carbon bond formation, these nucleophiles led to the introduction of carbonyl, alkene, allene, and cyano functional groups, as well as heterocyclic rings. The formation of the allylic azide **12** illustrates the possibility of carbon–heteroatom bond formation.

Experimental evidence suggests that these reactions proceed by ionization to an allylic carbocation.[6] For example, regioisomeric allylic alcohols **3** and **14** gave the same product **2**, the result of attack of the nucleophile at the least substituted end of a common intermediate carbocation. Grieco has also obtained evidence for a carbocation intermediate in his work with allyl vinyl ethers.[4] Although most of the examples in Table I involve trialkyl allylic or aryldialkyl allylic substrates which may give particularly well-stabilized allylic carbocations, less substituted examples are also successful, e.g., **19**, **23**, and **25**.

The lithium perchlorate-promoted substitution reaction allows convenient access to γ,δ-unsaturated esters, ketones, and aldehydes, 1,5-dienes, 1,2,5-trienes, allylated heterocycles, allylic azides, and allylic nitriles. The mild conditions, simplicity, and efficiency of this method for carbon–carbon bond formation make it an attractive alternative to transition metal-catalyzed processes.[7] The ability to employ allylic alcohols directly (e.g., **3**, **14**, and **17**) is also significant, since it obviates the acetylation step. A full account of this work will outline the scope and stereochemistry of this process.

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(6) (a) Winstein, S.; Smith, S.; Darwish, D. *J. Am. Chem. Soc.* **1959**, *81*, 5511. (b) Pocker, Y.; Buchholz, R. F. *J. Am. Chem. Soc.* **1970**, *92*, 2075.

(7) The following procedure for the preparation of compound **2** is typical. Commercial lithium perchlorate (Aldrich Chemical Co.) was used without drying or further purification, since doing so led to no significant improvement in yields or reaction rates. To a solution of the acetate **1** (139 mg, 0.534 mmol) in ether (2 mL) was added 1-[(*tert*-butyldimethylsilyl)oxy]-1-ethoxyethene (324 mg, 1.60 mmol). The mixture was cooled to 0 °C and lithium perchlorate (636 mg, 6.00 mmol) was added. After the mixture was stirred for 1 h, water (10 mL) was added and the layers were separated. The water layer was extracted with ether (3 × 25 mL), and the combined organics were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. Chromatography ($SiO_2$, 5% EtOAc/hex) gave 140 mg (92%) of the ester **2** as a clear, colorless oil, $R_f$ = 0.47 (25% EtOAc/hex): $^1H$ NMR ($CDCl_3$, 300 MHz) δ 6.88 (s, 1 H), 6.84 (d, $J$ = 8.1 Hz, 1 H), 6.74 (d, $J$ = 8.1 Hz, 1 H), 5.93 (s, 2 H), 5.84 (s, 1 H), 4.16 (q, $J$ = 7.2 Hz, 2 H), 2.75 (m, 1 H), 2.35 (m, 4 H), 1.88 (m, 2 H), 1.69 (m, 1 H), 1.31 (m, 1 H), 1.27 (t, $J$ = 7.2 Hz, 3 H); $^{13}C$ NMR ($CDCl_3$, 75 MHz, JMOD) δ 172.85 (–), 147.61 (–), 137.12 (–), 136.68 (–), 126.52 (+), 118.43 (+), 107.87 (+), 105.86 (+), 100.85 (–), 60.23 (–), 40.95 (–), 32.99 (+), 28.44 (–), 27.70 (–), 21.57 (–), 14.29 (+); IR (neat) 1731, 1606, 1504, 1487, 1444, 1371, 1278, 1244, 1219, 1176 $cm^{-1}$; MS (EI, 70 eV) $m/z$ (rel int) 288 ($M^+$, 17.9), 214 (14.6), 201 (100.0), 135 (43.4) 115 (11.2), 79 (18.4); HRMS calcd for $C_{17}H_{20}O_4$ 248.1362, found 288.1369. Anal. Calcd for $C_{17}H_{20}C_4$: C, 70.81; H, 6.99. Found: C, 70.88; H, 6.91. Compound **2** has also been prepared on a larger scale from allylic alcohol **14**. Thus, **14** (6.44 g, 0.030 mmol), 1-[(*tert*-butyldimethylsilyl)oxy]-1-ethoxyethene (11.87 g, 0.060 mol), and lithium perchlorate (19.0 g, 0.179 mol) were combined for 1.5 h as reported above to yield 7.31 g (86%) of ester **2** after chromatography.

## An Enantioselective Synthesis of the Spirotetronate Subunit of Kijanolide

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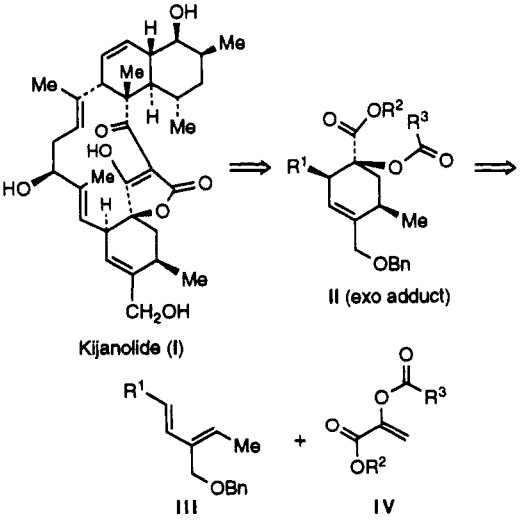
*Summary:* The Diels–Alder adduct **11** of α-bromoacrolein and triene **9** was converted to spirotetronate **21** through a sequence involving Pummerer rearrangement of the derived sulfoxide **16**, oxidation of the resulting aldehyde **17**, and Dieckmann cyclization of the diester **19** followed by in situ quench with MOMCl.

The spirotetronate subunit of kijanolide (**I**), the aglycon of the novel antitumor antibiotic kijanimicin,[1] has elicited significant synthetic activity in recent years.[2] Several routes to racemic equivalents of this subunit have been reported but to date no enantioselective synthesis has been achieved.[3] We have expended considerable effort on the design of α-acyloxy acrylic esters **IV** possessing chiral




(1) Mallams, A. K.; Puar, M. S.; Rossman, R. R.; McPhail, A. T.; Macfarlane, R. D.; Stephens, R. L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1497.

(2) (a) Roush, W. R.; Brown, B. B. *Tetrahedron Lett.* **1989**, *30*, 7309. (b) Okumura, K.; Okazaki, K.; Takeda, K.; Yoshii, E. *Tetrahedron Lett.* **1989**, *30*, 2233. (c) Takeda, K.; Yano, S.; Sato, M.; Yoshii, E. *J. Org. Chem.* **1987**, *52*, 4135. (d) Takeda, K.; Shibata, Y.; Sagawa, Y.; Urahata, M.; Funaki, K.; Hori, K.; Sasahara, H.; Yoshii, E. *J. Org. Chem.* **1985**, *50*, 4673. (e) Schmidt, R. R.; Hirsenkorn, R. *Tetrahedron Lett.* **1984**, *25*, 4357. (f) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041.

(3) Though not yet reported, the sequence employed by Roush,[2a] which led to a racemic analogue of **21**, could easily be used to prepare the enantioenriched modification of that analogue. In fact, we have repeated the Roush sequence with enantioenriched dienophile to obtain a comparison compound (see ref 9).

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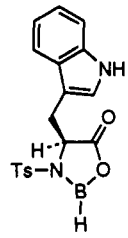
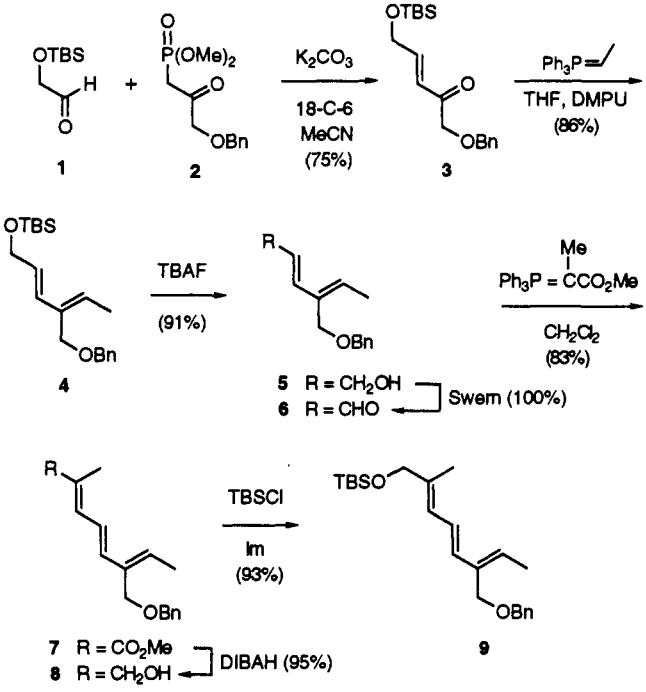
auxiliaries at $R^2$ or $R^3$ hoping to effect enantioselective Diels–Alder additions to dienes such as **III** that might lead to precursors **II** of such spirotetronates.[4] However, this approach encounters complications as a consequence of the unreactivity of such acrylates and the formation of diastereomeric exo and endo adducts.[5] Recently, Corey and Loh reported that the oxazaborolidine **V** catalyzes the



**V**

addition of α-bromoacrolein to both cyclopentadienes and isoprene to afford Diels–Alder adducts of high ee through a proposed complex in which the indole moiety associates with the acrolein through π-base/π-acid pairing.[6] These findings prompted our formulation of a strategy for the synthesis of enantioenriched spirotetronate **21** employing α-bromoacrolein as the Diels–Alder dienophile.

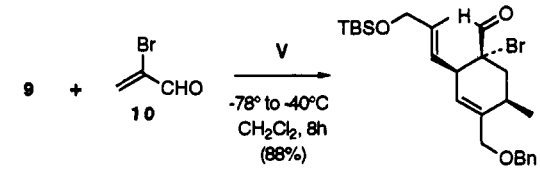
The dienic partner **9** for the approach was prepared by a straightforward route commencing with the Horner–Emmons condensation of aldehyde **1** and phosphonate **2**.




**1** **2** **3** **4** **9**

The ensuing Wittig ethylidenation was highly (*Z*) selective affording diene **4** as the sole isomer. Deprotection of the silyl ether then Swern oxidation[7] and ensuing Horner–Emmons condensation of the intermediate aldehyde **6** afforded trienoate **7** as a 94:6 mixture of geometric isomers. The derived triene **9** was obtained as a 91:9 mixture of geometric isomers.

Cycloaddition of diene **9** to α-bromoacrolein occurred smoothly but slowly in the presence of the Corey oxazaborolidine **V**. Best conditions to date require a full equivalent of the (recoverable) Lewis acid at −78 to −40 °C. Reactions at −10 °C gave product of significantly lower ee.

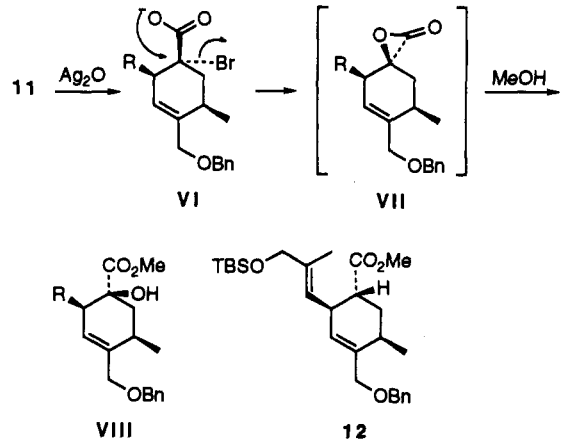



**11** (72% ee)

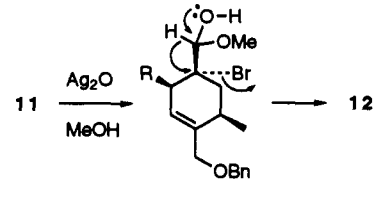
The assignment of relative configuration to adduct **11** is based on comparison of the $^1H$ NMR spectrum with those of known exo and endo analogues (OR in place of Br) reported in the literature and prepared in our laboratory.[2,4] The absolute stereochemistry is based on the mechanistic model of Corey and Loh.[6] Support for the assigned configuration and an evaluation of the ee came from $^1H$ NMR analysis of the *O*-methyl mandelates[8] of the derived alcohol **13**.[9]

It is noteworthy that under Corey–Loh catalysis the addition of α-bromoacrolein to 1,3-cyclopentadienes gives mainly the exo products.[6] With diene **9** the endo product **11** is formed exclusively.

Our initial plan for the inversion of bromo aldehyde **11** to the requisite exo diastereomer entailed a perceived oxidation with $Ag_2O$ in MeOH to the carboxylate **VI** and a hoped for solvolysis with participation to yield the hydroxy ester **VIII** via the α-lactone **VII**. In fact, treatment




of bromo aldehyde **11** with methanolic $Ag_2O$ led smoothly to a single methyl ester in high yield. However, careful analysis of the $^1H$ and $^{13}C$ NMR spectra pointed to **12** not **VIII** as the structure for this ester, an analysis corroborated by the high-resolution mass spectrum. A likely pathway for this transformation involves migration of the hemiacetal carbinyl H of **IX** to the bromine-bearing center with inversion of

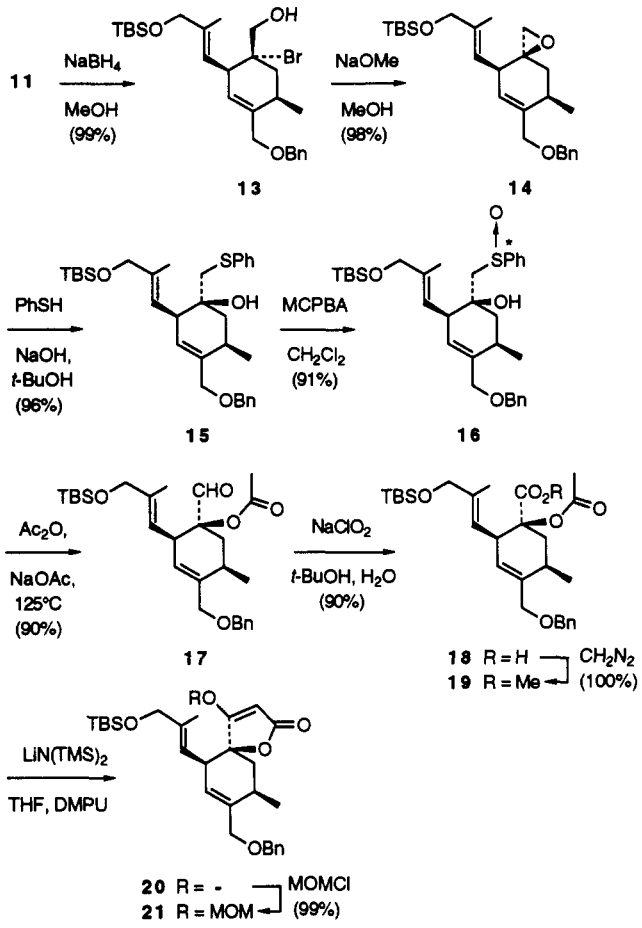



**IX**

In view of this unforeseen, but admittedly interesting, turn of events we explored an alternative inversion strategy. Accordingly, reduction of bromo aldehyde **11** with $NaBH_4$ followed by exposure to methanolic NaOMe at room temperature for 5 h gave the epoxide **14** in

(4) Unpublished studies with Shiping Xie.
(5) Cf. Creary, X.; Inocencio, P. A.; Undriner, T. L.; Kostromin, R. *J. Org. Chem.* **1985**, *50*, 1932. Mattay, J.; Mertes, J.; Maas, G. *Chem. Ber.* **1989**, *122*, 327. Takeda, K.; Igarashi, Y.; Okazaki, K.; Yoshii, E.; Yamaguchi, K. *J. Org. Chem.* **1990**, *55*, 3431.
(6) Corey, E. J.; Loh, T-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966.
(7) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

near-quantitative yield. Oxidation of the derived sulfide **15** with MCPBA afforded a separable 3:1 mixture of diastereomeric sulfoxides. Each was converted to the same acetoxy aldehyde **17** upon heating in $Ac_2O$ and NaOAc.[10]



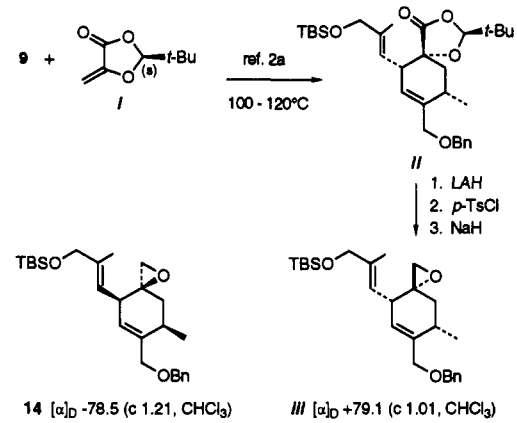

Completion of the synthesis was effected through the cyclization methodology of Ireland and Thompson, but substituting DMPU for HMPA as the cosolvent.[2f] Addition of MOMCl to the basic solution gave the spirotetronate **21**, $[\alpha]_D$-28.0(c1.70, $CHCl_3$), in 99% yield for the two steps. The $^1H$ NMR spectrum of this product was in excellent agreement with that of a close analogue (DPS in place of OBn) prepared by Roush and Brown.[2a]

**Acknowledgment.** We are indebted to Dr. Kevin Pinney for assistance with $^1H$ NMR analyses. We thank Dr. Michael Walla and Dr. William Cotham for their valuable assistance with mass spectra interpretation. Special thanks to Professor Roush for $^1H$ NMR comparisons of spirotetronates. Support for this work was provided by Research Grant CA34247 from the National Cancer Institute of the NIH.

**Supplementary Material Available:** Experimental procedures and $^1H$ NMR spectra for all key intermediates (43 pages). This material is contained in many libraries on microfiche, immediately follows this article in the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(8) For previous applications of this methodology, see: Marshall, J. A.; Welmaker, G. S.; Gung, B. W. *J. Am. Chem. Soc.* **1991**, *113*, 647. In the present case by making reasonable assumptions regarding the preferred conformation of the *O*-methyl mandelate in the relatively crowded environment of the carbinyl center, we can apply the method to the primary alcohol **13**. As a rule only secondary alcohols can be reliably assigned by this method: Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

(9) We also carried out a chemical correlation as follows:




(10) Cf. Lee, A. W.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Walker, F. J. *J. Am. Chem. Soc.* **1982**, *104*, 3515.

## Synthesis of an Oligonucleotide Suicide Substrate for DNA Methyltransferases

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*Summary:* The large-scale chemical synthesis of an oligodeoxynucleotide containing 5-fluoro-2′-deoxycytidine (FdC) and its characterization are described. The FdC residue is introduced via the corresponding 4-*O*-(2,4,6-trimethylphenyl)-2′-deoxyuridine derivative, which undergoes clean conversion to FdC during removal of the oligonucleotide protecting groups with ammonia. A double-stranded oligodeoxynucleotide containing FdC inactivated the DNA methyltransferase enzyme M.*Hae* III by irreversible formation of a covalent protein–DNA complex.

DNA (cytosine-5)-methyltransferases (DCMtases) catalyze the methylation of DNA by the cofactor *S*-adenosyl-L-methionine (SAM). This reaction has aroused widespread interest not only for its profound effects on genomic structure and function[1] but also for its unusual character, involving electrophilic substitution at a formally unactivated vinyl carbon in neutral aqueous solution (Figure 1, X = H). DCMtase-catalyzed methylations are believed to involve the intermediacy of a covalent pro-

(1) For general references on enzymatic DNA methylation, see: Razin, A., Cedar, H., Riggs, A. D., Eds. *DNA Methylation: Biochemistry and Biological Significance*; Springer-Verlag: Berlin, 1984. Adams, R. L. P.; Burdon, R. H. *Molecular Biology of DNA Methylation*; Springer-Verlag: New York, 1985.

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