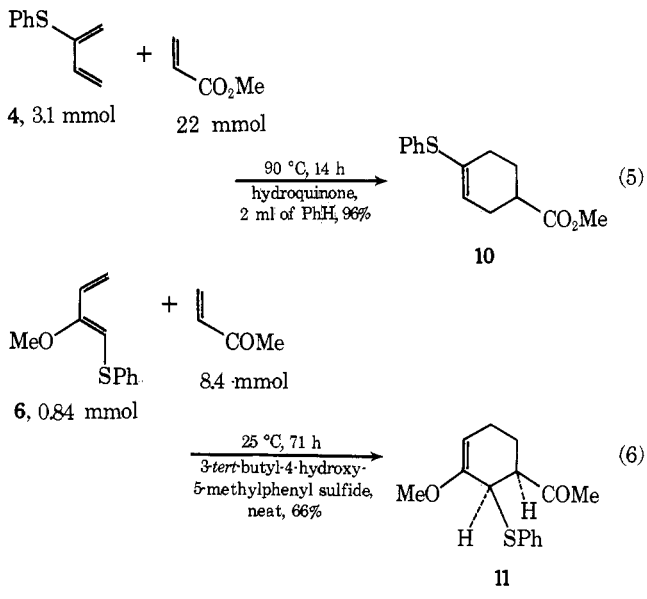


presence of a trace of radical polymerization inhibitor. The yields in the equations are not optimized and are for purified adducts.

Evans[14] has shown that **2** is capable of condensing with methyl vinyl ketone and maleic anhydride and that its sulfoxide forms useful Diels–Alder adducts with electron-rich dienophiles. In order to demonstrate that the adducts in reaction 4 do not include an allylic rearrangement product[15] of **8** and/or **9**, the C_1 proton of **1** was readily removed (CH_3Li–HMPA) and replaced by deuterium (D_2O); the resulting diene (**7**) gave an adduct lacking NMR peaks for the protons labeled Y in **8** and **9**. The structures of **8** and **9** (Y = H) were confirmed by 250-MHz ^1H NMR decoupling experiments on the mixture.

The structure of **11** was unequivocally established by the same technique. The absorption at 3.83 ppm for the CHS proton appeared as a broad doublet (J = 4.0 Hz) which collapsed to a broad singlet upon irradiation at the frequency of the methine hydrogen adjacent to the carbonyl. The signal for the latter, an eight-line multiplet centered at 2.71 ppm, collapsed to a clean doublet of doublets (J_{ax-ax} = 13 Hz; J_{ax-eq} = 2.5 Hz) upon irradiation at 3.83 ppm. Thus, the acetyl group is equatorial and adjacent to a quasiaxial phenylthio group.

The syntheses herein described of dienes substituted by phenylthio groups are far superior in yield, simplicity, and stereospecificity to any thus far reported.[11,13,14,16] The importance of these dienes lies in their Diels–Alder adducts which bear synthetically manipulatable functionality in fixed regiospecific relationships. Adduct **11** is a striking example in that the potential ketone function is meta to the acetyl group in contrast to the para orientation of the alkoxy groups in adducts of other 2-alkoxybutadienes.[17,18] The exploitation of these now accessible dienes and their adducts is receiving considerable attention in our laboratory and will be described in due course.

Acknowledgment. We thank Dr. Samuel Danishefsky for stimulating suggestions, Mr. Robert Bittner for recording the 250-MHz NMR spectra, Messrs. Vance Bell and Glen Herman for recording the mass spectra, and the National Institutes of Health for support of this work through Grant GM 20707.

References and Notes

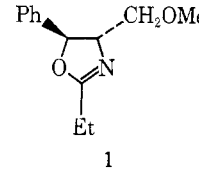
(1) Taken in part from the Ph.D. Thesis of Albert J. Mura, Jr., University of Pittsburgh, 1976.
(2) (a) T. Cohen, G. Herman, J. R. Falck, and A. J. Mura, Jr., *J. Org. Chem.*, **40**, 812 (1975); (b) T. Cohen, D. Kuhn, and J. R. Falck, *J. Am. Chem. Soc.*, **97**, 4749 (1975).
(3) New compounds gave satisfactory spectral and elemental composition data.
(4) In addition to these examples, we have prepared 1,3-bis(phenylthio)-1,3-butadiene by the procedures of eq 1 and 2 starting with commercial $MeCOCH_2CH(OMe)_2$ as well as 1-phenylthio-2-methyl-1,3-butadiene by elimination of thiophenol from 1,3-bis(phenylthio)-2-methyl-1-butene;[5] both undergo Diels–Alder reactions and are thus, presumably, of *E* configuration.
(5) T. Cohen, D. A. Bennett, and A. J. Mura, Jr., *J. Org. Chem.*, **41**, 2506 (1976).
(6) Preparation of bis(phenylthio)methane: K. Uneyama, H. Namba, and S. Oae, *Bull. Chem. Soc. Jpn.*, **41**, 1928 (1968). Preparation of lithio derivative: E. J. Corey and D. Seebach, *J. Org. Chem.*, **31**, 4097 (1966).
(7) R. G. Salomon and J. K. Kochi, *J. Am. Chem. Soc.*, **95**, 3300 (1973).
(8) If the amine is present during the first stage of the reaction at 0 °C, 2,4-bis(phenylthio)-1-butene, the undesirable product of Hofmann elimination, is also formed.
(9) Diene **2** gave a single peak on a support coated (OV-17) open tubular (SCOT) GC column[10] which is capable of almost complete separation of the *E* and *Z*[11] isomers. Diene **6** gave one TLC spot and its ^1H NMR spectrum exhibited a very sharp methyl peak at 3.70 and other absorptions at 4.98–5.60 (8-line multiplet, 2 H, CH_2), 5.78 (s, 1 H, SCH), 5.93–6.43 (quart., 1 H, vinyl), and 7.06–7.50 ppm (m, 5 H, aromatic).
(10) Perkin-Elmer Corp.
(11) E. N. Prilezhaeva, V. N. Petrov, and A. N. Khudyakova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **5**, 1097 (1968); *Engl. Trans.*, **5**, 1042 (1968).
(12) The Diels–Alder adduct of **4** with maleic anhydride was also prepared and was found to have the reported melting point.[13]
(13) K. D. Gundermann and P. Holtmann, *Angew. Chem., Int. Ed. Engl.*, **5**, 668 (1966).
(14) D. A. Evans, C. A. Bryan, and C. L. Sims, *J. Am. Chem. Soc.*, **94**, 2891 (1972).
(15) H. Kwart and N. Johnson, *J. Am. Chem. Soc.*, **92**, 6064 (1970).
(16) Samples of diene **2** prepared as in ref 2 and 14 (the latter kindly supplied by Dr. Sarah Danishefsky) were contaminated by *Z* isomer. A newly reported preparation of **2** proceeds in poor yield and in unspecified stereochemistry: I. Kuwajima, K. Sugimoto, and T. Murofushi, *Chem. Lett.*, 625 (1974).
(17) Reviews of Diels–Alder reactions: Y. A. Titov, *Russian Chem. Rev.*, **31**, 267 (1962); J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **5**, 211 (1966); **6**, 16 (1967).
(18) For a particularly elegant solution to the problem raised by the failure of 2-alkyl-1,3-butadienes to give meta Diels–Alder adducts as major products, see G. Büchi and J. E. Powell, Jr., *J. Am. Chem. Soc.*, **92**, 3126 (1970).
(19) (a) Andrew Mellon Predoctoral Fellow. (b) Undergraduate Research Participant.

Theodore Cohen,* Albert J. Mura, Jr.[19a]
David W. Shull, Elaine R. Fogel[19b]
Robert J. Ruffner,[19b] **J. R. Falck**
Chemistry Department, University of Pittsburgh
Pittsburgh, Pennsylvania 15260
Received July 27, 1976

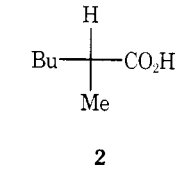
Preparation and Alkylation of a New Chiral Oxazoline from L-Serine

Summary: A new chiral oxazoline was prepared from L-serine, and its alkylation leads to asymmetric induction which is the reverse of that observed for other oxazolines.

Sir: The use of chiral oxazolines in the preparation of optically active α-substituted carboxylic acids has been demonstrated by Meyers. For example, lithiation of **1** followed by treatment



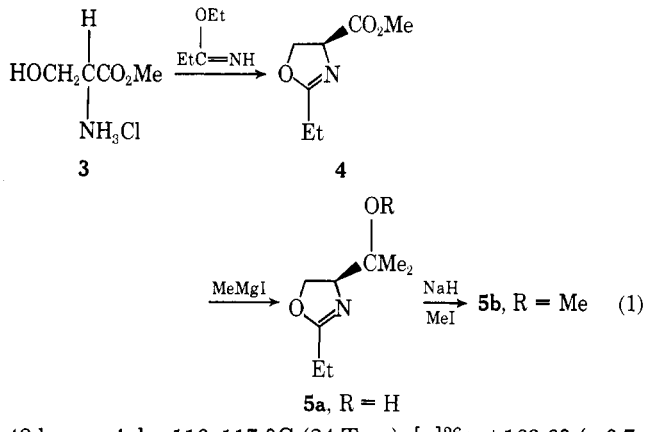
1



2

with 1-iodobutane gives an alkylated oxazoline which may be converted by acidic hydrolysis into (*S*)-(+)-2-methylhexanoic acid, **2**, with 78% optical purity.[1] We wish to report the preparation of a new chiral oxazoline related to **1**, along with some unexpected results from preliminary studies of its alkylation and hydrolysis.

The new chiral oxazoline was prepared from the methyl ester hydrochloride, **3**, of L-serine which was converted by sequence 1 through **4** and **5a** to **5b**.[2] Reaction of **3** with ethyl propionimidate[3] in dichloromethane at room temperature for



3 4

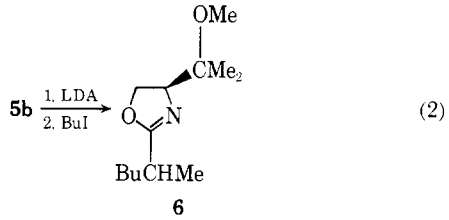
5a, R = H

48 h gave **4**, bp 116–117 °C (24 Torr), $[\alpha]^{26}D$ +163.6° (*c* 6.7, $CHCl_3$), in 90% yield.[4] The ir spectrum of **4** included absorptions at 1740 and 1660 cm^{-1} (C=O and C=N), while the NMR spectrum showed signals at 3.74 (s, 3 H, OMe), 2.32 (q, J = 7, 2 H) and 1.15 (t, J = 7, 3 H) (CH_2CH_3), and overlapping signals at 4.3–4.9 for the three ring protons.

Addition of **4** to 2.2 equiv of methylmagnesium iodide in ether to maintain reflux gave 75% **5a** which was isolated by treatment of the reaction mixture with saturated NH_4Cl and repeated extraction of the slurry with dichloromethane. Spinning band distillation gave a colorless liquid, bp 46 °C (0.1 Torr), $[\alpha]^{25}D$ +84.8° (*c* 8.4, $CHCl_3$). The ir spectrum included the expected broad absorption for OH at 3380 cm^{-1} along with the oxazoline absorption at 1665 cm^{-1}. The NMR spectrum, in addition to the overlapping signals at 3.8–4.3 for the three ring protons and the ethyl quartet and triplet at 2.30 and 1.14, included a broad singlet at 3.02 for OH and two three-proton singlets for the diastereotopic geminal methyl groups at 1.20 and 1.12.

The methyl ether was formed when **5a** in ether was treated with NaH and then stirred with iodomethane at room temperature for 5 days to give 87% **5b**, bp 94 °C (25 Torr), $[\alpha]^{26}D$ +81.7° (*c* 8.8, $CHCl_3$). The ir spectrum included the usual oxazoline absorption at 1665 cm^{-1}, while signals in the NMR appeared at 4.0–4.4 (overlapping, 3 H, ring protons), 3.18 (s, 3 H, OMe), 2.14 (q, J = 7, 2 H) and 1.12 (t, J = 7, 3 H) (CH_2CH_3), and 1.21 (s, 3 H) and 1.00 (s, 3 H) (CMe_2). The mass spectrum included as the base peak a fragment of *m/e* 73.[5]

Alkylation of **5b** was carried out under N_2 by dropwise addition of **5b** in tetrahydrofuran (THF) to a solution containing a 10% excess of lithium diisopropylamide (LDA) (from diisopropylamine and butyllithium) in THF at −78 °C and stirring for 45 min. The resulting solution was cooled to −98 °C (liquid N_2–MeOH), and a solution of 1-iodobutane (10% excess) in THF was added over 2 h. The mixture was warmed to room temperature, washed with saturated brine, and distilled to give 61% **6** (eq 2), bp 60–61 °C (0.1 Torr), $[\alpha]^{26}D$ +72.3° (*c* 9.9, $CHCl_3$). It was found that **6** could be hydrolyzed most conveniently by adding 6.2 g of the oxazoline to 100 ml of 4 N H_2SO_4 and carrying out a direct steam distillation, removing the carboxylic acid as it was formed, and adding water to the pot periodically to maintain relatively constant volume. In this way 88% **2** was obtained after about 90 min, during which 70 ml of distillate was collected. The product was isolated in very pure form (99.4% by GC) after ether extraction from the distillate and distillation as a colorless oil, bp 124–125 °C (30 Torr). The material was identical in the ir with authentic 2-methylhexanoic acid.[6]



6

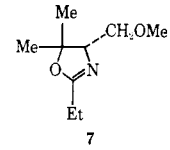
Measurement of the optical activity of **2** obtained as described led, unexpectedly, to a rotation of $[\alpha]^{25}D$ +14.1° (neat), indicating (*S*)-(+)-2-methylhexanoic acid with an optical purity of 75%. Meyers has presented evidence for the alkylation of **1** which indicates that the attack of the alkyl group on the lithio derivative occurs so that the alkyl group approaches from the side of the intermediate on which the ether substituent is located. Since the configuration of the chiral center in **5b** is opposite that of the corresponding center in **1**, then one might have predicted that the acid produced should have the *R* configuration, and the observed results are the opposite of what might have been predicted.

The above results suggest that with the new oxazoline, factors not observed in Meyers' cases, possibly steric influences of the bulky substituent, are operative. Further studies are in progress in order to determine the nature of these effects.

Acknowledgment. The authors thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. Stimulating discussion and helpful suggestions from Professor A. I. Meyers are appreciated.

References and Notes

(1) A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, *J. Am. Chem. Soc.*, **98**, 567 (1976), and references cited therein.
(2) All new compounds gave satisfactory analysis for C, H, and N. Data reported for all compounds are for samples analyzed by GC with a minimum purity of 99%. Ir data are for neat films, and NMR data are reported as δ in parts per million relative to TMS in $CDCl_3$.
(3) Ethyl propionimidate hydrochloride was prepared by the method of A. W. Dox, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1941, p 5. Free ethyl propionimidate was isolated by a modification of the method of F. C. Schaefer and G. Peters, *J. Org. Chem.*, **26**, 2778 (1961).
(4) The method was modeled after D. F. Elliot, *J. Chem. Soc.*, 589 (1949).
(5) The base peak is assigned as $Me_2C{=}O^+Me$. The prominence of this fragment effectively eliminates the possibility of rearrangement to **7** during the



7

synthetic scheme as an alternative explanation of the subsequent alkylation data.
(6) C. J. Pouchert, "The Aldrich Library of Infrared Spectra", 2nd ed, Aldrich Chemical Co., Milwaukee, Wis., 1975, p 259.

John F. Hansen,* Curt S. Cooper
Department of Chemistry, Illinois State University
Normal, Illinois 61761
Received May 25, 1976