Optically Active Heteroaromatic Compounds. VI. 3-Substituted Furans and Thiophenes from α,β-Unsaturated Aldehydes

C. Botteghi*

Technisch Chemisches Laboratorium, Eidgenössische Technische Hochschule, Zürich, Switzerland

L. Lardicci and R. Menicagli

Istituto di Chimica Organica, Facoltà di Scienze Mat., Fis., e Nat., Università di Pisa, 56100 Pisa, Italy

Received November 29, 1972

The hydroformylation of the acetals of the 2-substituted α,β-unsaturated aldehydes (**1**) in the presence of rhodium catalysts results in the exclusive formation of the monoacetals of the corresponding succinaldehydes (**2**) with 60–80% yield. Compounds **2** undergo cyclization reactions to the corresponding 3-substituted furans (**4**) and thiophenes (**5**) with satisfactory yields (40–77%). This synthesis is suitable for the preparation of optically active 3-*sec*-butylfuran (**4a**), thiophene (**5a**), and pyrrole (**6**). Although in the formation of **4a**, **5a**, and **6** racemization up to 26% was observed, the present method for obtaining such optically active heterocyclic compounds appears to be more convenient than others described in the literature.

Investigations of the steric course of the synthesis and of the chiroptical properties of simple optically active heteroaromatic systems[1-4] are in progress in our laboratories. The present report is concerned with 3-substituted furans and thiophenes, which are not readily accessible compounds and which represent the structural unit embodied in many natural products,[5-7] and are intermediates with increasing pharmacological interest.[8]

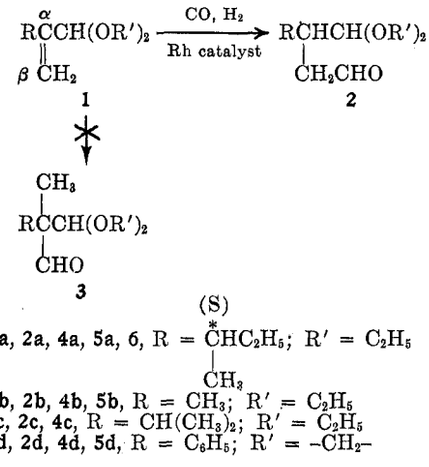
As previously pointed out by some authors,[5,7] the synthesis of a furan or thiophene ring bearing only a 3 substituent usually requires many steps with consequent low overall yields.[9,10] The best syntheses of such compounds appear to be those based upon the cyclization of suitable 1,4-dicarbonyl compounds or their derivatives.[6,11] Key precursors are the corresponding 2-substituted succinaldehydes, which are now readily available through rhodium-catalyzed hydroformylation[12,13] of suitable 2-substituted acrolein acetals.

We wish to describe here (1) examples of this convenient synthetic approach to 3-alkyl- or 3-aryl-substituted furans and thiophenes starting with the now easily available α,β-unsaturated aldehydes,[14] a method that may also be used for obtaining optically active 3-alkylfurans, thiophenes, and pyrroles; and (2) the relationship between the sign of the optical rotation, absolute configuration, optical purity, and rotatory power.

Results

Synthesis of Succinaldehyde Monoacetals (2).—The hydroformylation of α,β-unsaturated aldehyde acetals (**1**) was carried out in the presence of *trans*-bis(triphenylphosphine)carbonylchlororhodium(I)[15] as catalyst[12,16,17] and triethylamine in benzene solution.[16] The presence of the amine in the reaction mixture prevents side reactions during the hydroformylation. The hydroformylation of **1** in the presence of $RhCl(CO)(PPh_3)_2$ results in the exclusive formation of **2** (Scheme I), which corresponds to a β introduction of the formyl

Scheme I



group as confirmed by glpc and nmr analysis. The results obtained in hydroformylation experiments of **1** are summarized in Table I. Compounds **2**, which were recovered by simple distillation from the reaction mixture in the presence of small amounts of sodium or potassium carbonate, are quite stable intermediates, at least at room temperature.

Cyclization to Heterocycles.—Distillation of **2** in the presence of aqueous sulfuric acid promotes cyclization to the corresponding furan **4** in a 40–80% yield[19]

(1) C. Botteghi, L. Lardicci, E. Benedetti, and P. Pino, *Chim. Ind. (Milan)*, **49**, 171 (1967).
(2) L. Lardicci, R. Rossi, S. Pucci, M. Aglietto, C. Botteghi, and P. Pino, *ibid.*, **50**, 227 (1968).
(3) L. Lardicci, C. Botteghi, and P. Salvadori, *Gazz. Chim. Ital.*, **98**, 760 (1968).
(4) C. Botteghi, E. Guetti, G. Ceccarelli, and L. Lardicci, *ibid.*, **102**, 945 (1972).
(5) M. A. Gianturco and P. Friedel, *Can. J. Chem.*, **44**, 1083 (1964).
(6) P. Bosshard and C. H. Eugster, *Advan. Heterocycl. Chem.*, **7**, 378 (1966), and references cited therein.
(7) S. R. Ohlsen and S. Turner, *J. Chem. Soc. C*, 1632 (1971).
(8) S. Gronowitz, *Advan. Heterocycl. Chem.*, **1**, 119 (1963), and references cited therein.
(9) N. Elming, *Acta Chem. Scand.*, **6**, 605 (1952).
(10) D. Miller, *J. Chem. Soc. C*, 12 (1969).
(11) M. E. Garst and T. A. Spencer, *J. Amer. Chem. Soc.*, **95**, 250 (1973); see also ref 8 and literature cited therein.
(12) C. Botteghi and L. Lardicci, *Chim. Ind. (Milan)*, **52**, 265 (1970).
(13) C. Botteghi, G. Consiglio, G. Ceccarelli, and A. Stefani, *J. Org. Chem.*, **37**, 1835 (1972), and ref 12 therein.
(14) L. Lardicci, F. Navari, and R. Rossi, *Tetrahedron*, **22**, 1991 (1966).
(15) D. Evans, J. A. Osborn, and G. Wilkinson, *Inorg. Syn.*, **11**, 99 (1968).
(16) D. Evans, J. A. Osborn, and G. Wilkinson, *J. Chem. Soc. C*, 3133 (1968).
(17) The advantage of using rhodium catalysts in the hydroformylation of acrolein acetals was recently pointed out by Maeda and Yoshida.[18]
(18) I. Maeda and R. Yoshida, *Bull. Chem. Soc. Jap.*, **41**, 2969 (1968).
(19) The best yields were obtained when **4** was distilled off from the reaction mixture as formed.

TABLE I

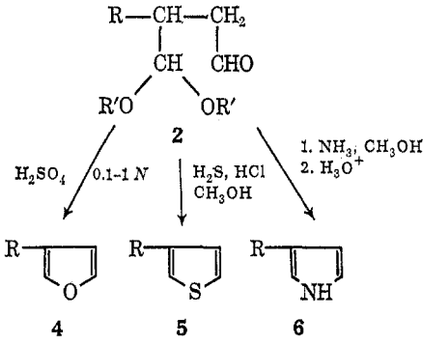
HYDROFORMYLATION OF α,β-UNSATURATED ACETALS (1) IN THE PRESENCE OF RHODIUM CATALYSTS TO THE CORRESPONDING ALKYL- AND ARYLSUCCINALDEHYDE MONOACETALS (2)

Substrate[a]	Concn, mol/l.	Catalyst	Concn, mmol/l.	Reaction pressure CO:H_2 1:1, atm	Reaction temp, °C	Reaction time, hr	$[\alpha]^{25}D$, deg (*n*-heptane)	Yield,[b] %
1a	1.23	$RhCl(CO)(PPh_3)_2$	5.82	100[c]	95	5	−6.94	85
	1.34		1.76	100[c]	80	*i*	−6.88	80
	1.50		2.10	100[c]	110	6	−6.84	79
	1.02		2.3	100[d]	80	6	*i*	80
1b	0.90	$RhCl(CO)(PPh_3)_2$	4.64	100[c]	75	50 min		70
	2.12		2.97	100[c]	80	2		76
	1.92		0.52	100[d]	80	24		70
1c	1.20	$RhCl(CO)(PPh_3)_2$	2.20	100[d]	105	5.5		75
	1.20		2.20	100[c]	110	5		60
	1.62	Rh[e,f]	4.00	10[c]	110	Very slow gas absorption		*i*
	1.62	Rh,[e] $P(OPh)_3$[g]	4.00	20[c]	110	73		60
1d	1.00	$RhCl(CO)(PPh_3)_2$	2.48	100[d]	90	5.5		80[h]

[a] The reaction mixture in benzene contains 0.7–0.75 mol of triethylamine per mol of substrate. [b] The yields are calculated on the isolated (by distillation) hydroformylation product. [c] Initial pressure at room temperature. [d] Experiment carried out at constant pressure at the reaction temperature. [e] 5% of rhodium on charcoal. [f] 0.5 ml of triethylamine was added to the reaction mixture. [g] 2.4×10^{-2} mol/l. [h] 15% of hydrogenation product was detected by nmr analysis. [i] Not determined.

(Scheme II). Cyclization of **2** to the corresponding thiophene **5** (50–60% yield) and pyrrole **6** (24% yield)

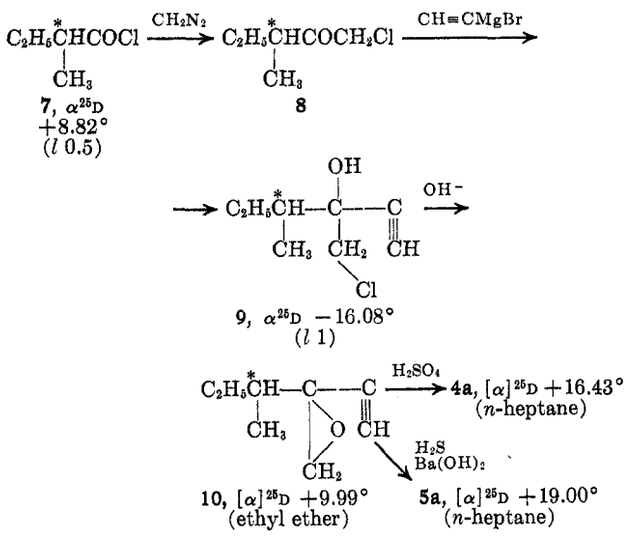
SCHEME II



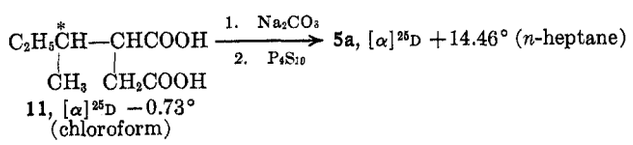
derivatives was accomplished in methanol solution by treatment with hydrogen sulfide and hydrogen chloride or by treatment with anhydrous ammonia followed by distillation in the presence of aqueous citric acid (Scheme II). The structures of **4**, **5**, and **6** were unequivocally confirmed by nmr and mass spectroscopy and, whenever possible, by direct comparison with authentic samples. The crude **4** and **5**, as recovered by distillation from the reaction mixture, were of satisfactory chemical purity ($\geq$95% by glpc).[20] Table II gives results obtained in the cyclization of optically active **2** to the corresponding **4a** and **5a**.

Results of ring closures with the optically active compound **2a** were compared with prior art methods: (1) those of Miller[10] and Perveev,[21] shown in Scheme III, and (2) the ring closure of optically active *sec*-butylsuccinic acid[22] (**11**) which is available by resolution methods[23] (Scheme IV). The yields in the cyclization of **10** and **11** and the chemical purity of the products **4a** and **5a** were similar to those using Schemes I and II.

SCHEME III



SCHEME IV



Discussion

The results reported in Table I clearly point out that the synthesis of the 2-substituted succinaldehyde monoacetals (**2**) can be achieved in satisfactory yield (60–85%) and with a high degree of chemical purity ($\geq$95%) through the hydroformylation of the α-alkylacrolein acetals **1**, which are readily available compounds.[24–26]

(20) In the cyclization of **2** to **5** a small amount of **4** (2–3% by glpc) was formed.

(21) F. Ya. Perveev and N. K. Kudryashova, *Zh. Obshch. Khim.*, **23**, 976 (1953); *Chem. Abstr.*, **48**, 8219 (1954); *Zh. Obshch. Khim.*, **23**, 1569 (1953); *Chem. Abstr.*, **48**, 10727 (1954).

(22) C. Botteghi, G. Ceccarelli, and G. Consiglio, *J. Prakt. Chem.*, **314**, 840 (1972).

(23) A. Fredga and U. Sahlberg, *Ark. Kemi*, **A18**, 8 (1944).

(24) J. A. Van Allan, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 21.

(25) R. Quelet and J. D'Angelo, *Bull. Soc. Chim. Fr.*, 1503 (1967).

(26) E. Elkik, *ibid.*, 283 (1968).

TABLE II

CYCLIZATIONS OF THE OPTICALLY ACTIVE 2-ALKYLSUCCINALDEHYDE MONOACETALS (2a) TO THE CORRESPONDING FURANS (4a) AND THIOPHENES (5a)

2a			4a		5a	
$[\alpha]^{25}D$, deg (*n*-heptane)	Reaction conditions	Reaction time, hr	$[\alpha]^{25}D$, deg (*n*-heptane)	Yield, %	$[\alpha]^{25}D$, deg (*n*-heptane)	Yield, %
−6.94	H_2SO_4 0.1 *N*[a]	1	+18.24	77		
−6.88	H_2SO_4 0.1 *N*[a]	1	+19.86	73		
−6.84	H_2SO_4 0.5 *N*[a]	1	+17.91	72		
−6.94	H_2O–CH_3OH[b] H_2S–HCl	2			+24.86	60
−6.94	H_2O–CH_3OH[b] H_2S–HCl	2			+23.96	58

[a] The reaction mixture was heated to the boiling point and **4a** was distilled off as formed. [b] Water–methanol, 1:9 (v/v); reaction temperature 60°.

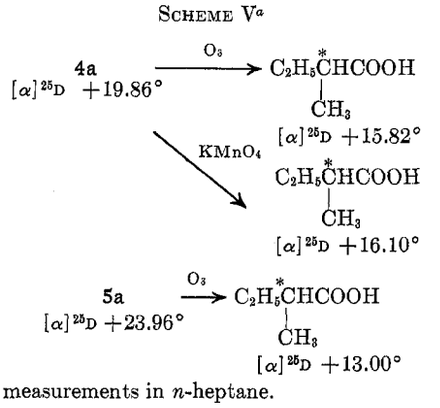
The nature of the α substituent in **1** does not seem to affect the reactivity of the double bond toward the addition of carbon monoxide and hydrogen.

It should also be noted that, while in the rhodium-catalyzed hydroformylation of similar substrates an appreciable extent of α addition can take place,[27,28] in the present case no significant amount (≤2%) of α isomer was detected by glpc and nmr analysis.[29] Compounds **2** represent a very interesting class of 1,4-dicarbonyl compounds which have so far not been described in the literature and appear to be difficult to prepare by classical methods.

While the yields obtained in the cyclization of **2** to (+)-(*S*)-3-*sec*-butylpyrrole are very small (24%), because of the simultaneous formation of high-boiling by-products, they are quite satisfactory (50–60%) in the preparation of the furans **4** and thiophenes **5**. The reaction sequences of Schemes I and II are therefore competitive with those reported in the literature[6,10,11] for similar synthesis.

In order to obtain information on steric course in the preparation of the optically active heterocyclic compounds, **4a** and **5a** were cleaved by ozonolysis to (+)-(*S*)-2-methylbutanoic acid according to a previously described procedure[3,4] (Scheme V). On this basis a

SCHEME V[a]



[a] $[\alpha]^{25}D$ measurements in *n*-heptane.

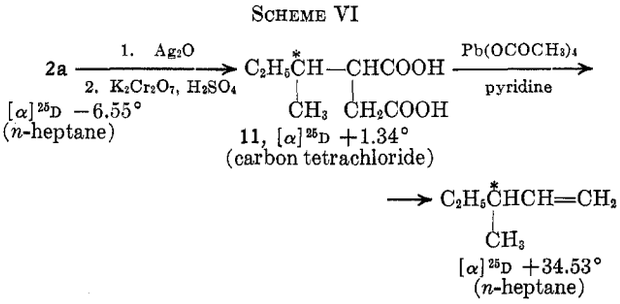
minimum optical purity of 65% for **5a** and 79% for **4a** was calculated; this last value was further confirmed by permanganate oxidation[30] (Scheme V).

The minimum optical purity of the (+)-(*S*)-3-*sec*-butylpyrrole,[31] prepared by us according to Scheme II, was estimated to be 73.5%.[32]

These results indicate, therefore, a 17–30% racemization with respect to the (+)-(*S*)-α-*sec*-butylacrolein[14] (optical purity ~96%) used as starting product.

Because the oxidative processes used have been successfully employed[3,4,30] in the breakdown of optically active heterocyclic systems and since a sample of **5a** does not racemize under the reaction conditions, it can be assumed that the overall racemization is to be attributed to the sequence (+)-(*S*)-α-*sec*-butylacrolein → **1a** → **2a** → **4a** or **5a**. In order to determine in which step of this sequence the maximum racemization takes place, a sample of (+)-(*S*)-α-*sec*-butylacrolein was converted *via* **2a** and its oxidation product, (*S*)-*sec*-butylsuccinic acid (**11**), to (+)-(*S*)-3-methyl-1-pentene[22] (Scheme VI). From the experimental data only

SCHEME VI



a ~5% racemization was found; this result indicates that the hydroformylation process has no effect on the asymmetric carbon atom of **1a**. Thus, it is concluded that racemization primarily takes place during the cyclization process. This is confirmed by the following: (1) poor reproducibility of the rotation power of **4a** and **5a**, which arise from the same substrate **2a**; in all cases the optical purity of **5a** is lower than that of **4a** (Scheme V); (2) an obvious dependence of the optical purity of **4a** on the acidity of the medium (Table II); and (3) the considerable loss of optical activity in the preparation of **6** from **2a** (~18%). Although we are not yet able to postulate reasonable reaction interme-

(27) J. Falbe and N. Huppes, *Brennst.-Chem.*, **48**, 46 (1967).

(28) R. L. Pruett and J. A. Smith, *J. Org. Chem.*, **34**, 327 (1969).

(29) The hydroformylation product obtained under the same reaction conditions from the diethyl acetal of acrolein in practically quantitative yield contained the straight-chain and branched isomer in a 58:42 ratio (glpc).

(30) P. S. Skell and G. P. Bean, *J. Amer. Chem. Soc.*, **84**, 4660 (1962).

(31) J. M. Patterson, L. T. Burka, and M. R. Boyd, *J. Org. Chem.*, **33**, 4033 (1968).

(32) This is based on an $[\alpha]^{25}D$ of +26.98° for optically pure (+)-3-*sec*-butylpyrrole, a value derived from the oxidation experiments of Skell and Bean,[30] but with correction made using a more reliable $[\alpha]^{25}D$ value[33] for 2-bromobutane and a corrected value for (+)-(*S*)-2-methylbutanoic acid.[14]

(33) G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, **91**, 4878 (1969), and ref 30 cited therein.

diates to account for the racemization of the 2-*sec*-butylsuccinaldehyde monoacetals (**2a**) in the cyclization process, it is tentatively concluded that species of considerable ionic character are involved in the ring-closure step, the observed partial racemization taking place in some way through these intermediates. In spite of the above-mentioned limitations, the method described provides a satisfactory synthetic approach to optically active 3-alkylfurans and thiophenes; in fact, using other optically active precursors and procedures already described[10,11,21] (Schemes III and IV), essentially lower optical yields (39–66%) in the preparation of **4a** and **5a** were obtained.

Experimental Section

Boiling points are uncorrected. Glpc analyses were performed on a Perkin-Elmer F-11 chromatograph, using the columns and the temperatures specified. Infrared spectral data were recorded on a Perkin-Elmer 221 spectrometer. Nmr spectra were recorded on a Varian A-60 spectrometer in CCl_4 solution (10%), with TMS as an internal standard (δ 0). Mass spectra were obtained with an Hitachi Perkin-Elmer RNU-6L mass spectrometer. All rotations were taken on a Perkin-Elmer 141 polarimeter in 1-dm or 0.1-dm tubes. Analyses were performed by the Microanalytical Laboratory of the Technical-Chemical Department of ETH (Zürich, Switzerland).

Acetals of 2-Substituted α,β-Unsaturated Aldehydes (1a–d).—Methacrolein from Fluka AG (Switzerland) was used without further purification. (+)-(*S*)-2-*sec*-Butylacrolein and 2-isopropylacrolein were prepared by a general method described in the literature.[14,34]

The corresponding ethyl acetals **1a–c** were prepared according to the procedure described by Van Allan[24] and employed by other authors.[25] The dioxolane of atropic aldehyde (**1d**) was obtained by the method of Elkik[26] in 23% overall yield. The physical constants of **1b–d** were consistent with those reported in the literature.[12,25,26]

Pure **1a** showed bp 73–75° (12 mm); $n^{25}D$ 1.4210; $[\alpha]^{25}D$ +23.75° (*c* 2.901, *n*-heptane).

Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 70.58; H, 12.07.

Monoacetals of 2-Substituted Succinaldehydes (2a–d).—The following two procedures are representative of the hydroformylation experiments.

A.—Into a 0.2-l. autoclave, evacuated from air and containing $RhCl(CO)(PPh_3)_2$ (0.300 g), a solution of **1** (21.6 g, 0.1 mol) and triethylamine (8.42 g, 11.5 ml) in dry benzene (40 ml) was introduced by suction. A mixture of CO and H_2 (1:1) was then introduced to a pressure of 100 atm; the autoclave was then rocked and heated to 80–100°. Reaction started immediately and was allowed to proceed until no more pressure drop was observed. After cooling and release of the pressure, the slightly yellow reaction mixture was evaporated under reduced pressure (100 mm) and the residue was distilled under vacuum over K_2CO_3 to give compounds **2a–d** (60–80% yield) as colorless liquids (Table I).

B.—Following the same experimental procedure, **1c** (0.4 mol) in benzene (200 ml) was hydroformylated (73% yield) in a 0.5-l. autoclave in the presence of 5% Rh/C (2.0 g)[28] and triethylamine (0.5 ml) at 20 atm (CO:H_2 1:1) and 110°. Glpc analyses of **2a–d** (on a 2 m × 2.2 mm 15% polypropylene glycol column at 120–140°) showed only one peak.

The same results were obtained for **2a** and **2b** using a 16 m × 0.5 mm Carbowax 20M support coated column at 160 and 140°, respectively.

2a had bp 67–70° (0.6 mm); $n^{25}D$ 1.4324; $[\alpha]^{25}D$ −6.94° (*c* 3.786, *n*-heptane); ir (liquid film) 1715 cm^{-1} (C=O); nmr (CCl_4) δ 9.64 (m, CHO), 2.21 (m, CH_2CHO).

Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.59; H, 11.03.

2b had bp 80° (13 mm); $n^{25}D$ 1.4190–1.4192; ir (liquid film) 1716 cm^{-1} (C=O); nmr (CCl_4) δ 9.70 (m, CHO), 2.38 (m, CH_2CHO).

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.10; H, 10.39.

2c had bp 110–112° (12 mm); $n^{25}D$ 1.4290; ir (liquid film) 1715 cm^{-1} (C=O); nmr (CCl_4) δ 9.50 (m, CHO), 2.18 (m, CH_2CHO).

Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.60; H, 10.87.

2d had bp 108–112° (0.3 mm); ir (liquid film) 1718 cm^{-1} (C=O); nmr (CCl_4) δ 9.57 (m, CHO), 2.70 (m, CH_2CHO); 2,4-dinitrophenylhydrazone mp 217–219° (*m*-xylene).

Anal. Calcd for $C_{22}H_{18}N_8O_8$: C, 50.58; H, 3.47; N, 21.45. Found: C, 50.67; H, 3.68; N, 21.21.

Cyclization of 2a–c to 3-Alkylfurans (4a–c).—A sample of **2** (0.15 mol) was rapidly added to a boiling solution of 0.1 *N* sulfuric acid (1 l.) and the reaction product was distilled as formed through a short-path distillation apparatus. The liquid product was separated from the water and washed with concentrated solutions of calcium chloride and ammonium chloride. After drying (Na_2SO_4), the crude **4** was distilled over sodium to give a colorless liquid (40–80% yield); glpc analysis (on a 2 m × 2.2 mm 15% polypropylene glycol column at 40–90°) showed only one peak.

4a had bp 130°; $n^{25}D$ 1.4415–1.4417; $[\alpha]^{25}D$ +19.86° (*c* 3.020, *n*-heptane); nmr ($CDCl_3$) δ 6.36 (m, H-4), 7.30 (m, H-2), 7.46 (m, H-5); mass spectrum (70 eV) *m/e* (rel intensity) 95 (100), 67 (30), 41 (23.5), 124 (M^+, 22), 96 (16), 39 (15.5), 81 (11), 27 (9), 28 (8), 109 (7).

4b had bp 62–63° (730 mm); $n^{20}D$ 1.4329–1.4330 (lit.[10] bp 65–66.5°, $n^{21}D$ 1.4299); nmr ($CDCl_3$) δ 6.29 (m, H-4), 7.27 (m, H-2), 7.38 (m, H-5).

4c had bp 111°; $n^{25}D$ 1.4348 (lit.[9] bp 111°, $n^{25}D$ 1.4344); nmr (CCl_4) δ 6.21 (m, H-4), 7.11 (m, H-2), 7.25 (m, H-5); mass spectrum *m/e* (rel intensity) 95 (100), 67 (50.5), 110 (M^+, 47.5), 41 (37), 39 (27.5), 65 (13.5), 27 (11), 18 (10), 28 (8.5), 96 (7.5).

In another experiment **4a**, $[\alpha]^{25}D$ +17.91° (*c* 1.87, *n*-heptane) (optical purity 71%), was prepared in 58% yield by cyclization of **2a**, $[\alpha]^{25}D$ −6.84° (*c* 2.294, *n*-heptane), with 0.5 *N* sulfuric acid.

3-Phenylfuran (4d).—The method of Miller[10] for the cyclization of 3,4-epoxy-3-phenyl-1-butyne was used. A sample of **2d** (3.0 g, 0.0145 mol) in ethanol (15 ml) was added in one portion to 2 *N* sulfuric acid (20 ml), and the mixture was refluxed for 20 min with vigorous stirring. After cooling, the reaction mixture was diluted with water (50 ml) and the resulting oil was extracted exhaustively with pentane. The extracts were dried ($MgSO_4$) and the solvent was evaporated to leave yellow crystals of crude 3-phenylfuran. Sublimation at 60–70° (13 mm) gave pure **4d** (1.16 g, 55% yield): mp 58–59°;[10] nmr (CCl_4) 6.59 (m, H-4), 7.62 (m, H-2), 7.38 (m, H-5), 7.05–7.52 (m, equal to five phenyl ring protons); mass spectrum *m/e* (rel intensity) 115 (100), 144 (M^+, 82.5), 29 (61.5), 63 (16), 89 (15), 33 (15), 116 (13.5), 145 (9.5), 39 (8.5), 65 (7).

Cyclization of 2a–d to 3-Substituted Thiophenes (5a–d).—A sample of **2** (0.1 mol) was dissolved in 90% methanol (200 ml), and a slow stream of hydrogen sulfide was bubbled into the stirred solution during 1 hr at room temperature. The reaction mixture was heated at 50–60° and a stream of hydrogen chloride was allowed to flow onto the surface of the solution. After 2 hr the reaction was complete. The mixture was cooled, diluted with water (600 ml), and extracted with pentane (200 ml). The pentane extracts were dried ($MgSO_4$) and the solvent was removed, yielding a yellow-brown residue which was distilled over sodium to give **5a** and **5b** as colorless liquids (50–60% yield) or crystallized from ethanol to give **5d** as white plates (50% yield).

5a had bp 63° (12 mm); $n^{25}D$ 1.5000; $[\alpha]^{25}D$ +24.86° (*c* 2.88, *n*-heptane); nmr ($CDCl_3$) δ 7.28 (m, H-5), 6.88–7.08 (m, equal to two hydrogens, H-2 and H-4); mass spectrum *m/e* (rel intensity) 111 (100), 140 (M^+, 54.5), 45 (20.5), 97 (20), 77 (19.5), 112 (18), 39 (14), 67 (12), 41 (11), 125 (9).

5b had bp 114–115°; $n^{25}D$ 1.5174 (lit.[35] bp 115.4°, $n^{25}D$ 1.5175). This compound was identified by comparison of its physical constants and its nmr spectrum with those of a commercially available sample.

5d had mp 89° (lit.[36] mp 89.5–90.5°); mass spectrum *m/e* (rel intensity) 160 (M^+, 100), 115 (33), 161 (13), 116 (11), 128 (9.5), 80 (7), 89 (6), 67 (6), 63 (5.5), 45 (4.5).

(+)-(*S*)-**3-*sec*-Butylpyrrole (6).**—Into a solution of **2a** (0.1 mol), $[\alpha]^{25}D$ −6.84° (*c* 2.294, *n*-heptane), in methanol (60 ml)

(34) M. B. Green and H. J. Hickinbottom, *J. Chem. Soc.*, 3266 (1957).

(35) H. D. Hartough in A. Weissberger, "The Chemistry of Heterocyclic Compounds," Interscience, New York, N. Y., 1952, p 72.

(36) S. Gronowitz and N. Gigs, *Acta Chem. Scand.*, **21**(3), 2823 (1967).

a stream of anhydrous ammonia was bubbled during 3 hr at 0°; then the mixture was heated for 1 hr at 40°. The resulting solution was added dropwise during 30 min to a boiling solution of citric acid (40 g) in 1.8 l. of water, and the reaction product was distilled as soon as formed. The recovered yellow oil (7 g) contained 43% of **6** and 36% of another compound (glpc). By preparative glpc at 170° (on a 3 m × 8 mm column packed with 15% polyglycol 4000 on Kieselgur, treated with potassium hydroxide) a pure sample of **6** was obtained:[31] bp 83° (12 mm); $n^{25}D$ 1.4870; $[\alpha]^{25}D$ +19.82° (neat) (optical purity 73%); nmr (CCl_4) δ 6.08 (m, H-4), 6.48 (m, H-2), 6.60 (m, H-5); mass spectrum *m/e* (rel intensity) 94 (100), 123 (M^+, 46), 80 (15.5), 67 (14.5), 108 (14), 93 (14), 95 (13.5), 41 (11.5), 39 (11), 28 (8).

The other compound proved to be recovered **2a** with $[\alpha]^{25}D$ −6.90° (*c* 2.78, *n*-heptane).

(*S*)-1-Chloro-3-methyl-2-pentanone (8).—To an ether solution of diazomethane at 0° was added during 2 hr 28.2 g (0.233 mol) of **7**, $\alpha^{25}D$ +8.82° (*l* 0.5).[37] The reaction mixture was allowed to stand for 12 hr and then saturated with hydrogen chloride at 0°. After stirring for an additional 8 hr at 0° the mixture was hydrolyzed by a described procedure[38] and the ether extracts were dried (Na_2SO_4). After removal of the solvent, distillation of the crude product yielded 16.24 g of **8** (51.5% yield), bp 62–63° (13 mm), $n^{25}D$ 1.4402.

(−)-(*S*)-3-*sec*-Butyl-4-chloro-1-butyn-3-ol (9).—A solution of ethylmagnesium bromide (0.160 mol) in dry THF was added dropwise to 70 ml of the same solvent saturated with acetylene. During this addition a stream of the gas was allowed to bubble into the solution. A sample of **8** (14.0 g, 0.104 mol) in THF (20 ml) was dropped (45 min) into the solution of ethynylmagnesium bromide at 0°. The reaction mixture was allowed to stand for 12 hr and then hydrolyzed by a cold saturated solution of NH_4Cl. The organic layer was separated, washed with water, and dried ($CaSO_4$). The solvent was removed and the residue was distilled, yielding 13.3 g (79.8%) of **9**: bp 83° (15 mm); $n^{25}D$ 1.4662–1.4664; $\alpha^{25}D$ −16.08° (*l* 1).

Anal. Calcd for $C_8H_{13}OCl$: C, 59.81; H, 8.15; Cl, 22.06. Found: C, 60.00; H, 8.06; Cl, 21.74.

(+)-(*S*)-3-*sec*-Butyl-3,4-epoxy-1-butyne (10).—A sample of **9** (13.0 g, 0.081 mol) in anhydrous ether (20 ml) was added during 3 hr to a stirred suspension of pulverized sodium hydroxide (15.8 g) in 60 ml of ether. After 5 hr, the reaction mixture was hydrolyzed by water at 0° and extracted with ethyl ether. After drying (Na_2SO_4) the solvent was evaporated, and distillation of the crude product afforded **10** (9.36 g, 93% yield): bp 133–134° (770 mm); $n^{25}D$ 1.4334; $[\alpha]^{25}D$ +9.99° (*c* 5.002, ethyl ether).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.20; H, 9.67.

Cyclization of 10 to (+)-(*S*)-*sec*-Butylfuran (4a).—A sample of **10** (5.68 g, 0.045 mol) was converted to the corresponding furan **4a** (3.93 g) by the procedure described by Miller[10] (69% yield). The fraction of bp 127–128° and $n^{25}D$ 1.4398 was 98.5% pure (glpc); $[\alpha]^{25}D$ +16.43° (*c* 3.166, *n*-heptane) (optical purity 66%).

Cyclization of 10 to (+)-(*S*)-3-*sec*-Butylthiophene (5a).—Into a stirred mixture of **10** (3.4 g, 0.027 mol) and barium hydroxide (1.3 g) in 15 ml of water a slow stream of hydrogen sulfide[21] was bubbled during 5 hr at 55–60°. After cooling, the reaction mixture was diluted by water (50 ml) and extracted with three 20-ml portions of *n*-pentane. The solvent was evaporated and the crude product was distilled over sodium to give **5a** as a colorless liquid (2.1 g, 50% yield): bp 65° (12 mm); $n^{25}D$ 1.5001; $[\alpha]^{25}D$ +19.00° (*c* 3.015, *n*-heptane) (optical purity 51%).

Oxidation of 2a to (*R,S*)- and (*S,S*)-*sec*-Butylsuccinic Acid (11).[39]—To a stirred mixture of **2a** (9.72 g, 0.045 mol), $[\alpha]^{25}D$ −6.55 (*c* 1.787, *n*-heptane), and $AgNO_3$ (25.3 g, 0.153 mol) in water (50 ml), 110 ml of a 7.0% aqueous solution of NaOH was added during 2.5 hr at room temperature. The reaction mixture was then stirred at 25° for 24 hr and at 50° for 7 hr. The silver was removed, and the alkaline solution was concentrated to 30 ml and extracted with four 30-ml portions of ether. The aqueous solution was then added dropwise during 1 hr to an oxidizing mixture, held at 20–25°, of 22.5 g of $K_2Cr_2O_7$ and 20 ml of 98% sulfuric acid in 100 ml of water. The mixture was stirred at 25° for 48 hr, and the organic layer was separated, washed with water, and dried (Na_2SO_4). Removal of the solvent afforded crude **11** as a slightly yellow oil, which was shaken with pentane for 2 hr and allowed to stand at −10° for 3 days. The crystalline **11** (5.60 g, 71% yield) was filtered, washed with pentane, and dried under vacuum, mp 82–86°, $[\alpha]^{25}D$ +1.34° (*c* 0.723, CCl_4). Glpc analysis on a 100-m polyethylene glycol succinate capillary column at 100° showed the presence of both diastereoisomers, for which the following composition was determined:[22] (*R,S*), ~54%, (*S,S*), ~46%.

Oxidation of 11 to (+)-(*S*)-3-Methyl-1-pentene.—To a solution of **11** (4.4 g, 0.0253 mol) and dry pyridine (3.05 ml) in benzene (40 ml) was added under nitrogen atmosphere 13.17 g of lead tetraacetate (~85% chemical purity). The reaction mixture was stirred at 50–60° for 1 hr and at 75° for 3 hr while the volatile reaction products were swept out by a slow stream of dry nitrogen and collected in a trap cooled to −70°. The olefin (0.656 g, 32% yield from the corresponding dibromide) was ≥99% pure (glpc): bp 53–54°; $n^{20}D$ 1.3844; $[\alpha]^{25}D$ +34.53° (*c* 1.717, *n*-heptane) (optical purity 91%).[40]

Cyclization of 11 to (+)-(*S*)-3-*sec*-Butylthiophene (5a).—A sample of **11** (6.2 g, 0.0356 mol), $[\alpha]^{25}D$ −0.73° (*c* 0.745, $CHCl_3$), was neutralized (phenolphthalein) by a solution of 1.0 *N* sodium hydroxide and the water was completely evaporated. The resulting **11** sodium salt was carefully dried under vacuum, mixed with 7.0 g of P_4S_{10}, and introduced into a reaction vessel containing 20 ml of high-boiling oil. The stirred reaction mixture was then heated to 250° until the reaction started. A slow stream of dry nitrogen removed the reaction product as formed; it was collected in a trap cooled at −30°. The crude **5a** (3.5 ml) in pentane (10 ml) was washed twice with 10% sodium hydroxide (20 ml). The dried (Na_2SO_4) pentane extracts were distilled over sodium to give **5a** (2.1 g, 40% yield) (≥99% pure, glpc): bp 118–120°; $n^{25}D$ 1.5002; $[\alpha]^{25}D$ +14.46° (*c* 3.458, *n*-heptane) (optical purity 39%).

Ozonization of 4a.—A sample of **4a** (4.0 g, 0.032 mol), $[\alpha]^{25}D$ +19.86° (*c* 3.02, *n*-heptane), was dissolved in methylene chloride (70 ml) and a stream of oxygen containing 3% ozone was allowed to flow into the solution for 5 hr at 20°. The resulting ozonide was decomposed and (+)-(*S*)-2-methylbutanoic acid was recovered by the usual procedure[3,4] (2.1 g, 75.6% yield): bp 82–83° (15 mm); $n^{25}D$ 1.4042; $[\alpha]^{25}D$ +15.82° (*c* 2.863, *n*-heptane) (optical purity 79%).[3]

Oxidation of 4a.—The method of Skell and Bean[30] was employed. To a solution of 22.12 g (0.014 mol) of $KMnO_4$ in water (300 ml), **4a** (2.0 g, 0.016 mol), $[\alpha]^{25}D$ +19.86° (*c* 3.02, *n*-heptane), was added portionwise at 5–10°. By working up the reaction mixture in the usual manner,[30] (+)-(*S*)-2-methylbutanoic acid (0.2 g) was recovered (≥98% pure, glpc), $[\alpha]^{25}D$ +16.10° (*c* 1.006, *n*-heptane) (optical purity 81%).[3]

Ozonization of 5a.—A sample of **5a** (4.3 g, 0.03 mol), $[\alpha]^{25}D$ +23.96° (*c* 3.522, *n*-heptane), in methylene chloride (70 ml) was ozonized by the above procedure and (+)-(*S*)-2-methylbutanoic acid (32%) was obtained (≥98% pure, glpc): bp 80° (13 mm); $n^{25}D$ 1.4044; $[\alpha]^{25}D$ +12.99° (*c* 2.455, *n*-heptane) (optical purity 65%).

Racemization Attempt of (+)-(*S*)-3-*sec*-Butylthiophene (5a).—A 0.5 *M* solution of **5a**, $[\alpha]^{25}D$ +24.86° (*n*-heptane) (optical purity 67%), in methanol–water (9:1, v/v) was treated with a stream of hydrogen chloride and hydrogen sulfide for 15 min and then heated in a polarimeter tube at 62° for 5 hr. During this time no decrease of the optical activity was noticed, $[\alpha]^{62}D$ +22.39° (*c* 1.054) ($[\alpha]^{25}D$ +25.71°).

Registry No.—**1a**, 26871-36-3; **1b**, 23553-27-7; **1c**, 16627-19-3; **1d**, 16486-91-2; **2a**, 26871-37-4; **2b**, 26870-43-9; **2c**, 39542-01-3; **2d**, 39542-02-4; **2d** dinitrophenylhydrazone, 39542-03-5; **4a**, 26871-39-6, **5a**, 26871-40-9; **6**, 17289-43-9; **7**, 27763-54-8; **8**, 39542-08-0; **9**, 39542-09-1; **10**, 39542-10-4; (*R,S*)-**11**, 39497-75-1; (*S,S*)-**11**, 39542-12-6; (+)-(*S*)-3-methyl-1-pentene, 5026-95-9; (+)-(*S*)-2-methylbutanoic acid, 1730-91-2.

Acknowledgment.—The authors wish to thank Dr. Carlo Battistini for his helpful cooperation in the synthesis of acetylenic derivatives.

(37) L. Lardicci, C. Botteghi, and E. Belgodere, *Gazz. Chim. Ital.*, **97**, 610 (1967).

(38) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 375 (1947).

(39) An attempt was made to oxidize directly compound **2a** to **11** with potassium permanganate in aqueous solution, maintaining the pH between 6 and 7 during the reaction; only a 14% yield of **11** was obtained.

(40) P. Pino, L. Lardicci, and L. Centoni, *J. Org. Chem.*, **24**, 1399 (1959).