m/e 296 (M^+). Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.95; H, 5.44. Found: C, 72.63; H, 5.56.

The reaction mixture from **11b** was treated as described above to afford crude quinone. Recrystallization from hexane gave 73 mg (60%) of **18a**.

***anti*-7,10,15,18-Tetrahydroxy[4.2]metacyclophane (20).** To a solution of 100 mg (0.338 mmol) of **18a** in 30 mL of acetic acid was added 1.0 g of zinc powder. Addition of zinc powder to the mixture produced a yellow to reddish brown color immediately. The reaction mixture was stirred at rt for a few min. After the reaction mixture became colorless, the reaction mixture was treated as described above to give 92 mg (91%) of **20**: colorless prisms; mp >300 °C; IR (KBr) 3500–3350 (broad, OH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.2–1.5 (4 H, m), 1.8–2.0 (2 H, m), 2.5–2.8 (6 H, m), 5.24 (2 H, s, internal OH, exchanged by D_2O), 6.17 (2 H, d, J = 2.8 Hz), 6.41 (2 H, d, J = 2.8 Hz), 8.44 (2 H, s, external OH, exchanged by D_2O); MS *m/e* 300 (M^+). Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.14; H, 6.81.

***anti*-7,10,15,18-Tetraacetoxy[4.2]metacyclophane (21).** Metacyclophane **21** was prepared in 80% yield using the same procedure as described above: colorless prisms (hexane–benzene (1:1)); mp 272–274 °C; IR (KBr) 1757 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.24–1.60 (4 H, m), 1.96 (6 H, s), 2.10–2.80 (8 H, m), 2.28 (6 H, s), 6.78 (2 H, d, J = 2.4 Hz), 6.97 (2 H, d, J = 2.4 Hz); MS *m/e* 468 (M^+). Anal. Calcd for $C_{26}H_{28}O_8$: C, 66.66; H, 6.02. Found: C, 66.34; H, 6.31.

Attempted Reaction of 18a and 20 To Give 19. Attempted preparation of *anti*-[4.2]metacyclophane quinhydrone (**19**) was carried out by reaction of **18a** and **20** in refluxing THF by the same procedure as for **13a**. Although the formation of **19** was observed by ^{1}H NMR, isolation of **19** in a pure state was not achieved.

Acid Catalyzed Racemization of 1-(Heterocyclyloxy)-2,3-propanediols

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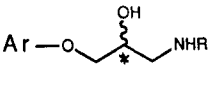
A number of enantiomerically pure heterocyclic ketals **5** have been prepared, and their acid-catalyzed hydrolysis to the corresponding diols **6** has been studied. During this reaction a rearrangement may occur to give racemic products, and so the kinetics of the two competing reactions have been studied to establish optimum conditions. The rate of rearrangement is independent of pH below the pK_a of the heterocycle, whereas the rate of ketal hydrolysis continues to increase as pH is lowered. Brief treatment with strong acid has allowed the formation of very pure diols in high yield.

Introduction

β-Adrenergic blocking drugs are of great importance in the treatment of cardiovascular disease,[1] and one class of drug, the (aryloxy)propanolamines, may be represented by structure **1**, in which the asterisked carbon atom in-



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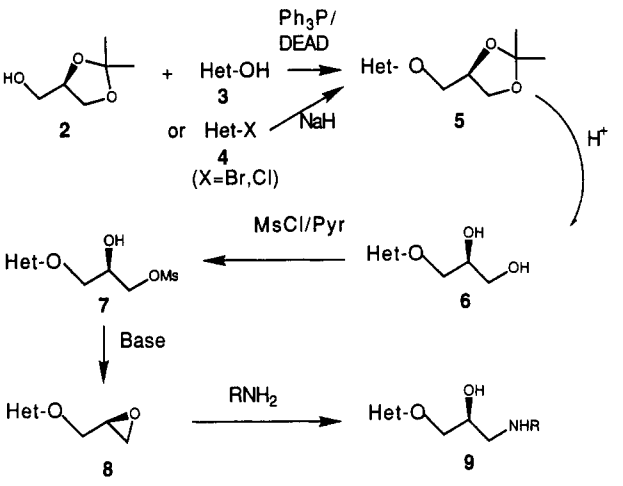
dicates that two enantiomers of **1** are possible. In practice most β-adrenergic blocking drugs are sold as racemates, although there is increasing interest in the synthesis and development of pure enantiomers.[2]

One useful synthetic sequence is shown in Scheme I, where the availability of enantiomerically pure glycerol acetonide (**2**) enables the ready synthesis of the heterocyclic ethers **5** from the appropriate hydroxy (**3**) or halo (**4**) heterocycles. These ketal–ethers may be cleaved to diols (**6**) which may be cyclized to epoxides (**8**) by a variety of means, of one of which involves the mesylates (**7**) shown.

An early report by Syntex workers[3] described the synthesis of the *S*-enantiomer of tazolol (**9**, Het = 2-thiazolyl, R = Pr^i) by this route which, however, led to a partially racemic product. The authors ascribed this to a lack of selectivity in the mesylation of **6**, but the reaction was

Scheme I



investigated further by McClure et al.,[4] who proposed that the acid-catalyzed racemization of the diol **6** during prolonged exposure to the hydrolysis conditions was partially responsible for the loss of chiral integrity. The mechanism proposed for this pseudo-Smiles rearrangement[5] is shown in Scheme II and involves the interconversion of (*S*)-**6** to (*R*)-**6** via the intermediate **10**.

As part of our cardiovascular research program we required a number of enantiomerically pure heterocyclic

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0022-3263/92/1957-5158$03.00/0

Table I. Heterocyclic Ketal Derivatives 5

no.	Het	synth method	yield (%)	bp	$[\alpha]_D$ (deg)	concn solvent	emp form.	anal.[a]
13	thiazole-2-	A	67	72–4 °C (0.1 mm)	+0.2	c = 2, MeOH	$C_9H_{13}NO_3S$	C, H, N, S
14	thiazole-4-	C	>100	oil	–[b]		$C_9H_{13}NO_3S$	–[b]
15	thiazole-5-	C	>100	oil	–[b]		$C_9H_{13}NO_3S$	–[b]
16	1,2,5-thiadiazole-3-	D	88	oil	+1.0	c = 1, MeOH	$C_8H_{12}N_2O_3S$	C, H, N
17	pyridine-2-	B	54	oil	–4.8	c = 7.3, MeOH	$C_{11}H_{15}NO_3$	C, H, N
18	pyridine-4-	B	23	oil	–[b]		$C_{11}H_{15}NO_3$	–[b]
19	pyrimidine-2-	B	95	oil	–5.85	c = 0.6, MeOH	$C_{10}H_{14}N_2O_3$	C, H, N
20	pyrazine-2-	B	97	oil	–[b]		$C_{10}H_{14}N_2O_3$	–[b]

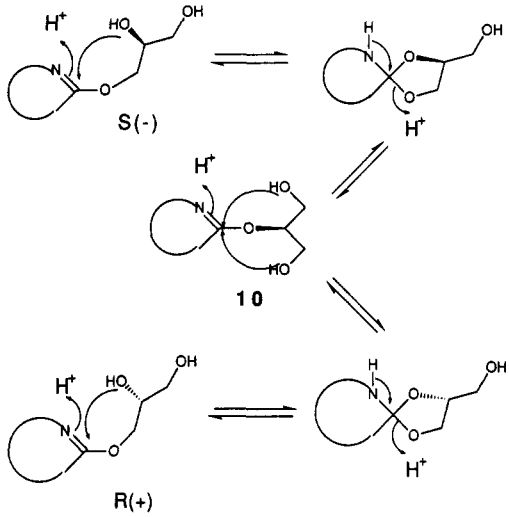
[a] Analyses were within ±0.4% of theory. [b] Not determined, as crude ketal was an oil, contaminated with 2.

Table II. Heterocyclic Diol Derivatives 6

no.	Het	yield (%)	recryst solvent	mp (°C)	$[\alpha]_D$ (deg)	concn solvent	opt. purity[a] (%)	emp form.	anal.[b]
21	thiazole-2-	96	toluene/hexane	62–3	+16.0	c = 2, MeOH	>99.8	$C_6H_9NO_3S$	C, H, N
22	thiazole-4-	44[c]	oil cryst.	69–70			>99.8	$C_6H_9NO_3S$	–[d]
23	thiazole-5-	44[c]	oil	–	+18.2	c = 2, MeOH	>99	$C_6H_9NO_3S$	–[d]
24	1,2,5-thiadiazole-3-	71	ether tritn	67–8	+19.5	c = 2, MeOH	99.8	$C_5H_8N_2O_3S$	C, H, N
25	pyridine-2-	95	oil	–	+12.8	c = 0.3, MeOH	>99.8	$C_8H_{11}NO_3$	–[d]
26	pyridine-4-	90	wax	–	+13.8	c = 0.3, MeOH	>98.5	$C_8H_{11}NO_3$	C, H, N
27	pyrimidine-2-	42	EtOAc/hexane	74–6	+13.6	c = 0.4, MeOH	98.0	$C_7H_{10}N_2O_3$	C, H, N
28	pyrazine-2-	88	oil	–	+15.8	c = 1.62 MeOH	>99.8	$C_7H_{10}N_2O_3$	C, H, N

[a] From HPLC assay. [b] Analyses were within ±0.4% of theory. [c] Overall yield from bromothiazole. [d] Not determined, as product was an oil.

Scheme II



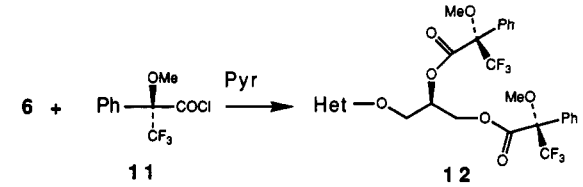
epoxides 8 and were concerned about the possible loss of chiral purity during the hydrolysis of the ketals 5. Consideration of the mechanism of the rearrangement suggested that the cautious hydrolysis with very dilute acid used by McClure was likely to be, in fact, inappropriate, as the racemization rate should be independent of pH below the pK_a of the heterocycle, while the rate of hydrolysis of the ketal should be accelerated by lowering the pH. A series of heterocyclic analogues was prepared and the rates of hydrolysis and racemization measured in order to determine the optimum hydrolysis conditions.

Synthetic Chemistry

The majority of ketals 5 were prepared by the reaction of the halo heterocycle with glycerol acetonide (2), using either the bromo derivative/NaH/DMF method (A, Scheme I) or the chloro derivative/KOBu^t/THF method (B). The 4- and 5-thiazolyl bromides were particularly unreactive, and sodium iodide/copper(II) oxide catalysis was necessary to achieve a reasonable yield (method C).

The 1,2,5-thiadiazol-4-yl compound was prepared from the corresponding hydroxy heterocycle and 2 (method D), the condensation being effected by triphenylphosphine-diethyl azodicarboxylate (Ph_3P/DEAD). The ketals

Scheme III



studied are listed in Table I.

All the diols were prepared by the hydrolysis methods outlined in the discussion and are shown in Table II.

Analytical Chemistry

It was essential to develop a sensitive chiral assay for the diols produced. Reaction of racemic 22 with (*S*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetyl chloride (11) gave a pair of diastereoisomers (Scheme III, 12) which were readily separable by HPLC and distinguished by ^{1}H NMR spectroscopy. As, in most cases, we only had one enantiomer of the diols it was necessary to react them, separately, with the two enantiomers of the acid chloride in order to prove that a separation was possible. This derivatization worked in all the cases studied and gave analyses with a detection limit of around 0.2%.

Kinetic Studies

Ketal hydrolysis rates at selected pH's were determined directly at 25 °C by monitoring the fall in concentration of ketal, and the appearance of diol product, by HPLC. Racemization rates for the Smiles rearrangements of the various diols were determined by following the change in optical rotation using a thermostated polarimeter. As this latter process is generally slower, measurements were conducted at a series of elevated temperatures which gave convenient reaction times (less than 12 h). Rates were then extrapolated to 25 °C using the measured Arrhenius parameters. The integrity of the diol samples was checked by HPLC at the end of each run to confirm that changes in optical rotation were not due to sample decomposition.

Results and Discussion

Ketal hydrolysis rates were rapid and did not vary widely between different heterocyclic analogues (Table III);

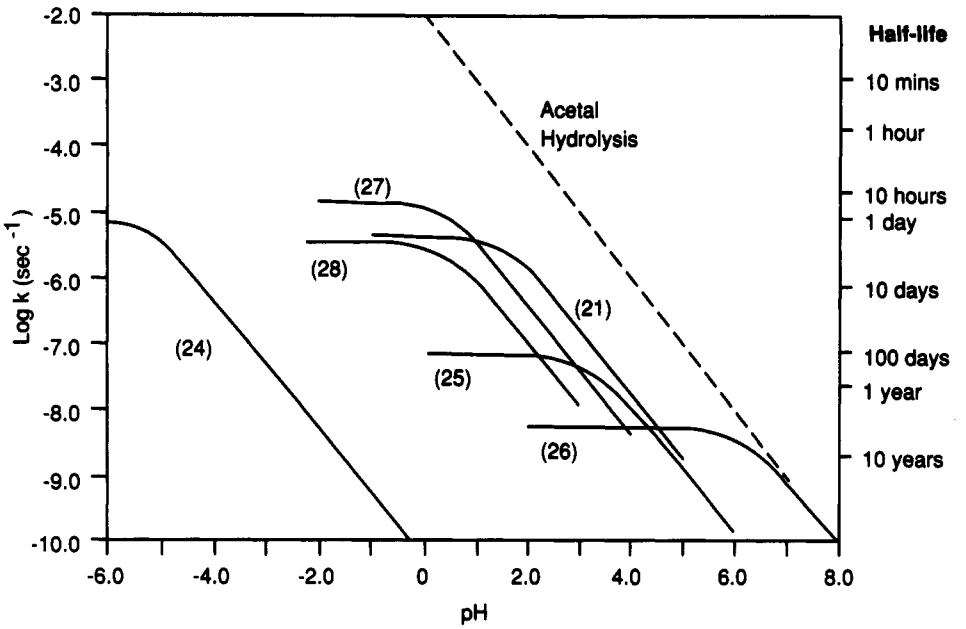


Figure 1. Comparison of the rates of heterocyclic diol rearrangement with acetal hydrolysis at 25 °C.

Table III. Hydrolysis Rates of Ketal 5 at 25 °C

no.	pK_a (25 °C)	k (M^{-1} s^{-1})
21	1.28	4.44×10^{-3}
22	−4.0 (est)	12.3×10^{-3}
23	2.95	5.0×10^{-3}
24	1.05	19.2×10^{-3}
25	0.83 (diol)	12.8×10^{-3}

Table IV. Arrhenius Data for Diol 6 and Predicted Racemization Rates at 25 °C

het	pK_a 25 °C	plateau rate[a] (s^{-1})	ΔH (kcal M^{-1})	ΔS (cal.deg^{-1} M^{-1})
21	1.64	4.6×10^{-6}	17.2 ± 1.6	−25.4 ± 4.9
22		8.8×10^{-6}[b]	21.1 ± 1.7	−10.9 ± 5.0
23	1.2	ND[b]		
24	−5.2 (diol)	ND[c]		
25	3.3	6.8×10^{-8}[d]		
26	6.2	5.6×10^{-9}		
27	0.6 (est)	1.6×10^{-5}	20.9 ± 1.3	−10.5 ● 4.1
28	0.83	3.2×10^{-6}	14.9 ± 1.8	−33.8 ± 5.2

[a] Calcd at 25 °C. [b] Very slow, dec rather than rearrangement. [c] Very slow, dec in addition to rearrangement. [d] Reaction too slow to measure rates over a range of temperatures. Value calculated by assuming the same temperature coefficient as the 2-pyrazine derivatives 28.

the rates of racemization, however, varied considerably (Table IV). The pH profiles (Figure 1) show that as acid concentration is increased the rate of diol formation increases, whereas the rate of rearrangement does not increase once the pH falls below the pK_a of the heterocycle. Thus, it was predicted that hydrolysis of **21**, **25**, **26**, **27**, and **28** at high acid concentration would give a large separation in the rates of hydrolysis and rearrangement, giving rise to the least amount of racemization. For **24** the gaps between the two rates should remain the same until very high acidity is reached, due to its low pK_a. However, even between pH −3 and +2 the difference in rate is still 1000-fold, enabling pure **24** to be prepared (Table II).

These predictions were investigated using the (*S*)-2-thiazole derivative **13**. Utilizing 3 M HCl for a brief period (experiment a, Table V) reasonably pure material was obtained, and reducing the reaction time to 5 min at 0 °C (experiment b) improved this further. Recrystallization of this material (experiment c) gave a good yield of a product containing no detectable amount of the *R* enantiomer.

Following the literature conditions as closely as possible (experiment d), we obtained a 17% yield of material with an optical rotation very close to that reported,[4] that is a purity of 97% (experiment e). If, however, the reaction was allowed to proceed to completion (experiment f) product purity fell to 71%. For completeness the experimental results of the Syntex group[3] are included as experiment g.

A number of other ketals were hydrolyzed using these optimum conditions, and good yields of pure products were obtained (Table II). The use of brief contact with strong acid enables rapid hydrolysis while minimizing the possible time for racemization. On the other hand, using very dilute acid slows the rate of ketal hydrolysis very much, so that extended reaction times and/or high temperatures are required. This allows rearrangement of the protonated heterocyclic diol, causing racemization.

Table V. Enantiomeric Purity of Diol 21 Formed under Different Conditions

exp	wt. ketal 13 (g)	concn of acid	vol. of acid (mL)	time and temp (°C) of reactn		yield (%)	cryst solvent	$[\alpha]_D$	%*S* (from $[\alpha]_D$)	%*S* (deriv)
a	0.058	3 M HCl	5	10 min	rt	95	none	ND[a]	ND[a]	94.4
b	5.0	3 M HCl	30	5 min	0	96	none	+15.8	99.4	99.4
c	5.0	3 M HCl	30	5 min	0	73.8	toluene/hexane	+16.0	100	>99.8
d	5.0	1 M AcOH/50% aq MeOH	100	72 h	rt	17	none	+14.9	96.5	98.1
e[4]	0.50	1 M AcOH/50% aq MeOH	not stated	72 h	rt	ND[a]	none	−15.1[b]	97.2	ND[a]
f	5.0	1 M AcOH/50% aq MeOH	100	34 days	rt	95	none	+6.7	71	ND[a]
g[3]	300	0.011 M HCl	2000	2 h	100	ND[a]	none	+9.6	80	ND[a]

[a] Not determined. [b] The R isomer of **13** was used in ref 3.

Experimental Section

General. Unless noted otherwise, materials were obtained from commercial suppliers and used without further purification. Dry solvents were dried over 3-Å molecular sieves, THF being first freed of antioxidant by passage through a short alumina column. Boiling and melting points are uncorrected. All products shown in Table II were characterized by ^1H NMR spectroscopy. Spectra were measured in $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane as internal standard.

The yields quoted were not optimized; flash chromatography refers to the technique described by Still, Kahn, and Mitra[6] using Merck Art. 9385 silica. All evaporations were performed on a rotary evaporator under reduced pressure.

(4*S*)-2,2-Dimethyl-4-[(2-thiazolyloxy)methyl]-1,3-dioxolane (13). Method A. NaH (60% in oil, 9.1 g, 0.237 mol) was washed twice with hexane and suspended in dimethoxyethane (70 mL) at rt. A solution of (4*R*)-**2** (26.1 g, 0.198 mol)[7] in dimethoxyethane (100 mL) was added over 30 min and the mixture stirred for a further 1 h. 2-Bromothiazole (25.0 g, 0.152 mol) was added and the mixture refluxed for 2 h. The white suspension was then stirred overnight. After the solution was diluted with ether (500 mL) and filtered through Celite the filtrate was washed with brine, dried ($MgSO_4$), and concentrated to a pale yellow oil, wt 39.0 g. This was distilled under reduced pressure and the fraction boiling between 82 and 83 °C at 0.1 mm of pressure (25.3 g) was redistilled to give 21.9 g of pure **13** (66.8%), bp 72–4 °C (0.1 mm): NMR δ 1.39 (s, 3 H), 1.46 (s, 3 H), 3.86 (m, 1 H), 4.14 (m, 1 H), 4.48 (m, 3 H), 6.71 (d, J = 4 Hz, 1 H), 7.11 (d, J = 4 Hz, 1 H); $[\alpha]^{23}_D$ + 0.2° (c = 2, MeOH). Anal. Calcd for $C_9H_{13}NO_3S$: C, 50.2; H, 6.0; N, 6.5; S, 14.9. Found: C, 50.2; H, 6.6; N, 6.1; S, 14.4.

(4*S*)-2,2-Dimethyl-4-[(2-pyridyloxy)methyl]-1,3-dioxolane (17). Method B. A solution of (4*R*)-**2** (15.0 g, 0.113 mol) in THF (200 mL) was stirred and cooled to 0 °C under Ar and $KOBu^t$ (15.3 g, 1.2 equiv) was added. The mixture was stirred 15 min, 2-chloropyridine (12 mL, 0.127 mol) was added, and the mixture was stirred 18 h at rt, diluted with H_2O (200 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated to give 25.8 g of **17** (>100%) as a pale yellow oil, still contaminated with 2-chloropyridine. This was purified by flash chromatography using 2% MeOH in CH_2Cl_2 to give 12.8 g of **17** (54%) as a colorless oil: $[\alpha]^{20}_D$ −4.8° (c = 7.3, MeOH); NMR ($CDCl_3$) δ 1.41 (s, 3 H), 1.47 (s, 3 H), 3.85 (dd, J = 8, 6 Hz, 1 H), 4.39 (m, 2 H), 4.50 (dd, J = 8, 7 Hz, 1 H), 4.51 (m, 1 H), 6.80 (d, J = 8 Hz, 1 H), 6.88 (m, 1 H), 7.57 (m, 1 H), 8.14 (m, 1 H); MS m/e 210 $(M + H)^+$. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.1; H, 7.2; N, 6.7. Found: C, 62.6; H, 7.2; N, 6.5.

(4*S*)-2,2-Dimethyl-4-[(5-thiazolyloxy)methyl]-1,3-dioxolane (15). Method C. Na metal (693 mg, 0.03 g atom) was added in small portions to (4*R*)-**2** (17 mL, 0.137 mol) and the mixture warmed to 90 °C (argon atmos) to aid solution. 5-Bromothiazole[8] (1.83 g, 0.011 mol), CuO (444 mg, 6 mmol), and KI (19 mg) were added and the mixture stirred for 24 h at 90 °C. The mixture was cooled, diluted with CH_2Cl_2 (35 mL), filtered through Celite, and evaporated under high vacuum (oil pump) with a water bath at 70 °C. The residue was stirred with CH_2Cl_2, refiltered through Celite, and evaporated to a brown gum. This was purified by flash chromatography using 4% EtOAc/CH_2Cl_2 as eluant to give 2.99 g 15 (>100%) as a pale yellow oil, still contaminated with **2**: NMR δ 1.37 (s, 3 H), 1.44 (s, 3 H), 3.65 (m, 3 H), 4.05 (m, 1 H), 4.25 (m, 1 H), 7.28 (s, 2 H); peaks for **2** seen at δ 1.39, 1.45, 4.43 and within complex patterns; MS m/e 216 (**15** + H)$^+$ and 133 (**2** + H)$^+$.

The product was not characterized further, but was hydrolyzed directly.

(4*S*)-2,2-Dimethyl-4-[[[3-(1,2,5-thiadiazolyl)]oxy]methyl]-1,3-dioxolane (16). Method D. A solution of 4-hydroxy-1,2,5-thiadiazole[9] (10.2 g, 0.10 mol), (4*R*)-**2** (13.2 g, 0.10 mol), Ph_3P (28.82 g, 0.11 mol), and dry THF (50 mL) was stirred and refluxed gently under Ar, and diethyl azodicarboxylate (26.1 g, 0.15 mol) was added dropwise (mild exotherm). After addition (10 min) reaction was virtually complete. The reaction mixture was evaporated (bath <40 °C) and purified by flash chromatography using CH_2Cl_2 to give 19.0 g (88%) of pure **16**: NMR δ 1.40 (s, 3 H), 1.47 (s, 3 H), 3.87 (m, 1 H), 4.18 (m, 1 H), 4.49 (m, 3 H), 8.02 (s, 1 H). Anal. Calcd $C_8H_{12}N_2O_3S$: C, 44.4; H, 5.6; N, 13.0. Found: C, 44.4; H, 5.7; N, 12.8.

(2*S*)-1-(2-Thiazolyloxy)-2,3-propanediol (21). Method E. 5.0 g of **13** was treated for 5.0 min with ice-cold 3 M HCl (30 mL), and then 15.0 g of K_2CO_3 was added as rapidly as possible (ca. 30 s). The solution was extracted with EtOAc (200 mL) and the extract washed once with brine, dried ($MgSO_4$), and evaporated to give 2.97 g of product. The extraction was repeated in the same way to obtain a further 0.94 g of product, making a total of 3.91 g (96%). A sample was retained and the remainder recrystallized from toluene/hexane giving 2.85 g pure **21**: mp 62–3 °C; $[\alpha]^{23}_D$ + 16.03° (c = 2, MeOH); NMR δ 3.48 (s, 2 H), 3.72 (m, 2 H), 4.08 (m, 1 H), 4.53 (m, 1 H), 6.70 (d, J = 4 Hz, 1 H), 7.09 (d, J = 4 Hz, 1 H). Anal. Calcd for $C_6H_9NO_3S$: C, 41.1; H, 5.1; N, 8.0. Found: C, 41.2; H, 5.2; N, 8.0.

(2*S*)-1-(2-Thiazolyloxy)-2,3-propanediol (21) by the Procedure in Reference 4. A solution of 5.0 g of **12** in a mixture of AcOH (6 mL), MeOH (47 mL), and H_2O (47 mL) was allowed to stand for 72 h at rt. The mixture was evaporated to an oil which was shaken with Et_2O (100 mL) and H_2O (100 mL). The aqueous layer was saturated with K_2CO_3 and extracted once with CH_2Cl_2 (100 mL). The organic phase was separated and evaporated to give an oil which was purified by flash chromatography using EtOAc to give 700 mg of **21** (17%) as a white solid. The optical rotation of this material was +14.9° (c = 2, MeOH, 589 nM). As the product was evidently impure no melting point was recorded.

On a separate occasion the same mixture of reactants was left until complete hydrolysis had occurred, which took 34 days, and the reaction worked up as above to give 3.87 g of **21** (95%) as an oil, $[\alpha]^{23}_D$ +6.7°.

Enantiomeric Purity Analysis of 12. A solution of **21** (35 mg, 0.2 mmol) in dry pyridine (0.5 mL) was treated with (2*R*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetyl chloride (160 μL, 0.8 mmol) via syringe. After 30 min the reaction was diluted with EtOAc (10 mL), washed with H_2O (20 mL), and evaporated. The residue was treated with toluene (20 mL) and reevaporated to remove H_2O and pyridine. The residual oil was purified using a Bond-elut 3-mL silica column and CH_2Cl_2 as eluant. All the fractions containing the diester **12** were combined and evaporated. For HPLC analysis 1 mg/mL solutions were chromatographed using a Gilson apparatus, a 25-cm 3-μm-silica column (Hichrom Ltd), 254-nm detector setting, and 15% EtOAc/hexane with a flow rate of 1 mL/min. The chromatogram was compared with that of the derivative prepared from **21** using (2*S*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetyl chloride. Retention times were 11.4 and 13.7 min, and adding 0.2% of one isomer to the other could be detected reliably. For other heterocyclic systems solvent mixtures containing between 10 and 40% EtOAc were suitable.

For NMR assay a Bruker AM400 instrument was used, with $CDCl_3$ solvent and TMS standard. Assay was possible using the two four-line patterns at δ 4.79 and 4.50 ((*S*)-**12**) and δ 4.68 and 4.54 ((*R*)-**12**). Sensitivity was approximately ±1%.

Kinetic Measurements. The rate of ketal hydrolyses were measured at 25 °C by HPLC using a Perkin-Elmer ISS 100 autosampler combined with an Altex 110A pump, an LDC spectromonitor III detector, and a Pye Unicam PU4850 video chromatography control unit using an S5 CN column. The eluant used was 20% CH_3CN, H_2O monitored at 240 nm which gave good separations for all ketals and their diol products. Rate coefficients were calculated from HPLC integrals using a linear regression of ln standard concentration versus time data sets. pH measurements were made using a Radiometer PHM 63 meter.

The Smiles rearrangements were followed by monitoring changes in optical rotation with a Perkin-Elmer 241-polarimeter using Hg lines at wavelengths of either 436 or 365 nm. 1×10^{-2} M solutions were used in a 10-cm polarimeter cell thermostated using a Haake bath. Initially, changes in optical rotation were followed manually and latterly using a recorder. Rate coefficients were calculated from ln OD versus time plots. Temperatures selected to obtain Arrhenius data covered the range 50–95 °C and were selected to give convenient rates.

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(8) US Patent 3,850,946 (1974).
(9) Weinstock, L. M.; Davis, P.; Handelsman, B.; Tull, R. *J. Org. Chem.* **1967**, *32*, 2823.

pK_a values were measured spectrophotometrically using standard perchloric acid solutions of known H_0 value.

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Supplementary Material Available: ^1H NMR spectra for compounds 14, 18–20, and 22–28 (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Convenient Synthesis of α-Hetero-Substituted Acyloxathianes

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In contrast to simple esters, α-alkoxy, α-alkylthio, and α-dimethylamino esters react with lithiooxathiane 1-Li in good yield to give the corresponding α-functionalized 2-acetylhexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin 2. In some cases, mixtures of diastereomers (2, 2′) are obtained. The reaction has been extended to α-methoxy- and α-[(triisopropylsilyl)oxy]propanoyl and α-(methylthio)butanoyl homologs which have chiral centers at C(α).

Introduction and Results

In connection with another problem[1] we had occasion to prepare chiral 2-acyloxathianes (2) with α-alkoxy, α-alkylthio, and α-dialkylamino substituents. In previous syntheses of corresponding 2-acyloxathianes devoid of α-substituents, we had found the reaction of 2-lithiooxathiane (1-Li) with esters to proceed in poor yield at best;[2] the preferred way of preparing these compounds (X = H or alkyl in Scheme I) was condensation of 1-Li either with aldehydes followed by Swern oxidation[3] or with nitriles followed by hydrolysis.[4] In contrast, the α-substituted acyloxathianes have now been synthesized in good yield and generally high conversion (see Table I) by condensation of esters with 1-Li (Scheme I). An interesting aspect of this reaction, not reported previously, is the isolation of the axial ketone 2′ along with the equatorial one (2) in the case of the α-alkoxy compounds (entries 1, 2 in Table I). Evidently, because of the greater acidity of the acylated products at C(2), proton transfer from the product 2 to the starting material 1-Li takes place, with formation of the more stable[5] equatorial anion of 2′; this process will be discussed in more detail below. In the case of the (triisopropylsilyl)oxy ("O-TIPS") compound, **2b′** was actually the major product, but was converted to **2b** by (slow) silica gel chromatography, indicating that, as expected, free **2b** is more stable than **2b′**. In the case of the synthesis of the alkylthio compounds (**2c**, **2d**, entries 3 and 4 in Table I) only a small amount of the axial isomers (**2c′**, **2d′**) was formed (as indicated by NMR spectroscopy) but not isolated; no axial isomer (**2e′**) was observed in the case of the dimethylamino compound (entry 5 in Table I).

Assignment of Configuration. Compound **2b** has been previously described.[6] That **2b′** is the diastereomer at C(2) of **2b** follows from its epimerization to the latter. In the other cases, **2a**/**2a′**, **2c**/**2c′**, **2d**/**2d′**, and **2e**, the assignment of the major isomer as the equatorial one was confirmed by comparison of the proton chemical shifts of the axial and equatorial methyl groups in the oxathiane moiety (Table II): corresponding protons resonate at higher field in the 2-axial (primed) series, presumably because of the shielding effect of the axial carbonyl moiety;

Scheme I

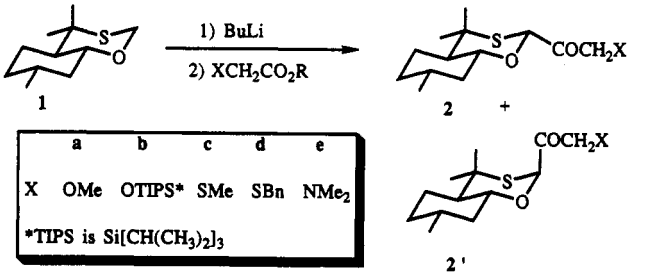

Table I. Reactions of 2-Lithiooxathiane with Substituted Acetates

entry	series	X	2/2′/1[a]	2[b]	2′[b]	1[c]
1	**a**	OMe	61/22/17	54	17	d
2	**b**	OTIPS	36/64/e	39	52[f]	d
3	*c*	SMe	85/*e*/15	76	*d*	13
4	**d**	SBn	74/*e*/26	55	*g*	17
5	**e**	NMe_2	*h*	82	*i*	*d*

[a] Ratio of crude product mixture determined by proton NMR. [b] Isolated yield. [c] Recovered yield. [d] Not isolated. [e] Too little material present, not calculated. [f] Converted to **2b** on silica gel. [g] Impure. [h] Almost complete conversion to **2e**. [i] Not observed.

Table II. Chemical Shifts (ppm) of the Geminal Ring Methyl Protons[a]

compd	2a	2a′	2b	2b′	2c	2d	2d′	2e
a-Me	1.43	1.25	1.43	1.25	1.44	1.43	1.23	1.44
e-Me	1.26	1.20	1.25	1.19	1.27	1.26	1.20	1.27

[a] **a.** Methoxy ketone. **b.** Triisopropylsiloxy ketone. **c.** Methylthio ketone. **d.** Benzylthio ketone. **e.** *N*,*N*-Dimethylamino ketone.

Table III. C=O Frequencies (cm^{-1}) in the IR spectrum

compd	IR (C=O)
2a	1740
2a′	1731
2b	1740
2b′	1729

† From the Ph.D. dissertation of X. Bai, University of North Carolina, Chapel Hill, NC, 1990.

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