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SYNTHESIS OF CHIRAL 2-METHYL-3-ALKENOIC ESTERS *VIA* 1,2-REARRANGEMENT OF ALKENYL GROUP[1)]

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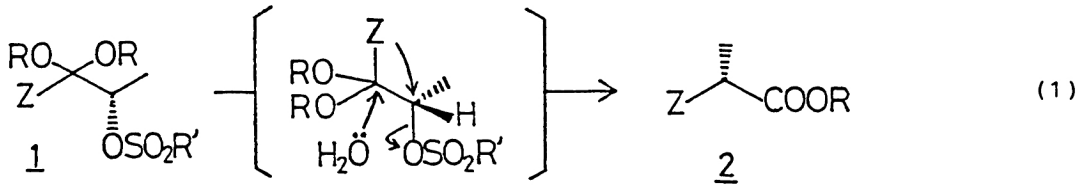
Hydrolysis of optically pure 1-alkenyl-2-sulfonyloxy-1-propanone acetals afforded optically and geometrically pure title compounds *via* stereospecific 1,2-rearrangement of alkenyl group.

We have already reported[2)] that hydrolysis of optically active 1-aryl-2-sulfonyloxy-1-propanone acetals (1) afforded 2-arylpropanoic esters (2) *via* 1,2-rearrangement of the aryl group with complete inversion of configuration on the carbon atom. The reaction is considered to involve the transition state illustrated in Eq. 1 (Z=aryl).

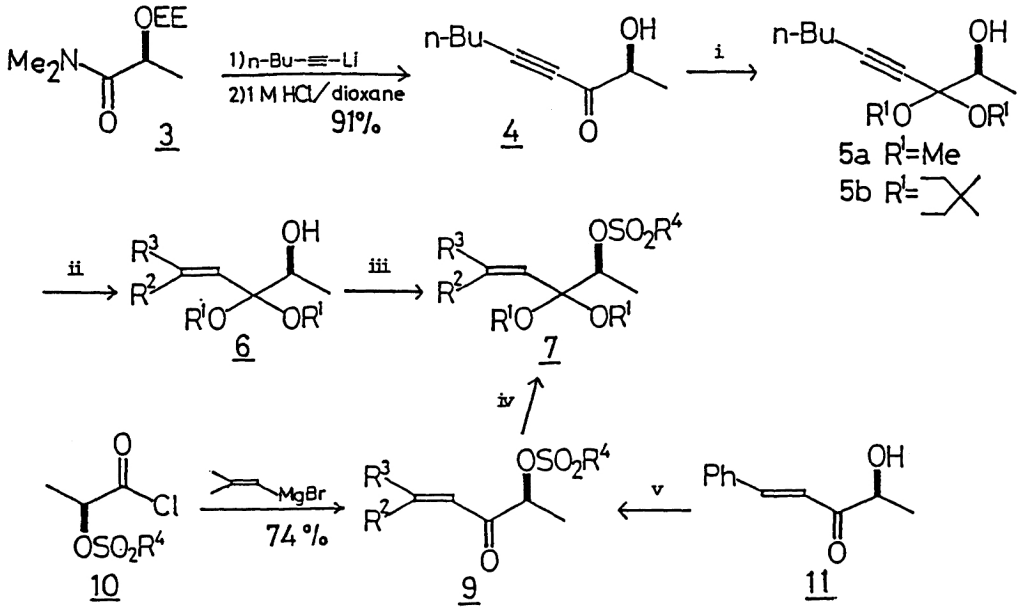


(1)

If this stereospecific rearrangement can be applied to a variety of substrates, it will present an effective synthetic tool. Under the strategy to widen the scope of the reaction, we tried the synthesis of title compounds (Eq. 1, Z=alkenyl), which are expected to be useful chiral building blocks for the asymmetric synthesis of natural products. In this letter, we wish to report that alkenyl groups also cleanly migrate in a stereospecific manner, with synchronous elimination of sulfonyloxy group.

The key intermediate, 1-alkenyl-2-sulfonyloxy-1-propanone acetal (7) was prepared in several ways. At first (S)-O-(1-ethoxyethyl)-N,N-dimethyl-lactamide (3)[3)] was treated with lithium acetylide (1.4 equiv.) at -78 °C, followed by acid hydrolysis to give α-hydroxyl ketone (4) in 91% yield. Dimethyl acetal (5a) was prepared from 4 by treatment with trimethoxymethane (5 equiv.)-methanesulfonic acid (1 equiv.)[4)] in methanol at 0 °C in 98% yield. 2,2-Dimethyl-trimethylene acetal (5b) was also prepared by treatment with 2,2-dimethyl-1,3-propanediol (10 equiv.)-trimethylsilyl chloride (2.5 equiv.)[5)] in methanol at 0 °C in 99% yield. The acetylenic acetals (5) were hydrogenated by H_2 over Lindlar catalyst in hexane to give (Z)-alkenols (Z-6), or by Na-NH_3 at -78 °C to give (E)-alkenols (E-6). Crude E-6 was revealed to be contaminated by *ca.* 2% of Z-6.[6)] Pure E-6 was obtained as follows: The mixture was benzoylated, purified by silica-gel column chlomatography (hexane-dichloromethane), and deprotected by a solution of NaOH (3 wt%) in methanol. Olefinic alcohols (6) were methanesulfonylated to give

7.[7] Table 1 (entries 1-4) shows the results. In other ways α-sulfonyloxy ketone (9) could be prepared by Grignard coupling between acyl chloride (10) and alkenylmagnesium bromide[8] or sulfonylation of 11.[9] Acetalization of 9 by the usual manner was all failed. Only one successful way was treatment of 9 with 2,2-dimethyl-1,3-bis(trimethylsilyloxy)propane (1.5 equiv.)- trimethylsilyl trifluoromethanesulfonate (0.1 equiv.) in dichloromethane[10] at room temperature which resulted sulfonyloxy acetal (7) in a high yield. But unfortunately, it was confirmed from the optical purity of final products (8) that a little racemization occured under these conditions (Tables 1 and 2, entries 5,6).



i) a: $HC(OMe)_3$ 5 equiv., $MeSO_3H$ 1 equiv., in MeOH, 0 °C, 2 h b: $HOCH_2CMe_2CH_2OH$ 10 equiv., Me_3SiCl 2.5 equiv., in MeOH, 0 °C, 2 h ii) Z: H_2(1 atm), Pd-Pb, rt, 2 h E: Na-NH_3-EtOH, in THF, -78 °C, 2 h iii) $MeSO_2Cl$-pyridine, rt iv) $TMSOCH_2$-CMe_2CH_2OTMS 1.5 equiv., $TMSOSO_2CF_3$ 0.1 equiv., in CH_2Cl_2, rt, 20 h v) $(Me\text{-}C_6H_4\text{-}SO_2)_2O$, pyridine, 0 °C, 1.5 h

Table 1. Synthesis of α-sulfonyloxy ketone acetals (7)

Entry	R^1	R^2	R^3	R^4	Yield / % 6	7
1	Me	Bu	H	Me	89[a]	91
2	Me	H	Bu	Me	83[a]	97
3		Bu	H	Me	91[a]	99
4		H	Bu	Me	83[a]	99
5		Me	Me	Me	74[b]	90
6		H	Ph	Me- 	79[b]	96

a) Yield from acetylenic acetal (5).

b) Yield of α-sulfonyloxy ketone (9).

Hydrolytic 1,2-rearrangement of alkenyl group of the key intermediate 7 was carried out in the analogous way with aryl rearrangement. When sulfonats (7) were heated in the presence of calcium carbonate (2 equiv.) in aqueous methanol (MeOH/H_2O=7/3 v/v), methyl esters (8a) or half esters (8b) were obtained in excellent yields. Table 2 shows the results. The products in entries 1-4 were optically pure within the limit of measurement,[11,12] indicating that the rearrangement reaction, as well as the each step for preparation of 7, proceeded in completely stereospecific manner. A small contamination by another enantiomer in entries 5,6 are thus concluded to be the result of acetalization step of sulfonyloxy ketone 9. Moreover it is worth noting that no geometric isomerization of migrating alkenyl group was observed in the rearrangement process.[15,16] It is supposed that elimination of sulfonyloxy group, migration of alkenyl group, and attack of water occured simultaneously without formation of cyclopropyl methyl cation[17] (Fig.1).

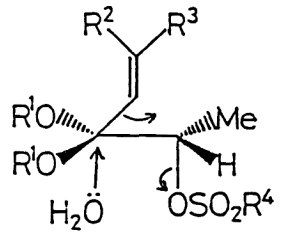
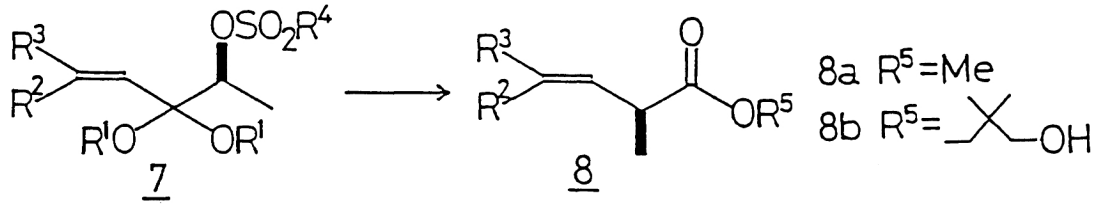


Fig. 1.

Table 2. Synthesis of 2-methyl-3-alkanoic esters (8)



Entry	R^1	R^2	R^3	R^4	Temp/°C	Time/h	Yield/%	$[\alpha]_D$/°(t/°C, c, in $CHCl_3$)	e.e./%
1	Me	Bu	H	Me	90	2	83	+166 (21, 1.00)	> 98[11]
2	Me	H	Bu	Me	90	3	85	+ 53 (19, 1.16)	> 95[12]
3		Bu	H	Me	90	3	97	+135 (21, 1.21)	> 98[11]
4		H	Bu	Me	90	4	98	+ 39 (19, 1.00)	> 95[12]
5		Me	Me	Me	70 80	14 13	92	+114 (27, 1.00)	93[13]
6		H	Ph	Me- 	70	22	92	+ 9 (21, 1.08)	95[11]

In conclusion, 2-methyl-3-alkenoic esters were obtained in optically and geometrically pure forms. Two functional groups of these compounds will serve as versatile synthons in derivation to more complex molecules.

References

1) A part of this work was presented at the 49th National Meeting of the Chemical Society of Japan, April 3, 1984, Abstruct II, 1469.
2) G. Tsuchihashi, s. Mitamura, K. Kitajima, and K. Kobayashi, *Tetrahedron Lett.*, 23, 5427 (1982).
3) Y. Honda, M. Sakai, and G. Tsuchihashi, *Chem. Lett.*, 1985, 1153.
4) Under the ice cooling condition, 1 equiv. of sulfonic acid was needed.
5) The synthetic procedure for ethylene acetals was applied; T. H. Chan, M. A. Brook, and T. Chaly, *Synthesis*, 1983, 203.
6) Determined by HPLC measurement of benzoyl derivatives by using Cosmosil 5SL (Japan Spectroscopic Co., LTD.); hexane/dichloromethane=10/1 (v/v), flow rate 0.5 ml/min, k'_Z=2.43, $\alpha=k'_E/k'_Z$=1.45.
7) Sulfonates (7) were relatively unstable, so they were purified by short flash column chromatography (dichloromethane).
8) α-Sulfonyloxyacyl chloride (10), prepared from free acid by chlorination, was treated with alkenylmagnesium bromide (1 equiv.) in THF at -42 °C.
9) α-Hydroxyl-α',β'-unsaturated ketone (11), available from 3 by trearment with alkenylmagnesium bromide, was sulfonylated by sulfonic anhydride in pyridine at 0 °C.
10) T. Tsunoda, M. Suzuki, and R. Noyori, *Tetrahedron Lett.*, 21, 1357 (1980).
11) Determined by ^{1}H-NMR measurement of (R)-MTPA ester[14] in the presence of $Eu(FOD)_3$ in CCl_4. The ester was prepared from the corresponding alcohol, which was obtained quantitatively by treatment of 8 with $LiAlH_4$ in diethyl ether.
12) Determined by 100 MHz ^{13}C-NMR measurement of (R)-MTPA ester.
13) Determined by ^{1}H-NMR measurement using $Eu(TFC)_3$. The difference in chemical shift for CH_2 group of (R)-and (S)-half ester (8b) was about 0.24 ppm in the presence of 1.1 equiv. of $Eu(TFC)_3$ in CCl_4.
14) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 34, 2543 (1969).
15) To our knowledge, this is the first case in the thermal rearrangement, but a similar result has been observed in the reductive rearrangement promoted by organoaluminum.[3]
16) Determined by the signal due to the proton at C-2 on 90 MHz ^{1}H-NMR measurement in $CDCl_3$. The difference in chemical shift for Z-isomer and E-isomer was about 0.4 ppm. For example, compounds listed in entries 3 and 4 in Table 2 exhibited the signal at δ 3.45 (Z-8) and 3.06 (E-8) ppm respectively.
17) In general, cyclopropyl cation is supposed in many cases as a relatively stable intermediate.

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