Chiral Acyl Anion Equivalents: Asymmetric Synthesis of α-Methoxytolualdehyde

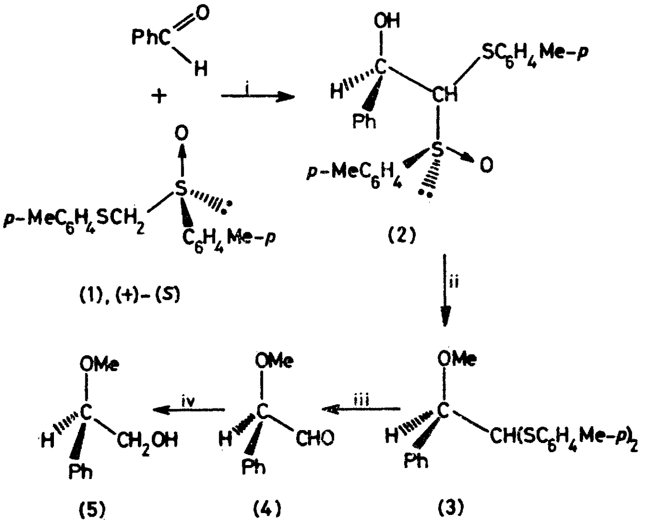
By LINO COLOMBO, CESARE GENNARI, and CARLO SCOLASTICO*
(*Istituto di Chimica Organica dell'Università, Centro C.N.R. per le Sostanze Organiche Naturali, Via Saldini* 50, 20133 *Milano, Italy*)

and GIUSEPPE GUANTI and ENRICA NARISANO
(*Istituto di Chimica Organica dell'Università, Palazzo delle Scienze, Corso Europa,* 16132 *Genova, Italy*)

Summary Condensation of a chiral dithioacetal mono-*S*-oxide anion with benzaldehyde leads to α-methoxytolualdehyde with high chemical and optical yield.

RECENTLY a stereospecific synthesis of optically active dithioacetal mono-*S*-oxides such as (**1**) was developed.[1]† It has been shown[2] that the anions from racemic dithioacetal mono-*S*-oxides are powerful nucleophiles and react with carbonyl compounds leading to the corresponding addition products. Here we report that, by using the chirality of (**1**), it is possible to develop an asymmetric synthesis of α-methoxyaldehydes such as (**4**).‡

To the anion of (**1**), prepared by treating (+)-(*S*)-(**1**) with Bu^{n}Li in tetrahydrofuran (THF) at −20 °C, benzaldehyde at −78 °C was added. After a few min at −78 °C, the usual work up gave (**2**) in 100% yield. A wide variety of procedures[3] was tried for selective *O*-methylation of the alcohol (**2**): sodium hydride–methyl iodide in THF or dimethyl sulphoxide, butyl-lithium–methyl iodide in THF, and silver oxide–methyl iodide in dimethylformamide. Epimerization, retro-aldol reaction, and dehydration made all these methods inefficient for methylation of (**2**). Accordingly, this compound was methylated in quantitative yield with dimethyl sulphate under phase-transfer conditions§ and reduced with NaI–I_2–Ph_3P (95%)[4] to provide (**3**). This product was then transformed in 70% yield into the aldehyde (**4**) using iodine[5] and $NaHCO_3$¶ (Scheme).



SCHEME. i, Bu^{n}Li, THF, −78 °C; ii, (a) Bu^{n}NOH, Me_2SO_4, H_2O–CH_2Cl_2, (b) NaI, I_2, Ph_3P; iii, I_2, $NaHCO_3$, H_2O–dioxan; iv, $NaBH_4$.

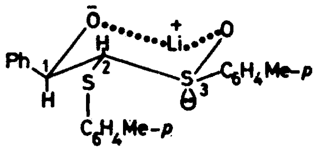
Reduction of (**4**) gave the alcohol (**5**) of known absolute configuration (Table).

TABLE

	$[\alpha]_D^{25}$ (*c* 1)	Absolute configuration	Enantiomer excess, %
(**3**)	+45·1° ($CHCl_3$)	(+)-(*R*)	⩾70
(**4**)	−66·0° ($CHCl_3$)	(−)-(*R*)	⩾70
(**5**)	−92·5°[a] (Me_2CO)	(−)-(*R*)	70[b]

[a] $[\alpha]_D^{25}$ −132° (acetone, *c* 1) is the value for optically pure (−)-(*R*)-(**5**). [b] Confirmed by n.m.r. ($CDCl_3$) spectroscopy in the presence of tris[3-(2,2,2-trifluoro-1-hydroxyethylidene)-(−)-camphorato]europium(III).

The diastereoisomeric ratio of (**2**) is *ca.* 50 : 35 : 15 : 0. On the basis of the absolute configuration and of the optical purity of the final compound, C-1 of the two major diastereoisomers has the *R* configuration (Figure). On the basis of previous studies,[6] we suggest that C-2 has the configuration also shown in the Figure. The asymmetric induction and the resulting high optical purity are probably due to the transition states as shown (Figure).



(a)

(a)	1*R*	2*S*	3*S*	50%
(b)	1*R*	2*R*	3*S*	35%
(c)	1*S*	2*S*	3*S*	15%
(d)	1*S*	2*R*	3*S*	0%

FIGURE

Recently two different asymmetric syntheses of α-hydroxy-aldehydes with high optical purity have been reported.[7] In the present procedure it is possible to obtain chiral hydroxy-aldehydes with an α-C–H bond.

The reaction sequence shown can also be used with aliphatic aldehydes; the potential asymmetric syntheses of secondary hydroxy-aldehydes, -acids, and -alcohols are being investigated.

(*Received, 2nd April* 1979; *Com.* 340.)

---

† Chiral thioacetal mono-*S*-oxides, such as (**1**) were previously obtained by reaction of α-halogeno-sulphoxides with sodium aryl sulphides, (see M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *J.C.S. Perkin I*, 1972, 1886; N. Kunieda, J. Nokami, and M. Kinoshita, *Bull. Chem. Soc. Japan*, 1976, **49**, 256).

‡ The idea of creating a chiral carbonyl equivalent group from a chiral thioacetal mono-*S*-oxide has also been suggested by other authors, (see R. F. Bryan, F. A. Carey, O. D. Dailey, Jr, R. J. Maher, and R. W. Miller, *J. Org. Chem.*, 1978, **43**, 90).

§ The diastereomeric ratio did not change during this reaction under the mild conditions used (3 min; 20 °C).

¶ Attempts to hydrolyse the dithioacetal mono-*S*-oxide directly into the aldehyde (**4**) were unsuccessful.

[1] L. Colombo, C. Gennari, and E. Narisano, *Tetrahedron Letters*, 1978, 3861.
[2] B. T. Gröbel and D. Seebach, *Synthesis*, 1977, 357, and references therein.
[3] C. A. Brown, D. Barton, and S. Sivaram, *Synthesis*, 1974, 434, and references therein.
[4] G. A. Olah, B. G. B. Gupta, and S. C. Narang, *Synthesis*, 1978, 137.
[5] G. A. Russell and L. A. Ochrymowycz, *J. Org. Chem.*, 1969, **34**, 3618.
[6] C. A. Kingsbury, *J. Org. Chem.*, 1972, **37**, 102.
[7] E. L. Eliel, J. K. Koskimies, B. Lohri, *J. Amer. Chem. Soc.*, 1978, **100**, 1614; T. Mukaiyama, Y. Sakito, and M. Asami, *Chem. Letters*, 1978, 1253.

Printed by Heffers Printers Ltd Cambridge England