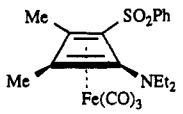
cm^{-1}, characteristic of a sulfone group, and the absence of bands in the region of 1045 ± 10 cm^{-1}, characteristic of a sulfoxide group; (3) broad, intense bands at 1620–1650 cm^{-1}, expected for C=C stretching absorptions; and (4) appropriate ^1H NMR signals for Me, Et, *t*-Bu, and $PhSO_2$ groups in the correct ratio. All such data accord with the presence, in each case, of a sulfonyl- and amino-substituted cyclobutadiene, such as **3**; conversely, such data are not consistent with the presence of a 2-sulfinyl-4-aminofuran such as **7** in the reaction product at this stage.

Furthermore, by treating cyclobutadiene **3a** with $Fe(CO)_5$ or by exposing cyclobutadiene **3b** to $Mo(CO)_6$, the corresponding complexes, **3a**·$Fe(CO)_3$ (**9**) and **3b**·$Mo(CO)_4$ (**10**), were obtained. Both complexes displayed mass fragments for their cyclobutadiene subunits, **3a** and **3b**, in their mass spectra, had characteristic metal carbonyl bands in the 1800–2000 cm^{-1} region and sulfonyl bands at 1140 ± 10 and 1335 ± 10 cm^{-1} in their infrared spectra, and showed proton absorptions and splittings in their ^1H NMR spectra only slightly shifted over those shown by uncomplexed **3a** and **3b**.



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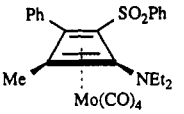
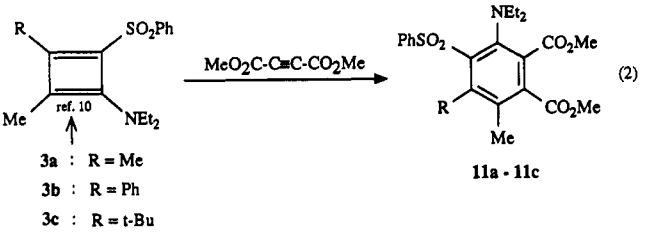


10

Finally, depending upon how soon 1 equiv of dimethyl acetylenedicarboxylate is added to cyclobutadiene **3a**, **3b**, or **3c** after its formation from ynamine **2** and the appropriate alkynyl sulfone **1a**, **1b**, or **1c**, modest to good yields of the Diels–Alder adduct, **11a**, **11b**, and **11c**, were isolated (eq 2). These products **11a–c** displayed weak parent ions, as well as intense fragment ions at $M^+ - PhSO_2$, in their mass spectra, infrared bands at 1150 and 1310 cm^{-1} consistent with the presence of the sulfonyl group, and ^1H NMR spectra appropriate for the expected substituents.

In conclusion, we have adduced compelling evidence that ynamines and 1-alkynyl sulfones combine initially with



(2)

3a : R = Me
3b : R = Ph
3c : R = t-Bu

11a - 11c

each other to provide metastable cyclobutadiene intermediates and that such cyclobutadienes can be chemically trapped, as metal complexes (**9** and **10**) or as Diels–Alder adducts (**11a–c**), in a potentially useful manner. In opposition to Himbert's contention (Scheme I), furans such as **7** are not formed directly from ynamines and alkynyl sulfones. Rather, at this point in our studies it appears that the initially formed cyclobutadiene eventually may isomerize to the furan **7** and, ultimately, to the enedione **8**.[11]

Acknowledgment. This research was supported, in part, by the National Science Foundation under Grant CHE-87-14911. Professor Marek P. Boleslawski and Ms. Gabriela Blaich provided valuable technical assistance.

Supplementary Material Available: Experimental details and data for the discussed reactions and their products (8 pages). Ordering information is given on any current masthead page.

(11) Himbert and co-workers repeated our reported interaction of **1a** with **2** and found that they "could confirm most of the ^1H NMR data quoted" in our work.[6] However, they were unable to "give a definite statement about the structure of the adduct or the new compound formed from it on distillation". We have not actually isolated furans or enediones of types **7** and **8** from this reaction either, but we do observe spectral changes in **3a**, upon standing, that are consistent with its isomerization into a furan like **7**: the ^1H NMR spectrum shows two new singlets as "shadows" on the methyl peaks at 1.88 and 2.25 ppm and the triplet and the quartet at 0.95 and 3.1 ppm display more complex splittings; the neat IR spectrum begins to develop new bands, especially one or more bands in the 1030–1045-cm^{-1} region, ascribable to the sulfoxide group.

Synthesis of the Mannosidase II Inhibitor Mannostatin A

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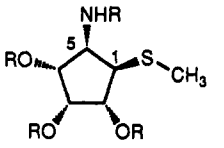
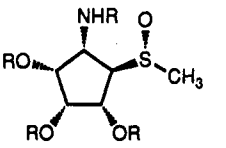
Summary: The synthesis of mannostatin A (**1**), a new inhibitor of glycoprotein processing, has been accomplished in stereocontrolled fashion starting from D-ribonolactone, **7** (~32% overall yield).

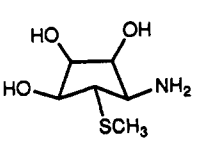
Two unusual aminocyclopentanetriols containing sulfur have recently been isolated from *Streptoverticillium verticillus* var. *quintum* and found to competitively inhibit the α-mannosidase from rat epididymus.[1] Dubbed mannostatin A and B, they were reported to have the sulfide and sulfoxide structures **1** and **3**, respectively, based on ^1H NMR, ^{13}C NMR, and mass spectroscopy, and on crystallographic analysis of mannostatin B tetraacetate (**4**).[2] Further biological evaluation by Elbein et al. led to the discovery that **1** powerfully and selectively inhibited Golgi processing mannosidase II, and in cell culture altered viral



1: R = H (mannostatin A)
2: R = Ac



3: R = H (mannostatin B)
4: R = Ac



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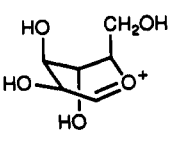

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glycoprotein processing so as to cause an increase in hybrid-type glycoproteins at the expense of complex type.[3] There is currently widespread interest in glycosidase inhibitors not only as biochemical tools for probing the

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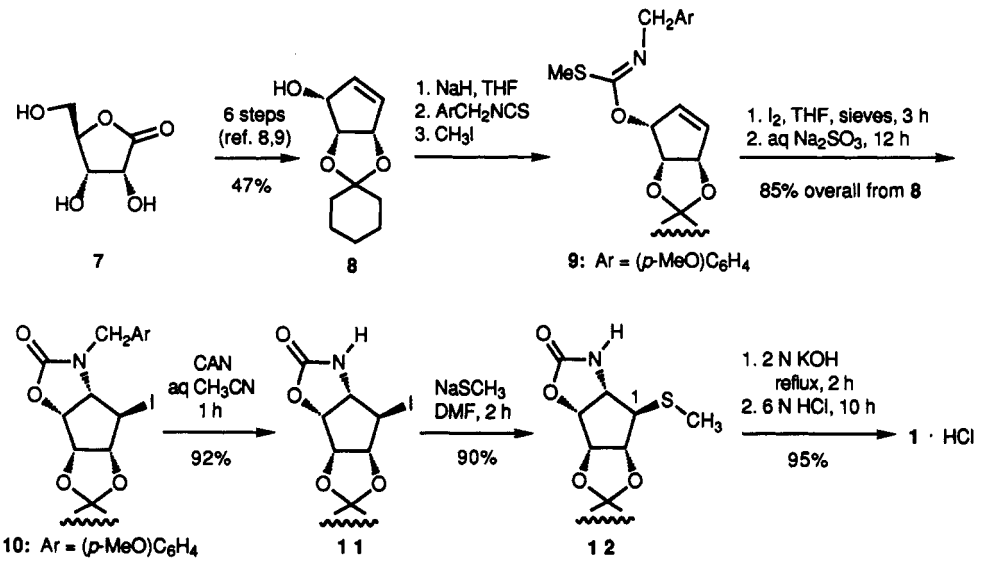
Scheme I. Synthesis of Mannostatin A



mechanisms and structures associated with glycoprotein processing,[4] but also for their diverse biological activities and potential for clinical and other applications.[5,6] The structures of 1 and 3 are provocative in that they closely resemble neither the alkaloidal mannosidase II inhibitor swainsonine[7] nor the transition state leading to formation of the mannopyranosyl cation 6 (the *enantiomer* 5 actually maps better onto 6 than does 1).[5,6] As a step toward understanding the structural basis for its activity and selectivity, we report the stereocontrolled synthesis of mannostatin A (1) from D-ribonolactone (7) via the known cyclopentenol 8 (Scheme I), and also the synthesis of the mannostatin A enantiomer 5 from the enantiomer of 8.[8,9]

Reaction of the sodium salt of 8 with *p*-methoxybenzyl isothiocyanate followed by iodomethane gave the carbonimidothioate 9,[10] which was directly cyclized using iodine[11] to afford the oxazolidinone 10. The structure assignment for 10 rests upon the precedent of trans alkene addition for similar cyclizations[10,12] and is also consistent with IR and ^{1}H NMR analysis.[13] Ceric ammonium nitrate cleanly removed the *N*-*p*-methoxybenzyl group, and subsequent displacement of the iodide of 11 using sodium methylmercaptide gave the methylthio derivative 12. The close similarity of the apparent proton coupling constants for the ring methines of 11 and 12 suggests that the displacement reaction has occurred with overall retention of configuration at C-1, perhaps as a result of participation by the oxazolidinone nitrogen.[11,12] Sequential removal of the protecting groups gave synthetic mannostatin A (1) as its hydrochloride ($[\alpha]_D$ +5.4°, *c* = 1, MeOH; compare natural 1·HCl +5.9°). The structure was confirmed by matching the well-resolved 400-MHz ^{1}H NMR and 50-MHz ^{13}C NMR spectra in D_2O solution with the reported values,[2,14] and with the ^{1}H NMR spectrum of natural 1·HCl. Acetylation of 1 gave the tetraacetate 2 (mp 119–120 °C dec; $[\alpha]_D$ +8.5°, *c* = 0.9, $CHCl_3$), which also proved identical with 2 derived from natural 1, according to its melting point and ^{1}H NMR spectrum in deuteriochloroform.[2] An identical route starting with the enantiomer of 8 produced the mannostatin A enantiomer 5·HCl with $[\alpha]_D$ –6.0° (*c* = 0.5).

Acknowledgment. We are grateful to the Charles and Johanna Busch Memorial Fund for financial support of this work, NSF grant CHEM-8300444 and NIH grant 1510RRO1486 for support of instrumentation, and Jeffrey Hale (Merck Co.) for measuring optical rotations. We thank Prof. Bruce Ganem for providing the ^{1}H NMR spectrum and $[\alpha]_D$ of natural 1·HCl.

Supplementary Material Available: Full experimental details for the preparation of 1 from 8 and the ^{1}H NMR spectrum of 1·HCl (3 pages). Ordering information is given on any current masthead page.

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(13) IR: 1750 cm^{-1} (cis-fused oxazolidinone). ^{1}H NMR: app *J* (H-1/H-2 and H-1/H-5) = 0. A similarly substituted cyclopentane also showed no vicinal ring coupling at the position corresponding to H-1 in 10, 11, and 12. See compound 9 in Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 1261–1263.
(14) The ^{1}H NMR spectrum reported for 1 in ref 2 probably refers to 1·HX and was corrected by –0.67 ppm to match the spectrum of synthetic 1·HCl.