Chemo-, Regio-, and Diastereoselective Alkylation via Lewis Acid Promoted Substitutions of Sulfones

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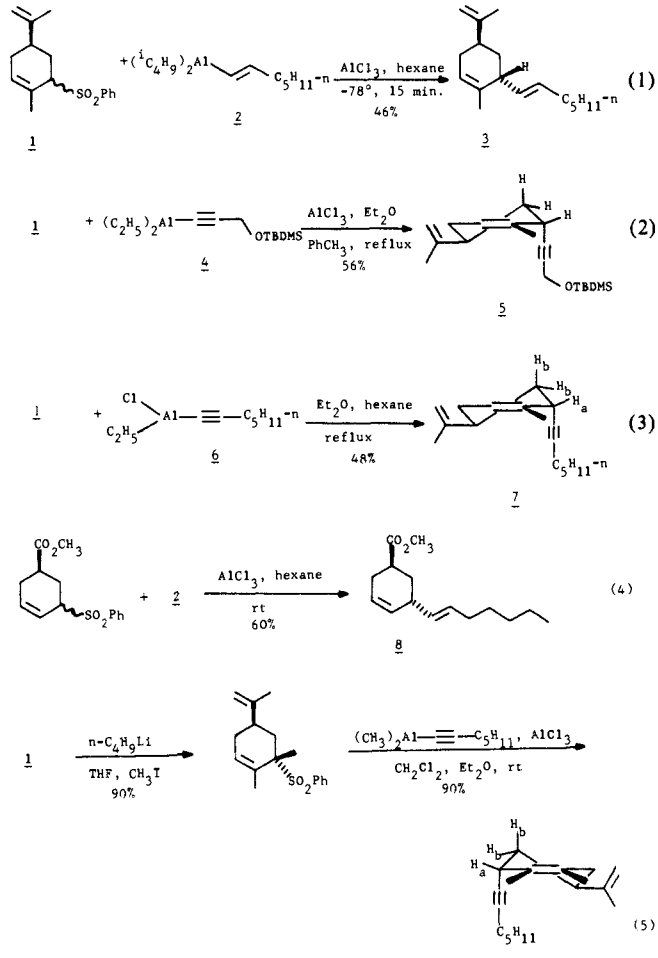
The versatility of sulfones as building blocks stems from their ability to acidify protons on carbons bearing this functionality. The subsequent step has normally been reductive cleavage[1,2] or elimination to olefins.[3] The possibility of replacing the carbon–sulfur bond of a sulfone with a carbon–carbon bond[4] would be a most useful direction since such a transformation permits a sulfone to be considered as a synthon for a 1,1- or 1,3-dipole (vide infra). Recent work has centered on the use of transition metals to activate a sulfone.[5] Our recent observation of a Friedel–Crafts-type cyclization of sulfones[6] suggested that alkylations using Lewis acid type alkylating agents, e.g., organoaluminum compounds,[7] may permit such substitutions. We wish to report the observation that Lewis acid initiated substitutions do proceed with remarkable ease, with good chemo- and regioselectivity, and with a strong bias for formation of an axial C–C bond in cyclohexenyl systems.

Reaction of an isomeric mixture of carvylphenyl sulfone **1**[8] with the vinylalane **2**, available by direct hydroalumination of 1-heptyne,[9] proceeds with remarkable facility at −78 °C in hexane in the presence of aluminum chloride (eq 1) (Scheme I). The product **3**[10] (46% isolated yield) consists of predominantly one isomer (9:1, capillary GC[11]). The same reaction with an acetylenic alane **4** gives also predominantly (5:1)[11] one isomer **5**[10] (eq 2, 56% isolated yield). In this case, use of ether as solvent slows the reaction dramatically compared to hexane but is required for chemoselectivity with respect to the TBDMS group. Increasing the Lewis acidity of the aluminum in the organoalane obviates the need for an exogeneous Lewis acid as in the case of **6** which gives **7**[10] (eq 3, 48% isolated yield) as a 13:1[11] diastereomeric mixture. The assignment of the axial stereochemistry rests upon the NMR data. For example, in **7**, J_{ab} = 4.5 Hz, which suggests that H_a (δ 2.90) is equatorial. For the minor isomer, the appearance of a large coupling (11.9 Hz) for H_a at δ 3.05 is consistent with this proton being axial. 5-Carbomethoxy-3-(phenylsulfonyl)cyclohexene[8] also condenses well with the vinylalane **2** to give **8**[10] (eq 4, 60% yield,[12] 7:1[11]). The presence of the ester slows the reaction compared to **1** but otherwise is compatible.

Scheme I



The unique advantage of the sulfone as a leaving group stems from the ease of alkylation α to the sulfone prior to the substitution. To illustrate this point, the sulfone **1** is methylated via its organolithium analogue (90% yield, 6:1 t/c)[8] and then substituted (90% yield,[10,12] 13:1 t/c[11]) as in eq 5. NMR spectroscopy establishes both the regio- and diastereoselectivity as depicted (e.g., H_a, δ 2.92, t, J_{ab} = 5.5 Hz). Equations 3–8 represent additional examples of alkylation–substitution.

Substitution at the less substituted side of an allyl system appears to be general regardless of the original location of the sulfone. In eq 5, 9, and 10, reactions proceed with allyl inversion but in eq 6–8 (Scheme II) with direct substitution. In cases of eq 5–8, only the isomer depicted is observed. This result indicates that in the competition between a secondary and tertiary center, a strong selectivity for the less hindered secondary position exists. On the other hand, the primary vs. secondary competition in eq 9 and 10 (only the major product is depicted) varies from 5:1 to 11:1.[11] That steric factors with respect to the organoaluminum play a role is suggested by the increase in selectivity in eq 9 from 5:1 to 8:1[11] upon switching from R = C_2H_5 to R = i-C_4H_9.

The ability to use this method to elaborate a side chain exocyclic to a ring is illustrated in eq 11. In this case, the regioselectivity

(1) Bremna, J.; Julia, M.; Launay, M.; Stacino, J.-P. *Tetrahedron Lett.* **1982**, *23*, 3265. Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477. Julia, M.; Uguen, D. *Bull. Soc. Chim. Fr.* **1976**, 513. Nakai, T.; Shiono, H.; Okawara, M. *Chem. Lett.* **1975**, 249. Posnere, G. H.; Brunelle, D. J. *J. Org. Chem.*, **1973**, *38*, 2747.

(2) Also see: Janssen, C. G. M.; Godefroi, E. F. *J. Org. Chem.* **1982**, *47*, 3274.

(3) For a few recent examples, see: Mandai, T.; Yanagi, T.; Araki, K.; Morisaki, Y.; Kawada, M.; Otera, J. *J. Am. Chem. Soc.* **1984**, *106*, 3670. Hsiao, C.-N.; Shechter, H. *Tetrahedron Lett.* **1984**, *25*, 1219. Cuvigny, T.; Herve du Penhoat, C.; Julia, M. *Ibid.* **1983**, *24*, 4315. Fehr, C. *Helv. Chim. Acta* **1983**, *66*, 2519. Kocienski, P.; Todd, M. *J. Chem. Soc., Perkin A Trans. 1* **1983**, 1777, 1783. Ochia, M.; Ukita, T.; Fujita, E. *Tetrahedron Lett.* **1983**, *24*, 4025. Ochia, M.; Sumi, K.; Fujita, E.; Tada, S. *Chem. Pharm. Bull.* **1983**, *31*, 3346. Tanaka, K.; Ootake, K.; Imai, K.; Tanaka, N.; Kaji, A. *Chem. Lett.* **1983**, 633.

(4) Sulfone has served as a leaving group for cyclopropane formation: Parker, W. L.; Woodward, R. B. *J. Org. Chem.* **1969**, *34*, 3085. Campbell, R. V. M.; Crombie, L.; Findley, D. A. R.; King, R. W., Pattenden, G.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 897. Julia, M.; Guy-Rouault, A. *Bull. Soc. Chim. Fr.* **1967**, 1411.

(5) Organocopper: Julia, M.; Righini-Tapie, A.; Verpeaux, J. N. *Tetrahedron* **1983**, *39*, 3283. Julia, M.; Verpeaux, J. N. *Ibid.* **1983**, *39*, 3289. Organopalladium: Trost, B. M.; Schmuff, N. R.; Miller, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 5979. Organonickel: Cuvigny, T.; Julia, M. *J. Organomet. Chem.* **1983**, *250*, C21.

(6) Trost, B. M.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 7260.

(7) For excellent reviews, see: Mole, T.; Jeffrey, E. A. "Organoaluminum Compounds"; Elsevier: Amsterdam, 1972. Bruno, G. "The Use of Aluminum Alkyls in Organic Synthesis"; Ethyl Corp.: Baton Rouge, 1970, 1973, 1980. Yamamoto, H.; Nozaki, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 169. Negishi, E. "Organometallics in Organic Synthesis"; Wiley: New York, 1980; Vol. 1, pp 286–393. Maruoka, K.; Yamamoto, H. *Angew. Chem., Int. Ed. Engl.*, in press.

(8) Trost, B. M.; Schmuff, N. R. *J. Am. Chem. Soc.* **1985**, *107*, 396.

(9) Wilke, G.; Muller, H. *Ann. Chem.* **1960**, *629*, 222. Eisch, J. J.; Amtmann, R.; Foxton, M. W. *J. Organomet. Chem.* **1969**, *16*, 55. Zweifel, G.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, *89*, 2753. Zweifel, G.; Lynd, R. A. *Synthesis* **1976**, 625.

(10) All new compounds have been fully characterized spectrally and have elemental compositions determined by high-resolution mass spectroscopy and/or combustion analysis.

(11) A 25 m × 0.25 mm poly(dimethylsiloxane) capillary VPC column (Alltech 932525) was employed for this analysis.

(12) Isolated yield.

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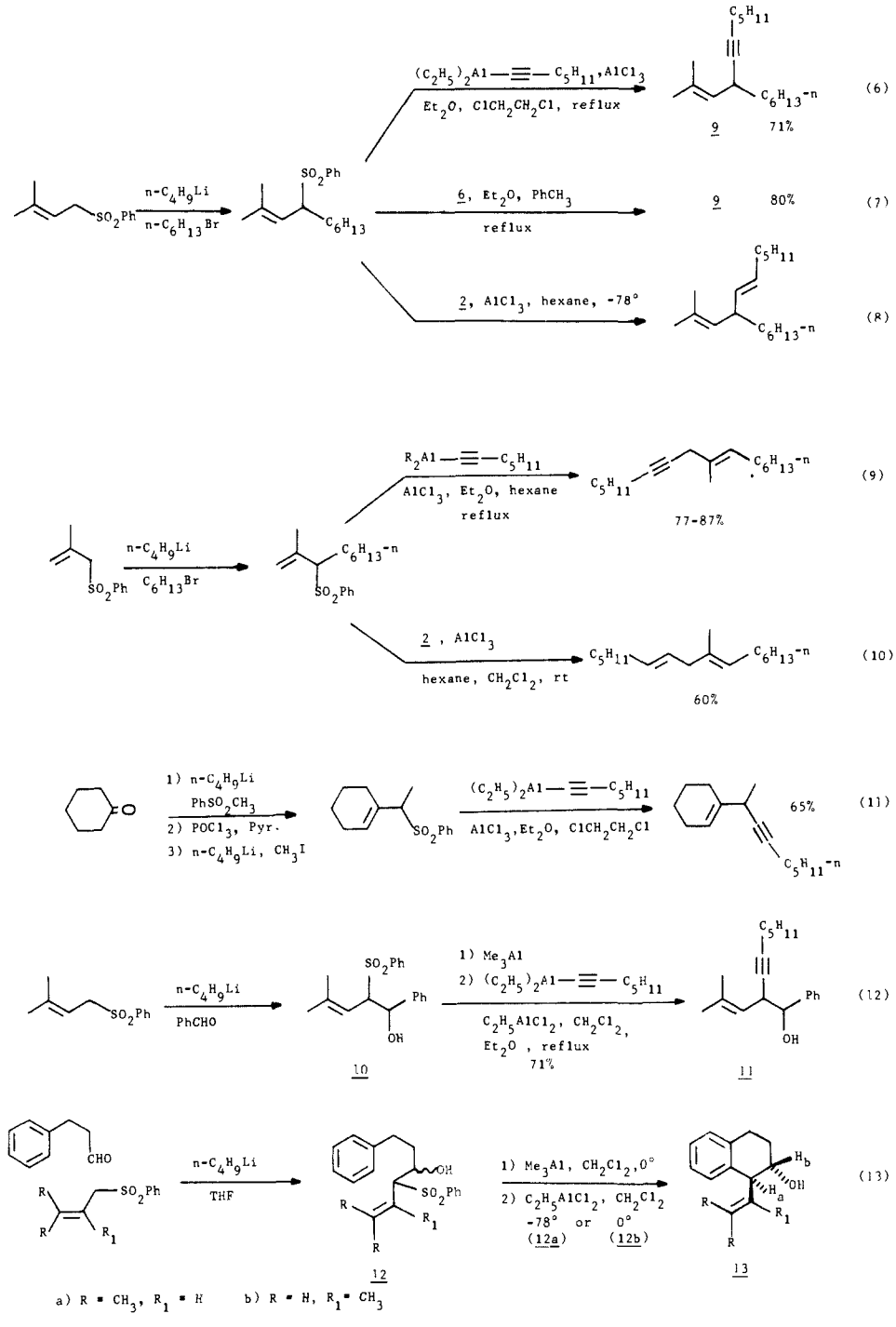
Scheme II



(6:1) competes at two secondary positions. The thermodynamic bias for a double bond to be endocyclic in a six-member ring accounts for the selectivity.

The chemoselectivity of the method is tested by the ability to employ carbonyl adducts as in **10**. Initial complexation of the free alcohol with trimethylaluminum followed by addition of the alkynylalane and ethylaluminum dichloride as the Lewis acid gives only the product of substitution of the allylic sulfone with formation of the new C–C bond at the secondary carbon, **11**[10] (eq 12, 71% yield[12]). The preferential ionization of the allylic sulfone in preference to the benzylic alcohol is particularly noteworthy.

The ability to employ β-hydroxy sulfones in the intermolecular substitution led us to briefly examine their chemo- and diastereoselectivity in the Friedel–Crafts cyclization.[6] Here, too, the cyclization is compatible with an unprotected alcohol and proceeds with good (68% yield,[12] 7:1[11] in **13a**[10]) to excellent (81% yield,[11] >50:1[11] in **13b**[10]) diastereoselectivity (eq 13). The trans stereochemistry assignment derives from J_{ab} = 5.0 and 9.0 Hz in **13a** and **13b**, respectively.

The Lewis acid mediated nucleophilic substitution of sulfone proceeds with unexpected facility. The scope of sulfones as building blocks increases greatly—especially in terms of the equivalence of either a 1,1-dipole when the starting sulfone has a substitution pattern as in **14** or 1,3-dipole with sulfones like **15**.

14 **15**

The mechanism most likely involves ionization to a carbonium ion followed by capture by the nucleophile. The independence of the stereochemistry of the product from the stereochemsitry of the starting sulfone supports this interpretation. For example, starting with a diastereomeric mixture of **1** ranging from 2:1 to

1:4 trans/cis gives the same product with high preference for the trans isomer (i.e., axial bond formation). Synthetically, the lack of dependence of stereochemistry of the product on that of the starting material and the bias for axial C–C bond formation are advantages of this approach. Clearly steric effects and not charge distribution determine regioselectivity. The compatibility with esters, silyl ethers, and hydroxyl groups and the diastereoselectivity in the latter instance enhances the utility of this methodology. At the moment, the reaction requires a somewhat stabilized carbon nucleophile such as an alkynyl or vinyl system. The high selectivity for transfer of such "stabilized" carbanions in preference to saturated alkyl groups is highlighted in the reaction of **10** where, in spite of the many methyl and ethylaluminum bonds, only alkynyl transfer occurs. Alternative Lewis acid type alkylating agents may provide the opportunity for alkyl transfer. Indeed, these results suggest that organosulfones are a new general class of substrates as electrophilic conjunctive reagents in the presence of Lewis acids as mild as alkylaluminum halides.

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Synthesis of (*R*)- and (*S*)-[1-$^{13}C_1$,2-$^{2}H_1$]Malonate and Its Stereochemical Analysis by NMR Spectroscopy

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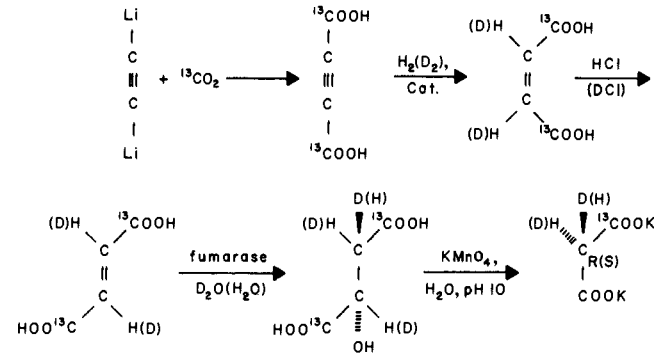
A wide variety of natural products are formed from malonylcoenzyme A by the so-called "polyketide pathway",[1-3] a biosynthetic route sharing many features with the biosynthesis of fatty acids.[4] The formation of the polyketides or acetogenins poses many stereochemical questions which have so far not been elucidated. The stereochemistry of fatty acid biosynthesis has been unraveled in the elegant studies of Cornforth and Sedgwick[5,6] using stereospecifically tritiated malonylcoenzyme A as the chiral substrate. This approach, however, is limited to work with isolated enzymes. Most polyketide biosyntheses have not yet been achieved in cell-free systems and must therefore be studied in in vivo fermentations. We therefore synthesized a chiral version of malonate, a pro-prochiral molecule of the Caabb type,[7] as a substrate for studies on the steric course of polyketide biosynthesis.

A major problem in the preparation and use of chiral malonate is the propensity of the molecule to undergo proton exchange and racemization in aqueous solutions[5] ($t_{1/2}$ for ^{1}H exchange at 30 °C 112 min at pH 8, 216 min at pH 9).[8] Clearly the compound must be generated and used at a pH above 8 and all operations must be carried out on a time scale of minutes, ruling out operations like chromatography or similar purification steps. We decided to prepare (*R*)- and (*S*)-[1-$^{13}C_1$, 2-$^{2}H_1$]malonate from configurationally stable precursors, (2*S*,3*R*)-[1,4-$^{13}C_2$, 3-$^{2}H_1$]-malate and (2*S*,3*S*)-[1,4-$^{13}C_2$-2,3-$^{2}H_2$]malate, which were synthesized as shown in Scheme I. The malate samples contained

Scheme I. Synthesis of Potassium (*R*)- and (*S*)-[1-$^{13}C_1$,2-$^{2}H_1$]Malonate



Scheme II. Derivatization of Chiral Malonate for NMR Analysis

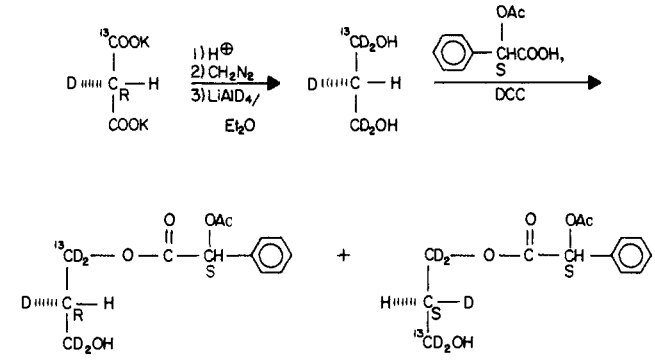
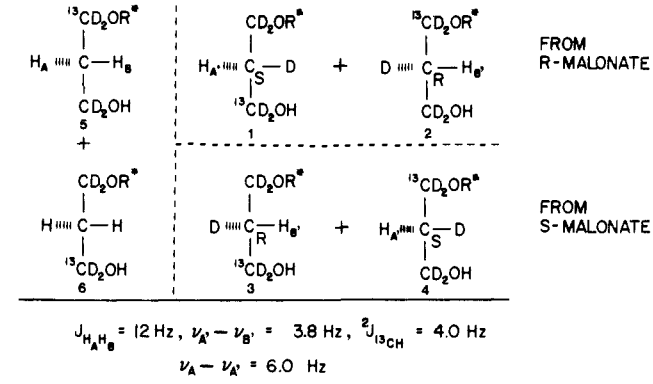


Chart I



99% ^{13}C and 90% ^{2}H per labeled position. Their configurations follow from the known[9,10] steric course of the fumarase reaction. Oxidation of the malate (134 mg, 1 mmol) with $KMnO_4$ (300 mg, 1.1 mmol) in aqueous solution (1.9 mL) adjusted to pH 10.0 for 5 min in an ice bath, followed by immediate filtration to remove MnO_2, gave a solution of the potassium salts of malic acid (less than 10%), malonic acid (20%), and oxalic acid (70%) as determined by HPLC. If desired, the oxalic acid could be removed by addition of a cold solution of $CaCl_2$ immediately before filtration. Proton NMR analysis of the oxidation product from [3-$^{2}H_2$]malic acid in H_2O and unlabeled malic acid in D_2O showed less than 10% exchange under these conditions.

To demonstrate that the samples of chiral malonate so generated did indeed contain an excess of one enantiomer, each product was converted to dimethyl malonate by rapid acidification and lyophilization followed by treatment with ethereal diazomethane. The ether solutions were then immediately reduced with $LiAl^2H_4$ and the 1,3-propanediol was converted to the (*S*)-(+)-*O*-acetyl-D-mandelate monoester[11] (Scheme II). The latter (25% yield based on malonate) was purified by HPLC (Hamilton PRP-1 column,

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(1) Packter, N. M. "The Biosynthesis of Acetate-Derived Compounds"; Wiley: London, 1973.
(2) Manitto, P. "Biosynthesis of Natural Products"; Wiley: New York, 1981.
(3) Herbert, R. B. "The Biosynthesis of Secondary Metabolites"; Chapman and Hall: London, 1981.
(4) Lynen, F. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1961**, *20*, 941.
(5) Sedgwick, B.; Cornforth, F. W.; French, S. F.; Gray, R. T.; Kelstrup, E.; Willadsen, P. *Eur. J. Biochem.* **1977**, *75*, 481.
(6) Sedgwick, B.; Morris, C.; French, S. J. *J. Chem. Soc., Chem. Commun.* **1978**, 193.
(7) Floss, H. G.; Tsai, M. D.; Woodard, R. W. *Top. Stereochem.* **1984**, *15*, 253.
(8) Huang, S. Ph.D. Thesis, Purdue University, West Lafayette, IN, 1984.
(9) Gawron, O.; Fondy, T. P. *J. Am. Chem. Soc.* **1959**, *81*, 6333.
(10) Anet, F. A. L. *J. Am. Chem. Soc.* **1960**, *82*, 994.
(11) Parker, D. *J. Chem. Soc., Perkin Trans. 2* **1983**, 83.

0002-7863/86/1508-1100$01.50/0