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ASYMMETRIC DITHIOACETALS II: A NOVEL AND VERSATILE METHOD FOR THE PREPARATION OF CHIRAL DITHIOACETALS

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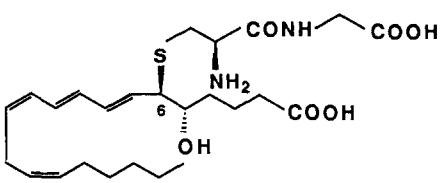
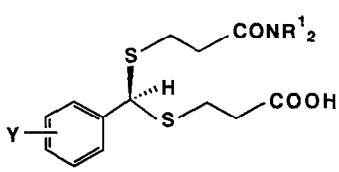
Summary: Reaction of aldehydes with one equivalent each of a thiol and a chiral thiolacid such as (R)-(-)-α-methoxyphenylthiolacetic acid in the presence of an acidic catalyst such as ZnI_2 or p-toluenesulfonic acid yields diastereomeric mixed thioacetals in good yields which are generally readily separable. Subsequent deacylation at low temperature with sodium methoxide and alkylation of the resulting thiolate anion with a variety of electrophiles provides chiral dithioacetals with no loss of enantiomeric purity.

Aryl and alkyl dithioacetals of mercaptopropionic acid have been used as mimetics of leukotriene D_4, providing potent receptor antagonists.[1,2,3] We have reported[4] on a novel method for the selective preparation of asymmetric dithioacetals developed in order to prepare such compounds in a selective and versatile manner. Given the receptor preference for the R configuration of the thiol bearing carbon (C-6) in leukotriene D_4 (I) we were prompted to develop a reliable and versatile method to obtain chiral dithioacetals (such as II) in order to define the stereochemical preference of such antagonists for the LTD_4 receptor. Initial attempts to resolve such structures by classical methods (eg. crystallization of the ephedrine salt, chromatographic or physical separation of diastereomic amides or esters) proved futile, presumably due to the relative similarity of the two thioalkyl chains.



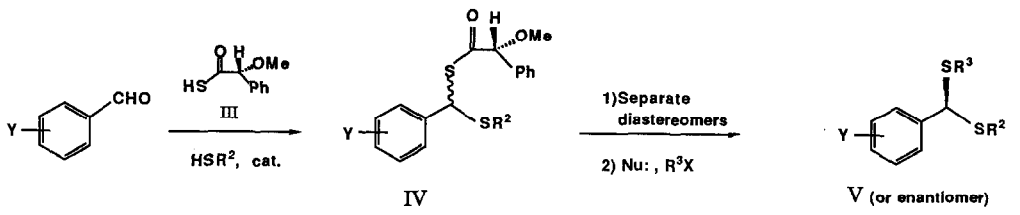
I



II

As an extension of our earlier work[4] we postulated that by utilizing an optically active thiolacid (such as III) in the first step of formation of the acylthio-alkylthio intermediate (Scheme 1) the diastereomeric intermediates IV would be more readily separable.

If subsequent deacylation-alkylation could be achieved without racemization of the thioacetal center then this would provide a versatile method for the preparation of a wide variety of chiral dithioacetals (V).



Scheme 1

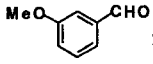
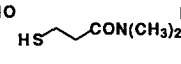
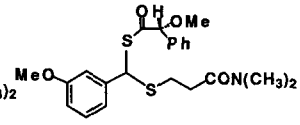
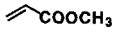
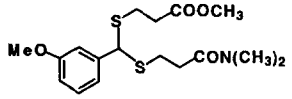
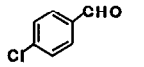
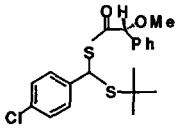
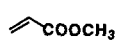
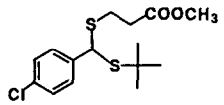
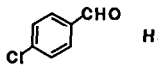
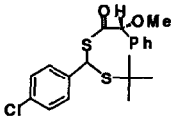
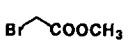
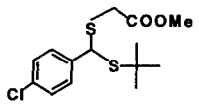
The preparation of the required chiral thiolacid (III) was easily achieved from (R)-(-)-α-methoxyphenylacetic acid (oxalyl chloride, benzene, trace DMF; followed by addition of the acid chloride to NaSH (2 equivalents) in ethanol at -10°C). Reaction of III with one equivalent of substituted benzaldehydes (eg. 3-methoxybenzaldehyde) and of N,N-dimethyl-3-mercaptopropionamide in the presence of catalytic amounts of p-toluenesulfonic acid or ZnI_2 in refluxing benzene smoothly provided the mixed thioacetal IVa as a 1:1 pair of diastereomers which were indeed readily separable by column chromatography (74% yield)[4] (see Table).

The success of the final deacylation and subsequent alkylation with methyl acrylate was potentially problematic in that we anticipated that removal of the thioacyl group in IV with sodium methoxide would proceed more slowly than the corresponding thioacetate used in the original procedure.[5] If the resulting thiolate anion intermediate were to equilibrate via the thioaldehyde this could lead to racemization.

In the event, reaction of the separated diastereomers with NaOMe at -78°C in THF followed after 5 min. by addition of an equivalent of methyl acrylate proceeded smoothly over one hour to provide the mixed dithioacetals Va1,2 in excellent yields (83% and 78% respectively). Equal and opposite optical rotations were observed for the pair of isomers ($[\alpha]_D$ = -3.2° (c = 2.0, acetone) and +3.6° (c = 1.54, acetone) respectively) but ultimate proof of the chiral purity of the two enantiomers was obtained by hydrolysis of the ester (1M LiOH, THF-H_2O) and reesterification with R-(-)-2,2,2-trifluoro-1-(9-anthranyl)ethanol (CMC metho-p-toluenesulfonate, DMAP, Pyr, CH_2Cl_2, RT, 18 h) to provide in each case a diastereomer whose purity could be determined by ^1H NMR analysis. Clearly resolved signals for the dithioacetal methine proton at 4.88 and 4.90 ppm showed that in each case the enantiomers had e.e. >95%. To further demonstrate the generality of the procedure the sequence was repeated using III, p-chlorobenzaldehyde and t-butylmercaptan to form the initial adduct (IVb) in 94% yield followed by separation of the diastereomers (flash

chromatography), alkylation with methylacrylate or with methyl bromoacetate (-78°C, 18 h) to give the corresponding enantiomeric mixed dithioacetals in excellent overall chemical and chiral yields (e.e. >95% in each case) (see Table). It was evident that no detectable racemization had occurred in the alkylation step and that the limiting factors for the chiral purity of the obtained products were the chiral purity of the starting thiolacid and the efficiency of separation of the diastereomers during the chromatography.

TABLE

Entry	Aldehyde	Thiol (HSR^2)	IV[a] (yield)	R^3X	V (yield)	$[\alpha]_D$
a			 IVa1,2 (74%)		 Va1 (83%) Va2 (78%)	-3.2° +3.6°
b			 IVb1,2 (94%)		 Vb1 (95%) Vb2 (87%)	-16.2° +15.9°
c					 Vc1 (91%) Vc2 (83%)	+14.8° -13.8°

a) **Isomers 1 and 2 refer to the less polar and more polar diastereomers as judged by t.l.c.(E. Merck plates silica gel 60, 20 EtOAc/80 Hex).**

This procedure thus makes available a wide variety of chiral dithioacetals via a versatile and efficient two step process. The application of this procedure to the preparation of the enantiomers of specific potent receptor antagonists of leukotriene D_4 will be described in detail elsewhere.

The ready availability of chiral dithioacetals by this method will also greatly facilitate studies on the chemistry of these novel compounds. The method can equally be applied to prepare chiral dithioacetals where there are no substituents which could be used to prepare diastereomeric salts, amides or esters and would thus not be amenable to classical resolution techniques. Such studies are ongoing in this laboratory and will be the subject of future reports.

References

1. C.D. Perchonock, M.E. McCarthy, K.F. Erhard, J.G. Gleason, M.A. Wasserman, R.M. Muccitelli, J.F. DeVan, S.S. Tucker, L.M. Vickery, T. Kerchner, B.M. Weichman, S. Mong, S.T. Crooke and J.F. Newton, J. Med. Chem., 28, 1145 (1985).

2. A.K. Saksena, M.J. Green, P. Mangiaracina, J.K. Wong, W. Kreutner and A.R. Gulbenkian, Tetrahedron Lett., 26, 6427 (1985).

3. a) R.N. Young and J.Y. Gauthier, U.K. Patent Application #2190377, November 18, 1987.
   b) R.N. Young, R. Zamboni and S. Leger, European Patent Application #233,763, August 26, 1987.

4. Diastereomers IVa1 and IVa2 have Rf values of 0.32 and 0.28 respectively on tlc (E. Merck plates, silica gel 60, EtOAc:hexane, 1:1) and were separated to >95% purity by flash chromatography using the same solvent system on a 1 gram scale. Diastereomers IVb1 and IVb2 have Rf values of 0.58 and 0.52 (15% EtOAc:hexane) and were similarly readily separated using flash chromatography on a 2.5 g scale.

5. J.Y. Gauthier, T. Henien, L. Lo, M. Thérien and R.N. Young, Tetrahedron Lett., 29, 000 (1988). See accompanying communication.

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