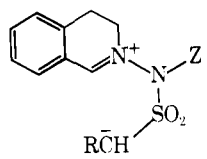
The most likely mechanisms for the formation of products **2** are either (a) a concerted $[_\pi4_s + _\pi2_s]$ cycloaddition process or (b) a stepwise addition of sulfene to **1**, leading to **2** by the ring closure of zwitterion **4**. Since it was observed



4

that under identical conditions of temperature (80°) and concentration (8 mmol of the dipole in 60 ml of benzene) adduct **2b** was produced with a complete lack of stereoselectivity, while **2j** was formed with a high degree of stereoselectivity, the intermediacy of zwitterion **4** in these reactions seems unlikely; the effect of the "Z" group on the stereochemical outcome of the ring closure of **4** is expected to be minimal. On the other hand, if it is assumed that the azomethine imines and sulfenes undergo a concerted $[_\pi2_s + _\pi4_s]$ cycloaddition,[11] the differences in the stereoselectivities with which **2b** and **2j** were formed may be rationalized by considering the reactivity of the dipoles **1**. Those azomethine imines in which the charge on the anionic nitrogen is stabilized by a carbonyl or a sulfonyl group may be less reactive and more selective than those in which the anionic charge is stabilized by a phenyl group. The more selective dipoles may discriminate between the two possible orientations of phenyl sulfene leading to the transition state and therefore may lead stereoselectively to the observed product.[14] The more reactive, less selective dipole **1** (Z = C_6H_5) may react indiscriminantly with phenyl sulfene to yield a mixture of two isomers.

A more complete evaluation of the scope and utility of these reactions is underway and will be reported at a later date.

Acknowledgment. Financial support was provided by the National Institutes of Health (CA-04536) and the Standard Oil Co. of Ohio, for which the authors are grateful.

Supplementary Material Available. Procedures for the preparation of all compounds **2** and **3**, along with spectral data for each, will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th Street N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2260.

References and Notes

(1) For reviews of sulfene chemistry, see (a) G. Optiz, *Angew. Chem., Int. Ed. Engl.*, **6**, 107 (1967); (b) W. E. Truce and L. K. Liu, *Mech. React. Sulfur Compd.*, **4**, 145 (1969); (c) T. Nagai and N. Tokura, *Int. J. Sulfur Chem. B.*, **7**, 207 (1972); (d) J. F. King, *Acc. Chem. Res.*, **8**, 10 (1975).
(2) W. E. Truce and C. I. Lin, *J. Am. Chem. Soc.*, **95**, 4426 (1973).
(3) S. Rossi and S. Maiorana, *tetrahedron Lett.*, 263 (1966).
(4) (a) R. Huisgen, R. Grashey, P. Laur, and H. Leitermann, *Angew. Chem.*, **72**, 416 (1960); (b) R. Huisgen, *Proc. Chem. Soc. (London)*, 363 (1961); (c) R. Grashey and K. Adelsberger, *Angew. Chem., Int. Ed. Engl.*, **1**, 267 (1962); (d) R. Grashey, H. Leitermann, R. Schmidt, and K. Adelsberger, *ibid.*, **1**, 406 (1962); (e) R. Huisgen, *ibid.*, **2**, 581 (1963).
(5) We wish to thank Professor R. Huisgen and Dr. R. Grashey for providing directions for the preparation of certain of the dimers of dipoles **1**.
(6) D. Walker and J. D. Hiebert, *Chem. Rev.*, **67**, 153 (1967).
(7) The NMR spectra of the crude products **2c** and **2d** indicated that both isomers had been formed in each case. Owing to the low yield of these reactions, detailed stereochemical investigations were not carried out. The low solubility of **2f** in organic solvents precluded the use of NMR spectroscopy as a means of determining the stereoselectivity with which it was formed.
(8) Because J_{ab} was 9.5 Hz for one isomer of **2b** and 10.5 Hz for the other, it was not possible to use the Karplus relationship[9] to assign absolute stereochemistries to these adducts.
(9) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Am. Chem. Soc.*, **85**, 2870 (1963).
(10) Peaks which may have been due to a small amount of a second isomer may also have been caused by impurities in the crude products.
(11) Recent molecular orbital calculations on the frontier orbitals of azomethine imine **1** (Z = C_6H_5)[12] and of sulfene[13] suggest that the orbital symmetries of these two species are compatible with a $[_\pi4_s + _\pi2_s]$ cycloaddition.
(12) K. N. Houk et al., *J. Am. Chem. Soc.*, **95**, 7287, 7301 (1973).
(13) J. P. Snyder, *J. Org. Chem.*, **37**, 3965 (1972).
(14) This argument suggests that the isolated isomers of **2h, 2j,** and **2l** are those in which H_a and H_b are trans. However, the absolute stereochemistry of these adducts has not yet been determined.

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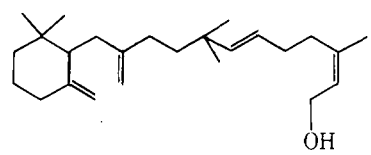
Received March 4, 1975

The Total Synthesis of (±)-Diumycinol

Summary: The first synthesis of the sesterterpene (±)-diumycinol (**1**) is reported featuring the reductive opening of a cyclopropyl ketone (**2**) which regiospecifically generates the β,β-disubstituted lithium enolate **3** and undergoes alkylation exclusively at C-2 with no loss of regiospecificity.

Sir: Diumycinol, the nonisoprenoid C_{25} lipid obtained by acid hydrolysis of the antibiotic diumycin, has been shown to possess structure **1**.[1] Diumycinol became of interest to



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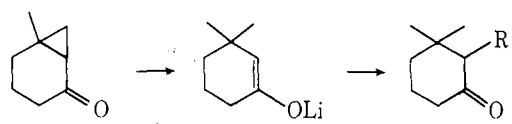
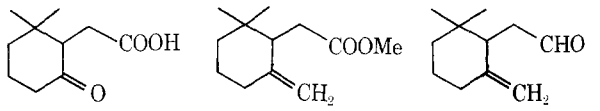
us, not only because of its polyolefinic nonisoprenoid nature, but also because it allowed us the opportunity to generate regiospecifically an enolate ion (e.g., from a cyclopropyl ketone[2]) which in principle should be capable of being alkylated without loss of structural integrity (cf. **2** → **3** → **4**).[2-5] We wish to report the first synthesis of (±)-diumycinol and demonstrate that the specifically generated β,β-disubstituted lithium enolate **3** undergoes alkylation as the exclusive process with no loss of regiospecificity.[5]



2 3 4

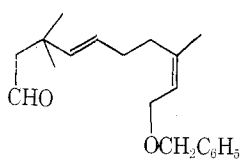
The synthesis of diumycinol outlined below involves the combination of two synthetic pieces, the six-membered-ring building block **7** and the sulfone moiety **12**.[7] The required intermediate **7**[8] was prepared from cyclopropyl ketone **2**[10] in the following manner. The β,β-disubstituted lithium enolate **3** formed during the metal–ammonia cleavage of cyclopropyl ketone **2** underwent exclusive C-2 alkylation (70%) with allyl bromide in 1,2-dimethoxyethane (glyme).[11] Oxidative cleavage of the double bond of **4** (R = allyl) in a two-phase system [benzene–water (1:1)] contain-

ing potassium permanganate and tetra-*n*-butylammonium bromide[12] resulted in a 42% yield of pure keto acid **5**. Methylenation[13] (methylenetriphenylphosphorane, DMSO, 60°, 96 hr) followed by esterification (ethereal diazomethane) provided a 76% yield of ester **6** which was smoothly converted to aldehyde **7** (58%)with diisobutylaluminum hydride in hexane (−70°).



5 6 7

The synthesis of sulfone **12** from the previously described[14] aldehyde **8** is detailed below. Reduction of aldehyde **8** (sodium borohydride, ethanol, room temperature, 1.5 hr) generated alcohol **9** which upon mesylation (methanesulfonyl chloride, pyridine, 0°, 1 hr) and exchange with iodide (sodium iodide, acetone, reflux, 15 hr) afforded a 90% overall yield (from **8**) of iodide **11** (*m/e* 412.1267). Treatment of iodide **11** with sodium *p*-toluenesulfinate in anhydrous DMF at 135° (15 hr) resulted in an 80% yield of chromatographically pure sulfone **12** (*m/e* 440.2385). The NMR spectrum of **12** exhibited peaks at 0.92 [s, 6 H, $C(CH_3)_2$], 1.68 (br s, 3 H, olefinic methyl), 2.41 (s, 3 H, $ArCH_3$), 2.85 (m, 2 H, $-CH_2SO_2$), 3.85 (d, 2 H, CH_2O), 4.38 (s, 2H, OCH_2Ar), 5.12 (m, 2 H, −CH=CH−), 5.30 (t, 1 H, =CH−), 7.18 (s, 5 H, $-C_6H_5$), and an AB quartet (4 H) centered at 7.42.



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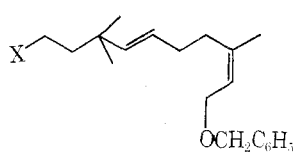
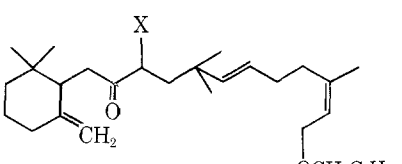


9, X = OH
10, X = OMs
11, X = I
12, X = $SO_2C_6H_4CH_3$

Metalation of sulfone **12** at −20° with *n*-butyllithium in tetrahydrofuran followed by addition of aldehyde **7** (−20°) afforded an adduct which was immediately oxidized (Jones reagent) to keto sulfone **13** in ~40% overall yield. The carbon-sulfur bond of **13** was readily cleaved (3% Na–Hg, ethanol, room temperature, 1 hr) in 77% yield producing intermediate **14** (*m/e* 450.3501).[15] Methylenation[13] of **14** (methylenetriphenylphosphorane, DMSO, 65°, 48 hr) afforded benzyl ether **15** (80%) (*m/e* 448.3692) which upon debenzylation (lithium, liquid ammonia, −78°, 30 min) resulted in an 83% yield of chromatographically pure (±)-diumycinol (**1**). The NMR and ir spectra of synthetic (±)-**1** were in agreement with reference spectra of natural diumycinol kindly provided by Dr. W. A. Slusarchyk. The NMR spectrum (60 MHz, $CDCl_3$) of synthetic **1** displayed three sharp singlets at 0.87 (3 H), 0.95 (3 H), and 0.98 (6 H), a broad singlet at 1.73 (3 H), a doublet centered at 4.12 (2 H), and multiplets located at 4.80–4.45 (4 H) and 5.40 (3 H). The 250-MHz NMR spectrum (CCl_4) of synthetic **1** cleanly separates the four terminal methylene protons from each other as well as the trisubstituted olefinic proton from the trans-disubstituted olefinic protons (Figure 1).



13, X = $SO_2C_6H_4CH_3$
14, X = H

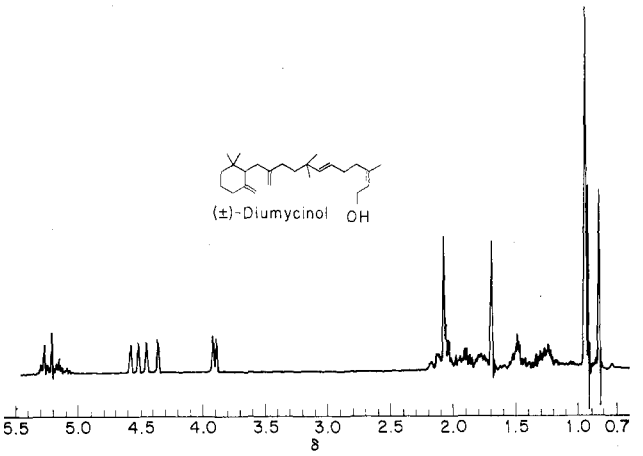
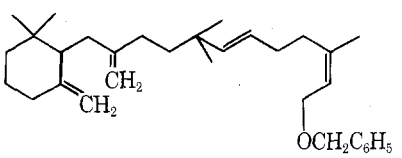


Figure 1. 250-MHz ^1H NMR spectrum of synthetic (±)-diumycinol in CCl_4 with TMS as internal standard.



15

Acknowledgment. This investigation was supported in part by a Public Health Service Research Grant from the National Cancer Institute (CA 13689) and Eli Lilly and Co. NMR spectra were obtained on facilities (250 MHz) partially supported by Public Health Service Grant RR 00297. We thank Dr. W. A. Slusarchyk (The Squibb Institute for Medical Research) for supplying us with reference spectra of natural diumycinol and Mr. Bernard Kane (Glidden Organics) for generous gifts of nerol.

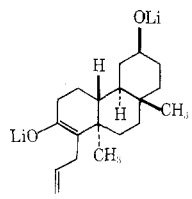
Supplementary Material Available. The Experiment Section will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2261.

References and Notes

(1) W. A. Slusarchyk, J. A. Osband, and F. L. Weisenborn, *J. Am. Chem. Soc.*, **92**, 4486 (1970); W. A. Slusarchyk, J. A. Osband, and F. L. Weisenborn, *Tetrahedron*, **29**, 1465 (1973).
(2) For the use and extension of enolate trapping[3] to a cyclopropyl ketone, see G. Stork, S. Uyeo, T. Wakamatsu, P. A. Grieco, and J. Labovitz, *J. Am. Chem. Soc.*, **93**, 4945 (1971); also see W. G. Dauben and E. J. Deviny, *J. Org. Chem.*, **31**, 3794 (1966).
(3) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Am. Chem. Soc.*, **87**, 275 (1965).

(4) For other methods of kinetic generation of enolates, cf. (a) M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964); (b) D. Caine, *J. Org. Chem.*, **29**, 1868 (1964); (c) G. Stork and P. F. Hudrlik, *J. Am. Chem. Soc.*, **90**, 4462 (1968); (d) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969); (e) R. K. Boeckman, Jr., *ibid.*, **39**, 275 (1974); (f) R. M. Coates and L. O. Sandefur, *ibid.*, **39**, 275 (1974).

(5) It has recently been suggested[4e] that, when β substitution is present, enolate equilibration, resulting in loss of regiospecificity, will be a major, if not exclusive, process. With reference to enolate **3**, we have found this not to be the case (vide supra).[6] To our knowledge two examples exist (cf. i[2] and ii[4f]) in which α,β,β,β-tetrasubstituted enolates undergo regiospecific alkylation with no enolate equilibration.



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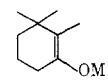
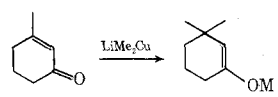


ii

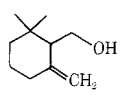
(6) S. Danishefsky and J. Eggler have regiospecifically generated enolate iii from 3-methylcyclohexenone and alkylated exclusively with methyl iodide at C-2 (private communication).



iii

(7) NMR spectra (CCl_4, 60 MHz) and ir spectra were obtained for all intermediates and were in every instance in accord with the assigned structure. Chemical shifts are expressed in parts per million downfield from TMS and coupling constants are expressed in hertz. Satisfactory C, H data and/or high resolution mass spectral data were obtained for all intermediates. Yields are for chromatographically pure substances unless indicated otherwise.

(8) Compound **7** was identical in all respects with a sample prepared from the homoallylic alcohol iv[9] via mesylation, displacement by cyanide ion, and reduction (DIBAL).



iv

(9) We thank Bernard Kane, Glidden Organics, Jacksonville, Fla., for a generous gift of iv.

(10) Treatment of 3-methylcyclohexenone with dimethyloxosulfonium methylide in DMSO afforded cyclopropyl ketone **2** in ~90% yield according to the procedure of E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).

(11) Reductive alkylation of 2 provided exclusively the C-2 allylated ketone **4** (R = allyl). A solution of 372 mg (3 mmol) of **2** in 12 ml of dry glyme and 0.28 ml (3 mmol) of *tert*-butyl alcohol was added to 63 mg (9 mmol) of lithium in 125 ml of anhydrous liquid ammonia. After 40 min, allyl bromide (2 ml) was added all at once. Evaporation of the ammonia gave the desired ketone **4** (R = allyl) in ~70% yield after chromatography. Similarly, methyl iodide (73%) and methallyl bromide (35%) underwent exclusive C-2 alkylation. No products resulting from enolate equilibration or polyalkylation could be detected by GPC analysis.[5] Attempts to alkylate **3** with methyl bromoacetate resulted in a disappointingly low yield (<10%) of C-2 alkylated product. It is apparent from the above that reductive alkylations can be accomplished regiospecifically, albeit in low yield in some instances, under mild conditions with β-substituted cyclopropyl ketones.

(12) A. W. Herriott and D. Picker, *Tetrahedron Lett.*, 1511 (1974).

(13) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(14) P. A. Grieco, Y. Masaki, and D. Boxler, *J. Am. Chem. Soc.*, **97**, 1597 (1975).

(15) Attempts to prepare **14** directly via the Grignard reagent derived from iodide **11** followed by oxidation were thwarted by our inability to prepare the required Grignard reagent. Presumably this was due to traces of water or peroxides which we were not able to get rid of.

(16) Fellow of the Alfred P. Sloan Foundation, 1974–1976.

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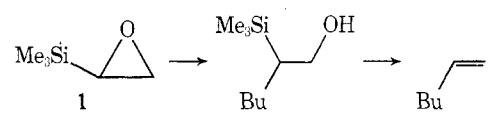
Received March 27, 1975

Reactions of α,β-Epoxysilanes with Organocuprate Reagents. A New Stereospecific Olefin Synthesis[1]

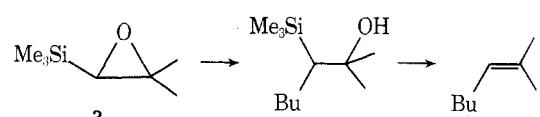
Summary: α,β-Epoxysilanes react with organocuprate reagents in a regio- and stereospecific manner to give good yields of β-hydroxyalkylsilanes, which can be stereospecifically converted to olefins in high yield under mild conditions.

Sir: Olefin-forming elimination reactions of β-hydroxyalkylsilanes have recently been used for the synthesis of a wide variety of compounds;[2] usually isomeric mixtures of cis and trans olefins have been formed. Using a diastereomerically enriched β-hydroxyalkylsilane, we have recently shown that these elimination reactions are stereospecific, and that the acid- and base-induced reactions take opposite stereochemical courses.[3] We now report the first method for the regio- and stereospecific synthesis of β-hydroxyalkylsilanes.[4] This method, coupled with the facile elimination reactions, provides a new, highly stereospecific olefin synthesis of potential generality, and in addition constitutes a definitive proof of the stereochemical course of the elimination reactions of β-hydroxyalkylsilanes.

We have found that the reactions of α,β-epoxysilanes[5] with organocuprate reagents[8] result in regiospecific opening of the epoxide ring to form β-hydroxyalkylsilanes in good yields.[9] Thus, treatment of trimethylsilylethylene oxide (**1**)[10] with lithium di-*n*-butyl cuprate[11] (2 equiv, ether, −25°, 5 hr) produced, in 88% yield, 2-trimethylsilyl-1-hexanol (**2**).[12,13] A similar reaction with epoxide **3**[12] (prepared from isobutenyltrimethylsilane[14] in 79% yield by treatment with *m*-chloroperbenzoic acid in CH_2Cl_2) yielded the alcohol **4**[12,15] in 75% yield.



1 2



3 4

Both silyl alcohols underwent facile β elimination reactions to the corresponding olefins. Treatment of alcohol **2** with potassium hydride (THF, room temperature, 1 hr) produced 1-hexene in 95% yield by VPC; treatment of alcohol **4** with sodium acetate in acetic acid (room temperature, 1 hr) gave 2-methyl-2-heptene in quantitative yield (by NMR; isolated yield 81%).

To determine the stereospecificity of these reactions, we have treated both cis and trans epoxysilanes **6c** and **6t** with an organocuprate reagent and have subjected the resulting β-hydroxyalkylsilanes to the conditions which we have previously shown to cause stereospecific β elimination.[3] The epoxides were synthesized in the following manner. *cis*-1-Pentenyltrimethylsilane (**5c**)[12,16,17] (98% cis by VPC) [ir (film) 6.23, 13.1 μm; NMR (CCl_4) δ 5.32 (d, 1 H, J = 14 Hz), 6.16 (m, 1 H)] was treated with *m*-chloroperbenzoic acid in CH_2Cl_2 to give, in 65% yield, the cis epoxide **6c**[12] [NMR (CCl_4) δ 1.90 (d, 1 H, J = 5 Hz), 2.83 (m, 1 H); mass spectrum *m/e* 158.1115 (calcd for $C_8H_{18}OSi$: 158.1126)]. An analogous sequence served to convert *trans*-1-pentenyltrimethylsilane (**5t**)[12,16b,19] [ir (film) 6.20, 10.1 μm; NMR (CCl_4) δ 5.52 (d, 1 H, J = 19 Hz), 6.02 (m, 1 H)] to the trans epoxide **6t**[12] [NMR ($CHCl_3$) δ 1.91 (d, 1 H, J = 4 Hz), 2.73