Table II. Diastereochemical Control as a Function of Solvent[a]

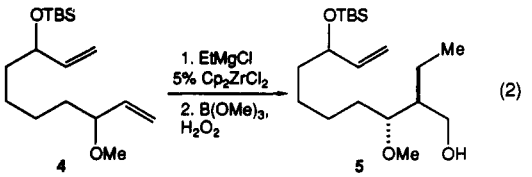
substrate	solvent	2:3	% yield
1a	Et_2O	95:5	70
1a	50% Et_2O/THF	73:27	70
1c	Et_2O	11:89	80
1c	50% Et_2O/THF	11:89	75

[a] Three equivalents of EtMgCl and 5 mol % Cp_2ZrCl_2 were used at 25 °C.

of THF as solvent results in higher yields but with diminution in stereocontrol (vide infra).

Ethylmagnesation of the allylic methyl ether **1c** and the methoxyethoxy ether **1d** affords the monoprotected diols **3c** and **3d** in 80% and 53% yields, respectively; however, it is the anti diastereomer that is formed predominantly with 89:11 and 90:10 selectivity.[5] In further contrast to the carbometalation of allylic alcohols, when the size of the β-alkyl substituent is increased from *n*-nonyl (**1c**) to cyclohexyl (**1e**), with 5 mol % Cp_2ZrCl_2 or Cp_2ZrBu_2 as catalyst, ethylmagnesation proceeds readily and the level of stereocontrol is enhanced to 96:4. Thus, *either syn or anti carbometalation products can be prepared with high stereochemical control, depending on the nature of the neighboring oxygen substituent.* The paucity of highly stereoselective functionalization of terminal alkenes renders such levels of asymmetric induction particularly noteworthy.

The carbomagnesation reaction shows sensitivity to steric encumbrance near the alkene center. Protection of the hydroxyl unit of **1a** as the *tert*-butyldimethylsilyl group completely inhibits the alkene from carbomagnesation; accordingly, carbometalation of diene **4** proceeds with >99% site selectivity and 90:10 stereoselectivity to afford the primary alcohol **5** in 70% isolated yield (eq 2).



(2)

70% yield; 90:10 diastereoselectivity; >99% site-selectivity

The reversal of diastereoselectivity observed with hydroxide (magnesium alkoxide) versus ether substrates is significant and might be attributed to the initial association of the metal alkoxide with the zirconium reagent. A set of observations that support this hypothesis are summarized in Table II. Stereoselectivity in ethylmagnesation of **1a** suffers severely when THF is employed as cosolvent; presumably, since THF is an effective ligand, it adversely affects the chelation of the magnesium alkoxide with the metal.[6] Stereochemical control in the carbometalation of allylic ethers (e.g., **1c**)[7] is not influenced by the presence of THF, and therefore, we project that reactions of these compounds probably do not involve two-point association of the substrate with the transition-metal complex.

A plausible mechanism for the carbometalation process may involve zirconocene ("Cp_2Zr") as the active catalyst. It has been established that decomposition of a dialkylzirconocene (prepared at −78 °C), which occurs upon warming to 25 °C, results in the formation of zirconocene.[8] An alkylmetallocene that has served as a reliable source of "Cp_2Zr" is the corresponding dibutyl derivative; that Cp_2ZrBu_2 is capable of serving as a potent initiator in the ethylmagnesation process indicates that zirconocene is involved in zirconium-catalyzed ethylmagnesations.[9] Formation of the zirconocene–alkene complex and its subsequent alkylation by the Grignard reagent may then lead to the final product.[10] Studies in connection with the further utility of transition-metal-catalyzed carbometalation of alkenes are in progress and will be reported in due course.

Supplementary Material Available: Experimental procedures and spectral and analytical data for all reaction products (9 pages). Ordering information is given on any current masthead page.

(5) Et_2Mg reacts with **1c** to afford **3c** with similar levels of stereocontrol but at a faster rate (3 h). The higher reactivity of Et_2Mg has been demonstrated by Dzhemilev (see ref 1).

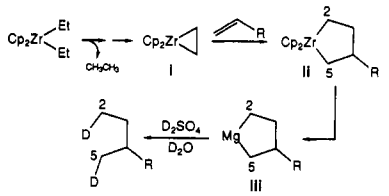
(6) The stereochemical outcome of the carbometalation of alcohols is not influenced by the nature of the metal alkoxide, as the sodium and potassium salts of **1a** afford similarly high levels of stereochemical control (92:8 and 94:6, syn:anti).

(7) With 100% THF, **1a** affords a 67:33 syn:anti ratio of isomers (85%), whereas stereoselectivity remains unaffected in the carbometalation of **1c** (70%).

(8) (a) Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 2544–2546. (b) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336–3346 and references cited therein.

(9) MeMgCl, unlike EtMgCl, under otherwise identical conditions, affords no desired product. This observation is consistent with the contention that "Cp_2Zr" is the active catalyst, since in the absence of a β-hydride required for elimination, "zirconocene" (the zirconocene source or the alkene–zirconocene complex) cannot form and reaction does not take place. Moreover, Cp_2ZrEt_2 and Cp_2ZrBu_2 (5–10 mol %) fail to catalyze the addition of MeMgCl; rapid ligand exchange leads to the immediate formation of Cp_2ZrMe_2.

(10) In analogy to the zirconium-catalyzed carboalumination of alkenes (Dzhemilev, U. M.; Ibragimov, A. G.; Zolotarev, A. P.; Muslukhov, A. R.; Tolstikov, G. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1989**, 207–208), a possible pathway may involve insertion of the alkene into i leading to the formation of ii, followed by ligand exchange to form iii. Where the reaction is quenched with H_3O^+, iii would yield the expected product. However, since the major product arises from trapping of 1 equiv of *other* electrophiles (see Tables I and II), and because <5% deuterium incorporation occurs at C2 (with 1-decene, **1a** and **1c** in Et_2O and Et_2O/THF, ^{13}C NMR analysis), such a mechanism is unlikely. Details of our mechanistic studies will be disclosed in a separate account.



Synthesis of the Core Trisaccharide of Esperamicin: Corroboration of the Proposed Structure for Its Rearrangement Product and Stabilization of the Core Trisaccharide Domain

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Received March 15, 1991

The discovery of esperamicin (**1**)[1] and calicheamicin[2] has stimulated interest at many levels.[3-6] The current perception is

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(2) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464.

(3) Synthesis: (a) Danishefsky, S. J.; Mantlo, N. B.; Yamashita, D. S.; Shulte, G. *J. Am. Chem. Soc.* **1988**, *110*, 6890. (b) Schreiber, S. L.; Kiessling, L. L. *Tetrahedron Lett.* **1989**, *30*, 433. (c) Magnus, P.; Bennett, F. *Tetrahedron Lett.* **1989**, *30*, 3637. (d) Kende, A. S.; Smith, C. A. *Tetrahedron Lett.* **1988**, *29*, 4217. (e) Magnus, P.; Lewis, R. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 6921. (f) Magnus, P.; Carter, P. A. *J. Am. Chem. Soc.* **1988**, *110*, 1626.

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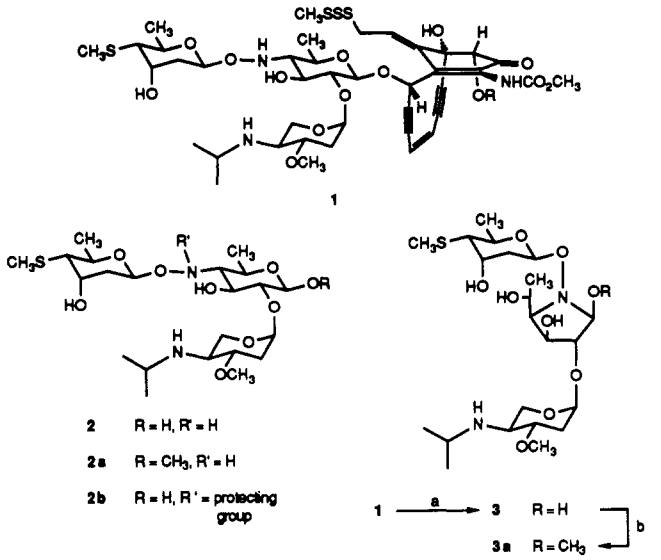
Scheme I[a]



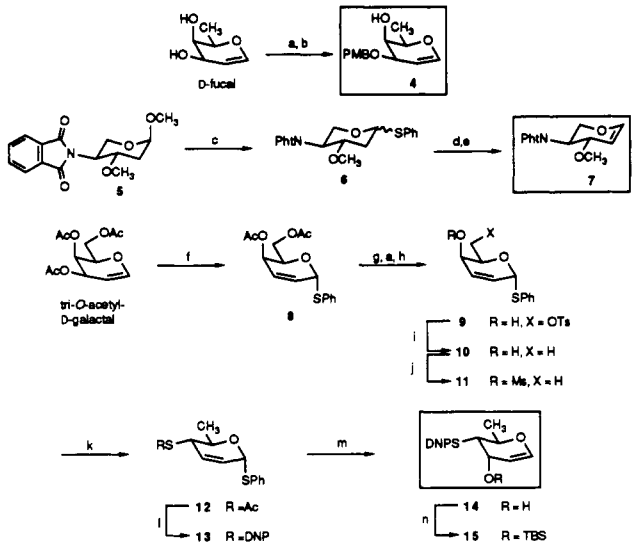
[a] (a) $NaBH_4$, MeOH; (b) MeOH, AcOH.

that the carbocyclic sector of these molecules constitutes the "effector" region for diyl generation. The carbohydrate domain apparently provides much of the sensing apparatus for achieving sequence selectivity in cutting duplex DNA.[5]

The total synthesis of these compounds represents a significant challenge to contemporary synthetic chemistry. As chemists pursue this and ancillary goals,[3-6] possibilities for dissecting the larger "complete drug" problem into components that can be evaluated individually are enhanced. The recently completed total synthesis of calicheamicinone[7] and the full carbohydrate–aromatic domain of calicheamicin[8] pave the way for major progress in this regard.

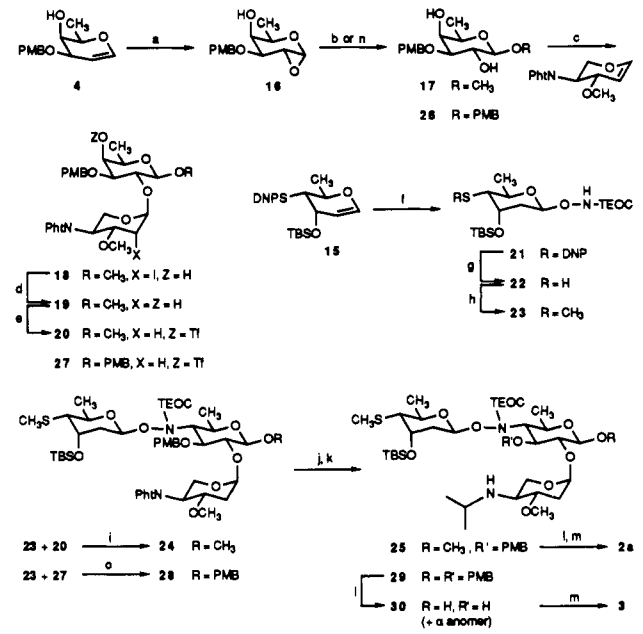
We, along with others, have been investigating the carbohydrate sector of the enediyne drugs. The Bristol-Myers group found that treatment of esperamicin with sodium borohydride led to the release of a trisaccharide, which was subsequently degraded further.[9] On the basis of spectral interpretation, the structure of the first isolated intermediate was assigned to be the rearrangement product **3** rather than the intact core system **2** (Scheme I). Upon exposure to acidic methanol, a methyl glycoside formulated as **3a** was obtained. In this communication we report

Scheme II[a]



[a] (a) Bu_2SnO, MeOH, reflux; (b) PMB-Br, CsF, DMF, 80 °C; (c) $PhSSiMe_3$, TMSOTf, CH_2Cl_2, room temperature; (d) *m*-CPBA, CH_2Cl_2, 0 °C; (e) benzene, reflux; (f) PhSH, CH_2Cl_2, $SnCl_4$, −20 °C; (g) NaOMe, MeOH; (h) TsCl, $CHCl_3$, *n*-Bu_4NBr, room temperature; (i) $LiAlH_4$, THF, reflux; (j) MsCl, CH_2Cl_2, Et_3N, 0 °C; (k) KSAc, DMF, room temperature; (l) (i) $LiAlH_4$, THF, 0 °C; (ii) DNP-F, room temperature; (m) (i) *m*-CPBA, CH_2Cl_2, −40 °C; (ii) Et_2NH, THF, room temperature; (n) TBSOTf, pyridine, CH_2Cl_2, 0 °C.

Scheme III[a]



[a] (a) 2,2-Dimethyldioxirane, CH_2Cl_2, acetone, 0 °C; (b) MeOH, room temperature; (c) **7**, $I^+ClO_4^-$(*sym*-collidine)$_2$, CH_2Cl_2, −48 °C → room temperature; (d) Ph_3SnH, AIBN, benzene, reflux; (e) Tf_2O, pyridine, CH_2Cl_2, 0 °C; (f) TEOC-NHOH, Ph_3P·HBr, CH_2Cl_2, room temperature; (g) EtSH, K_2CO_3, MeOH, room temperature; (h) MeI, DBU, benzene, room temperature; (i) (i) **23**, NaH, DMF, room temperature; (ii) **20**, DMF, 0 °C; (j) N_2H_4, EtOH, reflux; (k) acetone, $NaCNBH_3$, *i*-PrOH, $MgSO_4$, room temperature; (l) DDQ, CH_2Cl_2/H_2O, room temperature; (m) TBAF, THF, 0 °C → room temperature; (n) PMB-OH, room temperature; (o) (i) **23**, NaH, DMF, room temperature; (ii) **27**, DMF, 0 °C.

(i) a confirmation by total synthesis of the structures of **3** and **3a**, (ii) the first total synthesis of the fully deprotected glycoside of **2** (see **2a**), and (iii) the first synthesis of a core carbohydrate system in this series which contains a free "reducing sugar" terminus (generally depicted as compound **2b**). This is achieved by

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(7) (a) Cabal, M. P.; Coleman, R. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 3253. (b) For a study of the DNA cleaving properties of calicheamicinone, see: Drak, J.; Iwasawa, N.; Crothers, D. M.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. U.S.A.*, in press.

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(9) Golik, J.; Wong, H.; Krishnan, B.; Vyas, D. M.; Doyle, T. W. *Tetrahedron Lett.* **1991**, *32*, 1851. Cf.: Paulsen, H.; Todt, K. *Adv. Carbohydr. Chem. Biochem.* **1968**, *23*, 116.

a suitable protection of the hydroxylamino moiety. The constructions reported below illustrate the significant savings in protecting-group manipulations which arose from the use of glycals.[10] We first describe the preparation of our three glycal building blocks **4**, **7**, and **15** (Scheme II).[11]

Glycal **4**[12] was readily obtained in 73% yield from D-(+)-fucal[13] by stannylation and selective alkylation[14] with *p*-methoxybenzyl bromide (PMB-Br). Glycal **7** arose from the previously described methyl glycoside **5**,[15] which upon treatment with (phenylthio)-trimethylsilane (TMSOTf)[16] afforded thiophenyl anomers **6**. Oxidation of the latter with *m*-CPBA followed by thermolysis of the resultant sulfoxides[17] afforded **7**[12] (35% overall).

The construction of glycal **15** started with **8**,[11,12,18a] which is the product of Ferrier rearrangement[18b] of tri-*O*-acetyl-D-galactal with thiophenol (96%). Cleavage of the two acetyl functions was followed by selective tosylation at O-6 in 86% yield via stannylene methodology.[14] Reduction of **9**[12] with lithium aluminum hydride provided **10**[12,19] (91%), which was then converted to the mesylate **11**.[12] Reaction of the latter with potassium thioacetate in DMF provided **12**[12] (95% for two steps). Reductive deprotection of **12** with LAH followed by arylation of the resultant thiolate with Sanger's reagent (2,4-dinitrofluorobenzene, DNP-F)[20] afforded **13**[12] (89%). The anomeric sulfoxide derived from **13** was treated with diethylamine at room temperature[11,21] to effect [2,3] sigmatropic rearrangement, providing **14**[12] (76%), which was silylated to give **15**.[12]

The trisaccharide core was assembled from the three glycal building blocks as follows (Scheme III). Treatment of **4** with 2,2-dimethyldioxirane,[10a] followed by methanolysis of the resultant epoxide **16**, gave **17**[12] (68%) as well as 8% of its α methyl glycoside (not shown here). Reaction of **17** with glycal **7** in the presence of $I^+ClO_4^-(sym\text{-collidine})_2$[10b,22] afforded a 49% yield of disaccharide **18**,[12,23] which was deiodinated in 84% yield by using triphenyltin hydride. Treatment of **19**[12] with triflic anhydride in pyridine produced coupling partner **20**.

Treatment of glycal **15** with $Me_3SiCH_2CH_2OC(O)NHOH$ (TEOC-NHOH)[24] in the presence of catalytic triphenylphosphine hydrobromide[25] gave a 57% yield of the urethane **21**.[12,26] The C-4 thiol function was liberated through the action of ethanethiol/K_2CO_3, and the thiol **22** was subsequently methylated. Coupling partner **23**[12] was thus available in 87% yield. The coupling of **23** with **20** was achieved in DMF at 0 °C after prior deprotonation of the former with sodium hydride (according to the protocol of Kahne[27]). Trisaccharide **24**[12] was obtained in 78% yield.

Hydrazinolysis of **24** liberated the C-4′ primary amine which, upon Borch reaction with acetone,[28] afforded **25**[12] (85% over two steps). The PMB group was smoothly cleaved (99%) with DDQ. Finally, the fully deprotected methyl glycoside **2a**[12] was obtained (92%) by simultaneous removal of the TBS and TEOC protecting groups with TBAF.[24b]

We then focused on entering the rearranged trisaccharide series, **3**. Epoxide **16** was treated with *p*-methoxybenzyl alcohol[11a] to provide **26**[12] as a 1.5:1 mixture of β:α anomers (α anomer not shown here).[29] The triflate **27** was obtained by using exactly the same chemistry as in the synthesis of **20**, with very similar yields for each transformation. Coupling of this compound to the previously described **23** afforded **28**[12] and, after the hydrazinolysis–reductive isopropylation sequence,[28] the bis-PMB protected trisaccharide **29**.[12]

Deprotection of both PMB groups afforded **30**[12] (1:1 mixture of inseparable α and β anomers), which is the first nonrearranged trisaccharide in the calicheamicin–esperamicin series terminating in a reducing sugar. Treatment of **30** with TBAF generated the rearranged trisaccharide **3**, whose NMR spectrum was essentially identical with that of an authentic sample. A further comparison was achieved by treatment of **3** with methanol/acetic acid, whereupon the methyl glycoside **3a** was obtained (Scheme I). The high-field NMR spectrum of fully synthetic **3a** is identical with that of the same material arising from degradation of esperamicin. We believe that the rearrangement of the thus far hypothetical **2**, to **3**, is occurring under the conditions of the TBAF deprotection.

In summary, these studies reveal a direct route to the novel trisaccharide of esperamicin. They also identify the ease of rearrangement of **2** → **3** when the nitrogen of the hydroxylamino spacer is free. They demonstrate that the TEOC functionality provides suitable protection of this group to prevent rearrangement, and that only when the reducing terminus is contained in a suitable glycosidic linkage can the TEOC group be cleaved without provoking rearrangement. These studies serve to chart possible directions for attachment of these critical carbohydrate sectors to effector molecules of interest.

Acknowledgment. We thank Professor Daniel Kahne and his research group of Princeton University for providing us with valuable information on the use of urethane anions for coupling reactions. This research was supported by PHS Grant CA28824. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE7916210. An NIH postdoctoral fellowship to M.D.W. (Grant 1F32CA08641-01), an American Chemical Society Organic Division fellowship (sponsored by the Monsanto Corporation) to R.L.H., and a Department of Education fellowship to S.H.O. are gratefully acknowledged.

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(12) All new compounds were characterized by NMR and IR spectroscopy, HRMS, and optical rotation.

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(19) Treatment of di-*O*-acetyl-D-fucal with thiophenol and a variety of Lewis acids failed to give synthetically useful yields of the corresponding pseudoglycal. Therefore, the Ferrier rearrangement was conducted on tri-*O*-acetyl-D-galactal with subsequent deoxygenation of C-6.

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(23) Also produced were 6% of the O-4 glycosylated and 19% of the bis-glycosylated compounds.

(24) [2-(Trimethylsilyl)ethoxy]carbonyl chloride was prepared by following the procedure of Harris and Wilson[24a] for synthesizing *t*-BocNHOH: a solution of hydroxylamine hydrochloride in 50 mL of 1:1 H_2O/dioxane was adjusted to pH 11 with 0.1 N NaOH. TEOC-Cl[24b] was added, and the mixture was stirred for 12 h, readjusted to pH 11 with 0.1 N NaOH, and extracted with EtOAc to provide TEOC-NHOH. (a) Harris, R. B.; Wilson, I. B. *Tetrahedron Lett.* **1983**, *24*, 231. (b) Shute, R. E.; Rich, D. H. *Synthesis* **1987**, 346.

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