to a Substituted D-Glucal



synthesized. The glycosyl transfer steps that were commonly used in the syntheses may be summarized as nucleophilic displacements by aryl N, in many cases activated by base to form an anionic species, on an activated anomeric C. There are versions of the Koenigs–Knorr reaction with the aryl N displacing an anomeric halide.⁴ The Danishefsky variant has the aryl N attacking a glycal epoxide,⁵ and another variation uses Mitsunobu chemistry.⁶ In general, these glycosyl transfers have been problem-free.

Our group at Hunter College of the City University of New York, in collaboration with the Capozzi group at the Università di Firenze in Italy, has successfully developed a novel concept of glycosyl transfer via cycloaddition, patterned after pioneering work by Leblanc.⁷ Our groups' approach is illustrated for one aryl-*O*-glycoside in Scheme 1. Thus, the totally regio- and highly stereoselective [4 + 2] cycloadditions of *o*-thioquinone **6** to a D-glucal **7** afforded the 2-deoxy-2-thioglycoside in high yield. Raney nickel treatment afforded the 2-deoxyglycoside. The *o*-thioquinone **6** was generated in situ from the corresponding and easily prepared thiophthalimidonaphthol derivative **5**.⁸

This cycloaddition concept was also realized for *N*-glycosides as shown in Scheme 2. Here, the iminothiono diene **12** was formed from the phthalimidiothiosulfone

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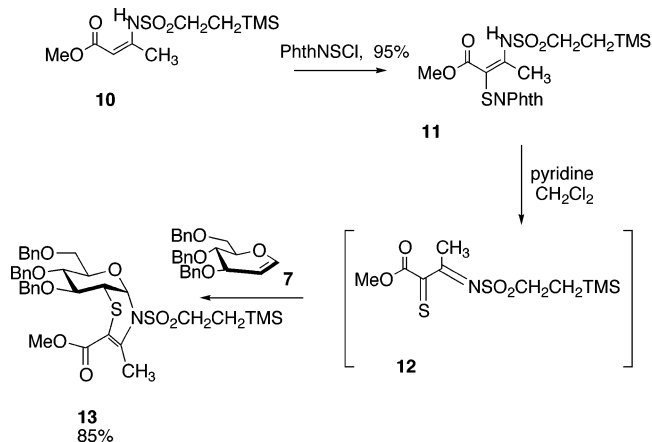
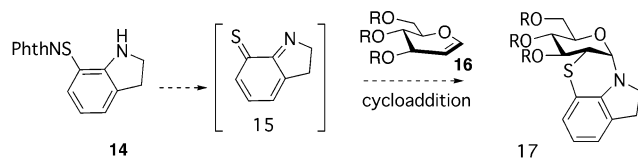
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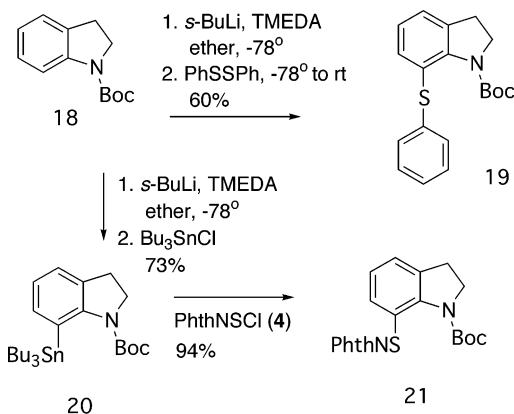
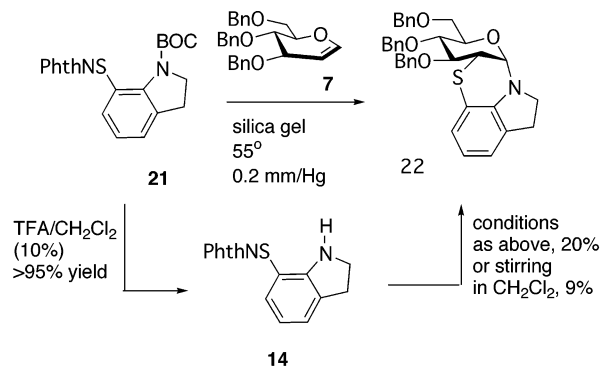
SCHEME 2. Example of Glycosyl Transfer to Nitrogen by Heterocycloaddition**SCHEME 3. Proposed Cycloaddition Approach to Indole-*N*-Glycosides**

imine **11**, and the subsequent glycosyl transfer to nitrogen was a clean process.⁹

Hence, as a logical extension of these discoveries, it was the purpose of this work to transfer an indolic nitrogen via the generation and subsequent cycloaddition of the *o*-iminothioquinone **15** to be generated from a thiophthalimidindoline **14**.

The challenge thus was to prepare this 7-thiosubstituted indoline **14**. After exploratory direct electrophilic thiations of indoline proved unprofitable, we turned to the work of Iwao.¹⁰ He described the peri lithiation of *t*-BOC indoline **18** followed by electrophilic trapping, and in the example shown in Scheme 4, with diphenyl disulfide, clean thiation at the 7 position was observed. However, when we employed *N*-phthalimidothiing agents, only traces of the desired product were obtained. We then turned to a two-step procedure where the lithiated indoline was trapped as a 7-stannyl derivative **20**, also described by Iwao. Then, in a very clean ipso electrophilic displacement, phthalimidodisulfenyl chloride replaced the tin function to form the necessary 7-phthalimidodisulfenyl derivative **21**.

We envisioned a one-pot cascade: deprotection of the indoline nitrogen to form **14** followed by elimination of phthalimide and generation of the iminothioquinone **15**, which would then undergo cycloaddition. The plan was to use the thermal elimination of *t*-BOC reported by Apelqvist and Wensbo where the *t*-BOC-*N* derivative is adsorbed on silica and then heated.¹¹ Hence, we adsorbed both the phthalimido species **21** and the glucal **7** onto silica (about 10× the weight of glucal) and then heated

SCHEME 4. Functionalization of C-7 via the Method of Iwao**SCHEME 5. Cycloaddition with Both *N*-BOC and NH precursors**

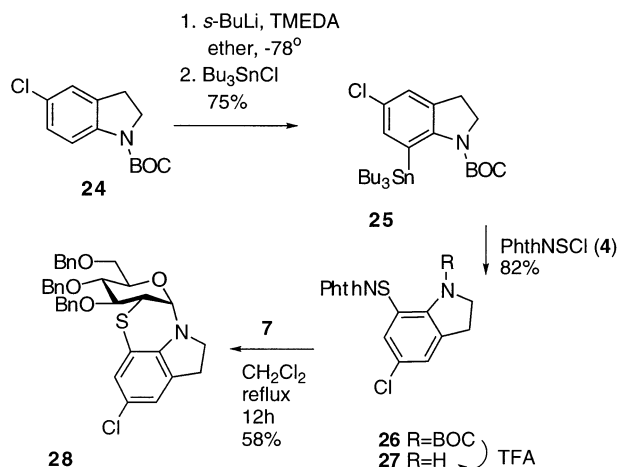
the solid mixture under vacuum (about 0.2 mm/Hg) as prescribed. To summarize dozens of experiments, it was found that low yields of cycloadduct **22** were obtained. The best yield was 18% when a 5:1 ratio of glucal:diene precursor was heated for almost 3 days. Silica gel was required since duplicating the conditions in the absence of silica gel afforded no adduct (Supporting Information). The material was isolated after loading the solid reaction mixture onto a chromatography column followed by elution. Accompanying the desired adduct was a material corresponding to a dimer of iminothioquinone whose structure is discussed below. The yield of dimer could be as high as 40% when 1:1 diene:glucal ratios were used. In some instances, a trace of deblocked indoline **14** was isolated. With this material as a TLC reference, conditions were developed using a limited amount of TFA with the *t*-BOC thio compound **21** to produce a usable quantity of **14**. This deblocked material was then separately tested in dozens of experiments as a precursor to the iminothioquinone **15**. Simple stirring at room temperature of **14** in dichloromethane with 2 equiv of glucal **7** afforded a 9% yield of adduct **22**. Higher temperatures or added Lewis acid catalysts or Bronsted base catalysts were useless (Supporting Information). Using the adsorbed silica technique described above, we were able to obtain a 20% yield of **22** with only a 2-fold excess of glucal (Scheme 5).

In our earlier work with aliphatic thiono/oxo diene cycloadditions, we had found a rough correlation with the HOMO–LUMO gap of the glucal/diene reactant pair.¹²

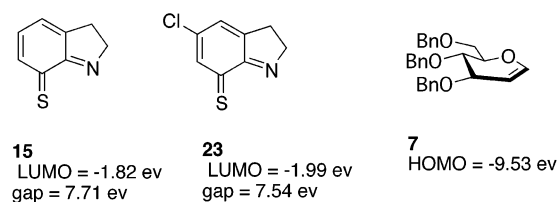
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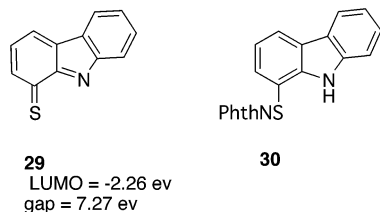
SCHEME 6. 5-Chloroindole as Starting Material for Heterodiene


Thus, we computed the LUMO of our diene **15** (-1.82 eV) and that of its 5-chloro congener **23** (-1.99 eV). Thus, use of the chloro material would result in a lowering of the HOMO–LUMO gap to presumably allow a more facile cycloaddition. We therefore repeated lithiation,



stannylation and phthalimidosulfonylation with *N*-BOC-5-chloroindolenine **24**. When the *t*-BOC of **26** was removed and the NH material **27** was heated in solvent in the presence of D-glucal **7**, we were pleased to observe a much cleaner cycloaddition to form glycoside **28** in 58% yield (Scheme 6).

Thus our LUMO-lowering gambit appeared to be a worthwhile concept. We then turned to the product of the carbazole analogue **29**, which we computed to have an even lower LUMO (-2.26 eV). However, when this was tested by the synthesis (using the same methodology described above) of phthalimidsulfonylcarbazole **30** followed by its decomposition in the presence of glucal, we were unable to isolate any cycloaddition material. This last case was not exhaustively investigated, so the claim that **29** is formed is not established and our LUMO argument is weakened.



The structure and stereochemistry of the cycloadducts depicted was perfectly consistent with ^1H and ^{13}C NMR data and with our experience with related cycloadducts obtained by both the Hunter and Firenze groups. For

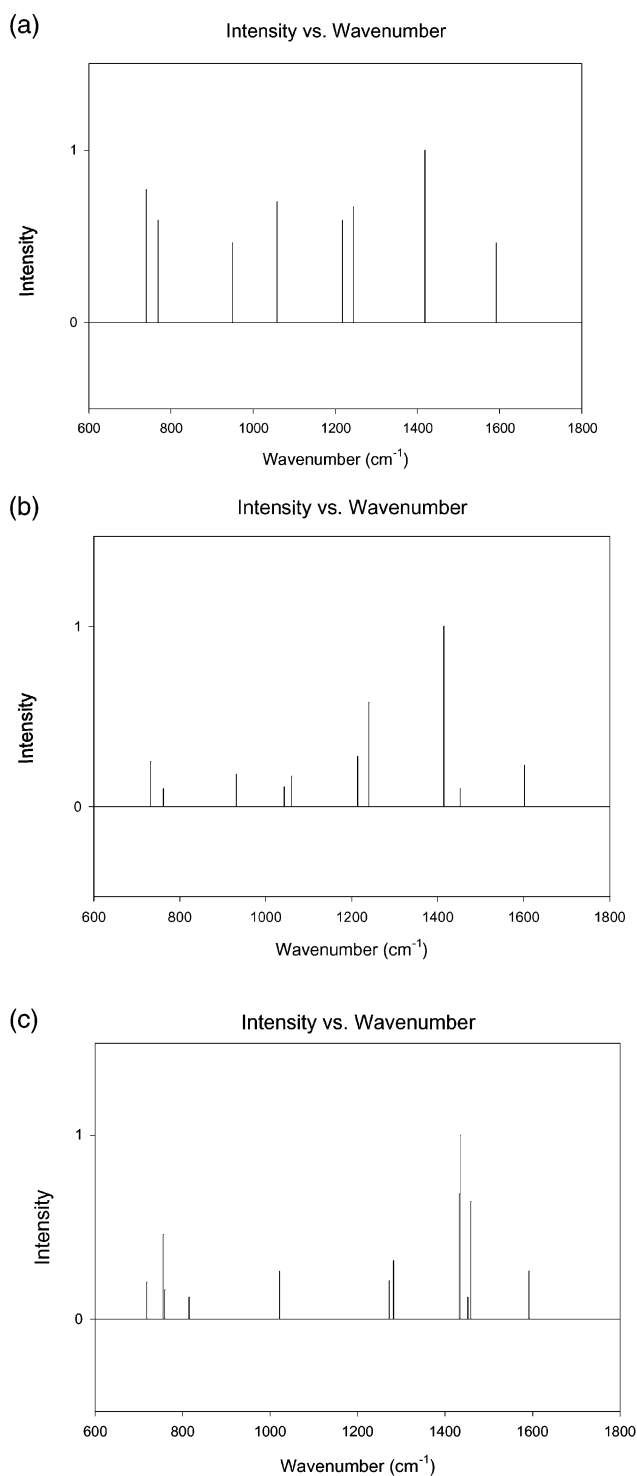
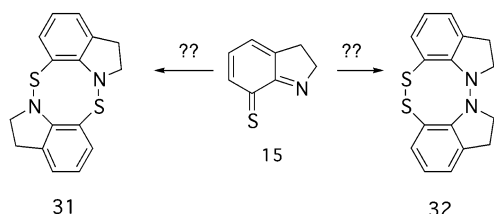


FIGURE 1. (a) Experimental IR spectrum of dimer (plotted from tabulated data). (b) Computed IR spectrum for **31**. (c) Computed IR spectrum for **32**.

added confirmation of regiochemistry, a NOESY experiment with **28** revealed a contact between the anomeric proton at δ 4.87 and an indoline α -H at δ 3.15. However, the dimerization byproduct of **15** on the basis of its mass spectrum and its NMR spectra, which was essentially identical to the indoline regions of **19** and **21**, could be formulated as either **31** or **32**; there was no precedent for either structure that we could find.



Since the development of accessible computational routines for density functional theory, there has been a surge of computations that successfully predict the IR spectra of fairly large organic molecules. This predictive ability has been a powerful tool for the detection of short-lived intermediates in organic reactions by in situ IR spectroscopy.¹³ Interestingly, we have not located many examples where the density functional calculations of IR spectra have been used to assist in structure proof by distinguishing between constitutional isomers.¹⁴

Prediction of IR Spectra. We performed molecular orbital calculations using a hybrid DFT method at the B3LYP/6-31G(d,p) level with the GAUSSIAN 98 suite of programs.¹⁵ This method combines Becke's 3-parameter functional,¹⁶ with the nonlocal correlation provided by the

TABLE 1. Calculated and Experimental IR Values of the Dimer

entry	exptl (cm ⁻¹)	calcd, 31 (cm ⁻¹)	calcd, 32 (cm ⁻¹)
1	739.1	732.1	718.0, 755.4
2	768.0	762.0	758.8
3	948.8	931.8	815.2
4	1057.7	1043.1, 1059.6	1021.4
5	1216.9	1213.6	
6	1244.2	1239.3	1272.1, 1282.0
7	1418.2	1414.0, 1451.3	1434.6, 1451.7, 1458.2
8	1592.1	1601.3	1591.9

correlation functional of Lee, Yang, and Parr.¹⁷ The geometries were completely optimized without any constraints. We calculated the vibrational frequencies using the normal harmonic approximations employed in the GAUSSIAN 98 program. All frequencies were real. The calculated frequencies reported here have been scaled by the factor 0.96, which is the accepted scaling factor for DFT frequency calculations.

Results of Calculations. For the two possible dimers, **31** and **32**, the two sets of IR values were compared with the IR that was obtained experimentally (Table 1, Figure 1a–c). Clearly, the experimental IR values of the dimer matched better with those of the calculated IR values of compound **31** than with those of compound **32**. On the basis of the IR comparisons, structure **31** was assigned to the dimer.

In conclusion, we have demonstrated that the Hunter–Firenze cycloaddition concept can be applied to the synthesis of indole-*N*-glycosides. Furthermore, we have shown that density functional calculations used for the prediction of IR spectra has potential as a structure-proof tool when NMR data does not provide a unique solution.

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Supporting Information Available: Experimental section including two tabulations of conditions for catalyzing the formation of **15** and spectra for **25**, **26**, and **31**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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