Chiral Heteroaryloxymethyloxiranes

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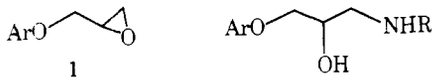
Several approaches to the synthesis of chiral heteroaryloxymethyloxiranes have been developed. The most direct method involves the reaction of an aromatic moiety bearing a readily displaceable leaving group with the sodium salt of chiral glycidol. An alternative procedure utilizes the sodium salt of chiral glycerol 1,2-acetonide in the displacement of a leaving group from an aromatic system to give the 3-(aryloxy)-1,2-propanediol acetonide. Controlled acid catalyzed deblocking of the acetonide yields chiral 3-(aryloxy)-1,2-propanediol. More vigorous hydrolytic conditions lead to a rearrangement of the diol, which ultimately produces racemization. A detailed study regarding the mechanism of this rearrangement is presented. The chiral 3-(aryloxy)-1,2-propanediol generated under the mild hydrolytic conditions could be converted through the monomesylate to the chiral oxirane. Finally, an example of the preparation of chiral aryloxymethyloxiranes from the corresponding chiral 3-amino-1-(aryloxy)-2-propanols is described.

Oxiranes, especially aryloxymethyloxiranes (**1**), are versatile intermediates useful in the synthesis of natural products and pharmaceuticals.[1,2] In compounds derivable from **1** chirality is often a key structural element,[3-5] and therefore the availability of synthetic methods for the preparation of (*R*)- and (*S*)-**1** should prove valuable. In principal, chiral **1** may be generated either from the reaction of a phenoxide with enantiomerically pure epichlorohydrin[6,7] or from the reaction of an aromatic moiety bearing a readily displaceable leaving group with chiral glycidol.[6,8] We should like to report herein the synthesis of chiral **1** utilizing the latter of these two possibilities.

As an alternative to this direct introduction of the chiral moiety, such oxiranes could, in theory, also be generated from enantiomerically pure 3-amino-1-(aryloxy)-2-propanols (**2**).[3]

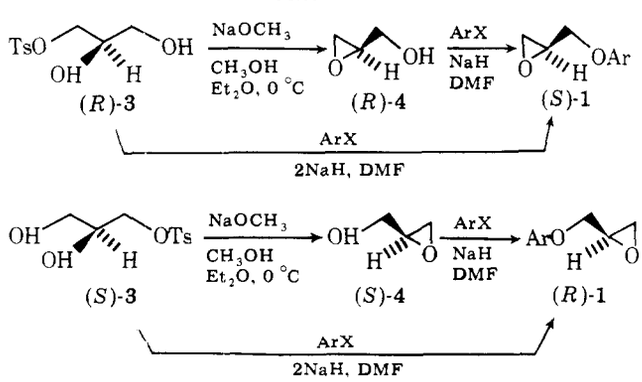


1 **2**

In such an approach, chirality would best be introduced during the synthesis of **2** through the use of a chiral glycolamine derivable from D-mannitol[3] or obtainable by resolution.[9] The utilization of this potential method of generating chiral **1** has been investigated and will also be described in this paper.

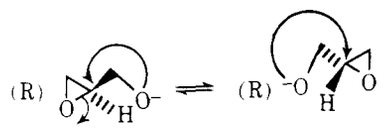
Although the preparation of racemic **1** utilizing the reaction of the sodium salt of glycidol with heteroaryl halides was described[10] while we were engaged in this work, studies directed toward the syntheses of these compounds in the more useful chiral forms have not been reported. The key intermediates in the syntheses of (*R*)- and (*S*)-glycidol (**4**), the corresponding (*R*)- and (*S*)-3-(tosyloxy)-1,2-propanediols (**3**),[6,8,11] are readily available from the diacetonide of D-mannitol[12]

Scheme I



using only slight modifications of the literature procedures. The methods by which these intermediates can be converted to chiral **1** are shown in Scheme I. To our knowledge, this is the first reported use of chiral glycidol (**4**) as a nucleophile; the indications are that this intermediate may have general use as a nucleophilic reagent when the base-induced polymerization is not a severe limitation (vide infra).

The metal salt of chiral glycidol is an interesting species. Although a cursory consideration of the rearrangement shown for the anion of glycidol may lead to the assumption that racemization would occur, a more careful examination reveals



that the chirality of this anion is retained during such a rearrangement. This fact allows for the use of chiral glycidol in a nucleophilic reaction. Retention of chirality has been recognized in the analogous cyclopropane system[13] undergoing a similar rearrangement.

Another potential problem in the utilization of glycidol as a nucleophilic reagent is a base-induced polymerization.[14] The success of the sequence indicated in Scheme I depends on the ability of the desired reaction to compete favorably with this polymerization pathway. Each of the following procedures was adopted with this in mind. In procedure A, a solution of chiral glycidol and the heteroaryl halide in DMF was added slowly to a DMF suspension of NaH, and in procedure B, a DMF solution of chiral glycidol was added slowly to a mixture of a heteroaryl halide and NaH in DMF. Comparable yields are obtained by these procedures as indicated in Table I. In addition, chiral glycidol may be generated in situ from the corresponding chiral **3** through the use of 2 equiv of NaH (procedure C). Although the yields presented in Table I for the in situ two-step procedure C are somewhat lower than those obtained from procedures A or B, the yields calculated for the latter methods are based on the last step only. Since the chiral glycidols are typically formed in 80–85% from (*R*)- and (*S*)-**3**, the overall yields of **1** from **3** according to procedures A and B are comparable to the in situ procedure (C). The tendency of isolated glycidol to polymerize makes this latter procedure (C) the method of choice in most instances.

While investigating an alternative sequence for the preparation of chiral **8** through the use of (*S*)-glycerol 1,2-acetonide [(*S*)-**11**][6] as shown in Scheme II, a rearrangement leading to racemization was uncovered. Initially, this sequence was successfully employed using racemic **11** to yield racemic **8** in

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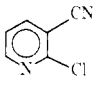
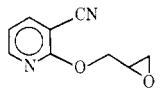
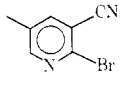
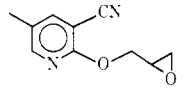
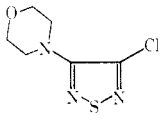
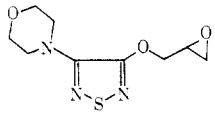
Table I. Chiral Heteroaryloxymethyloxiranes from Chiral Glycidol or its Equivalent

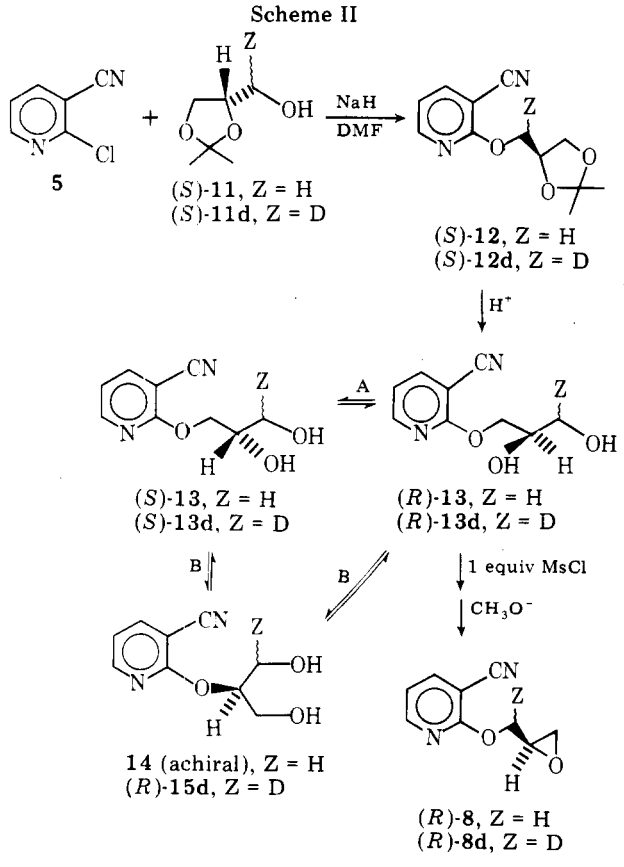
ArX[a]	product (chirality)[b]		glycidol[c]	procedure	% yield
 5[15]	 8	(*R*,*S*)	(*R*,*S*)-**4**	A	52
		(*R*,*S*)	(*R*,*S*)-**4**	B	50
		(*R*,*S*)	(*R*,*S*)-**4**	C	34
		(*S*)	(*R*)-**4**	A	48
		(*S*)	(*R*)-**4**	B	55
		(*S*)	(*R*)-**4**	C	39
		(*R*)	(*S*)-**4**	C	30
 6[16]	 9	(*R*,*S*)	(*R*,*S*)-**4**	A	45
		(*S*)	(*R*)-**4**	C	38
 7	 10	(*R*,*S*)	(*R*,*S*)-**4**	B	12
		(*S*)	(*R*)-**4**	B	7

[a] Registry no.: **5**, 6602-54-6; **6**, 65996-18-1; **7**, 30165-96-9. [b] Registry no.: (*R*,*S*)-**8**, 69470-18-4; (*S*)-**8**, 69500-51-2; (*R*)-**8**, 69500-52-3; (*R*,*S*)-**9**, 69515-56-6; (*S*)-**9**, 69470-19-5; (*R*,*S*)-**10**, 69470-20-8; (*S*)-**10**, 69500-53-4. [c] Registry no.: (*R*,*S*)-**4**, 61915-27-3; (*R*)-**4**, 57044-25-4; (*S*)-**4**, 60456-23-7.

good overall yield (~55%). However, in the chiral series it was found the acid-catalyzed removal of the acetonide group of (*S*)-**12** gave racemic **13**.

A reasonable process for this racemization would involve cleavage of (*S*)-**12** to (*R*)-**13** followed by the head-to-tail exchange of the cyanopyridyl substituent from one end of the glyceryl side chain to the other. It had been previously found that great care must be exercised in the isolation of the chiral monoacylated derivatives of glycerol,[17] which bear some structural similarity to **13**, since racemization can accompany their isolation. Two pathways for such a racemization can be envisioned and are outlined in Scheme II. Mechanism A would involve the direct exchange in (*R*)-**13** via a six-centered Smiles rearrangement[18] to give (*S*)-**13**. Mechanism B would involve two five-centered Smiles rearrangements,[18] the first yielding the achiral intermediate **14** and the second producing racemic **13** from **14**. Small amounts (≤10%) of **14** were detected in all samples of racemic **13** by the characteristic signal in the proton NMR spectrum at δ 5.4 attributable to the proton α to the aryloxy group. The presence of **14**, of course, may only be indicative of a minor side reaction and does not necessarily require that the rearrangement proceed through **14**. However, the related equilibrium observed with timolol,[3] which doesn't have the possibility of the direct exchange reaction via mechanism A, suggests that **13** and **14** would be in equilibrium in this case as well. Thus, both mechanistic pathways would appear to be viable.

Scheme II



Confirmation that the overall racemization process occurred via a head-to-tail exchange of the cyanopyridyl group was obtained through the use of (*S*)-glycerol 1,2-acetonide deuterated in the 3 position [(*S*)-**11d**].[19] According to both mechanisms A and B, racemic **13d** derived from (*S*)-**12d** should be composed of a 1:1 mixture of (*R*)-**13d** and (*S*)-**13d**; note that the position of the deuterium label varies with the chirality at the secondary alcohol center. Heating (*S*)-**12d** in aqueous acid for a few minutes produced racemic **13d**. Examination of the proton NMR spectrum confirmed the expectation that 50% of the deuterium label was located on each terminal carbon in the glyceryl side chain.

Under milder conditions (room temperature, 1 M HOAc in 50% CH_3OH/H_2O, 2–3 days) (*S*)-**12** was hydrolyzed to give (*R*)-**13** having good chiral purity [≥90% (*R*)] as determined by comparison of the proton NMR spectrum of (*R*)-**13** in the presence of a chiral shift reagent, Eu(hfbc)$_3$,[6] with that of racemic **13**. Hydrolysis of (*S*)-**12d** under these mild conditions gave, as expected, (*R*)-**13d** bearing a deuterium α to the aryloxy group. Heating (*R*)-**13d** produced racemic **13d** which now carried 50% of the deuterium label at each terminal position in the glyceryl side chain. It was also found that hydrolysis of (*S*)-**12d** in 50% CH_3OH/H_2O catalyzed with 2 drops of concentrated HCl at room temperature for 2.5 days gave partially racemic **13d**, which exhibited an approximate enantiomeric composition of 70:30 of (*R*)-**13d**/(*S*)-**13d** based on its optical rotation. The proton NMR spectrum of this material again

Table II. Chiral Purity of 17 from the Hydrolysis of (*R*)-16[d]

hydrolysis conditions	optical rotation $[\alpha]^{25}_D$ (conc)[a]	% enantiomeric excess	calc *R/S* ratio
1. 1 M HOAc, 50% CH_3OH/H_2O, room temperature, 2 days	−15.05° (2.02)	100	100 (*R*)[e]
2. dilute HCl,[b] Δ,[c] 2 h	−12.1° (4.17)	80	90/10
3. dilute HCl,[b] Δ,[c] 2 h	−7.6° (1.18)	50	75/25
4. dilute HCl,[b] Δ,[c] 2 h	−5.7 (1.57)	38	69/31
5. dilute HCl,[b] Δ,[c] 2 h	−6.0° (2.00)	40	70/30
6. dilute HCl[b] Δ,[c] 18 h	−2.3° (4.18)	16	58/42
7. dilute HCl,[b] Δ,[c] 40 h	0° (3.45)	0	50/50

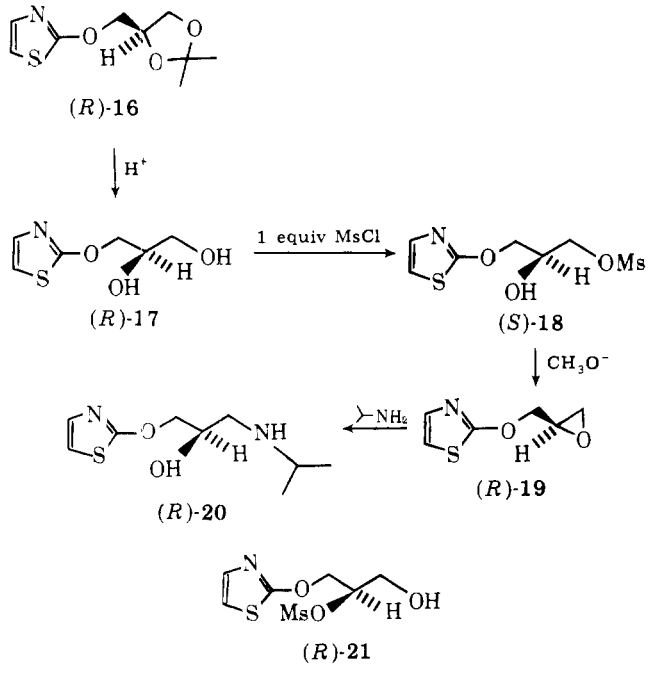
[a] g/100 mL in CH_3OH. [b] The HCl solution was prepared as previously described;[20] 2 mL concentrated HCl diluted with 2 L of H_2O. [c] Heated on a steam bath as previously described.[20] [d] Registry no.: 52120-95-3. [e] Registry no.: (*R*)-**17**, 52120-94-2; (*S*)-**17**, 52120-93-1.

confirmed the mechanistic expectation; the deuterium label was in each position of the glyceryl side chain in the ratio of 2:1, in agreement with the ratio indicated by optical rotation. Although these results are completely consistent with the overall head-to-tail exchange process, they do not allow for the selection of an actual mechanistic pathway from the possibilities A and B. It is interesting to note that the potential intermediate **14**, achiral in the protiated series, becomes chiral upon the introduction of deuterium [(*R*)-**15d**].

Reaction of each chiral diol, (*R*)-**13** or (*R*)-**13d**, with 1 equiv of methanesulfonyl chloride followed by treatment of the resulting monomesylate with base gave the corresponding oxiranes (*R*)-**8** and (*R*)-**8d**. The optical rotations observed for these samples showed them to be approximately 90% enantiomerically pure, a value in keeping with the minimum chiral purity established for the precursor diol, (*R*)-**13**. An analysis via the proton NMR spectrum exhibited by each in the presence of a europium chiral shift reagent [Eu(hfbc)$_3$][6] established a minimum chiral purity of 90% for (*R*)-**8** and (*R*)-**8d**.

It is possible that this head-to-tail exchange process had been observed previously in a related thiazole system,[20] but had not been recognized as such. Both chiral 2-[3-(isopropylamino)-2-hydroxy-1-propoxy]thiazoles (**20**) were previously synthesized according to the sequence of reactions shown in Scheme III starting with (*R*)-**16**. The final product

Scheme III



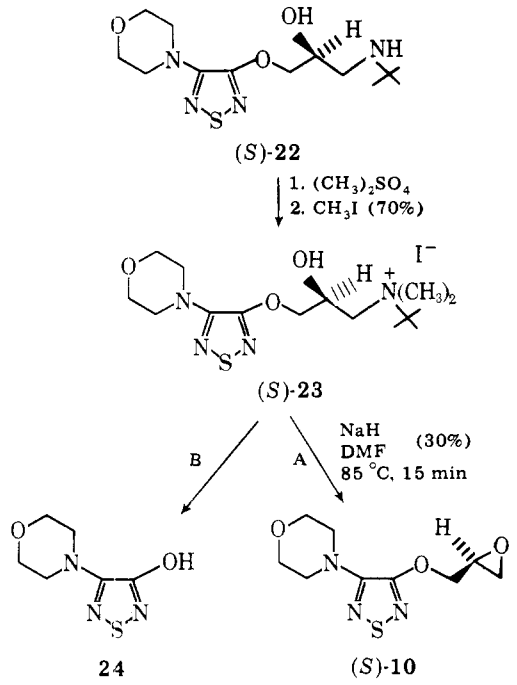
[(*R*)-**20**] obtained by this sequence was reported to have an actual isomeric *R/S* ratio of 80:20 when the optical rotation of this material was compared to that obtained by resolution.[20] Therefore, partial racemization occurred at some point between (*R*)-**16** and (*R*)-**20**. The previous workers suggested that the racemization probably resulted from the contamination of the desired monomesylate [(*S*)-**18**] with the corresponding secondary monomesylate [(*R*)-**21**].[21] Since an equally plausible explanation for the partial racemization would be a similar but slower head-to-tail exchange of the thiazole substituent during the hydrolysis of the acetonide (*R*)-**16**, experiments were performed to investigate this possibility.

The results obtained from the hydrolysis of (*R*)-**16** under various conditions are shown in Table II. By assuming that the diol **17** obtained under extremely mild hydrolytic conditions is enantiomerically pure, the isomeric *R/S* ratios obtained under other conditions can be calculated. The hydrolysis of (*R*)-**16** under the reported conditions as described in Table II was run several times and somewhat variable results were obtained with an enantiomeric purity ranging from an *R/S* ratio of 70:30 to 90:10 being found. Heating for longer periods of time (18 h) led to a 58:42 ratio, and finally to a racemic mixture (40 h). Although this system was not amenable to an estimation of the chiral purity using NMR chiral shift reagents, the decrease in optical rotation observed with increased reaction times certainly indicated that racemization of (*R*)-**17** occurred with heating in aqueous acid. In addition, the formation of the heteroaryloxymethyloxirane having a good chiral purity via this monomesylate route in the cyanopyridine system [(*R*)-**8** from (*R*)-**13**] argues against a major portion of the observed racemization in the thiazole series being the result of contamination of (*S*)-**18** by (*R*)-**21**, as proposed by the previous workers. Thus, our results support the conclusion that most, if not all, of the partial racemization in this sequence from (*R*)-**16** to (*R*)-**20** occurred at the stage of (*R*)-**17** via a mechanism involving head-to-tail exchange of the thiazole substituent.

The alternate approach which, in theory, could yield the aryloxymethyloxirane (**1**) from the corresponding aminohydroxypropoxy derivative (**2**) was next investigated. Since this approach requires the ready availability of a chiral **2**, it was decided to use timolol [(*S*)-**22**], one of the few β-adrenergic blocking agents that is readily available as a single enantiomer.[3] Such a synthetic strategy might circumvent the poor yields observed in the glycidol procedure for the synthesis of **10** from **7**. In addition, compounds represented by chiral **2** are generally readily available via procedures developed in the preparation of (*S*)-**22**.[3,9]

The overall conversion could be accomplished easily according to Scheme IV, based on the related conversion of ephedrine to the corresponding epoxide.[22] Treatment of the

Scheme IV



quaternary methiodide [(*S*)-**23**], derived in good yield from (*S*)-**22** in two steps, with NaH afforded only modest yields of (*S*)-**10** via path A along with approximately equal amounts of 3-hydroxy-4-morpholino-1,2,5-thiadiazole (**24**).[2] Apparently the elimination of the hydroxy heterocycle ($pK_a \approx 4.5$[23]) competes favorably via path B with the ejection of *tert*-butyldimethylamine. The formation of **24** was not unexpected, since a similar fragmentation has been reported with (*S*)-**22** under basic conditions.[3] As a result of the instability of **10** to basic conditions, the concentration of the desired product from this reaction follows a parabolic curve with respect to time, reaching a maximum at about 15 min. This base instability of **10** is likely to be an important factor in the low yield observed in the conversion of **7** to **10** using glycidol, as indicated in Table I.

To summarize, three different approaches to the synthesis of chiral heteroaryloxymethyloxiranes have been explored. The most direct method involves the reaction of an aromatic moiety bearing a readily displaceable leaving group with the sodium salt of chiral glycidol (isolated or generated in situ). An alternative procedure uses chiral glycerol 1,2-acetonide in place of glycidol as the nucleophilic reagent followed by the generation of the epoxide via the monomesylate of the corresponding 3-(aryloxy)-1,2-propanediol. Great care must be exercised during the acid-catalyzed deblocking of the acetonide to give the chiral 3-(aryloxy)-1,2-propanediol if a rearrangement process leading to racemization is to be avoided. Finally, the chiral aryloxymethyloxiranes may be prepared from the corresponding chiral 3-amino-1-(aryloxy)-2-propanols via base-induced epoxide formation from the quaternary methiodide.

Experimental Section

NMR spectra were determined in the indicated solvent on a Varian T-60 using tetramethylsilane as an internal standard. The NMR studies to determine the chiral purity of various products were conducted on a Varian SC-300 operating in the Fourier transform mode. Optical rotations were determined using a Perkin-Elmer 141 polarimeter. Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are uncorrected. Concentration of solutions was accomplished on a Buchi rotary evaporator at water aspirator pressure (20–25 mm).

(*S*)-2-(2,3-Epoxy-1-propoxy)-3-cyanopyridine [(*S*)-8]. Procedure A. An ice-cooled solution of 2-chloro-3-cyanopyridine (**5**)[15] (1.15 g, 8.3 mmol) and (*R*)-glycidol (0.63 g, 8.5 mmol) in DMF (25 mL) was added dropwise to an ice-cooled suspension of NaH (0.41 g of a 50% oil dispersion, 8.5 mmol) in DMF (15 mL) over 1.5 h. The reaction was allowed to stir overnight while slowly warming to room temperature. An equal volume of H_2O was added and the mixture was extracted with ether, dried (Na_2SO_4) and concentrated. The crude product was triturated several times with hot hexane and the washes were decanted. The combined hexane washes were cooled and filtered to give (*S*)-**8** (48%).

(*S*)-8. Procedure B. To an ice-cooled mixture of **5** (8.0 g, 58 mmol) and NaH (3.1 g of a 50% oil dispersion, 64 mmol) in DMF (20 mL) was added dropwise an ice-cooled solution of (*R*)-glycidol (4.2 g, 57 mmol) in DMF (40 mL) over 1 h. The reaction mixture was stirred overnight while slowly warming to room temperature and then worked up as in procedure A. Recrystallization from hexane gave (*S*)-**8** (55%).

(*S*)-8. Procedure C. To an ice-cooled mixture of **5** (1.39 g, 10 mmol) and NaH (1.0 g of a 50% oil dispersion, 21 mmol) in DMF (25 mL) was added dropwise (*R*)-**3** (2.5 g, 10 mmol) in DMF (50 mL) over 1½ h. The reaction was then conducted as in procedure A, and the product was recrystallized from hexane to give (*S*)-**8** (39%); mp 72–73 °C; $[\alpha]^{25}_D$ 16.8° (*c* 5.01, $CHCl_3$); $[\alpha]^{26}_D$ 28.7° (*c* 2.575, CH_3OH); ^1H NMR ($CDCl_3$) δ 2.9 (2 H, m), 3.4 (1 H, m), 4.4 (1 H, d of d, J = 12 and 5 Hz), 4.7 (1 H, d of d, J = 4 and 12 Hz), 7.0 (1 H, d of d, J = 8 and 5 Hz), 7.9 (1 H, d of d, J = 8 and 2 Hz), 8.35 (1 H, d of d, J = 5 and 2 Hz). An estimation of the chiral purity using Eu(hfbc)$_3$[6] indicated that this material was ≥98% (*S*)-**8**. Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.65; H, 4.50; N, 15.78.

(*R,S*)-8. Each of the three procedures above was used to prepare (*R,S*)-**8**, mp 57–60 °C. Anal. Found: C, 61.10; H, 4.37; N, 15.82.

(*R*)-8. Procedure C was used to prepare (*R*)-**8** (30%) starting with (*S*)-3-(tosyloxy)-1,2-propanediol [(*S*)-**3**] in place of (*R*)-**3**; mp 75–76 °C; $[\alpha]^{26}_D$ −30.7° (*c* 2.52, CH_3OH). An estimation of the chiral purity using Eu(hfbc)$_3$[6] indicated that this material was ≥98% (*R*)-**8**. Anal. Found: C, 61.40; H, 4.60; N, 15.84.

(*S*)-2-(2,3-Epoxy-1-propoxy)-3-cyano-5-methylpyridine [(*S*)-9]. Substituting 2-bromo-3-cyano-5-methylpyridine (**6**)[16] for **5** yields (*S*)-**9** (38%) according to procedure C: mp 83–85 °C; $[\alpha]^{25}_D$ 8.7° (*c* 2.65, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.3 (3 H, s), 2.9 (2 H, m), 3.4 (1 H, m), 4.3 (1 H, d of d, J = 12 and 4.5 Hz), 4.7 (1 H, d of d, J = 12 and 3.5 Hz), 7.6 (1 H, d, J = 2 Hz), 8.1 (1 H, d, J = 2 Hz). Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.10; H, 5.42; N 14.61.

(*R,S*)-9. Substituting **6** for **5** and following procedure A gave (*R,S*)-**9** (45%), mp 77–79 °C. Anal. Found: C, 62.96; H, 5.31; N, 14.63.

(*S*)-3-(2,3-Epoxy-1-propoxy)-4-morpholino-1,2,5-thiadiazole [(*S*)-10]. Substituting 3-chloro-4-morpholino-1,2,5-thiadiazole (**7**)[3] for **5** yields (*S*)-**10** (7%) according to procedure B, mp 113–114 °C.

(*R,S*)-10. Using racemic glycidol and procedure B as indicated for (*S*)-**10** above gave (*R,S*)-**10** (12%): mp 97–99 °C; ^1H NMR ($CDCl_3$) δ 2.8 (2 H, m), 3.2–3.9 (9 H, m), 4.2 (1 H, d of d, J = 12 and 6 Hz), 4.7 (1 H, d of d, J = 12 and 3 Hz). Anal. Calcd for $C_9H_{13}N_3SO_3$: C, 44.43; H, 5.39; N, 17.27. Found: C, 44.53; H, 5.59; N, 17.13.

3-(3-Cyano-2-pyridinyloxy)-1,2-propanediol Acetonide [(*R,S*)-12]. To NaH (2.4 g of a 50% oil dispersion, 52.5 mmol) in DMF (50 mL) was added glycerol 1,2-acetonide (6.9 g, 52.5 mmol) in DMF (20 mL) over 15 min. After stirring for 30 min, the solution was cooled in an ice bath and 2-chloro-3-cyanopyridine (7.5 g, 45 mmol) in DMF (50 mL) was added. After stirring for 3 h at room temperature, the mixture was filtered and the DMF was removed under reduced pressure. H_2O was added to the residue and the oil was extracted with $CHCl_3$. After drying (Na_2SO_4) and concentration, the residue was distilled to yield (*R,S*)-**12** (66.5%), bp 143–149 °C (0.3 torr). The distillate solidified and was recrystallized from hexane: mp 69–71 °C; ^1H NMR ($CDCl_3$) δ 1.4 (3 H, s), 1.5 (3 H, s), 3.8–4.6 (5 H, m), 7.0 (1 H, d of d, J = 7 and 2 Hz), 7.9 (1 H, d of d, J = 7 and 2 Hz), 8.3 (1 H, d of d, J = 5 and 2 Hz). Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.58; H, 6.16; N, 11.74.

3-(3-Cyano-2-pyridinyloxy)-1,2-propanediol [(*R,S*)-13]. A solution of (*R,S*)-**12** (6.0 g, 26 mmol) in 80% aqueous EtOH (70 mL) containing concentrated HCl (2 mL) was stirred at room temperature for 1 h and heated on a steam bath for 15 min. The solution was concentrated and distilled to yield (*R,S*)-**13** (64%): bp 190–195 °C (0.3 torr); ^1H NMR (D_2O) δ 3.9 (2 H, d of d, J = 6 and 4 Hz), 4.1–4.4 (1 H, m), 4.5 (2 H, m) 7.2 (1 H, d of d, J = 7 and 5 Hz), 8.2 (1 H, d of d, J = 7 and 2 Hz), 8.4 (1 H, d of d, J = 5 and 2 Hz). Anal. Calcd for $C_9H_{10}N_2O_3 \cdot \frac{1}{2}H_2O$: C, 53.19; H, 5.45; N, 13.79. Found: C, 53.34; H, 5.20; N, 14.21.

The presence of **14** or (*R*)-**15d** was detected by characteristic signals in the NMR of all samples of **13** prepared as described either above

or subsequently in the Experimental Section. The multiplet attributed to the proton α to the aryloxy group occurred at δ 5.4 (J = 5 Hz, see text), while the protons on the primary hydroxyl carbons appeared as a doublet (J = 5 Hz) at δ 3.95.

2-(2,3-Epoxy-1-propoxy)-3-cyanopyridine [(*R,S*)-8] from (*R,S*)-13. To (*R,S*)-**13** (1.94 g, 10 mmol) in pyridine (10 mL) at 0 to −10 °C in an ice–salt bath was added methanesulfonyl chloride (1.14 g, 10 mmol) over a few minutes. Cooling was discontinued and stirring was continued for 30 min. The mixture was diluted with CH_2Cl_2 (70 mL) and cooled in an ice–salt bath before NaOMe (1.2 g, 22 mmol) in MeOH was added. Stirring without cooling was continued for 1 h. The mixture was washed with H_2O, cold dilute HCl, and saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated to give crude (*R,S*)-**8** (82%). Recrystallization from hexane gave (*R,S*)-**8**, mp 56–58 °C.

(*S*)-12. Following essentially the procedure outlined for (*R,S*)-**12** and using (*S*)-**11**, (*S*)-**12** (90%) can be obtained which is suitable for further use without distillation. Recrystallization of a small sample from hexane gave (*S*)-**12**: mp 51–53 °C; $[\alpha]^{24}_D$ 27.2° (*c* 7.47, $CHCl_3$).

(*R*)-13. A mixture of (*S*)-**12** (500 mg, 2.1 mmol) and 1 M HOAc in 50% CH_3OH/H_2O was stirred at room temperature for 2–3 days. After concentration, the residue was taken up in H_2O and washed with ether, and the aqueous phase was saturated with K_2CO_3. Extraction with CH_2Cl_2, drying, and concentration gave (*R*)-**13**. Chromatography on a thick layer silica gel GF plate (Analtech, 2000μ) accomplished the removal of traces of the acetonide to yield pure (*R*)-**13**, $[\alpha]^{25}_D$ −5.0° (*c* 10.82, CH_3OH). An estimation of the chiral purity using Eu(hfbc)$_3$[6] indicated that this material was ≥90% (*R*)-**13**.

(*R*)-8 from (*R*)-13. Following the procedure described for the preparation of (*R,S*)-**8** from (*R,S*)-**13** and substituting (*R*)-**13** for (*R,S*)-**13**, (*R*)-**8** (46%) was obtained: mp 68–70 °C; $[\alpha]^{24}_D$ −24.7° (*c* 1.032, CH_3OH). An estimation of the chiral purity using Eu(hfbc)$_3$[6] indicated that this material was ≥90% (*R*)-**8**.

(*S*)-11d. Using the procedure previously described[6] for the preparation of (*S*)-**11** and substituting $NaBD_4$ (D = 98 atom %, MSD) for $NaBH_4$, (*S*)-**11d** (54%) was obtained: $[\alpha]^{24}_D$ 11.2° (*c* 5.36, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 1.3 (3 H, s), 1.45 (3 H, s), 2.9 (1 H, br s), 3.5–4.4 (4 H, m).

(*S*)-12d. According to the procedure described for (*R,S*)-**12** but substituting (*S*)-**11d** for (*R,S*)-**11**, (*S*)-**12d** (63%) was obtained without distillation. Recrystallization of a small sample from hexane gave pure (*S*)-**12d**: mp 51–53 °C; $[\alpha]^{24}_D$ 26.7° (*c* 5.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.4 (3 H, s), 1.5 (3 H, s), 3.8–4.6 (4 H, m), 7.0 (1 H, d of d, J = 8 and 5 Hz), 7.9 (1 H, d of d, J = 8 and 2 Hz), 8.4 (1 H, d of d, J = 5 and 2 Hz).

(*R*)-13d. Following the procedure described for (*R*)-**13** and starting with (*S*)-**12d**, (*R*)-**13d** was obtained: $[\alpha]^{24}_D$ −5.9° (*c* 1.60, CH_3OH); ^{1}H NMR (D_2O) δ 3.9 (2 H, d of d, J = 6 and 4 Hz), 4.1–4.4 (1 H, m), 4.5 (1 H, m), 7.2 (1 H, d of d, J = 8 and 5 Hz), 8.2 (1 H, d of d, J = 8 and 2 Hz), 8.4 (1 H, d of d, J = 5 and 2 Hz).

(*R,S*)-13d from (*R*)-13d or (*S*)-12d. Either (*S*)-**12d** or (*R*)-**13d** was heated in a mixture of equal volumes of 3 N HCl and acetone for 15–30 min. The residual aqueous phase was saturated with K_2CO_3, extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated to give (*R,S*)-**13d**; ^{1}H NMR (D_2O) δ 3.7–3.9 (1.5 H, m), 4.1–4.4 (1 H, m), 4.4–4.6 (1.5 H, m), 7.2 (1 H, d of d, J = 7 and 5 Hz), 8.2 (1 H, d of d, J = 7 and 2 Hz) 8.4 (1 H, d of d, J = 5 and 2 Hz).

(*R*)-8d from (*R*)-13d. Following the procedure described for the preparation of (*R,S*)-**8** from (*R,S*)-**13** and substituting (*R*)-**13d** for (*R,S*)-**13**, (*R*)-**8d** (60%) was obtained: mp 63–70 °C; $[\alpha]^{24}_D$ −23.4° (*c* 0.912, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 2.9 (2 H, m), 3.4 (1 H, m), 4.45 (½ H, m), 4.7 (½ H, m), 7.0 (1 H, d of d, J = 8 and 5 Hz), 7.9 (1 H, d of d, J = 8 and 2 Hz), 8.35 (1 H, d of d, J = 5 and 2 Hz). An estimation of the chiral purity using Eu(hfbc)$_3$[6] indicated that this material was ≥90% (*R*)-**8d**.

(*R*)-3-(2-Thiazolyloxy)-1,2-propanediol [(*R*)-17]. Following the procedure described for the preparation of (*R*)-**13** for the hydrolysis of (*R*)-**16**,[20] (*R*)-**17** was obtained. Chromatography on a thick layer silica gel GF plate (Analtech, 2000μ) removed small amounts of (*R*)-**16** to give pure (*R*)-**17**, $[\alpha]^{24}_D$ −15.05° (*c* 2.02, CH_3OH).

Anal. Calcd for $C_6H_9NO_3S$: C, 41.13; H, 5.18; N, 8.00. Found: C, 40.96; H, 5.15; N, 7.92.

(*S*)-1-(Methyl-*tert*-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol. The maleate salt of (*S*)-**22** (40 g, 0.09 mol) was partitioned between saturated sodium carbonate (150 mL) and ethyl acetate (150 mL). After drying thoroughly ($CaSO_4$), the organic phase was treated with dimethyl sulfate (12.6 g, 0.1 mol) and ethyldiisopropylamine (12.9 g, 0.1 mol). The reaction was refluxed for 3 h, followed by stirring overnight at ambient temperature. After washing the reaction with water (2 × 50 mL) and drying ($CaSO_4$), the solvent was evaporated to yield 25 g (82%) of the crude tertiary amine: ^{1}H NMR ($CDCl_3$) δ 1.05 (9 H, s), 2.2 (3 H, s), 3.3–3.9 (9 H, m), 4.0–4.7 (4 H, m).

(*S*)-1-(Dimethyl-*tert*-butylammonium)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol Iodide [(*S*)-23]. A solution of the tertiary amine derived from (*S*)-**22** (24.3 g, 0.074 mol) in DMF (20 mL) was treated with methyl iodide (11.4 g, 0.08 mol) at room temperature. After stirring for 15 h, ether (400 mL) was added slowly causing the salt to crystallize. The solid was filtered, washed with ether, and dried. Recrystallization from acetone–ethyl acetate afforded 29.5 g (85%) of the crystalline salt: mp 158–160 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.4 (9 H, s), 3.0 (3 H, s), 3.1 (3 H, s), 3.2–3.8 (10 H, m), 4.3–4.8 (3 H, m).

(*S*)-3-(2,3-Epoxy-1-propoxy)-4-morpholino-1,2,5-thiadiazole. [(*S*)-10]. To a solution of the salt (*S*)-**23** (9.4 g, 20 mmol) in dry DMF (20 mL) at 85 °C was added in one portion sodium hydride (0.48 g, 20 mmol) previously washed with petroleum ether (bp 30–60 °C) under a nitrogen stream. A 300-mL round-bottom flask was used in order to accommodate the vigorous gas evolution and foaming which occurs. After 15 min, the reaction was removed from the oil bath and diluted with ethyl acetate (150 mL). The resulting solution was washed with saturated NH_4Cl solution (1 × 50 mL) and water (3 × 60 mL). The organic portion was dried ($CaSO_4$) and evaporated to a crystalline solid. This residue was partitioned between ether (200 mL) and 6 N NaOH (50 mL). The ether extract was washed with water, dried ($CaSO_4$), and evaporated to afford 1.4 g of the crude product. Recrystallization from petroleum ether yielded 1.1 g (24%) of the crystalline (*S*)-**10**: mp 113–114 °C; $[\alpha]^{23}_D$ 24.8° (*c* 5.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.7 (1 H, d of d, J = 4.5 and 3 Hz), 2.9 (1 H, d of d, J = 4.5 and 4.5 Hz), 3.2–3.9 (9 H, m), 4.2 (1 H, d of d, J = 12 and 6 Hz), 4.7 (1 H, d of d, J = 12 and 3 Hz).

Anal. Calcd for $C_9H_{13}N_3O_3S$: C, 44.43; H, 5.39; N, 17.27. Found: C, 44.51; H, 5.53; N, 17.19.

Additional product can be recovered from the mother liquors via chromatography over silica gel, eluting with 5% Et_2O/CH_2Cl_2. Yields vary from 15 to 30%.

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Registry No.—(*R*)-**3**, 41274-09-3; (*S*)-**3**, 50765-70-3; **8d**, 69470-21-9; (*S*)-**11**, 22323-82-6; (*R,S*)-**11**, 22323-83-7; **11d**, 56165-50-5; (*S*)-**12**, 69470-22-0; (*R,S*)-**12**, 69500-54-5; **12d**, 69470-23-1; (*R,S*)-**13**, 69470-24-2; **13d**, (*R*)-**13**, 69500-55-6; **13d**, 69470-25-3; **14**, 69470-26-4; **15d**, 69470-27-5; (*S*)-**22** maleate, 60469-65-0; (*S*)-**23**, 69470-28-6; (*S*)-1-(methyl-*tert*-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol, 69493-62-5; glycerol 1,2-acetonide, 22323-83-7.

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Sesquiterpene Lactones of *Tithonia diversifolia*. Stereochemistry of the Tagitinins and Related Compounds[1]

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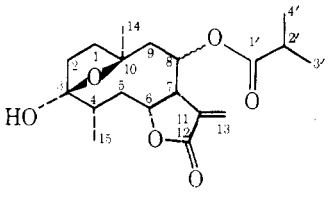
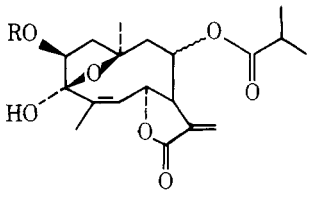
The sesquiterpene lactones tagitinins A, C, and F and tirotundin and the flavone hispidulin were isolated from Indian *Tithonia diversifolia* (Hemsl.) A. Gray. Complete stereochemical expressions are presented for these compounds as well as for tagitinin B and E, and the configuration at C-8 of zexbrevin, zexbrevin B, orizabin, ciliarin, calaxin, tifruticin, deoxytifruticin, viguiestin, and deacetylviguiestin is assigned.

Isolation of six sesquiterpene lactones, tagitinins A–F, from the antileukemic alcoholic extract of what was referred to as *Tithonia tagitiflora* Desf. [sic] has been reported recently.[2,3] We have isolated several of these compounds from an Indian collection of *Tithonia diversifolia* (Hemsl.) A. Gray which we believe represents the actual source of the lactones obtained by Pal and co-workers.[4] Our results which together with our previous work on tirotundin[6,7] and woodhousin[8,9] provide complete stereochemical expressions for the tagitinins and several related substances are described in the present report.

Tagitinin D was identical with tirotundin which we had isolated earlier[6] from *T. rotundifolia;* the name tagitinin D



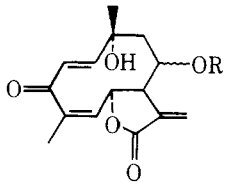
1a, H-8α, tirotundin
b, H-8β



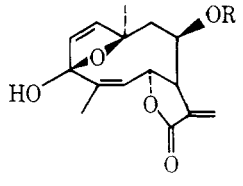
2a, R = H, H-8α, tagitinin D
b, R = Ac, H-8α, woodhousin
c, R = Ac, H-8β

should therefore be abandoned. The stereochemistry **1b** assigned originally[6] to tirotundin was recently[7] altered to **1a** as the result of an X-ray analysis.

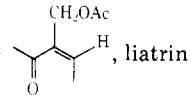
Tagitinin B had properties which suggested[3] that it was a deacetyl derivative of woodhousin;[8] hence formulas **2** (R = H) and **3** (R = H, stereochemistry at C-8 not specified) were assigned to it and to tagitinin C with which it had been correlated.[3] Since the C-8 stereochemistry of woodhousin has recently been revised from **2c** to **2b** as the result of an X-ray analysis,[9] tagitinin B and tagitinin C will have to be reformulated as **2a** and **3a,** respectively. This removes at least one element of confusion emanating from the work of Pal et al. who stated[3] that hydrogenation of tagitinin F (assigned[3] formula **4a** because of its similarity to liatrin, **4b**) furnished the



3a, R = *i*-Bu, H-8α, tagitinin C
b, R = Ang, H-8α
c, R = Ang, H-8β

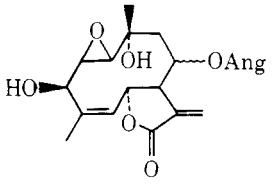


4a, R = *i*-Bu, tagitinin F

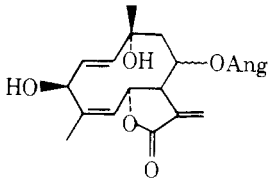


b, R = , liatrin

same hexahydro derivative as hydrogenation of **3a,** a result manifestly impossible if the stereochemistry at C-8 were different.[11] ^{13}C NMR spectra of tirotundin, woodhousin, and tagitinin C are listed in Table I for comparison.[12] Because of the close correspondence in chemical shifts and coupling constants between tagitinin C and dehydrodeoxytifruticin[6,13] and for other reasons cited earlier,[7,9] we conclude that the C-8 stereochemistry of dehydrodesoxytifruticin, and therefore also that of its congeners tifruticin and deoxytifruticin from *T. fruticosa,*[6] must be inverted from **3c** to **3b, 5b** to **5a,** and **6b** to **6a,** respectively.



5a, H-8α, tifruticin
b, H-8β



6a, H-8α, deoxytifruticin
b, H-8β

Formula **7** with a trans-lactone function but without specification of stereochemistry at C-1, C-4, and C-8 was proposed[3] for tagitinin A because of its similarity to tirotundin and its chemical behavior. We have established its stereochemistry at all centers in the following manner.

0022-3263/79/1944-1831$01.00/0