the characteristic apparent quartet (J = 12 Hz) for H_a that is also seen in the spectrum of **1d**.[1] Likewise the stereochemistry of **9b** was determined primarily from its high-field ^1H NMR spectrum which showed the expected coupling constants for the conformation drawn, namely: H_a dd, J = 11.8, 6.8 Hz; H_b dd, J = 10.7, 5.1 Hz.[7] Thus the cyclization does indeed proceed with good stereoselectivity to give only the isomers from the more stable transition states derived from **4a** in preference to those from **4b**. We have also carried out the cyclization of the des-chloro analogue of **3**, namely 1-((*tert*-butyldimethylsilyl)oxy)-2,6-dimethyl-5-hepten-2-ol, under similar conditions (TBCD, CH_2Cl_2, 25 °C, 40 min) and obtained an approximately 1:1 mixture of the analogous bromotetrahydrofurans and bromotetrahydropyrans in good yield.[8] Thus the chlorine atom does have an effect on the regioselectivity of the reaction, giving a higher proportion of the tetrahydropyran products. The synthesis was finished in short order by Swern oxidation of the alcohol **9a** to give in quantitative yield the crude aldehyde which was not purified but immediately subjected to chromium-promoted chlorovinylation using a slight modification of the conditions of Takai[9] to give aplysiapyranoid D (**1d**) in 76.6% isolated yield after chromatography.[10]

This ends a 7-step synthesis of **1d** from **2** with an overall yield of about 16% (Scheme II). This route should be a quite general one for the synthesis of the other aplysiapyranoids and related polyhalogenated ethers.

We have thus synthesized the cytotoxic marine natural product aplysiapyranoid D (**1d**) in excellent yield by a short route using a regio- and stereoselective bromoetherification as the key step. Further work in this area is in progress.

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(7) MM2 calculations suggest that the tetrahydrofuran ring will exist mainly in the envelope conformation drawn with the CH_2 group as the flap and predicts very similar J's to those obtained. Compound **9b** was shown to be a tetrahydrofuran since reduction with tributylstannane afforded a product with an isopropyl group in the proton NMR.

(8) Determination of the structures of the des-chloro analogues were again made primarily by high field proton NMR of the bromoethers and their derived debrominated alcohols.

(9) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

(10) The mixture of chromous chloride and chloroform in THF was refluxed for a few minutes until a purple color was observed, then it was cooled and the aldehyde added, followed by the usual procedure,[9] namely 1-h reflux, nonaqueous workup and chromatography.

Asymmetric Carbon–Carbon Bond Formation via Sulfoxide-Directed S_N2' Displacements of Acyclic Allylic Mesylates

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Summary: The addition of organocyanocuprates to acylic allylic mesylates bearing a chiral sulfoxide in the 2-position occurs with complete S_N2' regioselectivity, high E/Z stereoselectivity (15:1) and high asymmetric induction to produce enantiometrically pure trisubstituted vinyl sulfoxides.

Despite the development of new synthetic methods for alkene synthesis and asymmetric carbon centers in recent years,[1] acyclic stereocontrol remains a challenging problem in organic chemistry. In connection with our interest in using chiral vinyl sulfoxides in asymmetric synthesis[2a,b] and in organocopper chemistry,[2c] we sought new strategies for constructing systems containing chiral centers allylic to the vinyl sulfoxide unit. To this end we have found that the conjugate addition[3] of organocuprates to acyclic allylic mesylates activated with a chiral sulfoxide group in the β-position (**4** and **5**) occurs with complete S_N2' regioselectivity, high E/Z stereoselectivity and high asymmetric induction[4] to produce enantiomerically pure trisubstituted vinyl sulfoxides (**6**–**9**) in very good yields.

At the initial stage of this investigation, styryl sulfoxides **4a** and **5a** were studied; these substrates were prepared by lithiation of vinyl sulfoxide **1a**[5,6] and condensation with propionaldehyde to produce a 45:55 mixture[7] of readily separable diastereomeric alcohols **2a** and **3a**,[8] which were converted to their respective mesylates under standard conditions (MsCl, Et_3N, THF, 0 °C).[9] Unfortunately, most attempts to isolate styryl mesylates **4a** and **5a** were

(1) For some leading reviews, see: (a) Oare, D. A.; Heathcock, C. H. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1989; Vol. 19, pp 227–407. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Ibid.* Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; Wiley: New YOrk, 1982; Vol. 13, pp 1–115.

(2) (a) Marino, J. P.; Kim, M.-W.; Lawrence, R. *J. Org. Chem.* **1989**, *54*, 1782–1784. (b) Marino, J. P.; Fernández de la Pradilla, R.; Laborde, E. *Synthesis 1987*, 1088. (c) Marino, J. P.; Fernández de la Pradilla, R.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 4898.

(3) A related process was studied by Posner et al. See: Posner, G. H. *Acc. Chem. Res.* **1987**, *20*, 72–78 and references cited therein.

(4) For asymmetric induction during conjugate addition to acyclic ethylenic sulfoxides, see: Takaki, K.; Maeda, T.; Ishikawa, M. *J. Org. Chem.* **1989**, *54*, 58–62. See also: Pyne, S. G. *J. Org. Chem.* **1986**, *51*, 81–87.

(5) Posner, G. H.; Tang, P. W.; Mallamo, J. P. *Tetrahedron Lett.* **1978**, 3995–3998.

(6) Prepared by the Andersen method from β-bromostyrene. Andersen, K. K. *Tetrahedron Lett.* **1962**, 93–95.

(7) Low stereoselectivities have been reported for these processes. Posner, G. H.; Mallamo, P.; Miura, K.; Hulce, M. *Pure Appl. Chem.* **1981**, *54*, 2307–2314. It should be pointed out that all isomermic alcohols **2** and **3** were separated readily by column chromatography with CH_2Cl_2–ethyl acetate mixtures as eluents.

(8) All new compounds were fully characterized spectrally and analytically.

(9) For recent reports on chiraly transfer by S_N2' displacements on allylic mesylates, see: Ibuka, T.; Habashita, H.; Funakoshi, S.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 801–803 and references cited therein.

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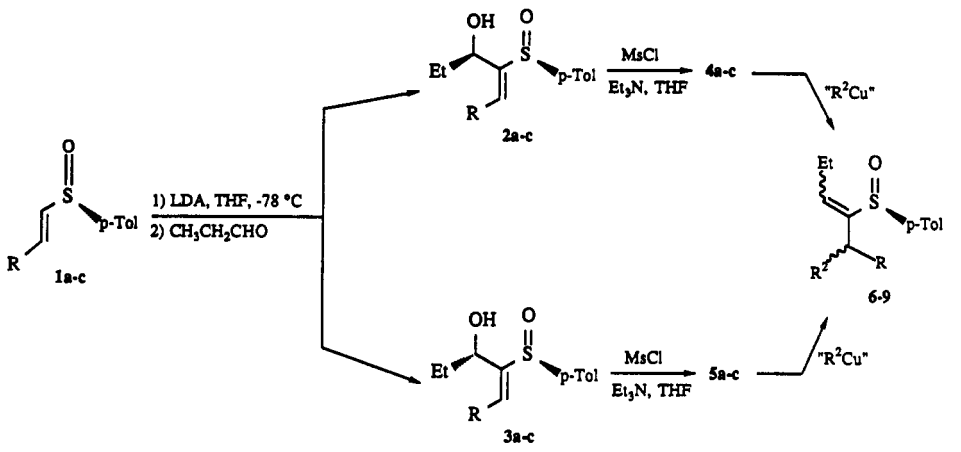
Scheme I[a]



[a] Throughout Scheme I: a, R = Ph, b, R = *n*-Bu; c, R = Me.

Table I. Reaction of Organocopper Reagents with Allylic Sulfinyl Mesylates

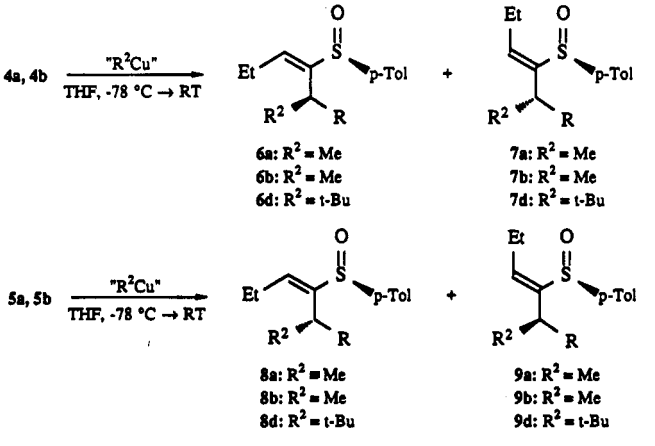
entry	substrate	R^2Cu[a]	6	7	8	9	yield (%)[b]
1[c]	4a	MeCuCNLi	6 (6a)	94 (7a)			81
2[c]	5a	MeCuCNLi			28 (8a)	72 (9a)	89
3[c]	5a	MeCuCNMgBr			6 (8a)	94 (9a)	80
4[c]	4a	*t*-BuCuCNLi	9 (6d)	91 (7d)			69
5[c]	5a	*t*-BuCuCNMgCl			6 (8d)	94 (9d)	71
6[d]	4b	MeCuCNLi	9 (6b)	91 (7b)			86
7	5b	MeCuCNLi			80 (8b)	20 (9b)	86
8	5b	Me_2CuLi			90 (8b)	10 (9b)	80
9	5c	PhCuCNMgBr	9 (6a)	91 (7a)			80
10	5c	$Ph_2CuMgBr$	6 (6a)	94 (7a)			70
11	4c	BuCuCNLi			15 (8b)	85 (9b)	74
12[d]	4c	PhCuCNLi			0 (8a)	100 (9a)	85

[a] Cuprates R^2Cu were prepared from the appropriate organolithium or Grignard reagent and CuI or CuCN. [b] Yields of pure products calculated from alcohols 2 and 3. [c] The crude mesylate solution was added to the organocuprate solution (6 equiv) at −78 °C. [d] The reaction was carried out in a DME/THF (9:1) solvent mixture; these conditions produced a slight increase of the selectivity of the reaction.

unsuccessful, and generally sulfinyl dienes were obtained instead. The cuprate reaction was then carried out by addition of the crude mesylate solution onto the preformed organocuprate reagent. In this fashion, when **5a** was treated with Gilman cuprate Me_2CuLi (6 equiv, THF, −78 °C → room temperature), a 45:55 mixture of displacement products **8a** and **9a** (Scheme II) was obtained in a disappointing 23% yield.[10] However, the use of cyanocuprate MeCuCNLi under the same conditions afforded a much better yield (89%) and a higher selectivity (28:72, Table I, entry 2). Furthermore, a significant improvement of the diastereoselectivity (6:94) of the process was realized when the cyanocuprate was generated from a Grignard reagent (entry 3). In contrast, diastereomeric mesylate **4a** reacted with MeCuCNLi to produce a 6:94 ratio of isomers **6a** and **7a** (entry 1).

The structures of alcohols **2a** and **3a** and of the corresponding displacement products (**6a–9a**, Scheme II) were tentatively assigned by inspection of their ^1H NMR data and on the basis of an anti attack of the nucleophile.[9] The stereochemistry of the double bond was deduced from the chemical shift of the vinylic proton (0.40–0.55 ppm more deshielded in *E* isomers, **6a** and **8a**). Additionally, the newly introduced methyl group appeared shielded in isomers **6a** (0.35 ppm) and **9a** (0.52 ppm) relative to **8a** ad **7a**, respectively (a similar unusual shielding had been observed for the CH_3–SO_2–methyl of mesyalte **4a**). All of

Scheme II[a]



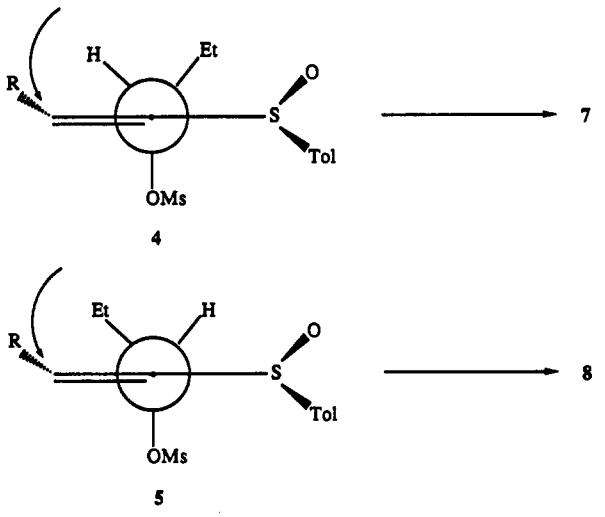
[a] Throughout Scheme II: a, R = Ph; b, R = *n*-Bu; d, R = Ph.

these spectral characteristics were consistent with a predominant conformation in solution which would place the aforementioned methyl groups in the shielding region of the anisotropic tolyl group. Nevertheless, in order to secure more definitive information on the absolute configurations of the carbon atom bearing the mesylate and of the newly formed chiral center, X-ray analyses of the styryl alcohol **2a**[11] and its adduct **7a**[12] were performed and the previously

(10) Under these conditions the major product was tentatively assigned as PhCH=C=CHEt. Interestingly, when the crude mixture was refluxed for 30 min the yield of vinyl sulfoxide was increased substantially (80%) and only traces of allene could be detected.

(11) X-ray data of alcohol **2a**: Allyl alcohol **2a** crystallized in the orthorhombic space group $P2_12_12_1$, with a = 8.346 (2) Å; b = 11.235 (2) Å; c = 16.919 (4) Å; and β = 90°. The structure was solved with direct methods and refined to a R = 0.0333 with a final R_w = 0.0519.

Scheme III



assigned structures were thus confirmed.

The interconversion of diastereomeric alcohols **2a** and **3a** was also examined. While oxidation to the keto sulfoxide proceeded smoothly (MnO_2, CH_2Cl_2, room temperature, 77%), we were unable to effect a clean stereoselective 1,2-reduction under a variety of reaction conditions.[13] However, both isomers could be interconverted via a Mitsunobu protocol[14] followed by debenzoylation (NaOMe, MeOH) in good overall yield (70%).

To extend the scope of the methodology, the introduction of a bulky *tert*-butyl group was addressed and good selectivities were encountered (entries 4 and 5 of Table I). The reactivity of *n*-butyl- and methyl-substituted vinyl sulfoxides **4b,c** and **5b,c**, respectively, prepared as described above from **1b**[15] and **1c**[16] (Scheme I), was also studied, and the results obtained are shown in Table I (entries 6-12). In the case of isomers **4b** and **5b**, excellent yields of displacement adducts were achieved with MeCuCNLi (entries 6, 7). An additional improvement in selectivity for **5b** was encountered when Me_2CuLi was employed (entry 8). In the case of **5c**, high diastereoselectivities were obtained upon reaction with Grignard derived phenyl organocuprates (entries 9, 10). Alternatively, the reactions between diastereomeric mesylate **4c** and *n*-BuCuCNLi and PhCuCNLi proceeded in very good yields and with good stereocontrol.

The above results may be tentatively rationalized in terms of an anti S_N2' process[9,17] on conformation **4** (for diastereomers **4a-c**) and **5** (for diastereomer **5b**)[18] (Scheme III) with oxidative addition of the cuprate opposite to the mesylate and away from the tolyl group. Conformation **5** represents a very delicately balanced case, highly dependent on the reaction conditions and on the steric requirements of the substrate. Thus, when the steric interaction between R and Et group is very strong (R = Ph, **5a**), adduct **9** becomes the main product of the reaction (entry 2), particularly when Grignard derived cuprates are employed (entries 3 and 5).[19] Overall, we feel that the reactions are primarily directed by the allylic mesylate system with the enantioselectivity controlled by the chiral sulfoxide group.

In conclusion, new methodology to effect the regio- and stereocontrolled S_N2' displacement of acyclic allylic mesyloxy vinyl sulfoxides has been developed. In this manner, the newly created chiral carbon center is attached to the synthetically useful functionality of a vinyl sulfoxide. The use of this methodology in synthesis is currently being pursued in our laboratories.

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Supplementary Material Available: ORTEP drawings, bond angles, and bond distances for compounds **2a** and **7a** and experimental and spectroscopic data for all new compounds (10 pages). Ordering information is given on any current masthead page.

(12) X-ray data of adduct **7a**: Sulfoxide **7a** crystallized in the orthorhombic space group *Pbc* 2_1, with a = 7.5133 (5) Å; b = 10.96 (1) Å; c = 20.175 (2) Å; and β = 90°. The structure was solved by direct methods and refined to a R = 0.0344 with a final R_w of 0.0518.

(13) DiBAL; DiBAL/$ZnCl_2$; LAH; $NaBH_4/CeCl_3$; LAH/$CeCl_3$; 9-BBN.

(14) Ph_3P, DEAD, $PhCO_2H$, THF, room temperature. See: Grynkiewicz, G.; Burzynska, H. *Tetrahedron* **1976**, *32*, 2109-2111.

(15) Prepared by the method of Kosugi and Uda; see: Kosugi, H.; Kitaoka, M.; Tagami, K.; Takahashi, A.; Uda, H. *J. Org. Chem.* **1987**, *52*, 1078-1082.

(16) Prepared from commercially available 1-bromo-1-propene.

(17) For reviews on S_N2' reactions, see: Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503-1511. Magid, R. M. *Tetrahedron* **1980**, *36*, 1901-1930.

(18) For a study on the conformation of single vinyl sulfoxides see: Kahn, S. D.; Dobbs, K. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 4602-4606.

(19) At this stage some participation of chelated forms involving the sulfoxide oxygen atom and the mesylate group when Grignard drived cuprates are employed cannot be conclusively ruled out.

A Study of the Kinetics of Diadamantylcarbene in Solution by Laser Flash Photolysis

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Summary: Laser flash photolysis of diadamantyldiazomethane produces diadamantylcarbene which reacts with oxygen to form a carbonyl oxide with λmax = 307 nm.

Recent years have witnessed considerable progress in the study of alkyl substituted carbenes by time resolved techniques.[1] These studies have to date been confined to the study of alkylhalocarbenes by photoacoustic calo-

(1) (a) Moss, R. A.; Turro, N. J. *Kinetics and Spectroscopy of Carbenes and Biradicals*; Platz, M. S., Ed.; Plenum: New York, 1990; p 213. (b) Platz, M. S.; Maloney, V. M. *Ibid.* p 239.

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