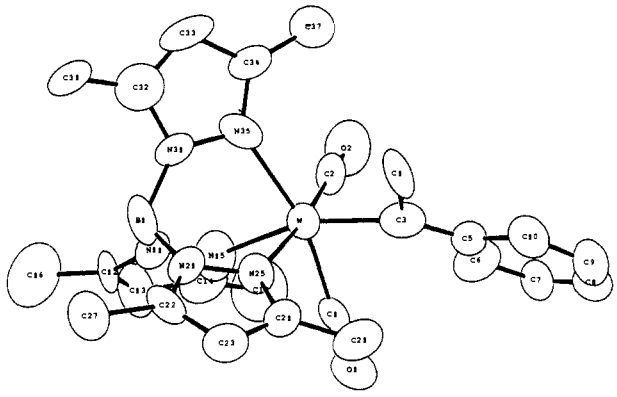

Figure 1. $[Tp'(CO)_2W{=}C(Ph)Me]^+$ with the β-agostic carbene lying between the two carbonyl ligands: W-C3, 1.94 (2) Å; C3-C4, 1.50 (3) Å; C3-C5, 1.45 (3) Å; W-C3-C4, 91 (1)°; W-C3-C5, 149 (2)°; C1-W-C2, 96 (1)°.

result from protonation of an η^2-vinyl ligand would leave the metal unsaturated.

The only unusual piece of spectral data we obtained for the methylphenylcarbene complex was a high-field ^{13}C chemical shift for the methyl carbon (-22.8 ppm). The $^1J_{CH}$ value of 132 Hz for this group could result either from a normal CH_3 moiety or from averaging one agostic C-H coupling constant with two olefin-like C-H coupling constants.[1] Partial deuterium incorporation did not cause a substantive change in either the methyl ^1H chemical shift or the methyl $^1J_{CH}$ coupling constant down to -70 °C.[11] Facile rotation of agostic methyl groups is known to obscure NMR evidence for agostic bonding in some complexes.[12]

The ethylphenylcarbene displays an unusually high field shift for the methylene carbon (-11.4 ppm), suggesting a close structural analogy to the methyl derivative. (In contrast, agostic spectral properties present in a scandium ethyl derivative disappear in the analogous propyl complex.[13]) The methylene $^1J_{CH}$ value of 121 Hz and several broad room-temperature NMR signals for $[Tp'(OC)_2W{=}C(Ph)CH_2Me][BF_4]$ encouraged us to undertake low-temperature NMR studies. Distinct proton signals for the methylene group of the ethyl substituent were evident at -60 °C (1.76 and 3.48 ppm, $^2J_{HH}$ = 17.5 Hz, $^3J_{HH}$ = 5.2 Hz). The absence of a mirror plane in the solution structure was also evident in the low-temperature ^{13}C spectrum as two carbonyl carbon signals were detected (211 ppm, $^1J_{WC}$ = 161 Hz; 215 ppm, $^1J_{WC}$ = 134 Hz).

The keystone that definitively characterizes the cationic ethylcarbene complex as agostic was the doublet of doublets revealed at -60 °C for the methylene carbon. The smaller $^1J_{CH}$ value of 96 Hz is the signature of an agostic bond,[1] and the larger value of 145 Hz reflects rehybridization from sp^3 toward sp^2 for the methylene carbon. The $^1J_{WC}$ value of 41 Hz to the carbene carbon is also noteworthy. Coalescence of the methylene protons at -5 °C indicates a barrier of 11.7 kcal/mol for enantiomer interconversion.

The X-ray structure[14] of $[Tp'(OC)_2W{=}C(Ph)CH_3][BF_4]$ is compatible with an agostic formulation (Figure 1). The Tp' and carbonyl ligands are unremarkable; details of the carbene geometry are the focus of attention here. The W=C distance of 1.942 Å lies near high oxidation state Schrock alkylidenes and below low oxidation state Fischer carbenes[15] [Bu^{t}CH=W(dmpe)(CBu^t)-(CH$_2$Bu^t), 1.94 Å;[16] $Ph_2C{=}W(CO)_5$, 2.14 Å[17]). The metal to methyl carbon distance of 2.49 Å is consistent with a three-center, two-electron linkage tying the W-H-C unit together. The W=C—C angles of 149° to the phenyl ipso carbon and 91° to the methyl carbon are reminiscent of protonated carbynes,[3,4] the analogy here being a methylated phenylcarbyne ligand.

The classical limits accessible to $[Tp'(OC)_2W{=}C(Ph)CH_2R][BF_4]$ are either an 18-electron η^2-vinyl hydride complex or a 16-electron carbene monomer. We believe that the steric requirements of the Tp' ligand[18] inhibit the formation of $[Tp'(OC)_2HW(\eta^2\text{-}CPh{=}CHR)]^+$, and thus this cationic third row metal complex adopts an agostic structure.

Acknowledgment. We thank PRF and the Department of Energy, Office of Basic Energy Sciences, for support (85ER13430) and Professor M. S. Brookhart for helpful discussions.

Supplementary Material Available: Synthetic details and complete characterization data as well as tables of X-ray structural parameters for $[Tp'(CO)_2WC(Ph)Me][BF_4]$ (19 pages); observed and calculated structure factors for $[Tp'(CO)_2WC(Ph)Me][BF_4]$ (14 pages). Ordering information is given on any current masthead page.

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Total Synthesis of the Oligosaccharide Fragment of Calicheamicin γ_1^I

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Model studies recently reported from these laboratories[1] suggested a strategy for the construction of the oligosaccharide fragment of calicheamicin γ_1^I (**1**),[2] which has been suggested as the main DNA-binding domain of this molecule.[3] We now report the first total synthesis of this unusual oligosaccharide as its methyl glycoside (**2**). The stereocontrolled synthesis reported herein is based on a novel 3,3-sigmatropic rearrangement that established the essential elements of the central ring B as presented in Scheme I and delivered the target molecule in enantiomerically pure form and high overall yield.

Designated on structure **2** are the strategic bond disconnections that allowed the tracing of the requisite intermediates to the readily available starting materials, L-rhamnose (ring D), 3,4,5-tri-

† Visiting scientist from Ono Pharmaceutical Co., Japan, 1989-1990.
‡ Feoder Lynen Postdoctoral Fellows of the Alexander von Humboldt Foundation, 1989-1991.
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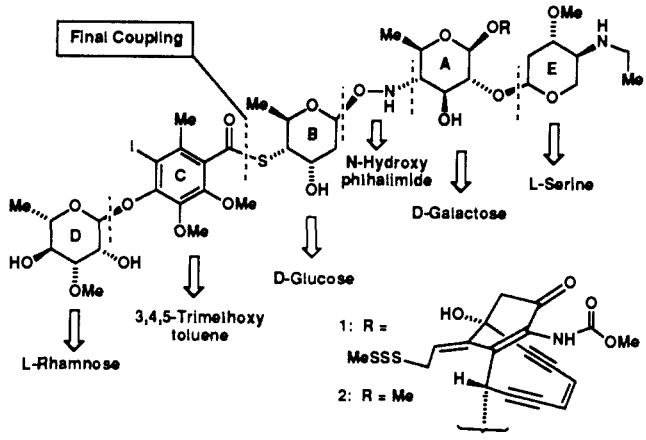
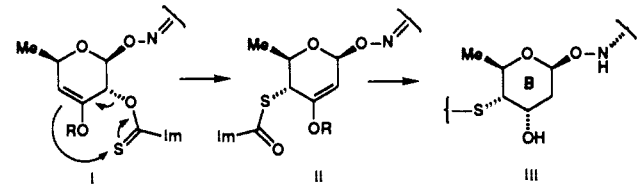
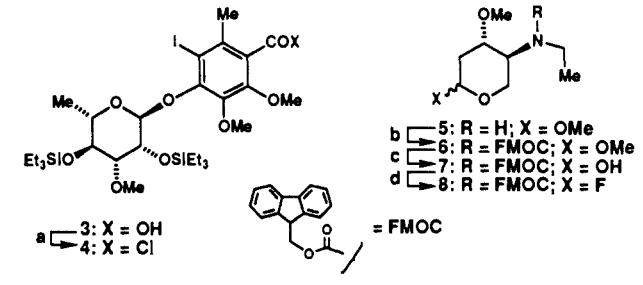
Scheme I. Strategic Bond Disconnections of **2**



Scheme II. Basic Strategy for Construction of the B ring of **2**



Scheme III. Construction of Key Intermediates **4** and **8**[a]



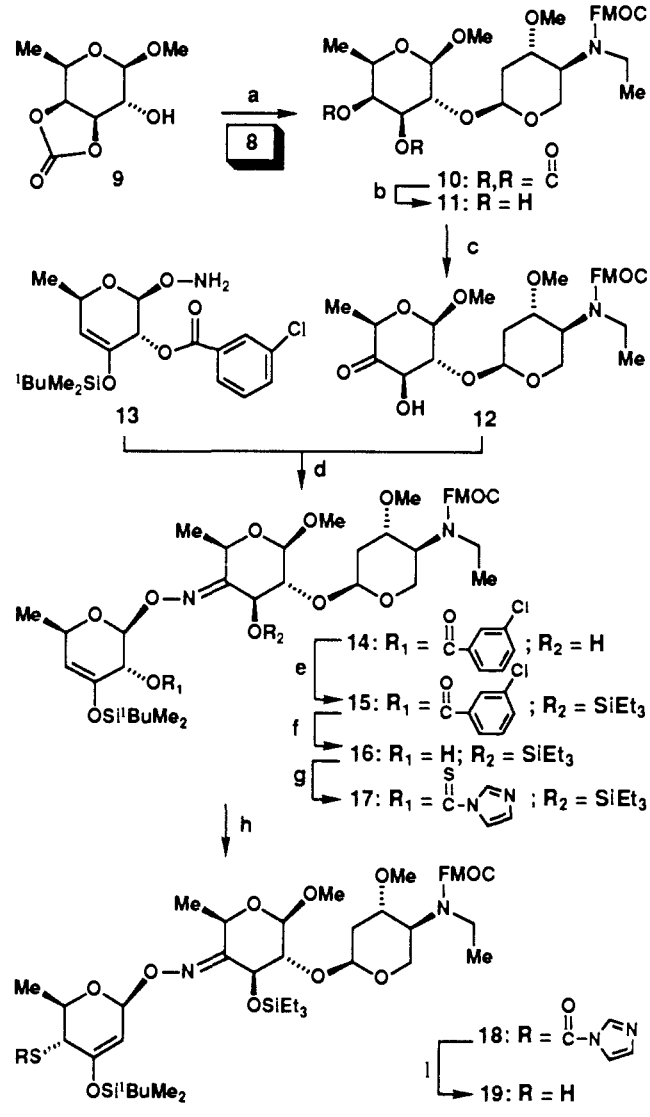
[a] Reagents and conditions: (a) $(COCl)_2$, 25 °C, 1 h, 100% (crude); (b) 1.5 equiv of FMOC-Cl, 3 equiv of K_2CO_3, THF–H_2O (7:3), 0 °C, 0.5 h, 96%; (c) AcOH–H_2O (4:1), 90 °C, 4 h, 85% plus 4% recovered **6**; (d) 3 equiv of DAST, THF, −78 → 0 °C, 1 h, 91%.

methoxytoluene (ring C), D-glucose (ring B), *N*-hydroxyphthalimide (O–NH moiety), D-galactose (ring A), and L-serine (ring E) (Scheme I). The CO–S linkage was chosen as the key bond for the final coupling reaction. Units **3**,[4] **5**[4] (Scheme III), **9**[5] (Scheme IV), and **13**[1] (Scheme IV) served as key building blocks for the total construction of **2**.

Scheme III summarizes the elaboration of intermediates **3**[4] and **5**[4] to the requisite key building blocks **4** and **8**, respectively. Thus, the acid chloride **4** was prepared by exposure of **3** to neat oxalyl chloride followed by removal of excess reagent under vacuum in essentially quantitative yield, whereas compound **8** was obtained from **5** via intermediates **6** and **7** by sequential FMOC[6] formation (96%), methyl glycoside hydrolysis (85% plus 4% recovered starting material), and glycosyl fluoride formation (91%).

Scheme IV summarizes the construction of key intermediate **19**, which utilized glycosidations based on glycosyl fluoride technology[7] and the Mitsunobu process[8] as well as an oxime-

Scheme IV. Construction of Key Intermediate **19**[a]



[a] Reagents and conditions: (a) 1.2 equiv of **9**,[5] 1.0 equiv of **8**, 2.0 equiv of $AgClO_4$, 2.0 equiv of $SnCl_2$, THF, −78 → −20 °C, 3 h, (α/β ratio 4.5:1), 86%; (b) 0.01 equiv of NaH, $HOCH_2CH_2OH$–THF (1:20), 25 °C, 0.5 h, 93%; (c) 1.0 equiv of Bu_2SnO, MeOH, 65 °C, 45 min, then 1.0 equiv of Br_2, 1.0 equiv of Bu_3SnOMe, CH_2Cl_2, 25 °C, 0.5 h, 70% plus 18% recovered **11**; (d) 1.2 equiv of **13**, 1.0 equiv of **12**, 0.05 equiv of PPTS, benzene, 25 °C, 2 h, 83%; (e) 1.3 equiv of Et_3SiOTf, 1.7 equiv of 2,6-lutidine CH_2Cl_2, 0 → 25 °C, 2 h, 100%; (f) 3.0 equiv of DIBAL, CH_2Cl_2, −78 °C, 0.5 h, 91%; (g) 3.0 equiv of thiocarbonyldiimidazole, CH_3CN, 25 °C, 1.5 h, 87%; (h) toluene, 110 °C, 0.5 h, 98%; (i) 0.5 equiv of NaSMe, 50 equiv of EtSH, CH_2Cl_2, 0 °C, 15 min, 95%.

forming reaction for assembling the key fragments. Thus, coupling of intermediate **9**[5] with glycosyl fluoride **8** afforded disaccharide **10** in 70% yield together with its anomer (16%). Chromatographic separation followed by selective deprotection of **10** led to diol **11** (93%), which was selectively oxidized with $^nBu_2SnO$–Br_2[9] at C-4, furnishing ketone **12** (70% plus 18% starting material). Compound **12** was then coupled with the previously prepared hydroxylamine derivative **13**[1] via oxime formation leading to trisaccharide **14** in 83% yield.[10] Elaboration of **14** as previously described for a model[1] led, via compounds **15** and **16**, to the key thiono imidazolide

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(5) The synthesis of this compound is summarized in the supplementary material.

(6) Although homogeneous by TLC, the FMOC derivatives described in this work exhibited multiple signals in their NMR spectra due to rotamers arising from restricted rotation around the C–N bond. Heating the NMR sample to ca. 80 °C often sharpened the peaks. Similar phenomena were observed by the Lederle group upon acetylation of the basic nitrogen in the calicheamicin series of compounds (personal communication with Dr. May Lee).

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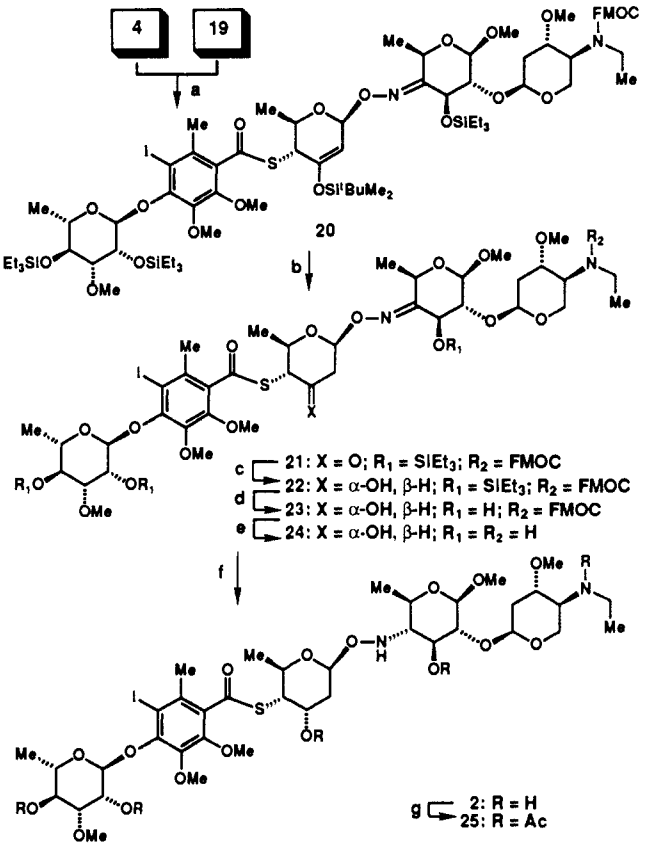
(10) While a single geometrical isomer about the oxime bond was obtained in this reaction, its stereochemistry was not assigned.

Scheme V. Construction of Compound **2**[a]



[a] Reagents and conditions: (a) 1.3 equiv of **4**, 1.0 equiv of **19**, 5 equiv of Et_3N, cat. DMAP, CH_2Cl_2, 0 °C, 10 min, 80%; (b) 1.0 equiv of TBAF, 4.0 equiv of AcOH, THF, -23 °C, 15 min; (c) 3.0 equiv of K-Selectride, DME-THF (8:1), -78 °C, 1.5 h, 75% overall from **20**; (d) HF·Pyr, CH_2Cl_2-THF (15:1), 0 °C, 1.5 h, 87%; (e) Et_2NH-THF (1:1), 25 °C, 2 h, 100%; (f) $NaCNBH_3$, MeOH-HCl(g) (pH 3), 0 °C, 2 h, 90% total yield, ca. 1:2 ratio; (g) 10 equiv of Ac_2O, 15 equiv of Et_3N, 2 equiv of DMAP, CH_2Cl_2, 0 °C, 2 h, 85%.

17 in 79% overall yield (Scheme IV). Thermolysis of **17** proceeded smoothly to afford the thioester **18** (98% yield) via the expected 3,3-sigmatropic rearrangement shown in Scheme II. Exposure of thio imidazolide **18** to catalytic amounts of NaSMe in CH_2Cl_2 in the presence of excess EtSH led to the rather labile thiol **19** (95% crude yield), which was reacted immediately with acid chloride **4** (1.3 equiv) in the presence of DMAP-Et_3N to afford coupling product **20** (80% yield based on thiol) (Scheme V).[11] Controlled monodesilylation of **20** (1.0 equiv of $^nBu_4NF$) resulted in the formation of ketone **21**, which was reduced selectively with K-selectride, as previously developed,[1] to afford hydroxy compound **22** in 75% overall yield from **20**. Removal of all three triethylsilyl groups from **22** with HF·Pyr, followed by exposure of the resulting intermediate **23** to Et_2NH in THF, led to the desired compound **24** in 87% overall yield. Finally, reduction of the oxime double bond in **24** with $NaCNBH_3$ in MeOH at pH 3 furnished the targeted oligosaccharide **2**, together with its C-4 isomer (90% yield, ca. 1:2 ratio). The two isomers were separated by flash column or preparative thin-layer chromatography (silica, ether-MeOH, 6:1), and the correct isomer (faster moving) was identified by ^1H NMR studies[12] and comparisons of the ^1H NMR spectrum of its pentaacetate (**25**, Scheme V) with that of a closely related derivative derived from calicheamicin γ_1^1 by degradation.[13]

(11) An alternative pathway to **20** from **18** which avoids the intermediacy of **19** was developed via the corresponding thioformate generated from **18** by the action of DIBAL (4.0 equiv, CH_2Cl_2, -78 °C, 2.5 h, 85%) followed by direct coupling with acid chloride **4** (10 equiv, DMAP, CH_2Cl_2, 25 °C, 4 h, 52% yield plus 41% recovered thioformate).

(12) Particularly revealing were the coupling constants for H-4: $J_{3,4} = J_{4,5} = 9.7$ Hz (500 MHz, $CDCl_3$, δ 2.32) indicating a diaxial relationship of this proton with its neighboring protons on ring A.

The described chemistry is expected to facilitate molecular recognition experiments between calicheamicin oligosaccharide fragments, such as **2**, and specific DNA strands, as well as pave the way for a total synthesis of the intact antibiotic (**1**).[14]

Acknowledgment. We express our many thanks to Drs. Dee H. Huang and Gary Siuzdak of the Research Institute of Scripps Clinic for their superb NMR and mass spectroscopic assistance, respectively, and to Dr. May Lee of Lederle Laboratories, Pearl River, NJ, for data and helpful discussions. This work was financially supported by the National Institutes of Health, Hoffmann-La Roche, and Merck Sharp and Dohme.

Supplementary Material Available: A summary for the synthesis of key intermediate **9** and a listing of selected R_f, $[\alpha]_D$, IR, ^1H and ^{13}C NMR, and mass spectral data for compounds **10**, **12**, **14**, **17**, **18**, **20**, **24**, and **2** (9 pages). Ordering information is given on any current masthead page.

(13) The ^1H NMR spectrum of **25** was very similar to that of the corresponding hexaacetate (replacement of anomeric OMe group of ring A with an OAc group) obtained by Lee et al.[2] by degradation of calicheamicin γ_1^1. We thank Dr. M. Lee of Lederle Laboratories for providing us with copies of ^1H NMR spectra of this and related compounds.

(14) New compounds exhibited satisfactory spectral and analytical and/or exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.

Tantazoles: Unusual Cytotoxic Alkaloids from the Blue-Green Alga *Scytonema mirabile*

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The terrestrial cyanophyte *Scytonema mirabile* (Dillwyn) Bornet (strain BY-8-1) produces a complex mixture of cytotoxins, the major and most potent one being tolytoxin.[1] Interestingly, some of the cytotoxins in the lipophilic extract of this alga show marginal solid tumor selectivity at the cellular level in the Corbett assay.[2] We report here the total structures of tantazoles A (**1**), B (**2**), F (**3**), and I (**4**), representatives of an unusual class of alkaloids that exhibit murine solid tumor selective cytotoxicity.[3]

The freeze-dried cyanophyte[4] was extracted with 70% ethanol in water, and the resulting extract was subjected to repeated reverse-phase (C-18) chromatography to give the tantazoles as amorphous white solids. During the purification of tantazole A (**1**), the major alkaloid, and tantazole I (**4**), extensive air oxidation of both compounds to the didehydro compound **5** occurred.

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(3) The tantazoles are named after the site (Mt. Tantalus, Oahu, HI) where the alga was collected. Details of the antitumor evaluation will be presented elsewhere.

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