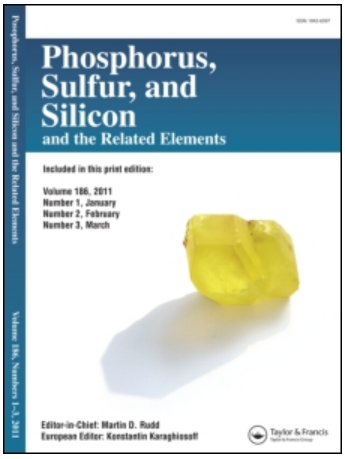

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Asymmetric Syntheses Based on Hexahydro-4,4,7-Trimethyl-1,3-Benzoxathians

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ASYMMETRIC SYNTHESES BASED ON HEXAHYDRO-4,4,7-TRIMETHYL-1,3-BENZOXATHIANS*

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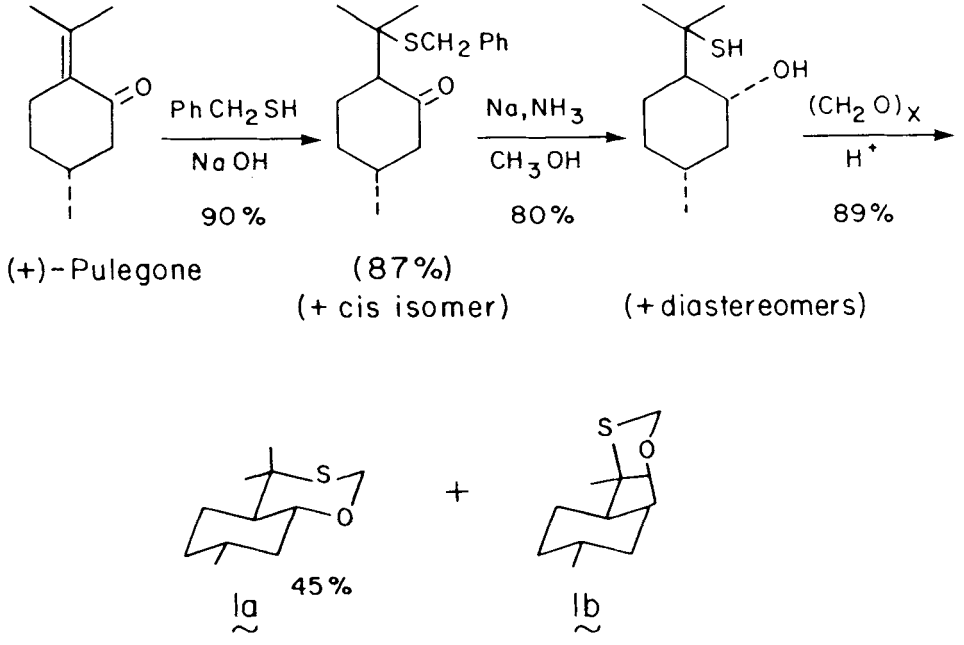
Abstract. Earlier work concerned with a highly stereoselective asymmetric synthesis based on a 1,3-oxathiane as the ciral auxiliary reagent is reviewed and recent applications to the synthesis of the four stereoisomers of malyngolide, of (R)-(+)-γ-caprolactone (a pheromone of the Trogoderma glabrum beetle) and of (S)-(+)-mevalolactone are presented. The mechanism underlying this asymmetric synthesis is discussed briefly.

Background

In the early 197o's we found [1,2] that electrophilic reactions [3] of conformationally locked 1,3-dithianes lead virtually exclusively to the equatorial product. Based on this finding, we devised [4,5] a highly stereoselective (generally ≥ 9o% e.e.) asymmetric synthesis of α-hydroxyaldehydes, RR'C(OH)CHO, and the corresponding acids, RR'C(OH)CO_2H, and glycols RR'C(OH)CH_2OH. Full details of the reaction, both for R'=alkyl [6] and R'=H [7] are available and the reaction sequence has been reviewed [8,9].

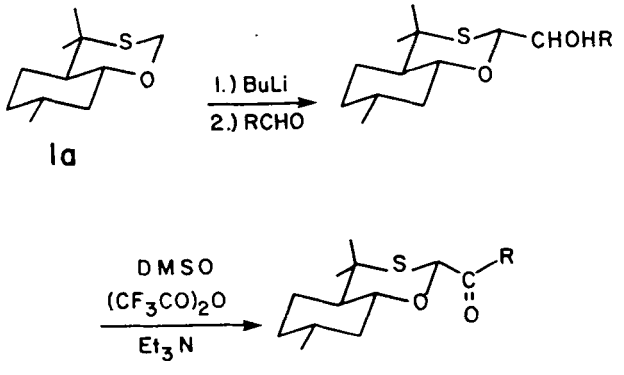
The asymmetric synthesis described proceeds in two steps. The first step is electrophilic substitution in a chiral 1,3-oxathiane. After some searching [4,1o] we found oxathiane 1a, derived from commercially available, enantiomerically pure pulegone by the reactions summarized in Scheme 1, [11]

*Dedicated to the memory of Harold Kwart



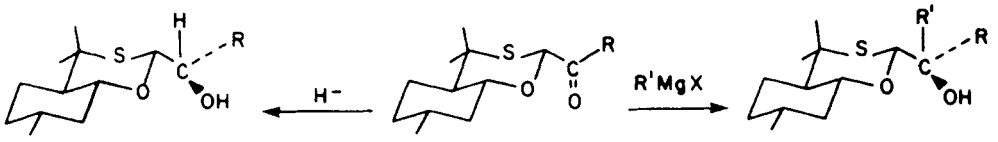
Scheme 1

the most suitable to use. Electrophilic substitution of the lithium salt of this oxathiane, (4a$\underline{R}$, 7$\underline{R}$, 8a$\underline{R}$)-hexahydro-4,4,7-trimethylbenzoxathiane , invariably proceeds so as to give exclusively the equatorial substitution product (Scheme 2). This constitutes the first step in the asymmetric synthesis.



Scheme 2

The second step (Scheme 3) involves the reaction of the ketone obtained from the carbinol by Swern oxidation [12]



Scheme 3

(shown in Scheme 2) with a Grignard reagent [6,13] or metal hydride [7]. Of a variety of organometallic reagents investigated [13], alkylmagnesium bromides or iodides have been found best; the presence of excess $MgBr_2$ is beneficial in some cases [14]. With phenyl ketones, stereoselectivity approaches 100%, even at room temperature whereas with alkyl ketones it is generally over 90% at -78°C. So far we have encountered only two failures: One occurs with alkoxyketones $R^*CO(CH_2)_nOR$ (n = 1-4; R^*= oxathiane moiety - see below) [15]. The other failure (low selectivity) involves reactions of alkyl ketones with allylmagnesium chloride (no difficulty is encountered with benzylmagnesium chloride) [15].

The selectivities observed in hydride reductions to secondary alcohols [7] are not quite so high. In the case of the phenyl ketone, $R^*COC_6H_5$ (R^*oxathiane moiety) selectivities up to 98:5:1.5 can be attained (with L-Selectride™ in toluene at -78°C). However, with an aliphatic ketone, $R^*COC_6H_{13-n}$, the highest attained selectivity has been 90:10 with L-Selectride™/LiI in toluene at -78°C. Interestingly, the reverse selectivity (i.e. for the diastereomer not favored by chelation followed by approach of the hydride from the least hindered side) is seen with Dibal (i-Bu_2AlH) in hexane at -78°C (10:90), but only with primary and tertiary alkyl ketones. (With phenyl ketones and secondary alkyl ketones

stereoselectivity with Dibal is low). Although these selectivities are generally not quite as good as in the Grignard additions, this drawback is counterbalanced by the fact that the two diastereomeric secondary alcohols formed in the reductions generally differ greatly in polarity (presumably, because one is strongly intramolecularly hydrogen bonded and the other is not) and can therefore be readily separated and purified chromatographically.

With ketones other than alkyl or aryl the stereoselectivity in hydride reductions (see also [9]) is often difficult to predict. In Table 1 are summarized the diastereomer ratios obtained in reductions of $R^*COC \equiv CC_8H_{17}$-n. [16]

In the case of the tertiary alcohols, reversal of carbinol configuration can be achieved in one of two ways: 1) By reversing the alkyl groups in the ketone and the Grignard reagent, i.e. by using R^*COR' + RMgX instead of R^*COR + R'MgX. This method has the potential drawback that one set of starting materials may be considerably less accessible than the other and also that the stereoselectivity may be less good in one combination than in the other. 2) By using the diastereomeric oxathiane 1b instead of 1a. The hydroxythiol precursor of 1b is formed as a byproduct in the synthesis of that of 1a (Scheme 1) and therefore a minor amount of 1b is formed along with the principal product 1a. After most of 1a has been crystallized from the reaction mixture (Scheme 1, last step) [11], isomer 1b can be isolated from the mother liquor by hplc [6]. Although 1b is a diastereomer of 1a, the oxathiane portions of the two reagents are mirror images and therefore will eventually give rise to hydroxyaldehydes, RR'C(OH)CHO, which are enantiomeric

TABLE I Hydride Reduction of Propargyl ketone $R^{*}COC{\equiv}CC_8H_{17}\text{-}n$[a]

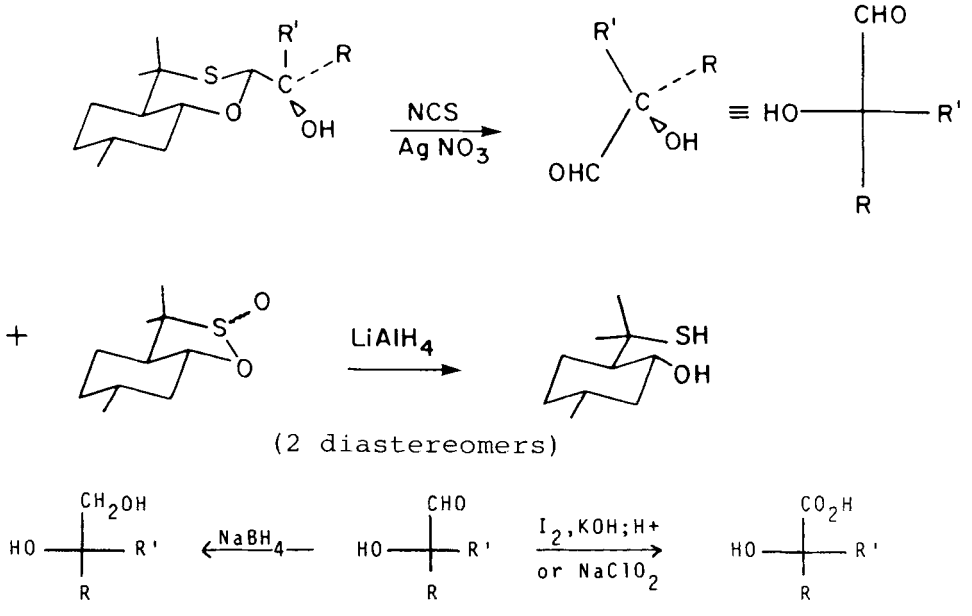
Reducing Agent	Solvent	Temp.°C	%R	%S	d.e.%
L-Selectride™	Toluene	-78	7.5	92.5	85
	THF	-78	14	86	72
K-Selectride™	Toluene	-78	1.5	98.5	97
$LiB(C_2H_5)_3H$	Toluene	-78	2	98	96
Dibal	Hexane	-78	67	33	34
S-Alpine-Hydride™	THF	-78	3o	7o	4o
	Toluene	-78	14	86	72
R-Alpine-Hydride™	THF	-78	36	64	28
	Toluene	-78	9	91	82
S-Alpine-Borane™	THF	RT	96	4	92
R-Alpine-Borane™	THF	RT	32	68	36
$LiAlH_4$	Ether	-78	24	76	52
	THF	-78	16	84	68
Bu_4NBH_4	THF	RT	73	27	46
	CH_2Cl_2	RT	61	39	22

[a] R^{*} = 2-(4aR, 7R, 8aR)-hexahydro-4,4,7-trimethylbenzoxathianyl

[b] Selectride™ is tri-sec.butylborohydride

[c] Alpine-Borane™ is (B)-isopinocampheyl-9-borabicyclo [3.3.1]nonane and Alpine-Hydride™ is the corresponding lithium hydride adduct.

(assuming that in both cases R'MgBr is added to R*COR where R* is the oxathiane moiety derived from 1a or 1b). Cleavage of the oxathiane is effected by N-chlorosuccinimide - silver nitrate [17] (Scheme 4). The method is generally reliable though somewhat costly. We have encountered only two failures so far, one in the cleavage of $R^*CHOHC{\equiv}C\text{-}C_8H_{17}\text{-}n$ which did not proceed at all, and one in the cleavage of $R^*C(OH)(CH_3)CH_2CH_2CH{=}C(CH_3)_2$,



Scheme 4

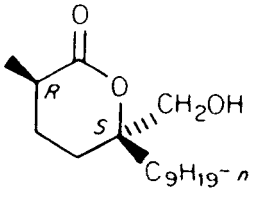
a precursor to linalool, where attack on the double bond apparently occurred concomitantly with cleavage [18]. It would be desirable to devise alternative methods of cleavage, but so far all attempts, e.g. via oxidation with chloramine-T[19] or the sulfoxides [20] or sulfones [21] have been unsuccessful [22]. Cleavage by $NCS/AgNO_3$ has the advantage that the oxathiane moiety is recovered in high yield in the form of a sultine

(cf. Scheme 4) which is readily reduced, by lithium aluminium hydride, to a hydroxythiol from which the oxathiane is regenerated as shown in Scheme 1. Although the hydroxyaldehydes obtained in the cleavage are not very stable (they seem to undergo reversible dimerization) they can be readily reduced to glycols by sodium borohydride or oxidized to acids, either by the method of Inch [23] (iodine/KOH in methanol) or by means of sodium chlorite (cf. Scheme 4, bottom) [24]. The latter reagent is best for secondary hydroxyacids, $RCHOHCO_2H$ since it is non-basic and thus does not lead to racemization. Harsh oxidants must be avoided since they cleave α-hydroxyaldehydes at the HOC-CHO bond. A convenient way of checking the enantiomeric purity of the glycols is to convert them into dioxolanes by means of benzaldehyde and then observe the acetalic hydrogen in proton nmr in the presence of a chiral shift reagent [7,25].

New Results

Malyngolide [26]

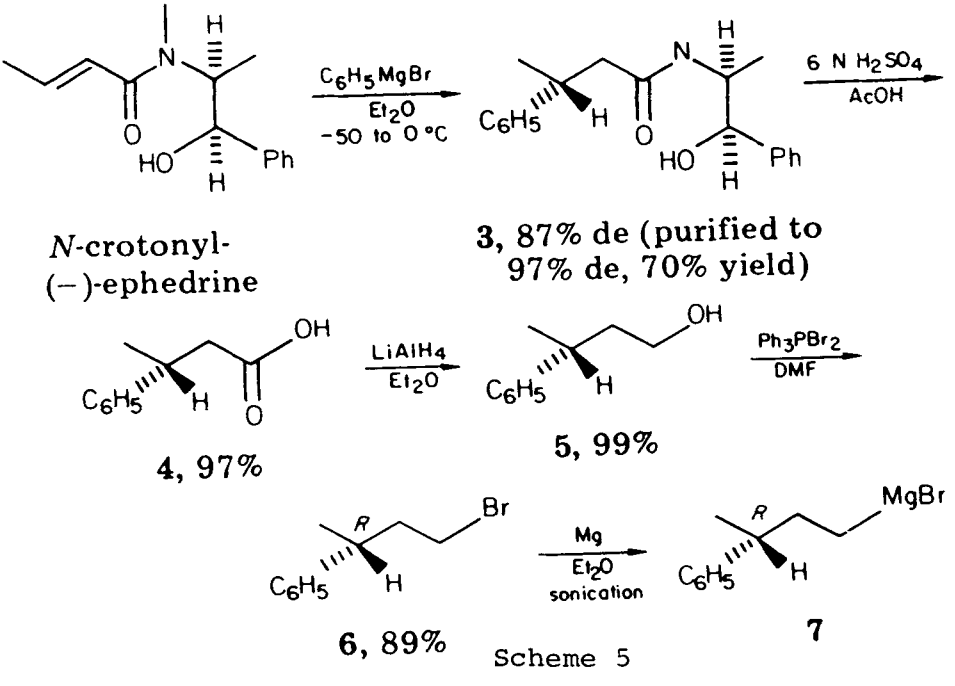
(-)-Malyngolide (2), an antibiotic of algal origin [27]



2

seemed to lend itself to the above asymmetric synthesis but contains a second chiral center α to the lactone carbonyl. It was decided to introduce the two chiral cen-

ters independently, each with a high degree of stereoselectivity, to use a phenyl group as a synthon for the carboxyl group of the lactone, and to use the method of Mukaiyama and Iwasawa [28] to obtain the needed second chiral precursor in nearly enantiomerically pure form. This method [28] is summarized in Scheme 5; its essential feature is the highly stereoselective 1,4-addition of the phenyl Grignard reagent to crotonylephedrine. Since both ephedrine enantiomers are commercially available, both enantiomers of 6 and 7 are readily obtainable in nearly enantiomerically pure form.



N-crotonyl-(−)-ephedrine

3, 87% de (purified to 97% de, 70% yield)

4, 97%

5, 99%

6, 89%

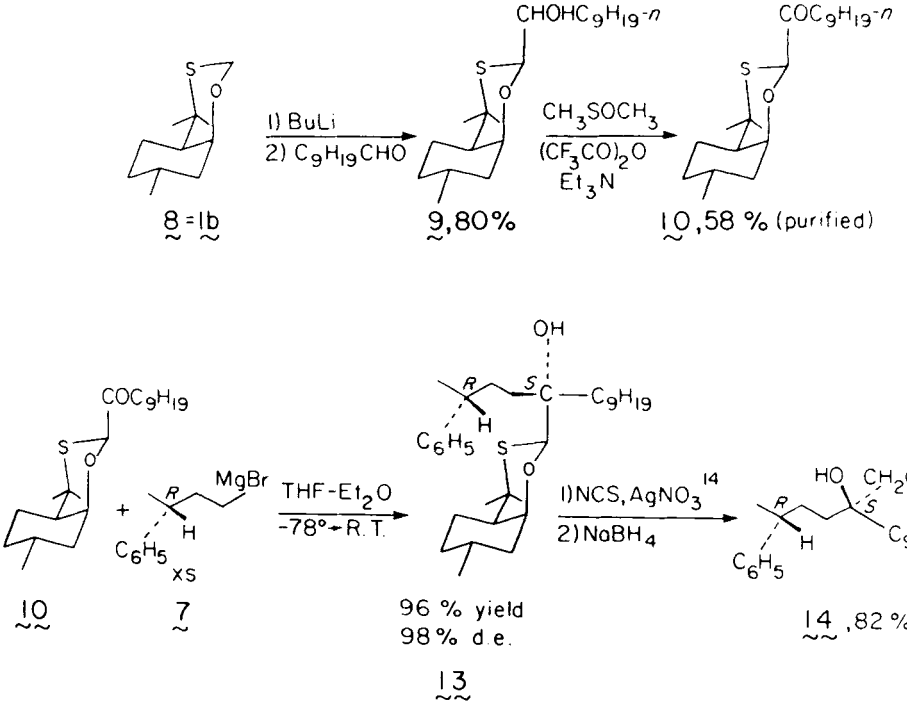
7

Scheme 5

The asymmetric synthesis of the carbinol center is shown in Scheme 6 and the conversion of the phenyl compound 14 to (-)-malyngolide in Scheme 7. Since either oxathiane 1a or 1b could be used in the synthesis (cf. Scheme 8), by appropriate combination of the enantiomers of 7 with

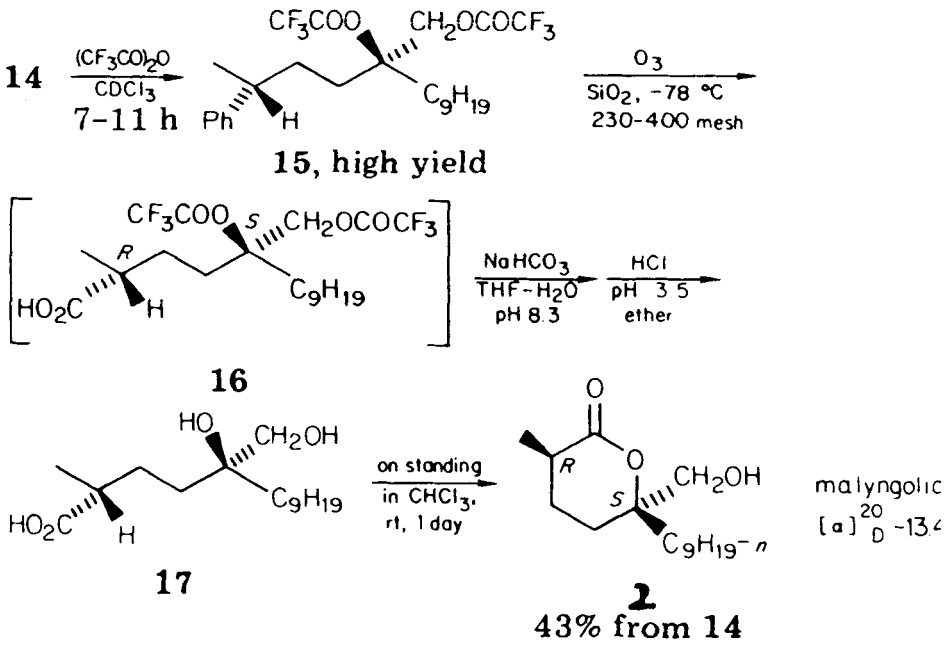
either 1o or 12, not only (-)-malyngolide and its enantiomer (+)-malyngolide but also its diastereomers (+)- and (-)-epimalyngolide were obtained [26].

It is relatively easy to determine the diastereomer excess formed in the reactions of ketones 1o and 12 with Grignard reagent 7 by analyzing the ratio of diastereo-

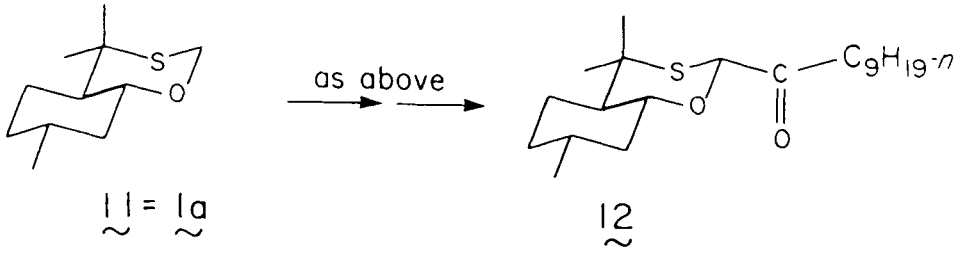


Scheme 6

mers in 13 (and its analog formed from 12) by proton nmr. The two diastereomers formed differ appreciably in the position of the C-2 proton in the oxathiane moiety (O-CHR-S). The diastereomeric purities of the four final products shown in Table 2 were then calculated



Scheme 7



Scheme 8

TABLE 2

Product	Purity		
	enantiomeric calc'd %	diastereomeric calc'd %	found %
(-)-Malyngolide	99.9+	97.4	96
(+)-Malyngolide	99.9	95.5	96
(-)-Epimalyngolide	99.8	87.6	87
(+)-Epimalyngolide	99.9+	95.4	98

by considering the enantiomeric purity of the starting Grignard reagent 7 and the stereoselectivity of conversion of ketones 1o and 12 to 13 or epimers thereof. Specifically, if A is the percent of the major enantiomer in the starting material 7 and B is the percent of the major diastereomer at the newly created carbinol center in the condensation of 7 with ketones 1o or 12, the percentage of the major stereoisomer in the product will be A.B/1oo, the percentage of the enantiomer of this product will be (1oo-A).(1oo-B)/1oo and the percentage of the two diastereomers will be [A.(1oo-B)+B.(1oo-A)]/1oo. If one normalizes the sum of the first two figures to 1oo%, one obtains the enantiomeric purity of the major product formed whereas taking the sum of the first two and normalizing the sum of all four to 1oo% will give the calculated diastereomeric purity. By way of example, in the (-)-malyngolide synthesis, the precursor 7 was 96.8% enantiomerically pure and the stereoselectivity in the Grignard addition (7 + 1o) was 98%. This means that the major enantiomer in 7 comprised 98.4% and the major diastereomer of 13 (at the carbinol center) 99% of total product; the percentage of the major product [(-)-malyngolide] is then 98.4 x 99/1oo or 97.4 and that of its enantiomer 1.6 x 1/1oo or o.o2 whence the enantiomeric purity of the (-)-malyngolide is 1oox(97.4-o.o2)/(97.4 + o.o2) or $\geq$ 99.9%. The fraction of the two diastereomeric products will be (98.4 x 1) + (99 x 1.6)/1oo or 2.6 and the diastereomeric purity of the malyngolide is calculated to be 1oo x (97.4 + o.o2)/(97.4 + o.o2 + 2.6) or 97.4%. These are calculated figures shown in Table 2, columns 2 and 3.

There is a question, of course, whether the actual purities correspond to those calculated, in other words,

whether or not there is any epimerization and/or racemization in the steps following the condensation of 7 and 10 (or 12). We have, at present, no way to check for the less than 0.1% enantiomer calculated to be present in the (-)-malyngolide; even capillary gas chromatography on a suitable chiral stationary phase (if one could be found) would be driven to the limits of its sensitivity in this situation. On the other hand, it is relatively easy to check for diastereomeric impurity (epimalyngolide in malyngolide or vice versa) since malyngolide and epimalyngolide are readily separable by column chromatography and also show different spectral pattern in the CH_2OH region of the proton spectrum (Malyngolide displays a well-spaced AB pattern, J=12 Hz, whereas epimalyngolide shows a very tightly coupled AB whose unresolved large inner peak is between the two halves of the malyngolide pattern and well separated from them). By a combination of chromatographic and nmr analysis the experimental diastereomeric purities shown in Table 2 (column 4) were determined. It is clear that they agree, within experimental error, with the calculated purities in column 3. It follows, therefore, that there has been no epimerization in the conversion of 13 to 2 in several steps. (The same is true for the three other stereoisomers). Since racemization (in contrast to epimerization) can only occur by inversion of both chiral centers in malyngolide, and since such an inversion must necessarily proceed stepwise, racemization would necessarly have to be accompanied by epimerization; conversely, the absence of epimerization thus guarantees the absence of racemization. The figures in Table 2, column 2 are therefore actual indicators of the enantiomeric purity of malyn-

golide and its three stereoisomers prepared by the present synthesis. The rotations of the malyngolide after purification by chromatography (which removes epimeric and other impurities) are shown in Table 3, along with literature values and enantiomeric purities from Table 2. It is evident, from the data in Table 2, that malyngolide and its stereoisomers were in fact obtained in high enantiomeric purity; overall chemical yields from 1o or 12 range from 25 to 38%.

TABLE 3

Product	e.e,calc'd %	$[\alpha]_D^{20}$ (deg.) found	lit.
Malyngolide	99.9+	-13.4	-13.o[a]
enantio-Malyngolide	99.9	+12.4[b]	(new)
epi-2-Malyngolide	99.9+	+21.1	+19.1[c]
epi-5-Malyngolide	99.8	-2o.8	(new)

[a] Ref. 27. [b] The material contained a small amount of chemical impurity. [c] Ref. 29.

(R)-(+)-γ-Caprolactone

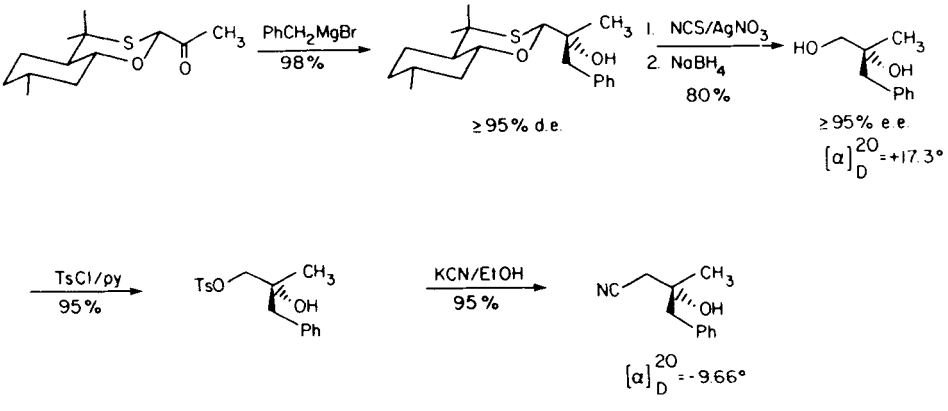
(R)-(+)-γ-caprolactone is a pheromone component of a dermestid beetle, Trogoderma glabrum. The compound has been synthesized from (S)-(+)-glutamic acid [3o]. We have synthesized the pheromone from the propionyloxathiane $R^*COC_2H_5$ by Dibal reduction (74% d.e.; further purification was achieved by chromatography), protection of the alcohol function by either benzylation or methoxymethylation, cleavage to (R)-$C_2H_5CHORCHO$ (R = $C_6H_5CH_2$ or CH_3OCH_2), reduction (or oxidation followed by reduction) to (R)-(-)-$C_2H_5CHORCH_2OH$, conversion to the tosylate, reaction with diethyl sodiomalonate to

give (R)-(-)-$C_2H_5CHORCH_2CH(CO_2C_2H_5)_2$ and saponification, acidification and decarboxylation to (R)-(-)-$C_2H_5CHORCH_2$-CH_2CO_2H. Debenzylation of this acid (R = $C_6H_5CH_2$) was sluggish and proceeded with considerable racemization, possibly by reversible dehydrogenation-hydrogenation over the palladium catalyst. The acid was therefore first esterified to the methyl ester, (R)-(-)-$C_2H_5CHORCH_2CH_2$-CO_2CH_3 which was then debenzylated (H_2, Pd/C); it spontaneously lactonized to (R)-(+)-γ-caprolactone (18). The overall chemical yield of the lactone 18 from the chiral alcohol R* $CHOHC_2H_5$ was 54% for R=$C_6H_5CH_2$ and the optical yield was 92%. Even for R=CH_3OCH_2O the optical yield was only 95%. Unfortunately these optical yields are not very reliable, since the enantiomeric purity of the final lactone 18 is based on measurement of rotation. We are presently studying better methods for determining the enantiomeric purity of the final product; with that information in hand we may be able to better the optical yield, if in fact it is as low as 92-95%.

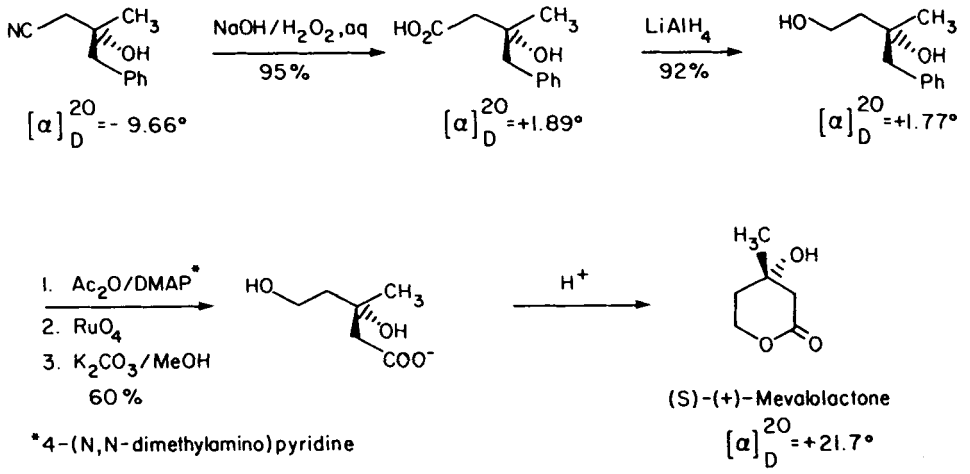
MEVALOLACTONE

Mevalolactone is the biogenetic precursor of steroids and a number of terpenes. It has been synthesized asymmetrically on a number of previous occasions [14,31-34] but mostly by enzymatic methods, from chiral precursors or in poor chemical or optical yields. Our own earlier synthesis of the natural (R)-(-)-Mevalolactone [14] proceeded in rather low yield, apparently because the final step, hydroboration-hydrolysis of (S)-β-hydroxy-β-vinylbutyronitrile, was insufficiently regioselective. Encouraged by our use of the phenyl group as a synthon for carbonyl in the malyngolide synthesis (vide supra) we have now synthesized (S)-(+)-Mevalolactone in high chemical

and optical yield [15] (cf. Schemes 9 and 10; yields refer to the racemic series). Most of the steps are straightforward; in the oxidation of the phenyl moiety we used ruthenium tetroxide [35] in preference to ozonization employed for malyngolide. The enantiomeric purity of the final product was estimated to be above 94% by optical rotation (which may, however, have been depressed by the presence of small amounts of chemical impurities) and by use of a chiral shift reagent [36] on the product as obtained and after dilution with a small amount of racemic material. The overall yield from the acetyl derivative of 1a is 37% in 7 steps. A synthesis of (R)-(-)-mevalolactone in ≥ 96% enantiomeric excess from (R)-(-)-β-benzyl-β-hydroxybutyronitrile (Scheme 9) in 56% yield (40% overall from 2-acetyl-1a) by acetylation, ruthenium tetroxide oxidation, diborane reduction and hydrolysis of the nitrile has also been accomplished.



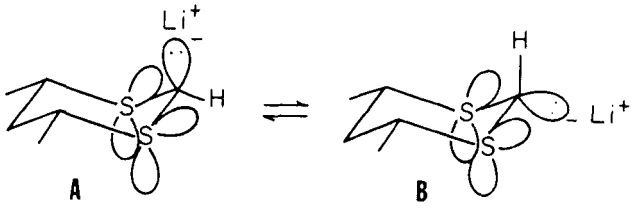
Scheme 9



Scheme 1o

Mechanism

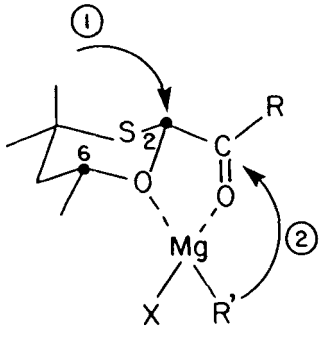
The first step in the asymmetric synthesis optical involves a virtually exclusively equatorial electrophilic substitution of an oxathiane. We have shown [37] that the corresponding substitution in dithianes is highly stereoselective regardless of whether or not tight ion pairing occurs and have postulated that the 2-lithio-1,3-dithiane exists exclusively (or nearly so) with the lithium equatorial, the subsequent electrophilic substitution taking place with retention of configuration [38]. The exclusively equatorial orientation of the lone pair in 2-dithianyl carbanions is a consequence of the gauche effect [39] and is supported by quantum-mechanical calculations [39,4o] as well as by X-ray study of the lithium salt of 2-phenyl-1,3-dithiane [41]. Scheme 11 shows the two diastereomeric lithium salts; the one on the right (B) is by far the more stable because it avoids the repulsive antiperiplanar arrangement of filled orbitals present in A. There is also stabilization of structure B through a favorable interaction of the unshared pair



Scheme 11

on C(2) with the σ^* orbital of the S-C(4) bond [40]. A similar situation undoubtedly exists in 2-lithio-1,3-oxathianes.

The second step of asymmetric synthesis follows Cram's rule [9], presumably - in view of the very high degree of selectivity - the chelate rule [42] (Scheme 12). Several pieces of evidence support this assumption: When-

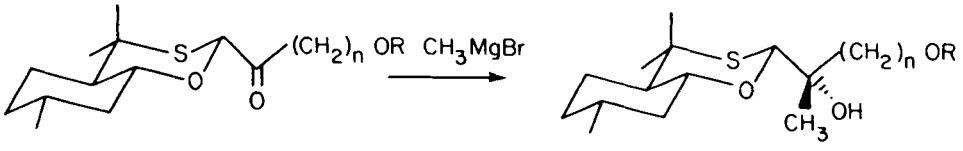


Scheme 12

ever the configuration of the product was established and correlated with that of the starting material [4,6], the results were in accord with Cram's rule (However, the chelate and the open-chain model lead to the same prediction, so the aforementioned criterion does not distinguish between the two). One piece of evidence favoring the chelate model is the finding [15] that an

ether group in the substituent at C(2) of the oxathiane will substantially lower the stereoselectivity of the Grignard addition of the 2-ketooxathiane (Scheme 13). Presumably chelation of the Grignard reagent with the exocyclic ether function competes with chelation with the oxathiane ring oxygen, thereby making the transition state for the Grignard addition less rigid and thus less selective.

Addition of CH_3MgBr to protected Oxathianyl hydroxy ketones

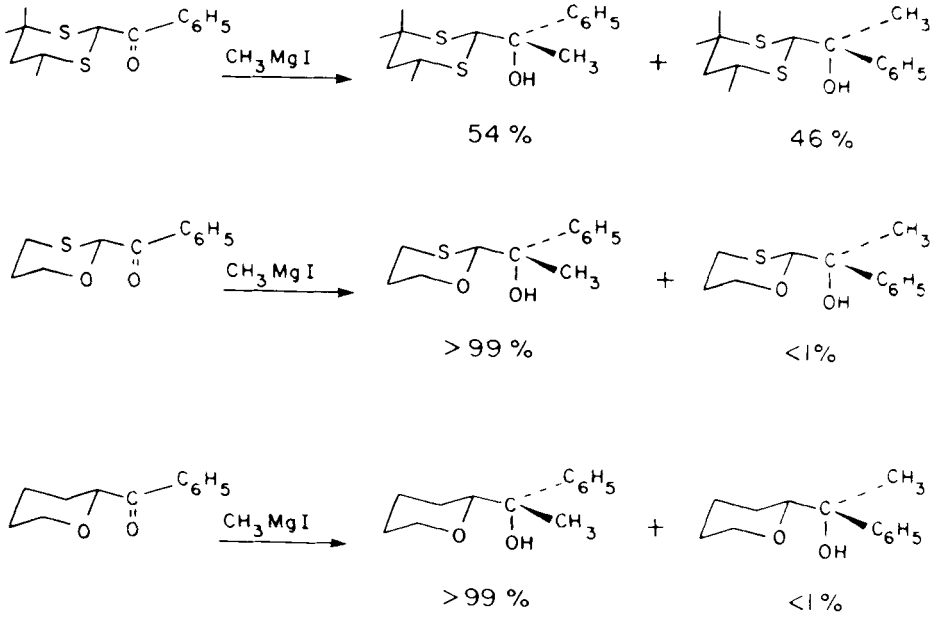


n	R	Diastereomeric excess*
1	CH_2Ph	36%
2	CH_2Ph	17%
3	CH_2Ph	62%
4	CH_2Ph	77%
2	CPh_3	72%

*13-Cnmr

Scheme 13

That complexation of the Grignard reagent with the ring oxygen is probably responsible for the stereoselectivity of the oxathiane alkylation step is also shown by the results in Scheme 14. The reaction of a chiral 2-acyl-1,3-dithiane with a Grignard reagent is nearly completely unstereoselective [43]. In contrast, the corresponding reaction with a simple 2-acyl-1,3-oxathiane, in which the only source of chirality is the chiral center at C(2),



Scheme 14

is, as far as we can tell, entirely stereoselective (Scheme 14) [43]. In fact, presence of the sulfur atom is not necessary at all for stereoselectivity: the reactions of various 2-acyloxanes with Grignard reagents (Scheme 14) are also completely stereoselective and in reductions of such ketones with lithium aluminium hydride or L-Selectride™, the major isomer predominates in ratios varying from 78:22 to 100:0 [44].

It is to be noted that despite the high stereoselectivity often observed in the application of Cram's chelate rule [9,42], processes involving this rule have rarely been used in asymmetric synthesis, because the new chiral center is generated right next to the existing one and it is generally not possible to separate the two centers, i.e. to isolate the only newly formed and,

at the same time, to regenerate the chiral auxiliary reagent. (Isolation of the newly formed chiral center and regeneration of the chiral auxiliary reagent are important considerations in an asymmetric synthesis [45]). In the synthesis here described, this difficulty is obviated by carrying out the asymmetric synthesis in two stages (cf. Scheme 12). Both stages - the electrophilic substitution in the chiral 1,3-oxathiane and the addition of an organometallic reagent to the 2-acylthiane are highly stereoselective, as indicated above. The first step transfers the chirality from the "backbone" of the oxathiane to C-2, the second from C-2 to the exocyclic chiral center. Subsequent hydrolysis destroys the chiral center at C-2 but preserves not only the newly formed exocyclic one [in the aldehyde RR'C(OH)CHO)] but also the one in the oxathiane backbone (in the form of the chiral sultine from which the chiral oxathiane can be regenerated).

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