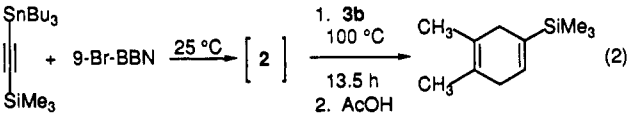
A variety of dienes (**3a–e**) reacted smoothly with **2** at 100 °C (Scheme I). As is normal for acetylenic dienophiles, **2** was less reactive than the corresponding vinylborane, but the formation of Diels–Alder adducts (**4a–e**) was clean and quantitative by NMR. Workup of **4** with acetic acid afforded cyclohexadienes **5** (contaminated by 2–10% of aromatized **6**) in excellent yield. The regiochemistry of these reactions was readily determined after the DDQ- or chloranil-mediated conversion of **5** to **6**. The difficulties associated with the isolation and manipulation of the air-sensitive **2**·THF may be avoided by forming **2** in situ (eq 2).[8] The formation of **2** from 9-bromo-9-BBN



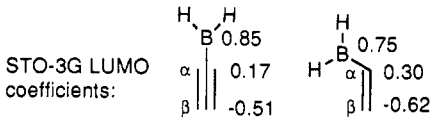
(2)

7 **5b** (89%)

and [(trimethylsilyl)ethynyl]tributyltin[9] (**7**) appeared by NMR to be instantaneous and quantitative at 25 °C. The absence of the weakly complexing THF made little difference in the reactivity of **2**; the reaction of **3b** with **2** formed in situ proceeded at 100 °C, as with **2**·THF, to afford **5b** in 89% yield after an acetic acid workup.

The unusual regiochemistry of these reactions is apparent. 2-(*tert*-Butyldimethylsiloxy)butadiene (**3c**) afforded the adduct **4c**, with a meta orientation of siloxy and BBN groups,[10] as the only observable regioisomer. With isoprene, the meta adduct **4d** was preferentially formed over the para adduct **4d'**. If this preference for the meta products (**4c** and **4d**) was due to some unknown steric factor, enhanced formation of the meta product would be expected with 2-*tert*-butylbutadiene. Instead, a majority of the para product (**4e'**) was formed with 2-*tert*-butylbutadiene, indicating that sterics favor the para product while electronic effects favor the meta product. Thus, the regiochemistry of the reactions of **2** is consistent with the ab initio prediction.

This regiochemistry is difficult to explain in any other way. The "normal" regiochemistry of Diels–Alder reactions has most popularly been rationalized either by FMO[11] theory or by postulating a *biradicaloid*[12] transition state. Because boranes are powerful radical-stabilizing groups,[13] the observed regiochemistry with **2** would not be expected of a biradicaloid transition state. If only the LUMO



coefficients in the reacting π bond of ethynylborane are considered, FMO theory also predicts the regiochemistry incorrectly. However, the regiochemistry is predictable from FMO theory based on the large LUMO coefficient on boron, once it is recognized that the boron is not an "innocent bystander" in these reactions. The advanced bonding of C_1 and B in **1** may be understood as the normal preferential bonding with the atom of the dienophile having the largest LUMO coefficient. In contrast, the LUMO of vinylborane is more evenly distributed between B and C_β, and low regioselectivity is observed in the absence of steric effects.

From a synthetic standpoint, products such as **4c** should be extremely versatile building blocks for further synthetic elaboration. Diels–Alder reactions of ethynylboranes should find broad use in organic synthesis, and we are continuing to explore both their synthetic utility and their intriguing physical organic properties.

Acknowledgment. We thank the Institute of General Medical Sciences of the National Institutes of Health and The Robert A. Welch Foundation for support of this research.

Supplementary Material Available: Experimental procedures and spectral data for all reactions, and the final geometry and energy of **1** (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(8) For a similar procedure for vinylboranes, see: Singleton, D. A.; Martinez, J. P.; Ndip, G. M. *J. Org. Chem.* In press.
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(11) For a leading reference to the application of FMO theory to the regioselectivity of Diels–Alder reactions, and a discussion of its limitations, see: Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, L. E. *J. Am. Chem. Soc.* **1986**, *108*, 7381.
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Generation and Use of a Zinc Derivative of a Functionalized 1,3-Oxazole. Solution of the Virginiamycin/Madumycin Oxazole Problem

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Summary: 2-(Bromomethyl)-4-carbethoxy-1,3-oxazole reacts with Zn dust to give a new heteroaromatic "benzylic" organozinc derivative which undergoes nucleophilic addition to a variety of aldehydes and ketones; application to the synthesis of virginiamycin and other streptogramin antibiotics is envisioned.

Efforts in our laboratory have been aimed at the synthesis of members of the type A family of streptogramin

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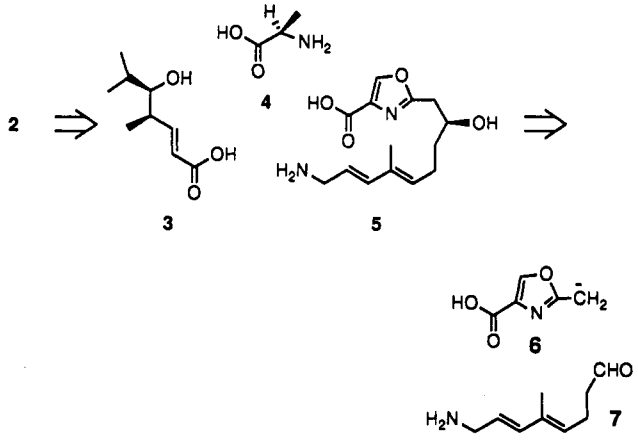
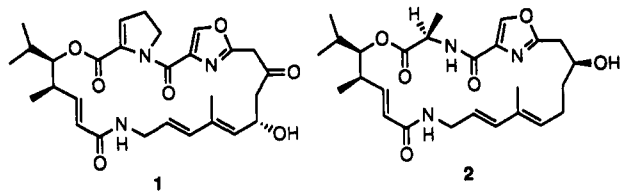
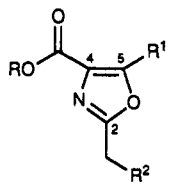
Scheme I



antibiotics.[1] These antibiotics, which include virginiamycin M_1 (VM_1, 1), A15104 (2), and the closely related madumycins, are among the most widely used antibiotics in the world. In addition to their use as animal growth promotors, they have a number of therapeutic applications.[2]



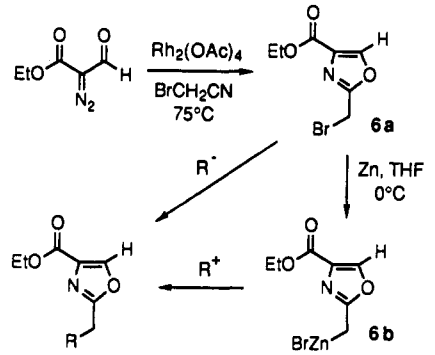
A retrosynthetic analysis of 2 shows three main fragments: a 5-hydroxy-2-alkenoic acid derivative 3, a D-alanine residue 4, and an oxazole–pentadienylamine portion 5 (Scheme I). In turn, 5 should in principle be obtainable by reaction of a suitably metalated oxazole derivative, represented by the formal carbanionic species 6, with an aldehyde corresponding to 7.



	R	R^1	R^2
6a	Et	H	Br
6b	Et	H	ZnBr
6c	alkyl	H	H
6d	alkyl	H	Li
6e	*t*-Bu	H	SO_2Ph
6f	H	TMS	H

Although this general strategy has been recognized by several investigators, the generation and use of species corresponding to 6 for this and other synthetic applications have proven to be problematical.[5-8] Meyers and co-workers[5] found that direct metalation of the 2-alkyl derivatives 6c using *n*-BuLi to give 6d was untenable, with deprotonation instead occurring at the 5-position on the oxazole ring. This difficulty was overcome by an indirect approach using a metaled derivative of a precursor in the Cornforth oxazole synthesis followed by acid-promoted cyclization to give 4-carboalkoxyoxazoles substituted at the 2-position.[5b] Fujita et al.[4b] activated the 2-methyl position by introducing a phenylsulfonyl group (6e) before performing alkylations. The phenylsulfonyl was reductively removed afterwards. Wood and Ganem[6] blocked the 5-position with a trimethylsilyl group and used the dianion of 6f in alkylations with various electrophiles. Desilylation using CsF in methanol completed the route to give 2-functionalized 4-carboxyoxazoles. In a related vein, Lipshutz and Hungate were able to effect direct lithiation of the 2-methyl group of other 2,4,5-trisubstituted oxazoles.[7,8] In the present paper, we report a simple means of generating a metalated species corresponding to 6 which has the advantage of being more direct than previous routes in that no additional functionalization is required on the oxazole moiety followed by later removal. Also, the use of Cornforth precursors is avoided.

Scheme II



Utilizing methodology already developed in our laboratory,[3] we synthesized 2-(bromomethyl)-4-carbethoxy-1,3-oxazole (6a) from α-formyl ethyldiazoacetate and bromoacetonitrile in 65% yield (Scheme II). Our original intent was to use 6a as an electrophile with appropriate carbanionic reagents[4a] to form 5 or to permit chain extensions in general. However, we have now found that the organozinc derivative 6b, which has an *umpolung* relationship[9] to 6a, is of much more general use in chain extensions, especially through use of aldehydes as the electrophilic components.

The work of Knochel[10] and others[11] has demonstrated the wide applicability of organozinc intermediates. In particular, Knochel's work with benzylic halides[10c,e,f,g] is relevant to our studies. The bromomethyl group of oxazole

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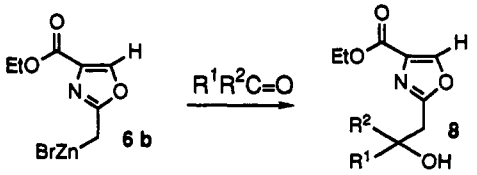
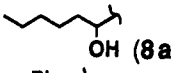
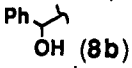
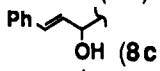
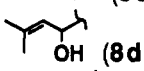
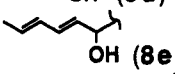
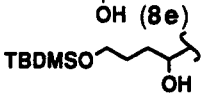
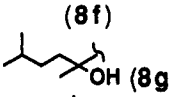
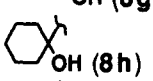
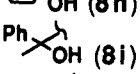
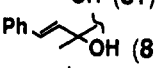
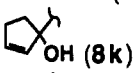
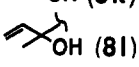
Table I. Addition of 6b to Aldehydes and Ketones



substrate	product	yield (%)
hexanal	 (8a)	92%
benzaldehyde	 (8b)	96%
PhCH=CHCHO	 (8c)	97%
$(Me)_2C$=CHCHO	 (8d)	62%
2,4-Hexadienal	 (8e)	40%
TBDMSO$(CH_2)_3$CHO	 (8f)	62%
$Me_2CH(CH_2)_2C(O)Me$	 (8g)	39%
cyclohexanone	 (8h)	49%
PhC(O)Me	 (8i)	47%
PhCH=CHC(O)Me	 (8j)	93%
cyclopentenone	 (8k)	90%
H_2C=CHC(O)Me	 (8l)	52%

6a can be considered as being heteroaromatic "benzylic". Knochel has published two examples of related "benzylic" halides[10e] (substituted furan and thiophene derivatives) which form organozinc derivatives which are then converted in situ into mixed Zn/Cu organometallics. The method presented here bypasses the need to form a mixed Zn/Cu derivative in reactions with aldehydes and ketones. Also, in Knochel's work with aldehydes as the electrophile,[10b] a Lewis acid (BF_3·OEt_2) was needed to activate the organometallic addition. However, our present route proceeds well without the need for added Lewis acids.

The range of different types of aldehydes and ketones which participate in this reaction[12] is seen in Table I. Aliphatic, aromatic, conjugated, and doubly conjugated aldehydes give fair to excellent yields of the corresponding secondary alcohols. Likewise, cyclic and acyclic (both aliphatic and conjugated) as well as aromatic ketones give the corresponding tertiary alcohols in fair to good yields. In reactions with α,β-unsaturated aldehydes and ketones, no products resulting from Michael additions are detected by ^1H NMR in the crude mixtures. Compound **8f** is particularly attractive as a possible intermediate for the synthesis of A15104 or 13-dehydroxy VM_1. The secondary alcohols **8a–8f** can be oxidized to ketones. For example, alcohol **8a** undergoes oxidation to the corresponding ketone using the Swern oxidation[13] (31% yield).

At present, acid chlorides do not react cleanly with **6b** when the organozinc is formed first and the acid chloride is added afterwards. However, the fact that a secondary alcohol β to the oxazole can be oxidized to a ketone bodes well for application of this methodology to the synthesis of streptogramin antibiotics.

In conclusion, a new heteroaromatic "benzylic" organozinc derivative has been generated and shown to react with a variety of aldehydes and ketones. Investigations are continuing using other types of electrophiles in reactions with **6b** and with other organometallic derivatives of the oxazole system. These results will be reported in due course.

Acknowledgment. We thank Dr. Tobias Rein and Nina Kann (Royal Institute, Stockholm) for many valuable discussions. A.R.G. acknowledges support received from a Fulbright Fellowship. We are also grateful for funding provided by the National Institutes of Health, the National Science Foundation (USA), and the Natural Science Research Council (Sweden).

Supplementary Material Available: Compound characterization data for **6a** and **8a–8l** (7 pages). This material is contained in many libraries on a microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(12) The simplicity of our procedure is demonstrated by the following representative example. Zinc dust (49 mg, 0.75 mmol) and THF (1 mL) under argon is cooled to 0 °C, and hexanal (55 mg, 0.55 mmol) is added, followed by the slow dropwise addition of **6a** (117 mg, 0.50 mmol) in THF (1 mL) from a 1000-μL syringe (1 drop every 10 s). The reaction is stirred at 0 °C for 2 h until TLC and GC show no **6a** remaining. The reaction is quenched with saturated aqueous NH_4Cl and extracted with ether. The organic phase is dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (40% EtOAc in hexanes) gives 104 mg (92%) of **8a** as a white solid (mp 34–36 °C). Most reactions were run only once, and the yields are not optimized.

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Synthesis of C–D–E Trisaccharide Precursors of Olivomycin A

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Summary: Syntheses of functionalized C–D–E trisaccharide precursors (**16**, **5**) of olivomycin A are reported. A stereoselective C–D β-glycosidation was accomplished by employing 2-deoxy-2-(phenylthio)-α-glucotrichloroacetimidate **8**. The α-D–E glycosidic linkage was introduced by using 2-deoxy-2-iodo-α-glycosyl acetate donor **14** as the glycosyl transfer agent.

Olivomycin A (**1**) is a member of the aureolic acid family of antitumor antibiotics which also includes mithramycin

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