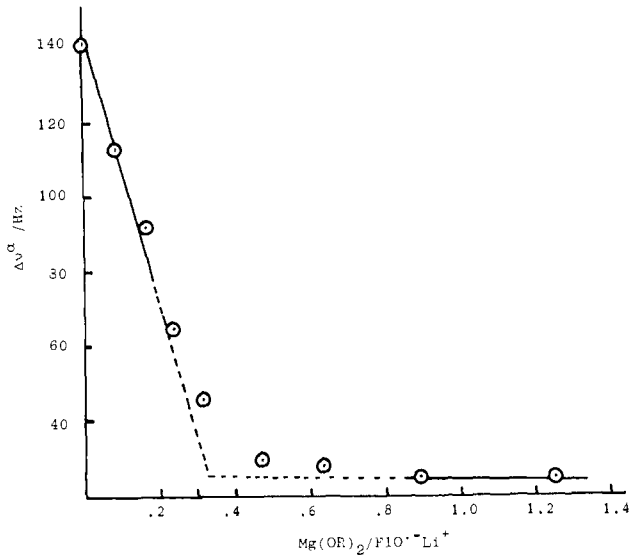

Figure 3. Magnetic titration of ca 1 M $FlO^{\bullet-}Li^+$ against 1.65 M of $Mg(OCH_2CH_2OEt)_2$ in THF (The indicated shift is referred to the α-proton band of THF.).

interaction could be estimated. The stoichiometries $(FlO^{\bullet-}M^+)/(\mathbf{2})$ for M = Li, Na, and K, respectively, were 3.00/1, 2.94/1, and 1.92/1. Again, we observe a cation-dependent stoichiometry, being 3/1 for Li^+ and Na^+ and 2/1 for K^+. If disappearance of paramagnetism takes place by a spin-pairing mechanism, then six molecules of $FlO^{\bullet-}Li^+$ and $FlO^{\bullet-}Na^+$ interact with two molecules of **2** at the stoichiometric point, whereas two of four $FlO^{\bullet-}K^+$ interact with one or two molecules of **2**, respectively. These results could indicate the existence of tetrameric and exameric paramagnetic $FlO^{\bullet-}M^+$ clusters. Hirota[8] besides identifying triple and quadruple ions[11] identified higher clusters and proposed structures for tetrameric and pentameric alkali metal fluorenone ketyls.

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A Highly Stereoselective Total Synthesis of the Natural Enantiomer of Olivin

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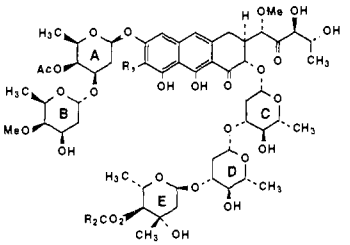
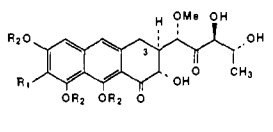
The aureolic acid antibiotics are a group of clinically effective antitumor agents.[2] As illustrated by **1** and **2** below, these compounds are structurally complex, each having a di- and a trisaccharide attached to a central aglycone, either olivin (**3**) or chromomycinone (**4**). While two syntheses of tri-*O*-methylolivin (**5**) have been reported,[3] no syntheses of the natural, *unprotected*



1, R_1 = H; R_2 = iPr olivomycin A
2, R_1 = R_2 = Me chromomycin A_3



3, R_1 = R_2 = H
4, R_1 = Me; R_2 = H
5, R_1 = H; R_2 = Me

aglycones have yet appeared.[4] As a continuation of our work on the total synthesis of olivomycin A (**1**),[5] we have completed and are pleased to report here the first total synthesis of olivin in the naturally occurring enantiomeric form.

The synthesis (see Scheme I) commenced with the reaction of threonine-derived aldehyde **6**[5a] with in situ generated[6] dimethyl (*Z*)-γ-methoxyallylboronate [prepared from 2.2 equiv of methyl allyl ether, 2.2 equiv of *n*-BuLi–TMEDA, and 2.2 equiv of $FB(OMe)_2$] that provided **7**, mp 61–62 °C, in 75–83% yield following chromatographic purification. After protection of **7** as the TBDMS ether, the vinyl unit was cleaved by ozonolysis, and the resulting aldehyde condensed with 1.2 equiv of $Ph_3P{=}CHCHO$ in benzene at reflux (5 h) to give unsaturated aldehyde **8** in 55% yield after one recycle of recovered saturated aldehyde.[8] The critical C(3) stereocenter of **3** was next introduced with very high stereoselection (>20:1) and in excellent yield by treatment of **8** with $(CH_2{=}CH)_2CuLi$ in an ether–THF mixture containing TMS-Cl.[5b,9,10] It is notable that use of the corresponding unsaturated ester as in our original studies[5b] gave highly variable yields and that very poor results were obtained on attempted scale up. By comparison, the conversion of **8** to **9** has proven to be highly reproducible, and multigram quantities of **9** are easily prepared in this way.

With a highly selective and efficient solution to the major stereochemical problems well in hand, we turned our attention to the construction of the anthracenone nucleus of **3**. Naphthoate

(1) Current address: Indiana University.
(2) For reviews, see: (a) Remers, W. A. *The Chemistry of Antitumor Antibiotics*; Wiley-Interscience: New York, 1979; Chapter 3. (b) Skarbeck, J. D.; Speedie, M. K. *Antitumor Compound Natural Origin: Chemistry and Biochemistry*; Aszalos, A., Ed.; CRC Press: 1981; Chapter 5.
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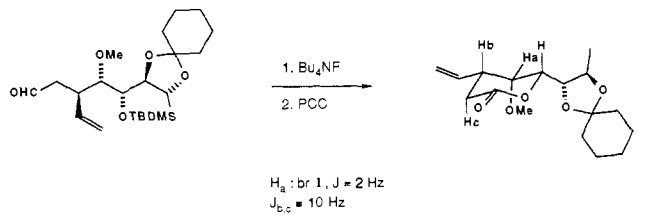
(7) The spectroscopic properties of all new compounds are fully consistent with the assigned structures.
(8) This reaction also produced substantial quantities (6–25%, depending on reaction conditions and stoichiometry) of the corresponding diene aldehyde. For large scale work, therefore, it was preferable to perform the RCHO to RCH=CHCHO conversion by a three-step operation: (i) Ph_3PCHCO_2Me, CH_2Cl_2, 23 °C; (ii) DIBAL-H, Et_2O, −78 °C; (iii) PCC, CH_2Cl_2. The overall yield of **8**, a 4:1 mixture of *E*–*Z* isomers, from **7** was 55–60%. The presence of (*Z*)-**8** did not noticeably influence the stereoselectivity of the subsequent cuprate reaction.
(9) The yield is 75% if TMS-Cl is omitted. For other studies on the use of TMS-Cl in organocuprate conjugate additions, see: (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015, 6019. (b) Alexakis, A.; Berlan, J.; Besace, Y. *Ibid.* **1986**, *27*, 1047. (c) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Ibid.* **1986**, *27*, 4025. (d) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Ibid.* **1986**, *27*, 4029.
(10) The stereochemistry of the vinylcuprate addition was established as shown below. The stereochemical outcome is identical with that reported previously for reactions of the corresponding enones and unsaturated esters (ref 5b). For other examples of high diastereoface selectivity in organocuprate conjugate additions, see: Bernardi, A.; Cardani, S.; Poli, G.; Scolastico, C. *J. Org. Chem.* **1986**, *51*, 5041.



H_a: br 1, J = 2 Hz
$J_{b,c}$ = 10 Hz

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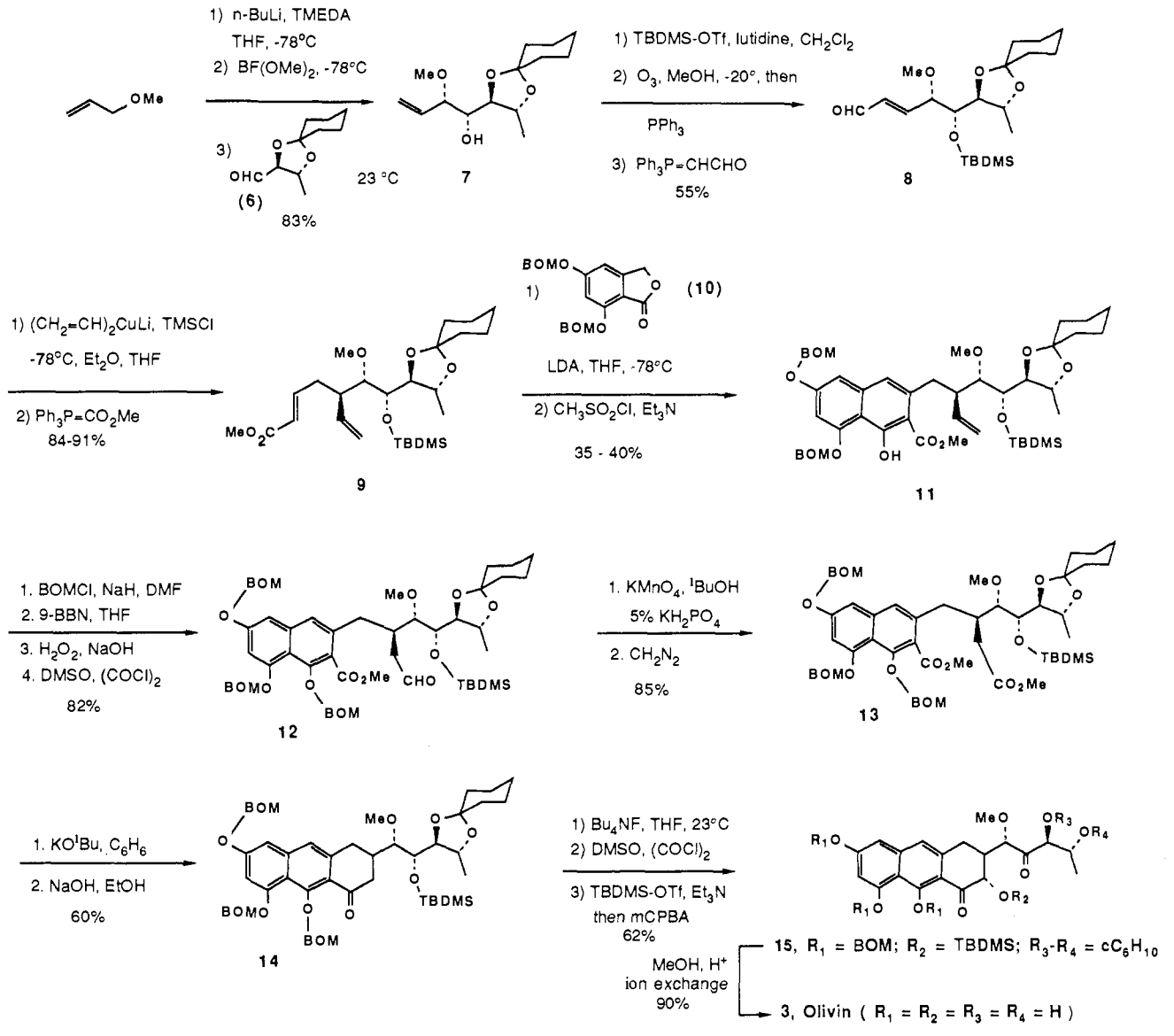
Scheme I



derivative **11** was prepared in 35–40% yield by coupling **9** and **10**[11] via modifications of Sammes' procedure.[12] Also obtained was 10–15% of the corresponding phenolic mesylate. The free -OH of **11** was protected as a BOM ether, and then the vinyl appendage was oxidized via aldehyde **12** to diester **13**. Of the numerous oxidation procedures examined, only Masamune's recently introduced method was suitable for the efficient oxidation of **12** (85%).[13] The final C–C bond of **3** was then established by treatment of **13** with excess of KO-*t*-Bu in C_6H_6 at 23 °C. Subsequent exposure to 0.4 M NaOH in aqueous EtOH at reflux effected decarbomethoxylation, thereby providing anthracenone **14** in 60% yield.

The side chain TBDMS ether was next cleaved by treatment with Bu_4NF in THF (93%), and the resulting hydroxyl group was oxidized to the C(2′) ketone via a standard Swern procedure (90%).[14] Selective conversion of the C(1) carbonyl to the corresponding TBDMS enol ether was smoothly accomplished according to Mander's method,[15] and as reported previously by Franck,[3b] thus setting the stage for the oxidative conversion to **15** by using Na_2HPO_4 buffered MCPBA (76%). The success of this last step was dependent on the purity of the TBDMS enol ether, and it proved necessary to filter this intermediate through silica gel before exposure to MCPBA. Finally, all five protecting groups in **15** were removed by treatment with Dowex 50W-X8 H^+ resin in MeOH at 23 °C for 5–6 days. Direct crystallization of the crude reaction product from ether–hexane provided synthetic olivin (mp 139–141 °C, $[\alpha]^{23}_D$ +53° (*c* 0.04, EtOH)) in 90% yield. Synthetic **3** so obtained was identical by all the usual criteria with an authentic sample (mp 137–139 °C, $[\alpha]^{23}_D$ +56° (*c* 0.05, EtOH)) prepared by acidic methanolysis of olivomycin A.[16]

In summary, a highly stereoselective synthesis of olivin has been accomplished. Efforts to complete a total synthesis of olivomycin A are in progress and will be reported in due course.

Acknowledgment. This research was supported by the National Institutes of Health (Grants CA 29847 and AI 20779). We are

(11) Phthalide **10**, mp 82–83 °C, was prepared by a four-step sequence in 50% overall yield starting from methyl 3,5-dihydroxybenzoate: (i) $BzlOCH_2Cl$, NaH, DMF; (ii) $LiAlH_4$, THF; (iii) NBS, $CHCl_3$, reflux; (iv) *n*-BuLi (1.0 equiv) then *sec*-BuLi (1.0 equiv), THF, −78 °C, 10 min; then CO_2 quench followed by an acidic aqueous workup. For related syntheses of the dimethyl ether, see: (a) Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Link, J. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 6885. (b) Noire, P. D.; Franck, R. W. *Synthesis* **1980**, 882.

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grateful to Professor R. W. Franck for a gift of natural olivomycin A used in the preparation of a reference sample of olivin.

Supplementary Material Available: Spectroscopic data and physical constants for all synthetic intermediates (5 pages). Ordering information is given on any current masthead page.

Tetrahydrofurans via Isoxazoline: A Tandem 1,3-Dipolar Cycloaddition/Electrophilic Cyclization Sequence

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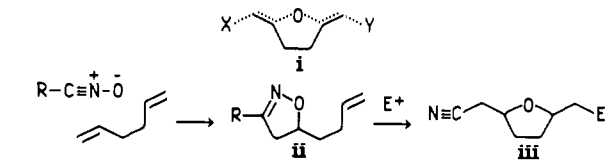
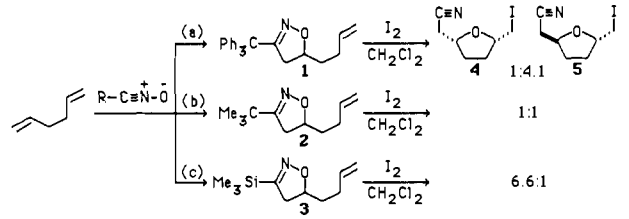
Development of methodology for the stereocontrolled synthesis of tetrahydrofuran containing natural products (e.g., polyether antibiotics) continues to receive significant attention.[2] Of the numerous strategies for tetrahydrofuran construction,[3] bis addition of an oxygen nucleophile across a 1,5-diene moiety (i) (Scheme I) represents a particularly attractive approach. Noteworthy examples of this strategy include potassium permanganate promoted oxidative cyclizations of 1,5-dienes[4] and epoxidation/oligoepoxide cascade cyclizations from 1,5-dienes.[5] We reasoned that exposing 1,5-hexadiene to a tandem 1,3-dipolar cycloaddition[6]/electrophilic cyclization sequence would furnish 1,5-disubstituted tetrahydrofuran **iii** via the intermediacy of isoxazoline **ii**. To our knowledge, there are no reports of an isoxazoline moiety participating in electrophilic cyclization reactions. Clearly, the nature of R is important in this strategy, and, based on the assumption that cation stabilizing R groups would favor the **2** → **3** transformation, the first substrates investigated were those with R = triphenylmethyl and *tert*-butyl.

Cycloaddition of 1,5-hexadiene (5 equiv) and triphenylacetonitrile oxide (prepared from triphenylmethyl chloride and silver fulminate)[7] furnished isoxazoline **1** in quantitative yield (Scheme II). As hoped, treating this heterocycle with iodine resulted in electrophilic cyclization giving tetrahydrofurans **4** and **5** in a 1:4.1 ratio (capillary GLC)[8] in 60% isolated yield. Apparently the triphenylmethyl moiety in **1** is initially lost as a triphenylcarbenium ion giving triphenylmethyl iodide which on aqueous workup undergoes solvolysis giving triphenylmethanol. Cis/trans stereochemical assignments for **4** and **5** were made in analogy with known 2,5-disubstituted tetrahydrofurans[9] on the basis of ^{1}H data for the corresponding deiodinated derivatives[10] (prepared by tributyltin hydride reduction).[11]

Scheme I



Scheme II



(a) benzene, 25°C; (b) ^{t}Bu-C(Cl)=N-OH, Et_3N, Et_2O; (c) $Hg(CNO)_2$, Me_3SiBr, benzene

Scheme III

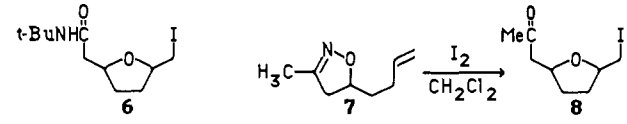
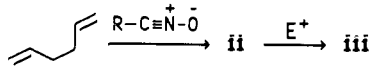


Table I. Electrophilic Cyclization of Isoxazoline **ii**



electrophile	R = ( )[a]	cis/trans[b]	yield (iiii, %)[c]
Br_2	Ph_3C-(**1**)	1:2.8	66
PhSeBr	Ph_3C-(**1**)		*d*
PhSeBr	Me_3Si-(**3**)	5.7:1	40
I_2	MeCH($OSiMe_3$)-(**9**)	1:1.4	59
I_2	*i*-PrCH($OSiMe_3$)-(**10**)	1:1.6	55

[a] Isoxazoline compound number. [b] Ratios determined by capillary GLC analysis of the crude reaction mixture. [c] Isolated, purified yields of **iii** from 1,5-hexadiene. [d] No tetrahydrofuran products were obtained.

Employing dimethylpropionitrile oxide (generated in situ from the hydroximic acid chloride with triethylamine)[12] gave isoxazoline **2** (70%) which, upon treatment with iodine, underwent electrophilic cyclization with concomitant loss of the *tert*-butyl moiety, again giving the anticipated tetrahydrofurans **4** and **5** (59% isolated yield). However, **2** also gave tetrahydrofuran **6**, a Beckmann rearrangement product, in 22% isolated yield (Scheme III). The fact that **1** gives no Beckmann rearrangement product while **2** does appears to reflect the ability of -R to serve as a stabilized cation source (ii → iii). Interestingly, treating a CH_2Cl_2 solution of isoxazoline **7** with iodine resulted in formation of ketone **8** (50%; 1:1 cis/trans): none of the corresponding nitrile or amide products were detected.

The next substrate investigated was (3-trimethylsilyl)isoxazoline **3**, prepared in a one-pot process by cycloaddition of 1,5-hexadiene (5 equiv) and trimethylsilylcarbonitrile oxide (generated in situ from trimethylsilyl bromide and mercury fulminate).[13] Upon treatment with iodine, **3** underwent electrophilic cyclization, again furnishing **4** and **5** but this time with cis selectivity (cis/trans, 6.6:1; 40% isolated yield). This intriguing reversal in product selectivity is clearly a function of the R group in ii, yet each electrophilic cyclization (**1**/**2**/**3** → **4** + **5**) is certainly a kinetic process.

(1) Recipient of an Alfred P. Sloan Research Fellowship, 1987–1989.

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(10) In analogy with literature data,[9] stereochemical assignments for the cis and trans isomers of 2-(cyanomethyl)-5-methyltetrahydrofuran were made on the basis of C_5-CH_3 chemical shifts (the $-CH_3$ doublet for the trans isomer resonating at higher field:[9c] cis at δ 1.28 and trans at δ 1.24).

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