fact that they generally exhibit high levels of diastereoface selectivity (90–94% de) under the optimized reaction conditions [TMSOTf (1.0 equiv), CH_2Cl_2, -78 °C]. The data also indicate that the relative stereochemistry (syn/anti) of the crotylsilanes does not have an effect on the selectivity of the addition reaction, as both the syn and anti diastereomers exhibited comparably high levels of selectivity (compare entries 1 and 2, Table II). In contrast, the position of the benzyl ether on the acetal appears to influence the level of diastereoselection. The β-alkoxy acetal undergoes addition with lower (C5,C6 syn/anti ratio 20:1) but still useful levels of selectivity. When a sterically larger dibenzyl acetal (entry 7) was used rather than the dimethyl acetal, the selectivity was slightly diminished. Pyruvic aldehyde dimethyl acetal (**2d**) successfully undergoes addition with crotylsilane **1a** (entry 8), demonstrating that a α-keto acetal can also serve as a useful electrophile and effectively participate in the enantioselective addition process.

For the cases examined in this study, the additions proceed with predictable and consistently high levels of diastereoface selectivity for the formation of the C5,C6-syn diastereomer. These findings are consistent with a stereospecific anti-S_E' process as previously reported for cases involving intermolecular additions of chiral allyl- and crotylsilanes,[10] allylstannanes,[11] and more recently chiral allenylstannanes.[12] The sense of asymmetric induction is regulated by the absolute configuration at the stereogenic center bearing the silicon group.[4,13,14] For example, the (*E*)-(2*S*,3*R*)-crotylsilane **1d** adds preferentially to the *re* face of the oxonium ion or activated acetal and (2*S*,3*S*)-**1a** adds to the *si* face (Figure 1).

In summary, the use of nearly enantiomerically pure (*E*)-crotylsilanes in Lewis acid catalyzed asymmetric addition reactions to hetero-substituted acetals represents an effective method for producing highly functionalized seven- and eight-membered acyclic chains with high levels of diastereo- and enantioselectivity. The ability to achieve the simultaneous controlled introduction of the 1,4- and 1,5- remote stereocenters with high levels of enantioselection to our knowledge is unprecedented in acyclic diastereoselective bond-forming processes. The levels of selectivity exhibited by the silane reagents and the high degree of functionalization embodied in the homoallylic ether products suggest that this methodology may be a useful alternative to a variety of existing asymmetric transformations. Further exploration of these reagents including reactions with chiral electrophiles and their applications in asymmetric synthesis are underway in our laboratories and further advances in this area will be reported in due course.

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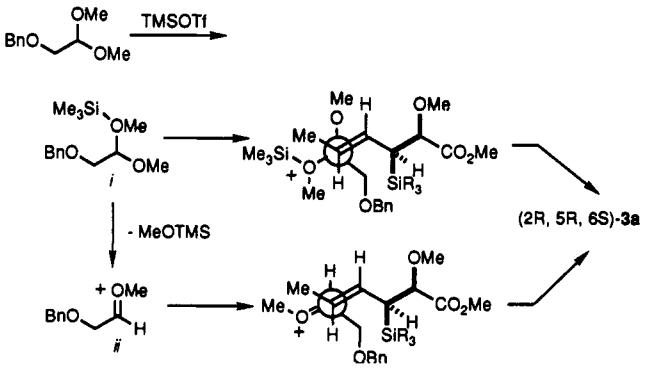
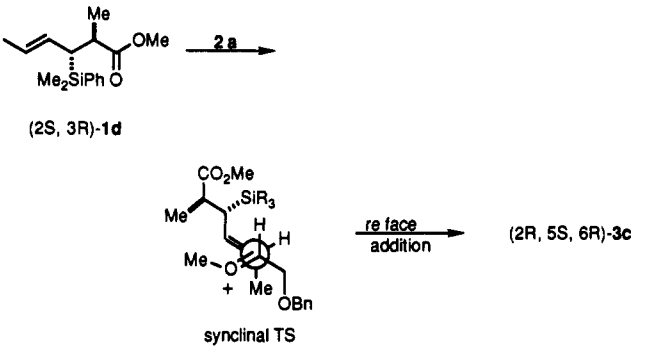
Supplementary Material Available: Methods for the absolute stereochemical assignment and determination of enantiomeric excess as well as experimental procedures for the addition reactions and spectral data for all reaction products including ^1H NMR and ^{13}C NMR spectra (35 pages). Ordering information is given on any current masthead page.

(12) For diastereoselective S_E' additions of optically active allenylstannanes, see; Marshall, J. A.; Wang, X. *J. Org. Chem.* **1991**, *56*, 3211.

(13) We have depicted the free oxonium ion (Figure 1) as the reactive intermediate; however, we would like to stress that the alternative, nondissociated activated acetal i can, in principle, exhibit the same levels of selectivity for the addition reaction, albeit through a seemingly more crowded transition state than oxonium ion ii.

(14) A synclinal orientation of the participating olefinic partners is illustrated with diastereomer (2*S*,3*R*)-**1d**. This arrangement would be a viable alternative transition state that would lead to the same C_5C_6-syn stereochemistry in the homoallylic ether products **3**.





Total Synthesis of (-)-(9*R*)-7,11-Dideoxy-13-deoxodaunomycinone

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Summary: The first enantioselective total synthesis of (-)-(9*R*)-7,11-dideoxy-13-deoxodaunomycinone (**8a**) is described. The route is based on enantioselective Diels–Alder methodology for construction of an optically active 1-(4*H*)-naphthalenone, which serves as an AB synthon.

The important biological activity of anthracycline antibiotics continues to foster strong interest in their syn-

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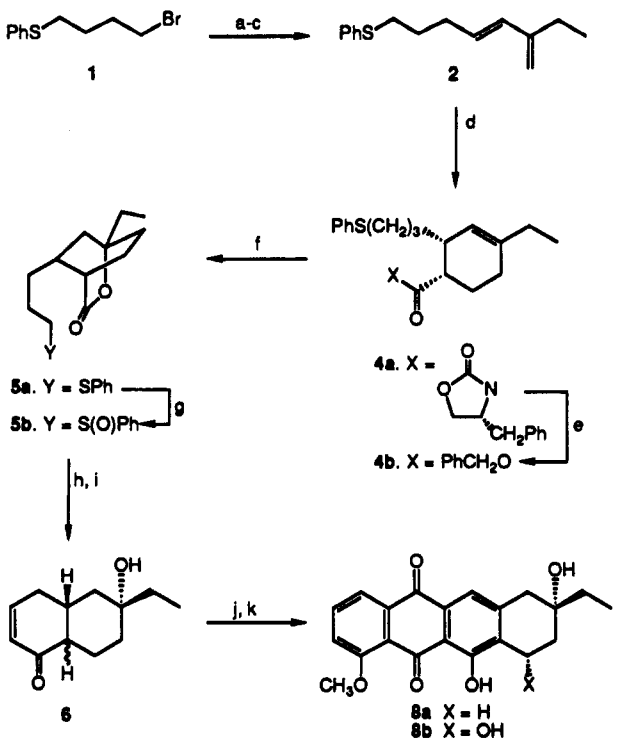
Scheme I[a]



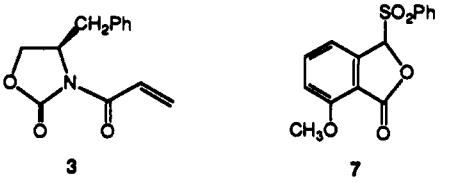
[a] (a) Mg, ethacrolein, H_3O^+, 60%; (b) Ac_2O, Py, DMAP, 100%; (c) $PdCl_2$, PPh_3, K_2CO_3, dioxane, Δ, 71%; (d) Me_2AlCl, **3**, CH_2Cl_2, −78 °C, 50%; (e) LiOBn, THF, −78 °C, 80%; (f) TMSCl, NaI, CH_3CN, 55 °C, 85%; (g) MCPBA, CH_2Cl_2, RT, 100%; (h) LDA, THF, −78 °C; (i) Δ, CCl_4, Na_2CO_3, 72% from **5b**; (j) LiOtBu, **7**, THF; (k) O_2, DMF, 45 °C, 85% from **6**.

thesis. Much of the current work is directed toward the development of methods for synthesis of this class of compounds in optically active form.[1]

We report herein the first enantioselective total synthesis of (−)-(9*R*)-7,11-dideoxy-13-deoxodaunomycinone (**8a**), the aglycone of an anthracycline antibiotic isolated concurrently with 11-deoxydaunorubicin.[2] Enantioselective total syntheses of anthracyclinones, especially 4-deoxy analogues, have been reported previously; however, these preparations either did not address the issue of regiochemical control or were only regioselective. The preparation described in this paper is the first enantioselective total synthesis that is also regiospecific.

The overall route, which is shown in Scheme I, is notably brief. Key elements of the plan are stereospecific preparation of the (*E*)-1,3-diene **2**,[3] use of Evans' asymmetric Diels–Alder methodology[4] to produce the optically active cyclohexene **4**, a novel intramolecular ring closure to efficiently construct the 1(4*H*)-naphthalenone **6**, and the use of **6** as an AB synthon for regiospecific synthesis of the naphthacenone ring system.[5]

The (*E*)-1,3-diene **2**, stereospecifically prepared in three steps from 4-bromobutyl phenyl sulfide[6] and 2-ethylacrolein, underwent dimethylaluminum chloride catalyzed Diels–Alder reaction with the oxazolidinone **3**[4,7] to furnish selectively the cyclohexene **4a** (endo/exo 23:1; de >100:1,[8] $[\alpha]_D$ −111.4° [*c* 13, CH_2Cl_2]). Removal of the chiral auxillary with LiOBn[4] (THF, −78 °C) gave the benzyl ester **4b** (80%; $[\alpha]_D$ −139.0° [*c* 6.7, CH_2Cl_2]). Debenzylation with concomitant lactonization to **5a** (85%; $[\alpha]_D$ −28.9° [*c* 4.9, CH_2Cl_2]) was uniquely achieved in a single step through treatment of **4b** with TMSCl and NaI.[9] This process effects a chirality transfer from C-1 to C-4 and thereby sets the key stereocenter at what will ultimately be C-9 of the anthracylinone.



The cis relationship of the (phenylthio)propyl side chain and the lactone functionality permitted straightforward conversion of **5a** to the 1(4*H*)-naphthalenone **6**. Thus, oxidation of **5a** to the sulfoxide **5b** (MCPBA; 100%), intramolecular cyclization of the derived carbanion of **5b** (LDA) with the proximate lactone carbonyl, and then thermolysis (Na_2CO_3, CCl_4, Δ) to eliminate benzenesulfinic acid provided **6** (72% from **5b**; $[\alpha]_D$ +49.9° [*c* 4.1, CH_2Cl_2]). Condensation of the anion of the sulfone **7**[5] (LiOtBu, THF) with the naphthalenone **6**, followed by oxidation (O_2, DMF, 45 °C) of the hydronaphthacene intermediate, furnished the optically active anthracyclinone **8a** (85% from **6**; mp 182–183 °C; $[\alpha]_D$ −19.8° [*c* 1.0, CH_2Cl_2]), which had identical IR, ^1H NMR, ^{13}C NMR, and TLC behavior with that of an alternatively prepared racemic sample.[10] Since introduction of the C-7 hydroxyl has been accomplished in the racemic compound,[10] this preparation constitutes a formal total synthesis of (+)-11-deoxy-13-deoxodaunomycinone (**8b**).

Currently, we are exploring generalization of this plan to include synthesis of other anthracyclinone A-ring substitution patterns.

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(7) Polymerization of this material proved to be a problem. We have now developed an alternative procedure for preparation of gram quantities, which we will soon publish.

(8) The endo/exo ratio was determined by ^1H NMR. The diastereomeric excess was determined by ^{19}F NMR of the Mosher ester derived from the alcohol obtained from reduction of the benzyl ester. Comparison of the Mosher ester derived from the racemic compound was performed.

(9) Undoubtedly, hydrogen iodide, produced through incipient hydrolysis of TMSI, is the proton source for the lactonization. With added sodium carbonate, the lactonization does not occur.

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