View Article Online / Journal Homepage / Table of Contents for this issue

## Chiral Acyl Anion Equivalents: Asymmetric Synthesis of a-Methoxytolualdehyde

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Summary Condensation of a chiral dithioacetal mono-Soxide anion with benzaldehyde leads to  $\alpha$ -methoxytolualdehyde with high chemical and optical yield.

RECENTLY a stereospecific synthesis of optically active dithioacetal mono-S-oxides such as (1) was developed.<sup>1†</sup> It has been shown<sup>2</sup> 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  $\alpha$ methoxyaldehydes such as (4).<sup>‡</sup>

To the anion of (1), prepared by treating (+)-(S)-(1) with Bu<sup>n</sup>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<sup>3</sup> 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%)<sup>4</sup> to provide (3). This product was then transformed in 70% yield into the aldehyde (4) using iodine<sup>5</sup> and NaHCO<sub>3</sub>¶ (Scheme).



SCHEME. i, Bu<sup>n</sup>Li, THF, -78 °C; ii, (a) Bu<sup>n</sup>NOH, Me<sub>2</sub>SO<sub>4</sub>, H<sub>2</sub>O-CH<sub>2</sub>Cl<sub>2</sub>, (b) NaI, I<sub>2</sub>, Ph<sub>3</sub>P; iii, I<sub>2</sub>, NaHCO<sub>3</sub>, H<sub>2</sub>O-dioxan; iv, NaBH4.

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

	TABLE	
$[\alpha]_{\mathbf{D}}^{25}$ (c 1)	Absolute configuration	Enantiomer excess, %
<b>3</b> ) $+45 \cdot 1^{\circ}$ (CHCl <sub>3</sub> ) <b>4</b> ) $-66 \cdot 0^{\circ}$ (CHCl <sub>3</sub> ) <b>5</b> ) $-92 \cdot 5^{\circ a}$ (Me <sub>2</sub> CO)	(+)-(R) (-)-(R) (-)-(R)	≥70 ≥70 70 <sup>b</sup>

<sup>a</sup>  $[\alpha]_{\rm D}^{25}$  -132° (acetone, c 1) is the value for optically pure (-)-(R)-(5). <sup>b</sup> Confirmed by n.m.r. (CDCl<sub>3</sub>) 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).



Recently two different asymmetric syntheses of  $\alpha$ hydroxy-aldehydes with high optical purity have been reported.<sup>7</sup> In the present procedure it is possible to obtain chiral hydroxy-aldehydes with an  $\alpha$ -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.

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† 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).

<sup>‡</sup> 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.

- <sup>1</sup> L. Colombo, C. Gennari, and E. Narisano, Tetrahedron Letters, 1978, 3861.
- <sup>2</sup> B. T. Gröbel and D. Seebach, Synthesis, 1977, 357, and references therein. <sup>3</sup> C. A. Brown, D. Barton, and S. Sivaram, Synthesis, 1974, 434, and references therein.
- <sup>4</sup>G. A. Olah, B. G. B. Gupta, and S. C. Narang, Synthesis, 1978, 137.

<sup>&</sup>lt;sup>5</sup> G. A. Russell and L. A. Ochrymowycz, J. Org. Chem., 1969, 34, 3618.
<sup>6</sup> C. A. Kingsbury, J. Org. Chem., 1972, 37, 102.
<sup>7</sup> 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.