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STUDIES IN ASYMMETRIC SYNTHESIS. HIGHLY STEREOSELECTIVE REACTIONS OF ORGANOSULFUR COMPOUNDS

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Abstract—The history of and need for asymmetric syntheses are reviewed briefly with special mention of recently developed methods of high efficiency. The conditions for a viable asymmetric synthesis are stated. Highly stereoselective syntheses involving sulfonium salts and 1,3-dithianes are detailed.

INTRODUCTION

Pasteur's work on optical resolution[1] antedates by a quarter of a century Le Bel and van't Hoff's celebrated contributions to the understanding of optical activity on a molecular basis. All three of Pasteur's original methods: mechanical separation[1a] resolution via diastereoisomers[1b] and enzymatic asymmetric destruction[1c] are still used (the first one in modified[2] form), but his second method—resolution via diastereomers—has been the wheelhorse of enantiomeric separation over the last 100 odd years. Unfortunately, this method (as well as asymmetric destruction) leads to the recovery, at best, of 50% of the racemic material in the form of the desired enantiomer. Such low recovery is quite acceptable as long as resolution is performed mainly for academic purposes (e.g. in the total synthesis of a chiral natural product) or for the commercial production of materials of high unit value (such as chiral drugs or vitamins). In the last few years, however, as a result of the mounting thrust toward adequate nutrition world-wide and the resulting increases in price of commodities rich in essential amino acids (such as soybeans), the synthesis of chiral compounds of much lower unit value, such as L-amino acids, has become of vital interest. Here the wastage of over 50% of the racemic material synthesized cannot be tolerated economically; either the "wrong" enantiomer must be racemized and the racemic modification once again resolved (which obviously adds to cost unless the two steps can be telescoped in a "second-order asymmetric transformation"[3]) or else the desired chiral material must be synthesized asymmetrically in the first instance.

Asymmetric synthesis (as distinct from the related asymmetric destruction discovered by Pasteur) as a concept was first put forward* by Le Bel; but its reduction to practice was realized only twenty years later by Emil Fischer in the homologation of sugars.[5-7] Unfortunately, for many years asymmetric synthesis suffered from inefficiency: the excess of one enantiomer over the other produced in the known asymmetric syntheses was generally quite small and thus hardly of practical utility. It was not until 1961 when H. C. Brown and G. Zweifel[8] discovered the asymmetric hydroboration–oxidation of *cis*-olefins by means of tetra-3-pinanyldiborane, which leads to chiral alcohols of over 90% optical purity, that nonenzymatic asymmetric synthesis became a practical method.

Before proceeding, it might be well to state the requirements of a viable asymmetric synthesis:

(1) It must lead to the desired enantiomer in high optical as well as chemical yield.

(2) The chiral product must be readily separable from the chiral auxiliary reagent which is needed in the synthesis.

(3) Unless the chiral auxiliary reagent is very much cheaper than the desired product,† the auxiliary reagent must be capable of being recovered in good yield and undiminished optical purity.

It might be noted that, although asymmetric hydroboration fulfills conditions (1) and (2), it does not fulfil condition (3): tetra-3-pinanyldiborane is not recovered in the synthesis. Several other recent elegant asymmetric syntheses which fulfil condi-

*"Lorsqu'il se forme un corps dissymétrique dans une réaction ou l'on n'a mis en présence les uns des autres que des corps symétriques, il y aura formation dans la même proportion des deux isomères de symétrie inverse..... Il n'en est pas nécessairement de même pour les composés dissymétriques formés en présence de corps actifs eux-mêmes ou traversés par de la lumière polarisée circulairement....." (Ref. 4, pp. 346–347.)

†Sucrose might be one of the few potential chiral auxiliary reagents cheap enough to be considered expendable.

tions (1) and (2) also fall short on the third point; among these may be mentioned the following:

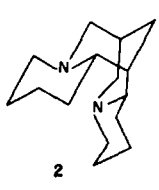
(1) The synthesis[9] of nearly optically pure (*S*)-(+)-aspartic acid from dimethyl acetylenedicarboxylate and (1*S*,2*R*)-(+)-1,2-diphenyl-2-aminoethanol [which is degraded to (1*S*,2)-diphenylethanol].

(2) The potential asymmetric synthesis of α-aminoacids from α-ketoacids and the above diphenylaminoethanol.[9]

(3) Homogeneous hydrogenation of α-acetamidoacrylic acids, $RCH=C(NHCOCH_3)COOH$, to chiral acetylamino acids, $RCH_2CH(NHCOCH_3)COOH$ by means of rhodium catalysts bearing chiral ligands.[10,11] The catalysts are eventually degraded and the phosphine ligands, RR'R"P (either chiral at phosphorus[10] by virtue of $R \neq R' \neq R''$ or with a chiral R-ligand[11]) cannot be recovered. However, this case almost fulfils condition (3) since a large amount of substrate can be hydrogenated (catalytically!) before the catalyst becomes deactivated; thus the chiral auxiliary reagent is potentially "cheap" in that a small amount of it generates a large amount of chiral product.

(4) The synthesis[12] of (*S*)-(−)-methyldopa, $3,4\text{—}(CH_3O)_2C_6H_3CH_2\text{—}C(CH_3)(NH_2)\text{—}COOH$ by a Strecker synthesis from 3,4-dimethoxyphenylacetone, 3, 4-$(CH_3O)_2C_6H_3CH_2COCH_3$, HCN and (4*S*, 5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane (a by-product in chloramphenicol synthesis). The synthesis proceeds via 4-3, $(CH_3O)_2C_6H_3CH_2\text{—}C(CH_3)(NHR)\text{—}COOH$, where R = $C_6H_5CHOH\text{—}CH\text{—}CH_2OH$, in 86–100% stereoselectivity* but requires a subsequent cleavage reaction in which the residue R loses its 2-amino substituent and is thus degraded and no longer recyclable to the aminodioxane which constitutes the chiral auxialiary reagent in the synthesis.

The author is aware of only two non-enzymatic† reactions which fulfil all three above conditions. One is the synthesis of α-amino acids from α-keto acids using various hydrazines of type 1 as chiral auxiliary reagents.[14] The hydrazines are, in fact, converted to amines from which they may, however, be readily regenerated by nitrosation followed by reduction. The other case is the synthesis of nearly optically pure ethyl β-hydroxy-β-phenylpropionate, $C_6H_5CHOHCH_2COOC_2H_5$ from benzaldehyde and ethyl bromoacetate in the presence of zinc (Reformatskii reaction) and the chiral auxiliary reagent starteine (**2**),[14] which is presumably recoverable.



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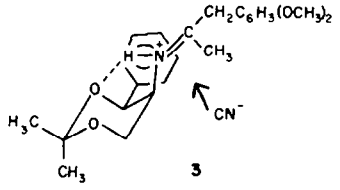

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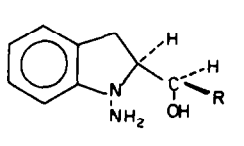
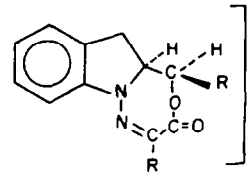
While it is undoubtedly premature to try to circumscribe the factors which make for a highly efficient non-enzymatic asymmetric synthesis, the following circumstances appear propitious: (1) Formation of a relative rigid ring which can be approached by a reagent much more readily from one side (e.g. the equatorial side in a 6-membered ring) than from the other (e.g. the axial side). This factor seems to be involved in the synthesis involving compound **1**[14] and also in the earlier-mentioned syntheses involving acetylenedicarboxylic ester.[9] (2) Formation of a bidentate metal chelate. The function of sparteine (**2**) and other polyfunctional chiral auxiliary reagents may be to make the two remaining coordination sites a and b of a tetrahedral metal reagent,

(R↑ and/or R↕ chiral) diastereotopic[15a] and thereby capable of inducing chirality in a prochiral[15b] substrate.[16] (3) Other types of formation of relatively tight complexes which are readily accessible from only one of two prochiral faces. This factor may be involved in the earlier-



Via hydrogenation and hydrogenolysis of

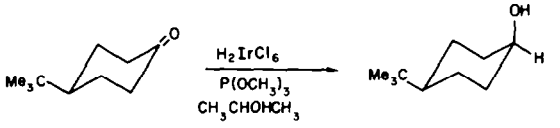


*The highest values of optical purity achieved in this synthesis probably involve a second-order asymmetric transformation of the intermediate aminonitrile as well as an asymmetric synthesis.

†Enzymatic reaction frequently do fulfil the three conditions and the production of chiral products from achiral precursors by *in vitro* enzymatic synthesis, e.g. using "fixed" enzymes,[13] is potentially a viable large-scale synthetic method.

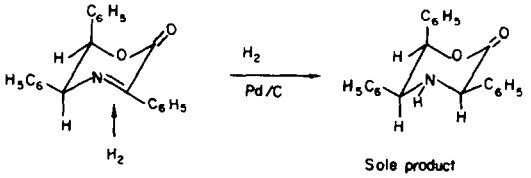
mentioned Strecker synthesis employing a *cis*-4-phenyl-5-amino-1, 3-dioxane (via 3).[12]

Before discussing our own attempts directed toward an asymmetric synthesis fulfilling the above conditions, we should like to point out that high stereoselectivity is not infrequently achieved in the synthesis of optically inactive diastereomers. An example[17] is shown in Scheme 1. In this case, since



SCHEME 1

the products are achiral, there is no *direct* application to asymmetric synthesis. In other cases, such as the earlier-mentioned potentially highly stereoselective synthesis[9] of α-amino acids involving intermediates **4** and **5**, although the starting material was *dl*-erythro-2-amino-1, 2-diphenylethanol



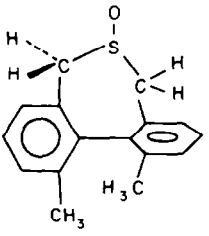
4 **5**

SCHEME 2

and the product therefore a diastereomerically pure *dl* pair rather than a pure enantiomer, the synthesis (Scheme 2) can easily be converted into an asymmetric one by using the optically active aminoalcohol as the chiral auxiliary agent.

Sulfur compounds

In recent years there has been considerable interest in sulfur compounds as vehicles of asymmetric synthesis. This interest is occasioned by the fact that (a) Hydrogen atoms at carbon next to sulfur tend to be acidic and thus readily replaced, via carbanions,[18] by a host of other groups. The transformation $-S-\underset{*}{C}H_2-R \rightarrow -S-\underset{*}{C}HX-R$ generates a new chiral center (starred). The underlined protons are particularly acidic when the adjacent sulfur function is sulfoxide, sulfone or sulfonium or when there are two sulfur atoms adjacent (R = S–). (b) The sulfur atom can be made chiral in sulfoxides and sulfonium salts and a transfer of chirality from sulfur to carbon is, in principle, possible. The first example of preferential exchange, with D_2O/OD^-, of one of the diastereotopic benzylic hydrogens in benzyl methyl sulfoxide, $C_6H_5\underline{C}HHSOCH_3$, was observed in 1965 by Wolfe and Rauk.[19,20] This sulfoxide has since been investigated extensively not only in exchange but also in other reactions[21]; reactions of considerably greater selectivity are found in the H/D exchange and the alkylation[22] of benzyl t-butyl sulfoxide, $C_6H_5CH_2SOC(CH_3)_3$ and the exchange of the α-hydrogens in sulfoxide **6**;[23] in both instances rate ratios of over 1000 are observed in the relative reactivity of diastereotopic H atoms.



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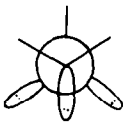

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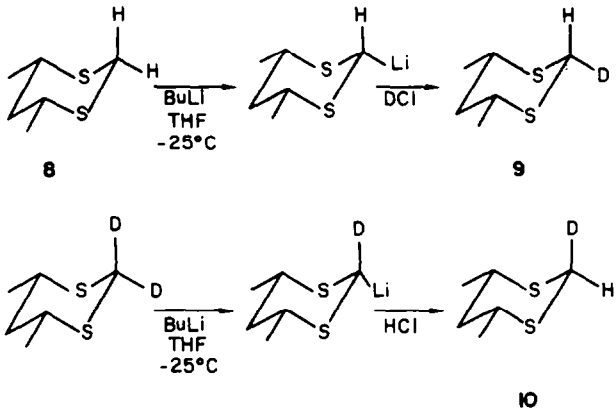
The high stereoselectivity in all these reactions has attracted attention from the theoretical point of view. For some years, the favored explanation for the enhanced acidity of C–H alpha to sulfur has been p–d overlap of the unshared p-electrons of the carbanion C^- with the empty d-orbitals on sulfur.[24] This effect may or may not have a directional component; it does explain satisfactorily why analogous high acidity is not found for C–H groups alpha to oxygen functions. More recently, both enhanced acidity and stereochemistry have been explained on the basis of the so-called "*gauche* effect"[25,26] *viz* a tendency, predicted by quantum mechanical calculations (in the gas phase!) for bonding electrons to be gauche to each other in preference to unbonded ones, which leads to the preferred conformation shown in **7**. Unfortunately this explanation is impaired by the finding that, at least in compound **6**, the relative acidity of the four methylene hydrogens next to sulfoxide is strongly solvent dependent, the implication being that solvation of the various carbanions is at least as important in determining their relative stability as is their intrinsic relative energy in the gas phase as calculated on the basis of quantum mechanical principles. We shall return to this point later.

Our own work on the stereochemistry of carbanions next to sulfur has been mainly concerned with the 1,3-dithiane system whose 2-anion was found, some years ago, to be an important intermediate in synthesis.[27,28] Having available, from earlier work,[29] conformationally fixed ("anancomeric"[30]) 1,3-dithianes, we converted[31,32] the *cis*-4,6-dimethyl compound **8** to the corresponding lithium derivative and then deuterated it with DCl with the startling result shown in Scheme 3. Scheme 3 also shows the fate of the 2,2-dideuterio analog of **8** (prepared from **8** by exchange with dimethyl sulfoxide-d_6 and base) when treated with butyllithium followed by



SCHEME 3

HCl. The methylene portions of the NMR spectra of **8**, **9**, and **10** are shown in Fig 1; it is clear, from consideration of these spectra, that in **9** the equatorial proton (upfield signal,[29] broadened, in the spectrum of **8**, by long-range coupling with H_{5e}) is replaced by deuterium whereas in **10** it is the axial proton (downfield signal) which remains, the equatorial one being replaced by hydrogen. Fig 1 clearly shows that the equatorial replacement is quite specific: no signal for **10** appears in the spectrum of **9** or *vice versa*; experiments in which **9** and **10** were deliberately mixed in a 100:1 or 1:100 ratio show that 1% of cross-contamination could have been clearly detected in the NMR spectrum. Thus the stereoselectivity of the lithiation-deuteronation (or -protonation) sequence involves nearly exclusive introduction of an equatorial D or H; quantitatively, it may be expressed as $\Delta G = -RT \ln K = -RT \ln 1/100 = 2{\cdot}3$ kcal/mol at −25°C; this value is a minimum one, since the stereoselectivity may have been greater than 100:1.

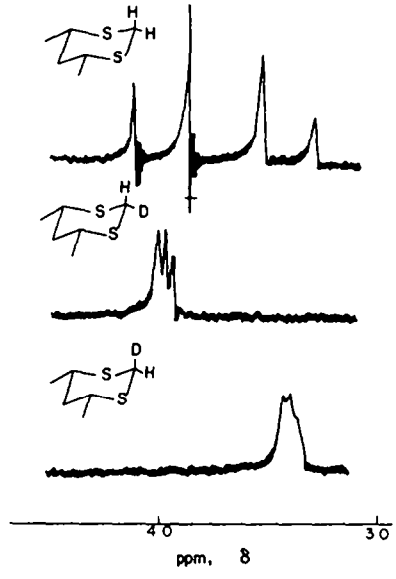
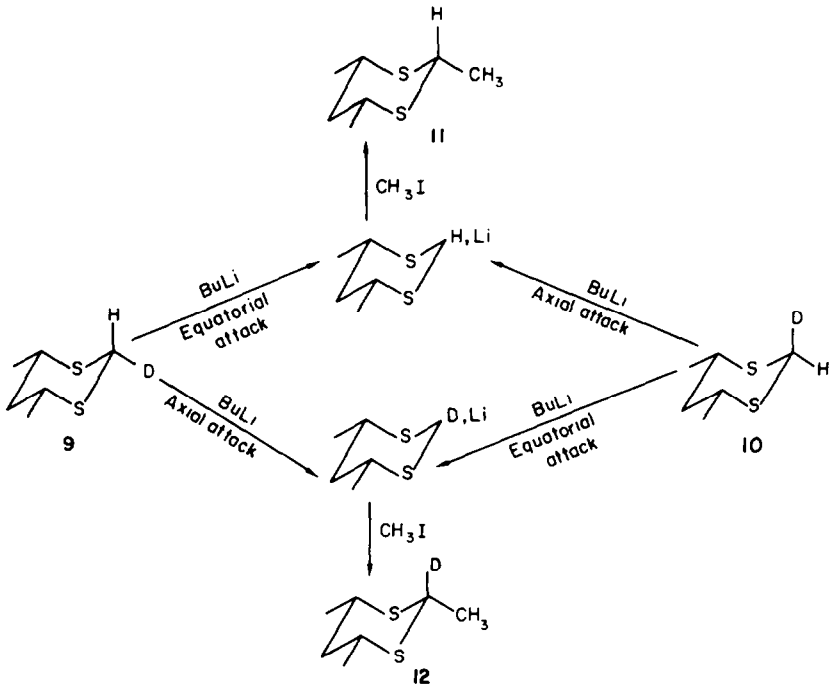


Fig 1. NMR spectra (3·2–4·2 ppm) of *cis*-4,6-dimethyldithiane (**8**) and its 2-monodeuterio analogs **9** and **10**.

It was of importance to find out whether the stereoselectivity was of kinetic origin, i.e. involved a preferential removal of the equatorial hydrogen in **8** with direct formation of a presumed equatorial lithium derivative followed by protonation with retention; or whether its source was thermodynamic, involving, presumably, equilibration of whatever intermediate is formed initially to the more stable equatorial lithium compound shown in Scheme 3 followed again by protonation with retention.* To this end, we carried out[32,33] the experiments represented by Scheme 4. Compound **9** was converted to the lithium derivative and treated with methyl iodide; as will be detailed below, this leads exclusively to the equatorial Me compound **11**. If **9** had been lithiated entirely from the equatorial side, the product would have been **11**, free of deuterium; by the same path **10** would have been converted totally to the deuterated Me compound **12**. In fact, as shown in Table 1, this extreme course was not followed; rather, both **9** and **10** gave mixtures of **11** and **12**, indicating that axial as well as equatorial attack occurs in the lithiation. Inspection of Table 1 shows that more axial attack occurs in the case of **9** than in the case of **10**, as might have been expected through operation of a primary isotope effect. From

*Strictly speaking, we only know the configuration of products **9** and **10**, not of the lithium intermediates leading to them. However, for reasons to be detailed below, the alternative possible interpretations, namely (a) formation of an exclusively axial lithium compound followed by complete inversion in the protonation or (b) formation of a lithium compound which is stereochemically heterogeneous followed by exclusive protonation from the equatorial side appear highly unlikely.



SCHEME 4

Table 1. Lithiation–methylation of **9** and **10**

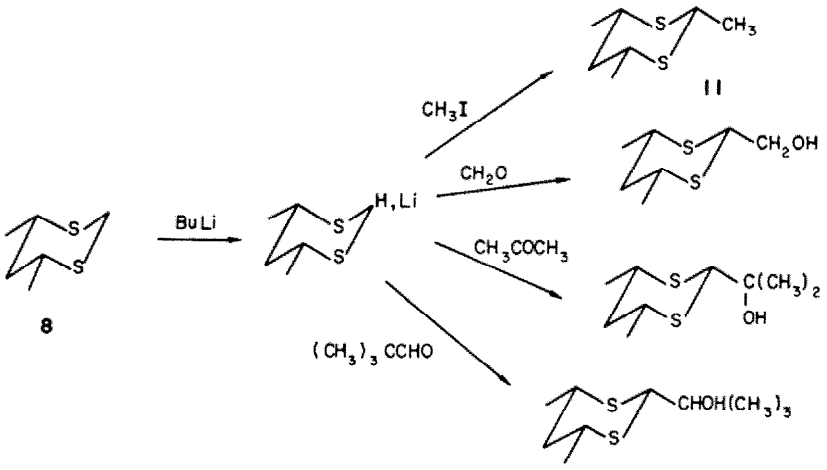
Run	Starting Material	Product d_0, %	Product d_1, %	k_e/k_a	IE[a]
1	**10**	3·2	96·8		
	9	84·3	15·7	12·9	2·41
2	**10**	4·4	95·6		
	9	73·5	26·5	9·9	3·73
3	**10**	6·8	93·2		
	9	74·85	25·15	7·3	2·55
4	**10**	6·42	93·58		
	9	77·2	22·7	8·5	2·57

[a] Isotope effect.

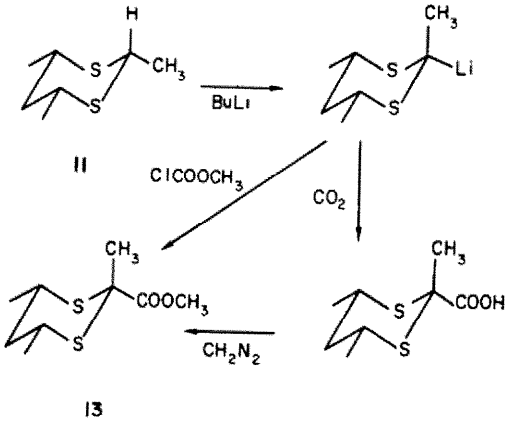
the product composition, it is possible, by a simple calculation,[34] to determine the intrinsic k_e/k_a ratio (ratio of specific rate of equatorial lithiation to specific rate of axial lithiation) as 8·6 ± 1·3 and the isotope effect as 2·5 ± 0·1. Clearly, although equatorial abstraction of hydrogen is favored kinetically, the ratio of equatorial to axial proton abstraction is considerably less than the ratio of equatorial to axial protonation mentioned earlier. Most probably the intermediate lithium derivative rapidly reorients itself in such a way as to have the lithium in the equatorial position; this point will be discussed further below.

In addition to protonation, we studied reaction of the lithium intermediate with methyl iodide, various carbonyl compounds (formaldehyde, acetone, pivalaldehyde), and carbon dioxide. The outcome of the reaction with carbonyl compounds and with methyl iodide is shown in Scheme 5. Only equatorial products were formed except in the case of the formaldehyde reaction where 0·2% of axial contaminant was found in the mother liquors of crystallization; since analysis in these cases was by gas chromatography, we estimate that in the other cases as little as 0·3% of the minor isomer would have been detected had it been present. Thus, in these cases we can raise our estimate of the stereoselectivity to 99·7:0·3 or 332 corresponding to a free energy difference of 3·4 kcal/mol at room temperature (the temperature of reaction). In the case of carboxylation, a mixture of carboxylic acids comprising 80% of the axial (*trans*) acid and 20% of the equatorial (*cis*) acid was obtained, but this lack of stereoselectivity is probably the consequence of at least partial thermodynamic control, since the acids are capable of epimerization under the conditions of the experiment and since it had previously been found[35] that the axial acid is the more stable. To avoid the epimerization problem, we resorted to carboxylation and also carbomethoxylation of the 2-*cis*-4,6-trimethyldithianes (Scheme 6); with these compounds, the reaction was highly stereoselective yielding, as far as we could discern, only the equatorially carboxylated products (e.g. ester **13**).

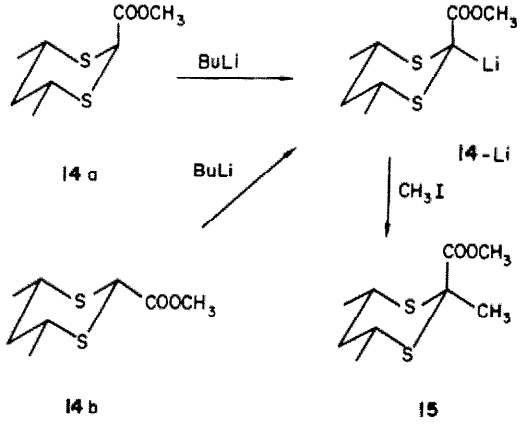
Rather surprisingly, even methylation of the 2-carbomethoxy compounds **14** (**a**,**b**) proceeded in



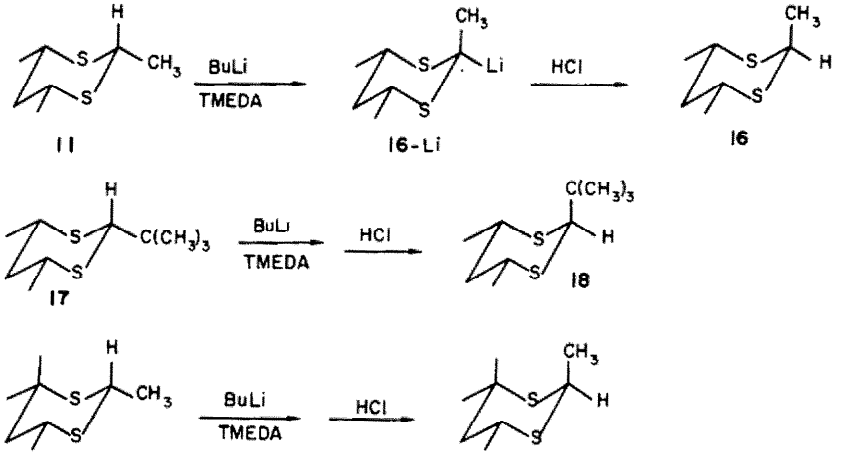
SCHEME 5



SCHEME 6



SCHEME 7

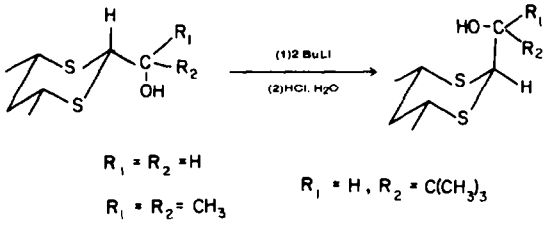


SCHEME 8

highly stereoselective fashion (Scheme 7) to give compound **15**, the epimer of **13** formed by introduction of the functional groups in reverse order. Since a free anion would no doubt have become delocalized by the carbomethoxy group in **14**-Li and therefore could hardly have given rise exclusively to the equatorial product, it would appear that the lithium derivative, at least in THF solution, exists as an ion pair rather than as a free ion. We shall deal with this point in more detail later.

In accord with the finding (*cf* Scheme 3) that equatorial hydrogen is abstracted more readily than axial hydrogen, we found, in preliminary experiments, that the conversion of the axial isomer, **16** (Scheme 8) to its lithium derivative is considerably more facile than corresponding conversion of the epimer **11**. In order to transform **11** to its lithium derivative efficiency, it is necessary to add tetramethylethylenediamine to the butyllithium reagent in THF; this is known[36] to disaggregate the oligomeric alkyllithium and thus to convert it to a much stronger base. Using the modified reagent it is easy to lithiate either **16** or **11**; subsequent quenching of the lithium compound formed from either precursor yields exclusively (i.e. >99·7%) the axial epimer **16** (Scheme 8).[37] Since this corresponds to a preference of 3·4 kcal/mol of the lithium derivative of the axial isomer **16** whereas normally the *equatorial* isomer **11** would be preferred at equilibrium by 1·8 kcal/mol,[29] the preference of the lithium *per se* to be equatorial (i.e. to favor **16**) might be estimated to be 3·4 + 1·8 or 5·2 kcal/mol.* We were able to extend this limit even further upward by bringing about a similar "contrathermodynamic"[38] i.e. equatorial → axial transformation in the case of 2 - t - butyl - *cis* - 4,6 - dimethyl - 1,3 - dithiane (Scheme 8, middle line). Here the isomer with the equatorial 4-t-butyl (**17**) is normally preferred by 2·7 kcal/mol[29] and the "driving force" in the reverse direction must therefore be worth at least 2·7 + 3·4 or 6·1 kcal/mol.† Another interesting "contrathermodynamic" equilibration is the conversion of *cis*-2,4,4,6-tetramethyl-1,3-dithiane to the *trans* isomer (which has highly unfavorable *syn*-axial Me groups) shown at the bottom of Scheme 8.

In similar fashion, the equatorial carbinols prepared as shown in Scheme 5 were converted quantitatively to their axial epimers by treatment with two moles of alkyllithium followed by quenching with acid (Scheme 9). While it might at first glance appear surprising that the dilithium compound required as an intermediate‡ for the "contrathermodynamic" transformation shown in Scheme 9 is formed with such ease, it should be recalled that similar intermediates are involved in the synthesis of methyl ketones from lithium salts of acids and methyllithium;[39] in fact, it appears that lithium alkoxides actually serve to stabilize alkylithiums,[40] presumably by some kind of complexing.



SCHEME 9

In summary of this part of the discussion, it would appear that we have found methods of synthesizing pure diastereomers of 2,X- and 2,2,X-substituted 1,3-dithianes at will. For the 2-monosubstituted compounds, appropriate reaction of the lithium compound will give the equatorial isomer (unless it epimerizes rapidly, as in the case of COOH) whereas epimerization of the equatorial isomer through stoichiometric formation of the alkyllithium derivative followed by acidification will give the pure axial epimer. In the case of 2,2-disubstituted compounds, appropriate reaction of the lithium derivative of a 2-monosubstituted precursor will always place the substituent introduced *second* in the equatorial position.

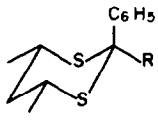
At this stage in the investigation it became a matter of vital interest to find out more about the nature of the organolithium intermediates, since

*We must concede that this figure is somewhat uncertain. It is based on the assumption of geminal additivity of conformational free energies—*cf* E. L. Eliel and R. M. Enanoza, *J. Amer. Chem. Soc.* **94**, 8072 (1972)—and, in particular, on the assumption that the $-\Delta G°$ value of the Me group in **16** is the same as that in its lithium derivative **16**-Li. If **16**-Li has substantial carbanion character at C-2, the bending potential of the axial Me group might be softer, and its $-\Delta G°$ value therefore lower, than corresponding quantities in **16**. We have recently observed—E.L. Eliel, R. L. Willer, A. T. McPhail and K. D. Onan, *J. Amer. Chem. Soc.* in press—that the bending potential, and the $-\Delta G°$ value, in a thicyclohexyl methyl sulfonium salt (unshared pair on sulfur!) is much smaller (0·275 kcal/mol) than the corresponding value in methylcyclohexane (1·7 kcal/mol).

†Apart from being subject to the same uncertainty mentioned in the previous footnote, which might make this value too high, there is here an additional factor working in the opposite direction: The lithium derivative of the *trans-trans* isomer **18** must presumably maintain the (unfavorable) chair conformation with axial t-butyl in order to preserve the favored equatorial position of the lithium whereas the free dithiane is believed to be in the somewhat less strained boat form.[29] In the boat form, the lithium cannot readily assume a position stereoelectronically equivalent to equatorial lithium in the chair.

‡Although, strictly speaking, the term is a misnomer, it does pointedly express the fact that the equilibrium of two complexed organic species may be entirely different from that of the free species and that thus, by complexing, one may convert the normally more stable isomer into the normally less stable one.

clearly these intermediates must be responsible for the high stereoselectivity of the overall reactions (protonation, alkylation, reaction with carbonyl compounds, carboxylation). The lithium intermediates are both air and moisture sensitive and thus not very easy to handle; we decided that NMR spectroscopy would be the easiest method of studying them. The first compound to be investigated[37] was the lithium derivative (**19**) of the axial phenyl compound **20** since the resonances of the phenyl



19 R = Li

20 R = H

protons in this compound could easily be observed in a wide variety of solvents. Table 2 summarizes the change in chemical shifts of these protons relative to their position in the parent hydrogen compound (**20**). Also reported in the Table, for those experiments carried out with TMEDA complexes, are the changes in chemical shift of the methyl and methylene protons of TMEDA, $(CH_3)_2NCH_2CH_2N(CH_3)_2$, in the dithianyllithium complex in various solvents compared to the corresponding shifts in the same solvent in the absence of the dithianyllithium. Reported in parentheses in the Table are corresponding data for the lithium complex of 2-phenyl-1,3-dithiane; it is clear that the chemical shifts for the aromatic protons in this complex are very nearly the same as for the biassed (4,6-dimethyl) homolog.

The following facts stand out from Table 2: (1) The lithium derivative **19** displays substantial upfield shifts of the aromatic protons compared to the parent compound **20**. The shift is generally greater for the *meta* hydrogens than for the *ortho*; it is greatest for the *para* hydrogen. Since the *ortho* protons in **20** are about 0·5 ppm downfield from the *meta* and *para*, the overall effect of the upfield shifts in **18** produces a near first-order spectrum for the aromatic hydrogens as shown in Fig 2. The

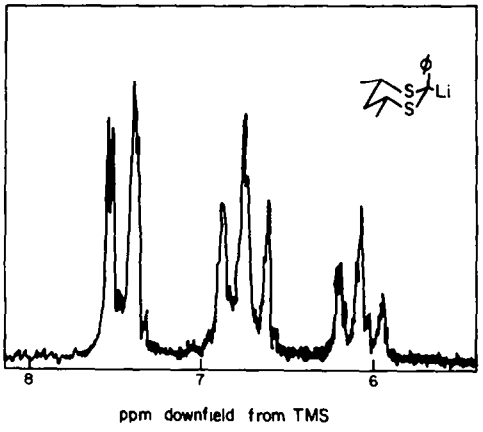


Fig 2. Proton NMR spectrum of 2-lithio-2-phenyl-*cis*-4,6-dimethyldithiane (**19**) in THF.

Table 2. Upfield shift of aromatic protons in lithium complexes of *r*-2-phenyl-*trans*-4, *trans*-6-dimethyl-1,3-dithiane (**19**) and 2-phenyl-1,3-dithiane[a] at 60 MHz[37]

Solvent	$\Delta\nu$, Herz				
	H_o[b]	H_m[c]	H_p[d]		
C_6H_6	6 (4)	6 (–)	40 (40)		
C_6D_6–THF[e] (1:1)	(5)	(17)	(57)		
C_6H_{12}[f]–THF (1:1)	27 (20)	37 (30)	74 (70)		
THF	24 (18)	34 (30)	74 (70)		
HMPTA[g]–THF–Hexane (1:1:1)	59 (65)	58 (59)	120 (122)		
				N–CH_3	N–CH_2
C_6H_{12}[f]	(22)	(26)	(62)	(–1)	(7)
C_6H_{12}[f]–THF (1:1)	23 (21)	34 (32)	74 (72)	–(–4)	2 (3)
C_6H_6	2	–[i]	47	18	39
C_6H_6–THF (1:1)	3 (11)[j]	–[i] (22)[j]	53 (62)[j]	3 (–1)[j]	15 (8)[j]
THF	24 (22)	33 (32)	75 (73)	–(–2)	2 (2)
THF–TMEDA[k]	(20)	(28)	(68)		

[a] Parenthesized data refer to 2-phenyl-1,3-dithiane derivative. [b] Shift in **20**: 482 Hz (band center). [c] Shift in **20**: 450 Hz (band center). [d] Shift in **20**: 450 Hz (band center). [e] Tetrahydrofuran. [f] Cyclohexane. [g] Hexamethylphosphoramide. [h] Shifts below this line refer to dithianyllithium-teramethylethylene diamine (TMEDA) complexes. The columns headed N–CH_3 and N–CH_2 refer to the chemical shifts of the methyl (132 Hz) and methylene (142 Hz) protons in TMEDA. These shifts, like the shifts of the aromatic protons in **20**, are nearly solvent independent. [i] Obscured by solvent. [j] Data in C_6D_6. [k] Excess tetramethylethylene diamine used as co-solvent.

spectrum very closely resembles that previously reported[41] for triphenylmethyllithium—much more so, in fact, than it resembles the spectra[41] of benzyl- or diphenylmethyllithium. This suggests that the negative charge is substantially delocalized in the dithianyllithium compound. (2) The shifts in hexamethylphosphoramide are substantially larger than those in less ionizing solvents, such as tetrahydrofuran or mixtures containing tetrahydrofuran.* This suggests that one is dealing with at least two types of anions or anion pairs, one of which (in THF) is tighter than the other (in HMPTA). The two species might be intimate and solvent-separated ion pairs or they might be an ion pair (in THF) and a free ion (in HMPTA). (3) In the same solvent, the lithiodithiane and its TMEDA complex display nearly the same shifts for the aromatic protons. This suggests that TMEDA complexing does not materially affect the anion in solution. Moreover, in tetrahydrofuran, there is no effect on the shift of the methyl and methylene protons of TMEDA for the complex as compared to free TMEDA. This suggests that the complex is entirely or nearly entirely dissociated in THF, THF molecules presumably having displaced the TMEDA molecules in the solvent sphere of the lithium cation. Contrariwise, in benzene (and, to a lesser extent, in cyclohexane and in a 1:1 benzene–THF mixture) the methylene protons of TMEDA show a substantial upfield shift—so much so that in pure benzene the N-methylene protons appear upfield from the N-Me protons. Thus in benzene the cation apparently remains complexed with TMEDA.

Despite the fact that the anion in **19** is delocalized in THF, quenching **19** with D_2O/DCl gave exclusively **20-*d*** and none of its *cis-cis* isomer (**21-*d***). In contrast, when the solution of **19** in the solvent mixture containing HMPTA was quenched, a mixture of **19-*d*** and **20-*d*** resulted (Scheme 10), with **19 *d***, the product of the more facile equatorial approach, predominating.

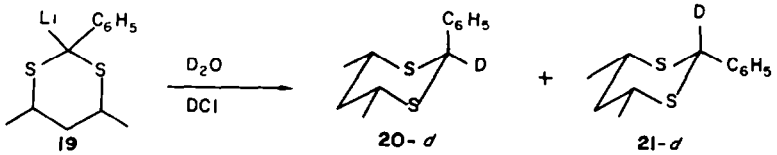
We consider these results very significant. The stereochemical outcome of the quenching shown in Scheme 10 clearly shows that if one has a solvent-separated ion pair or a free anion, the quenching reaction is non-stereoselective. One might blame this lack of stereoselectivity on the delocalization of the anion by the phenyl substituent, but since the PMR spectrum in less ionizing solvents, such as THF, in which the quenching reaction is highly stereoselective, also reveals substantial (though somewhat less extensive) delocalization of charge, the delocalization *alone* cannot be the cause for non-stereoselectivity. Accepting that the lithium compound in THF (in contrast to that in HMPTA) is an ion pair (*vide supra*), one is thus forced to the conclusion that it is the ion pairing itself which is largely responsible for the high stereoselectivity of the reaction rather than any intrinsic preferred stereochemical disposition of the anion. We therefore believe that the ion pair should be depicted as shown in **22** and that the bidentate coordination of the S atoms, while not responsible for the relatively high basicity of the dithiane,† largely accounts for the high stereoselectivity of its anion in that it holds the lithium gegenion of the pair quite rigidly in the equatorial position.‡

Interesting as the extraordinarily high stereoselectivity of the 1,3-dithianyllithium compounds is, it is unlikely, in itself, to lead to an asymmetric synthesis. This is not because most of the compounds discussed in this series are achiral: chirality could easily be introduced by leaving out one of the 4,6-dimethyl groups or by adding an extra one (as in Scheme 8, bottom). However, the

*Benzene apparently produces a downfield shift in **19** (although no such shift is evident in **20**). This becomes evident when one compares pure THF with THF-benzene mixtures (in contrast, it may be noted that THF and THF-cyclohexane mixtures show nearly the same shifts). This "benzene effect" makes the interpretation of the shifts in pure benzene difficult.

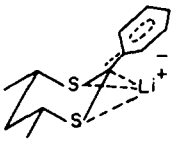
†We have so far found it impossible to prepare lithium derivatives from 1,3-dioxanes save in one case of a compound with an axial 2-phenyl substituent.

‡This leaves open the question as to why the electrophile approaches exclusively from the equatorial rather than the axial side. It has been suggested to us[42] that a simultaneous attack on sulfur and on C-2 may be involved, with the electrophile "sliding in" from the side where the sulfur can bond, i.e. the equatorial side.



Solvent	20-*d*	21-*d*
THF	~100%	~0%
HMPTA-THF-Hexane	85–89%	11–15%

SCHEME 10



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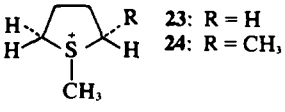
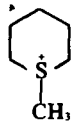
task of carving the chiral center (of type –S–CHX–S–) out of the molecule without destroying its chirality (i.e. meeting our condition 2 for a viable asymmetric synthesis) would be formidable, and performing this task while not destroying the chiral auxiliary reagent (the dithiane or at least its precursor dithiol) so as to meet condition 3 would be well-nigh impossible. We should therefore like to end this account by discussing a route more likely to lead to ultimate success, namely one involving chiral sulfonium salts.[43]

In 1971 it was reported[44] that the thiacyclopentyl methyl sulfonium salt **23** would exchange one pair of its diastereotopic alpha-hydrogens (later found[45] to be the pair *cis* to the Me group) over 400 times



23: R = H
24: R = CH_3

readily than the other pair. It occurred to us that this might be a convenient way for transferring chirality from sulfur to carbon[46] by starting from the chiral homolog **24** and proceeding as shown in Scheme 11. We actually realized[43] the ring opening envisaged in Scheme 11 (starting with the hydrogen analog **24** rather than with the deuterium compound), despite the fact that it requires attack of a nucleophile at a methylene in preference to a competing Me on sulfur. In fact, it was found, in compound **23**, that azide attack on the methylene group of the ring proceeded about 1·8 times as fast as attack on Me, the yield of ring-opened product (as compared to product of Me displacement) being 78%. This situation is in contrast to that pertaining in the 6-membered homolog **25** where methyl displacement proceeds over seven times as fast as ring opening. Since a similar contrast has been observed[47] in neighboring group participation reactions involving 5- and 6-membered oxonium rings (albeit in solvolysis rather than bimolecular displacement reactions), the cause would appear to reside mainly in the strain of the 5-membered as compared to the 6-membered cycle. Our hopes to parlay the synthesis outlined in Scheme 11 into a highly asymmetric one were dashed, however, when it was discovered[48,49] that selectivity of the H/D exchange in **23** was only between 12:1 and 28:1 rather than over 400:1; in any case, condition 3 (recovery of the chiral auxiliary reagent) can clearly not be fulfilled in the synthesis outlined in Scheme 11. Regardless of this fact, we believe that the high stereoselectivity observed by several investigators in reactions involving carbanions alpha to sulfur functions is a good omen and we are now looking for examples where such reactions can be harnessed to an asymmetric synthesis fulfilling all three conditions laid down at the beginning of this article.



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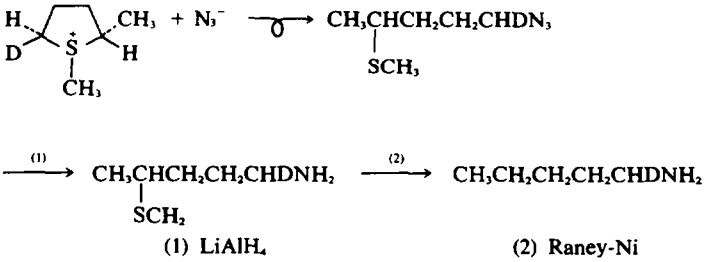

SCHEME 11

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