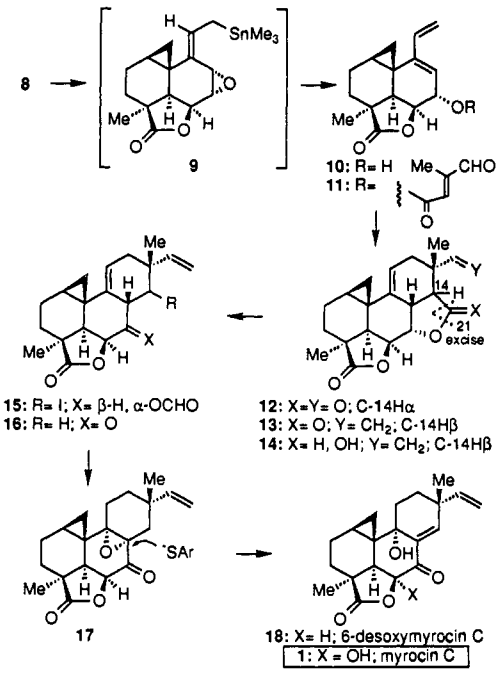
Scheme II



Photolytically mediated iodinative cleavage[16] ($PhI(OAc)_2$, I_2, cyclohexane) of the lactol linkage gave rise to iodo formates **15** (7:1 β/α), which upon reductive deiodination/deformylation (neat[17] Bu_3SnH, AIBN) and oxidation (Dess-Martin periodinane,[18] CH_2Cl_2) provided ketone **16**. Concomitant enone conjugation and stereospecific epoxidation (H_2O_2, NaOH, MeOH) gave **17** in 50% overall yield from **14** (Scheme II).

Oxirane opening (4-OMePhSAlMe_3Li,[19] THF) followed by sulfoxide formation (2,2-dimethyldioxirane, acetone/CH_2Cl_2) and spontaneous elimination provided desoxymyrocin C (**18**) in 55% overall yield. Finally, C-6 hydroxylation[20] (O_2, *t*-BuOK, THF/*t*-BuOH) was achieved via the presumed, but uncharacterized, C-6 hydroperoxide which was immediately reduced ($P(OEt)_3$, THF) to give *dl*-myrocin C (**1**), mp >214 °C dec, in 68% yield. While the spectral properties of the fully synthetic material corresponded very closely to those recorded for the natural product, a sample of the latter was not available to us for direct comparative measurements. *That the total synthesis of racemic* **1** *had in fact been achieved was rigorously demonstrated by a single-crystal X-ray determination of our fully synthetic material.*[21]

We shall in due course report on the mechanistic aspects of the cyclopropanation reaction as well as the interesting chemistry of **18** and **1** and the possible implications of the latter findings on the mode of action of myrocin C.

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Supplementary Material Available: A chart of reactions including specific conditions and yields for all transformations reported herein with listings of compiled analytical data for **2**, **10**, **13**, **18** and **1**, as well as ^1H and ^{13}C NMR spectra of synthetic and natural **1** (8 pages). Ordering information is given on any current masthead page.

n-Pentenyl Glycoside Methodology for Rapid Assembly of Homoglycans Exemplified with the Nonasaccharide Component of a High-Mannose Glycoprotein[1,2]

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Complex saccharides play critical roles in biological regulation,[3] and the triantenary oligosaccharide **1** which, though well-known as one of several high-mannose glycoproteins occurring in animals and plants,[4,5] now attracts special attention because of its presence on the conserved V3 loop of the viral coat of HIV1, known as GP-120.[6]

The mannan moiety of **1** can be dissected into three zones (Scheme I) whose components carry three, two, and one sugar units A, B, and C, respectively. Further retroanalysis of A leads to the retron **2** with permanent protecting groups at O2 and O4 and different temporary protecting groups at O3 and O6. Retrons B and C lead to the same synthon **3**, where the C2 ester serves for temporary protection, as required in B, or permanent, as required in C. Thus the nonasaccharide component of **1** could conceivably be constructed from only two mannopyranose precursors, **2** and **3**. In this manuscript we describe the realization of this objective based on the novel chemistry of *n*-pentenyl glycosides.

The armed/disarmed strategy for saccharide coupling emanated from our exploratory work on NPGs,[7] and two developments from

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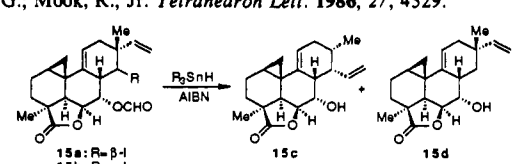

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(19) Cf. Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 361.

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(21) Crystallographic parameters and specifications will be reported in a subsequent disclosure.

(1) This work was supported by grants from the NIH (GM 41071, AI-31863) and NSF (CHE 8920003).

(2) Presented at the XVth International Carbohydrate Symposium, Paris, France, July 5-10, 1992, and at the 204th National Meeting of the American Chemical Society, August 23-28, 1992, Washington, D.C.

(3) See, for example: Ferguson, M. A. J. *Curr. Biol.* **1991**, *1*, 522. Robinson, P. J. *Immunol. Today* **1991**, *12*, 35. Findley, J. *Chem. Br.* **1991**, 724. von Boehmer, H.; Kisielow, P. *Sci. Am.* **1991**, 74. Springer, T. A.; Lasky, L. A. *Nature* **1991**, *349*, 196.

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(6) LaRosa, G. J.; Davide, J. P.; Weinhold, K.; Waterbury, J. A.; Profy, A. T.; Lewis, J. A.; Langlois, A. J.; Dreesman, G. R.; Boswell, R. N.; Shadduck, P.; Holley, L. H.; Karplus, M.; Bolognesi, D. P.; Matthews, T. J.; Emini, E. A.; Putney, S. D. *Science* **1990**, *249*, 932. Larkin, M.; Childs, R. A.; Matthews, T. J.; Thiel, S.; Mizuochi, T.; Lawson, A. M.; Savill, J. S.; Haslett, C.; Diaz, R.; Feizi, T. *AIDS* **1989**, *3*, 793.

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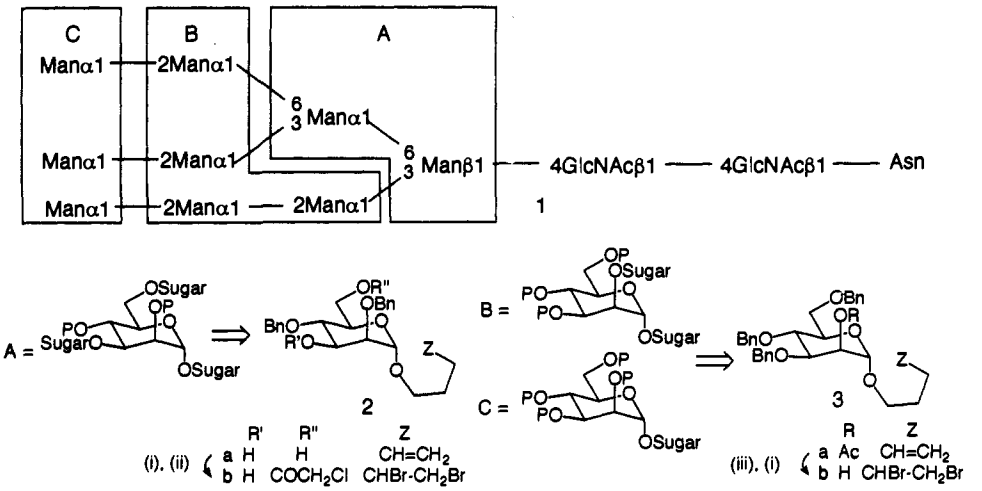
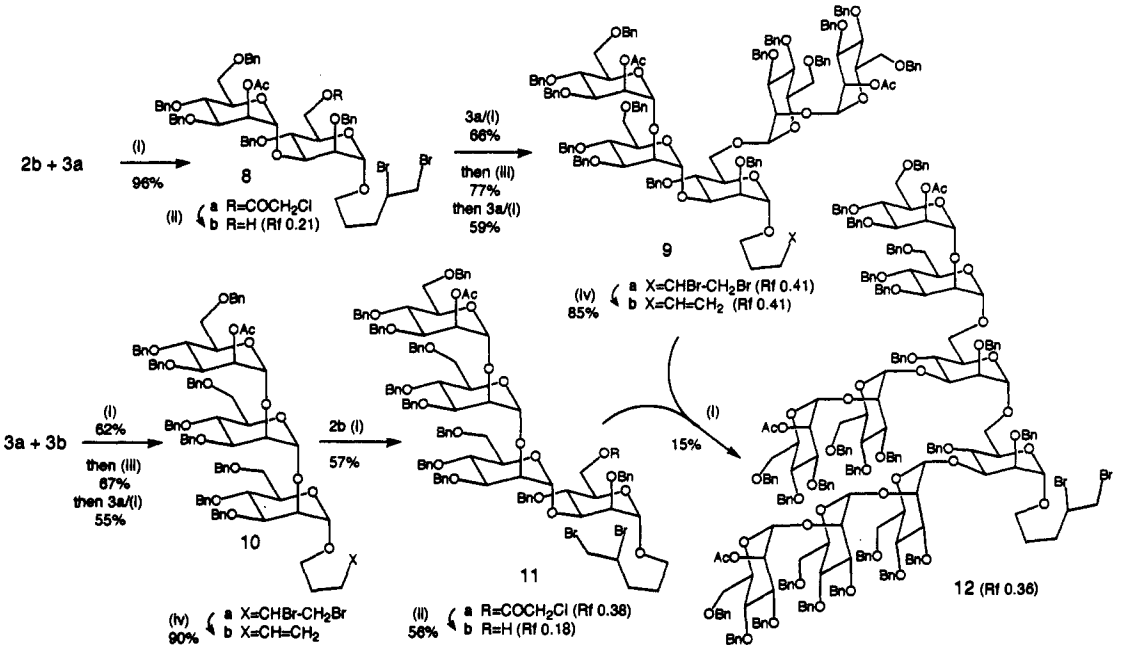
Scheme I[a]



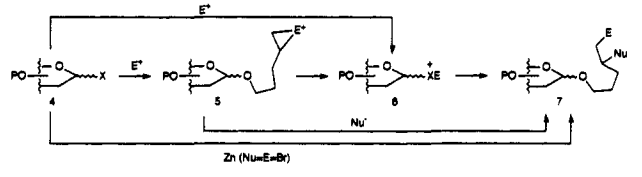
[a] (i) Br_2/Et_4NBr, CH_2Cl_2; (ii) $(ClCH_2CO)_2O$/pyr; (iii) K_2CO_3/MeOH.

Scheme II[a]



[a] (i) NIS/Et_3SiOTf, CH_2Cl_2; (ii) thiourea/$NaHCO_3$, EtOH; (iii) NH_3/MeOH; (iv) Zn/Bu_4NI, EtOH/EtOAc. R_f's shown in brackets were determined in 30% EtOAc/petroleum ether.

our subsequent mechanistic studies[8] have been leveraged into the methodology reported herein. (i) NIS/Et_3SiOTf[9] provides such a potent source of I^+ that disarmed glycosyl donors, e.g., **3**, react virtually instantaneously.[9] (ii) Whereas other glycosyl donors



are activated in a single step, **4** → **6**, NPG activation occurs in two stages, **4** → **5** → **6**, the second of which can be averted by the use of excess nucleophile to give **7**. A given NPG (**4**, X = *O*-pentenyl) can therefore serve immediately as a glycosyl donor (**4** → **6**) or be sidetracked by dibromination to **7** (Nu = E = Br) to serve as a glycosyl *acceptor* and, subsequently, after reductive elimination to regenerate the pentenyl group (**7** → **4**) as a glycosyl donor.

A portion of **2a**[10] was dibrominated and then selectively chloroacetylated to give **2b** (Scheme I), which reacted with the disarmed donor **3a** instantly,[11] with neighboring group participation, to afford **8a** in virtually quantitative yield (Scheme II). Sequential episodes of hydroxyl uncovering followed by coupling with **3a** afforded the pentasaccharide **9a**.

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(10) Compounds **2a** and **3a** were prepared by adopting Ogawa's procedures for the corresponding methyl mannosides: Ogawa, T.; Katano, K.; Sasajima, K.; Matsui, M. *Tetrahedron Lett.* **1981**, *37*, 2779.

(11) (a) The standard procedure for NPG coupling was as follows: The glycosyl acceptor (1 equiv) was taken up in CH_2Cl_2 (distilled over P_2O_5) to give a 0.1 M solution, and NIS (1.3 equiv) and Et_3SiOTf (0.3 equiv) were added as the solution was stirred under Ar. The glycosyl donor (1.3 equiv) was taken up in CH_2Cl_2 to give a 0.4 M solution, which was then added by syringe to the glycosyl acceptor solution. The reaction was stirred until all NIS had dissolved. More CH_2Cl_2 was added, and the solution was washed with 10% aqueous sodium thiosulfate solution and saturated aqueous $NaHCO_3$. The organic layer was collected and dried over Na_2SO_4. The solvent was removed on a rotary evaporator. (b) For this coupling the glycosyl donor **9b** was the limiting partner, and this undoubtedly contributed to the low yields.

Since the lowest antenna of **1** is made up of B (= C) components, compound **3a** served both as the glycosyl donor and, after dibromination and deacylation to **3b**, as the glycosyl acceptor, thereby permitting rapid assembly of the trisaccharide segment **10a**.

The building blocks **9a** and **10a** would now become glycosyl donors. Reductive elimination, carried out most efficiently by sonication overnight with zinc in the presence of tetra-*N*-butylammonium iodide, gave **9b** and **10b**, respectively. Coupling of **2b** gave the tetrasaccharide **11a** (Scheme II) which, after deacylation, was ready for coupling with the pentasaccharide **9b**[10b] to give the protected nonasaccharide **12**.

From Scheme II, it is apparent that once the properly designed monosaccharide precursors are in hand, subsequent synthetic manipulations are confined to liberation of (a) a hydroxyl group or (b) the pentenyl double bond. The fact that these alterations do not tamper with the anomeric center greatly facilitates the use of ^{1}H NMR to monitor the progress. With NIS/Et_3SiOTf as promoter, coupling is immediate, a circumstance which makes for rapid assembly.

It required 3 weeks to prepare 450 mg of pentasaccharide **9a** from mannose,[12] with a total of 8 days being required for the deacetylation steps. We anticipate that with proper attention to logistics it should be possible to assemble the entire nonasaccharide within 2 weeks.

Supplementary Material Available: Listings of experimental procedures for the preparation of compounds **2a,b**, **3a,b**, **8b**, **9a,b**, **10a,b**, **11a,b**, and **12** and their ^{1}H NMR data (9 pages). Ordering information is given on any current masthead page.

(12) We thank Miss Elizabeth Naisang, an undergraduate summer research assistant, for carrying out this experiment.

A Transition-State Model for the Rhodium Porphyrin-Catalyzed Cyclopropanation of Alkenes by Diazo Esters

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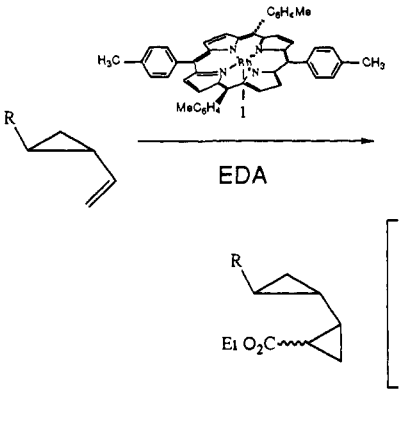
A number of metal complexes catalyze the cyclopropanation of alkenes by diazo esters.[1] Rhodium(III) porphyrins are particularly interesting in that they often produce *syn*-cyclopropyl esters preferentially. The syn selectivity increases with the size of the meso substituents, and synthetically useful ratios are achieved with bulky macrocycles.[2] All other metal catalysts exhibit the opposite selectivity, including several recently developed asymmetric catalysts.[3-7] Thus, the porphyrin-catalyzed reactions are of potential utility in organic synthesis, and particularly so if chiral porphyrins could be developed that would render the reaction highly asymmetric. We have recently reported preliminary work directed toward this goal, but high enantiomeric excesses have not yet been realized.[8,9] In order to rationally design more selective catalysts, it would be useful to understand the detailed mechanism of carbene transfer from the putative metallocarbene intermediate[10] to the alkene. The experiments reported here suggest that the exchange occurs without detectable intermediates and has a very early transition state.

The cyclopropanation of *trans*-β-deuterio-*p*-X-styrene (X = H, OCH_3)[11] was examined using RhTTPI[12] as the catalyst and ethyl diazoacetate (EDA) as the carbene donor. In both cases the stereochemistry about the C_α–C_β bond was retained, as deduced by ^{2}H NMR spectroscopy.[13] Furthermore, the ratio of *syn*- to *anti*-cyclopropyl esters produced by the RhTTPI-catalyzed reaction of EDA with a series of para-substituted styrenes is essentially invariant (X = Cl, H, Me, MeO, syn/anti = 0.96 ± 0.05). Finally, when a competitive cyclopropanation reaction was carried out between equimolar amounts of styrene and *p*-methoxystyrene in the presence of EDA and RhTTPI, the ratio of products was 1.0. These data suggest that, for the rhodium porphyrin-catalyzed reactions, cationic species are unlikely to be intermediates in the product-determining step.[14]

Carbon radicals adjacent to a cyclopropyl ring are known to undergo rapid rearrangement to homoallyl radicals. The RhTTPI-catalyzed cyclopropanation of vinylcyclopropane and *anti*-2-phenyl-1-vinylcyclopropane[15] with EDA resulted in the formation of only the dicyclopropane products (eq 1). The possible rearrangement products **1a** and **1b** were not observed by either ^{1}H NMR or GC/MS. The cyclopropane products and unreacted olefin accounted for over 97% of the substrate present, eliminating the possibility that a rearranged radical intermediate is formed, but polymerization occurs rather than cyclization to **1**. Since the rates of rearrangement for both cyclopropylcarbinyl radicals are known (R = H, $k = 1.0 \times 10^8$; R = Ph, $k = 2.1 \times 10^{11}$),[16,17] our data demand that if a radical intermediate is formed, it must close very rapidly.



(1)

The secondary kinetic isotope effect for the cyclopropanation of styrene and styrene-d_8 by EDA was determined in a competitive

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(12) RhTTPI is an abbreviation for iodorhodium(III) tetra-*p*-tolylporphyrin.
(13) ^{2}H NMR data for labeled ethyl 2-*p*-X-phenylcyclopropanecarboxylates: X = OCH_3 5.20 (D_a), 1.55 (D_c), 1.25 ppm (D_b); X = H 4.95 (D_a), 1.60 (D_c), 1.30 ppm (D_b). Chemical shifts reported are relative to $CDCl_3$ (7.24 ppm). All resonances are broad singlets due to proton–deuterium coupling. The detection limit is ≥5%. NMR data are available as supplementary material.
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(17) Newcomb, M.; Manek, M. *J. Am. Chem. Soc.* **1990**, *112*, 9662.

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