CHEMISTRY LETTERS, pp. 1153-1156, 1985.

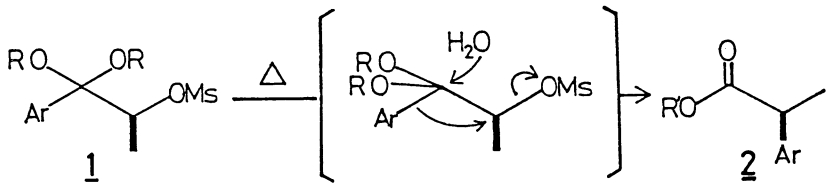
A NOVEL SYNTHETIC METHOD OF OPTICALLY PURE α-SUBSTITUTED ALDEHYDE ACETALS BY THE USE OF REDUCTIVE 1,2-REARRANGEMENT[1)]

Yutaka HONDA, Mitsuru SAKAI, and Gen-ichi TSUCHIHASHI*
Department of Chemistry, Faculty of Science and Technology,
Keio University, 3-14-1, Hiyoshi, Kohoku-ku, Yokohama 223

A new reductive 1,2-rearrangement of aryl (or alkenyl) groups of α-sulfonyloxy acetals to give the title compounds was developed by using the combination of *i*-Bu_2AlH and Et_3Al, and this method was applied to the synthesis of optically pure (R)-(−)-α-curcumene.

Recently, chiral α-alkenyl (or aryl) substituted aldehydes have been used widely as the building block for the asymmetric synthesis of natural products.[2)] Requisite chiral aldehydes were usually prepared by optical resolution of the corresponding acids, followed by a sequence of reduction to alcohols and oxidation. This method, however, requires rather tedious resolution procedures and, in some cases, the resulting aldehydes are labile and suffer from racemization. Thus we envisioned to develop a new method of synthesizing the title compounds (stable equivalent of aldehydes) without using optical resolution and oxidation. These acetals are not only easily convertible to aldehydes[3)] but also serve as useful building blocks for the formation of C-C bonds *via* the aldol-type condensation,[4)] reactions with allylsilane,[5)] and reactions of 1,3-dithiane derivatives.[6,22)]

Previously, we reported that the hydrolysis of optically pure 1-aryl-2-sulfonyloxy-1-propanone acetals (1) afforded 2-arylpropanoic esters (2) *via* 1,2-rearrangement of aryl group with 100% inversion of the C-2 chiral center.[7,12)]

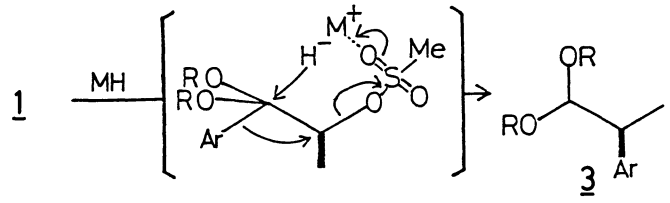


(1)

We assume that this rearrangement proceeded through a concerted process which involves concomitant attack of H_2O, 1,2-shift of aryl group, and elimination of sulfonyloxy group (Eq. 1). Thus it is regarded as a substitution type rearrangement, in contrast to the elimination type one, such as Pinacol, Favorskii, and quasi-Favorskii rearrangement. In the former, one of the driving forces is the push effect by electron pairs of oxygen of acetal oriented antiperiplanar to the migrating group and the attacking nucleophile, whereas in the latter an electron pair of oxygen anion plays the role.[8)]

Then, we supposed that if hydride ion serves as a nucleophile in the same manner, aldehyde acetals (3) could be obtained directly. Therefore, we decided to ex-

ploit this new reductive rearrangement by using a Lewis acid as an activator (Eq. 2).



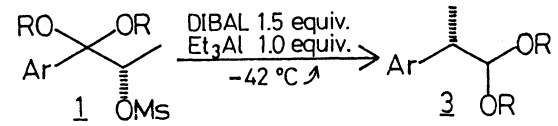
(2)

Optically pure α-sulfonyloxy acetals (1) were synthesized by the reaction of ArMgBr with (S)-O-(1-ethoxyethyl)-N,N-dimethyl lactamide,[9] followed by deprotection, acetalization, and methanesulfonylation.[12] When 1 was treated with i-Bu_2AlH (DIBAL) in toluene at -42 °C,[13] no reaction took place. However, when Et_3Al was added to the above system, reaction proceeded smoothly to give aldehyde acetal (3). In this reaction, two equivalents of activators are always needed (Fig. 1, Z=Ar).

A typical procedure was as follows: Under an argon atmosphere, DIBAL (1.5 equiv., 1 M hexane solution) was added to a solution of α-sulfonyloxy acetal (1, 1 equiv.) in toluene at -42 °C. Then Et_3Al (1 equiv., 1 M hexane solution) was added and the reaction mixture was stirred for 2 h. Reaction temperature was raised up slowly to -20 °C, and mixture was quenched by an aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was purified by silica-gel column chromatography (hexane-ethyl acetate) to give aldehyde acetals (3) in a quantitative yield (Table 1).[14] Dimethyl acetals were optically pure within the limit of the measurement.[15]

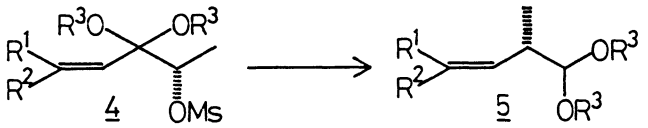
If this highly stereoselective rearrangement proceeds similarly with alkenyl analogs, useful optically pure α-methyl-β,γ-unsaturated acetals (5) will be obtained. In practice, 1-alkenyl-2-sulfonyloxy-1-propanone acetals (4),[1] gave *optically and geometrically pure* acetals (5) in quantitative yields (Table 2).[14]

Table 1. Yields of acetals (3)



Ar	R	Y/%	$[\alpha]_D$/°(t/°C,c,$CHCl_3$)
◯	Me	96	+ 3.3 (22,1.01)
"	⟩X	98	+29.6 (22,1.01)
Me-◯	Me	98	+ 0.5 (25,1.00)
"	⟩X	95	+17.4 (20,1.00)
MeO-◯	Me	97	- 3.0 (22,0.99)
"	⟩X	97	+21.6 (24,1.00)

Table 2. Yields of acetals (5)



R^1	R^2	R^3	Y/%	$[\alpha]_D$/°(t/°C,c,$CHCl_3$)
Bu	H	Me	97	+11.4 (16,1.01)
"	"	⟩X	98	+65.5 (16,1.00)
H	Bu	Me	97	-18.9 (20,1.00)
"	"	⟩X	96	+ 1.9 (16,1.00)

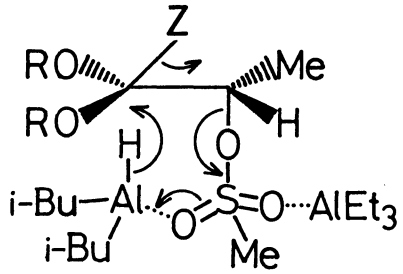
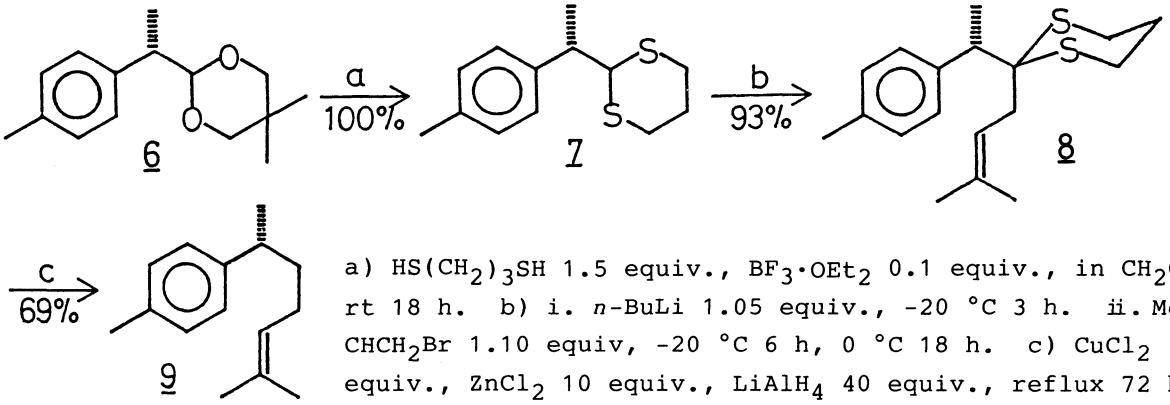


Fig. 1.

This will be explained by assuming that the alkenyl group retains the character of the double bond throughout the migration (Fig. 1, Z=alkenyl).

The utility of this new methodology was demonstrated by a short-step synthesis of an optically active terpene,[16] (R)-(−)-α-curcumene (9).[11] Cyclic acetal (6) was converted to the dithio cyclic acetal (7) by the use of $BF_3 \cdot OEt_2$ and 1,3-propanedithiol.[6] Dithio acetal (7) was prenylated by a usual manner,[22] and reductively desulfurized with $CuCl_2$-$ZnCl_2$-$LiAlH_4$[23] to give optically pure 9, $[\alpha]_D^{23}$ -46.2° (c 0.95, $CHCl_3$), in a 69% yield without isomerization of double bond[20] (Scheme 1).



a) $HS(CH_2)_3SH$ 1.5 equiv., $BF_3 \cdot OEt_2$ 0.1 equiv., in CH_2Cl_2, rt 18 h. b) i. *n*-BuLi 1.05 equiv., -20 °C 3 h. ii. $Me_2C=CHCH_2Br$ 1.10 equiv, -20 °C 6 h, 0 °C 18 h. c) $CuCl_2$ 10 equiv., $ZnCl_2$ 10 equiv., $LiAlH_4$ 40 equiv., reflux 72 h.

Scheme 1. Synthesis of (R)-(−)-α-curcumene (9).[24]

References

1) A part of this work was presented at the 49th National Meeting of the Chemical Society of Japan, April 3, 1984, Abstract II, 1469.

2) C. H. Heathcock, *Science*, 214, 395 (1981); S. Masamune and W. Choy, *Aldrichimica Acta*, 15, 47 (1982).

3) E. W. Colvin, R. A. Raphael, and J. S. Robelts, *J. Chem. Soc., Chem. Commun.*, 1971, 858.; F. Barbot and P. Miginiac, *Synthesis*, 1983, 651.

4) T. Mukaiyama and M. Hayashi, *Chem. Lett.*, 1974, 15; T. Mukaiyama and A. Ishida, *ibid.*, 1975, 319.; S. Murata, M. Suzuki, and R. Noyori, *Tetrahedron Lett.*, 21, 2527 (1980).

5) A. Hosomi, M. Endo, and H. Sakurai, *Chem. Lett.*, 1976, 941; 1978, 499; T. Tsunoda, M. Suzuki, and R. Noyori, *Tetrahedron Lett.*, 21, 71 (1980); H. Sakurai, K. Sasaki, and W. Hosomi, *ibid.*, 22, 745 (1981).

6) J. A. Marshall and J. L. Belletire, *Tetrahedron Lett.*, 1971, 871.

7) G. Tsuchihashi, M. Mitamura, K. Kitajima, and K. Kobayashi, *Tetrahedron Lett.*, 23, 5427 (1982).

8) P. Deslongchamps, "Stereoelectronic Effects in Organic Chemistry," Organic Chemistry Series Vol.1, Pergamon Press (1983).

9) N,N-Dimethyl lactamide [10] was successively treated with ethyl vinyl ether - PPTS[11] and solid $NaHCO_3$. Concentrated residue was purified by silica-gel column chromatography (hexane-acetone) followed by distillation.

10) K. Freudenberg, W. Kuhn, and I. Bumann, *Ber.*, 63b, 2380 (1930).

11) N. Miyashita, A. Yoshikoshi, and P. A. Grieco, *J. Org. Chem.*, 42, 3772 (1977).
12) This result was presented at the above meeting,[1] Abstract II, 1468.
13) The rearrangement proceeded by treatment with DIBAL at the room temperature. However more than two equivalents of DIBAL were needed to complete the reaction. and ether was generated as a by-product.
14) All new compounds were characterized by ^{1}H-NMR, IR, and high resolution MS.
15) Enantiomeric exess was determined to be over 99% by ^{1}H-NMR measurement using $Eu(TFC)_3$. The difference in chemical shift for OMe group of (R)- and (S)-3 was about 0.1 ppm in the presence of 0.6 equivalent of $Eu(TFC)_3$ in CCl_4. When 1% of the racemic 3, prepared from the racemic lactamide, was added into the sample, OMe peak due to 0.5% of (R)-3 was observed clearly in the higher field.
16) (R)-(−)-9 has been separated from the essential oil occurred in rhizomes of *Curcuma aromatica salisb*, but not completely purified so far. Optically pure (S)-(+)-9 has $[\alpha]_D^{20}$ +45.1° (*c*1.16, $CHCl_3$).[17] Total synthesis of optically active (R)-(−)-9 by the application of Grignard cross coupling in 66% *e.e.* has been reported.[18] (S)-(+)-9 has been synthesized in 95% *e.e.*[19]
17) N. P. Damodaran and S. Dev, *Tetrahedron*, 24, 4113 (1968).
18) K. Tamao, T. Hayashi, H. Matsumoto, H. Yamamoto, and M. Kumada, *Tetrahedron Lett.*, 1979, 2155.
19) S. Takano, E. Goto, and K. Ogasawara, *Tetrahedron Lett.*, 23, 5567 (1982).
20) Similar pathway for the synthesis of racemic 9 has been reported,[21] but racemic 8 was desulfurized with Raney nickel in absolute ethanol to give racemic 9 in 24% yield with isomerization of the double bond.
21) H. H. Bokel, A. Hoppmann, and P. Weyerstahl, *Tetrahedron*, 36, 651 (1980).
22) D. Seebach and E. J. Corey, *J. Org. Chem.*, 40, 231 (1975).
23) T. Mukaiyama, K. Narasaka, K. Maekawa, and M. Furusato, *Bull. Chem. Soc. Jpn.*, 44, 2285 (1971).
24) 6: ^{1}H-NMR ($CDCl_3$) δ; 0.42 (s, 3H), 1.16 (s, 3H), 1.31 (d, 3H, *J*=7.2 Hz), 2.30 (s, 3H), 2.94 (dq, 1H, *J*=4.8 Hz, *J*=7.2 Hz), 3.2-3.9 (m, 4H), 4.49 (d, 1H), 7.0-7.3 (m, 4H) ppm. IR (film) ν; 1104 cm^{-1}. MS *m/e*; 234.1603(M^+,$C_{15}H_{22}O_2$).
7: ^{1}H-NMR ($CDCl_3$) δ; 1.46 (d, 3H, *J*=7.3 Hz), 1.6-2.3 (m, 2H), 2.36 (s, 3H), 2.6-3.0 (m, 4H), 3.06 (quintet, 1H, *J*=7.3 Hz), 4.24 (d, 1H, *J*=7.3 Hz), 7.23 (s, 4H) ppm. $[\alpha]_D^{18}$ -4.1° (*c*1.12, $CHCl_3$). MS *m/e*; 238.0858 (M^+, $C_{13}H_{18}S_2$).
8: ^{1}H-NMR ($CDCl_3$) δ; 1.50 (d, 3H, *J*=7.2 Hz), 1.58 (d, 3H, *J*=1.5 Hz), 1.77 (d, 3H, *J*=1.5 Hz), 1.7-2.1 (m, 2H), 2.33 (s, 3H), 2.3-3.0 (m, 6H), 3.17 (q, 1H, *J*=7.2 Hz), 5.37 (m, 1H), 7.07 (d, 2H, *J*=8.7 Hz), 7.26 (d, 2H, *J*=8.7 Hz) ppm. IR (film) ν; 1668 cm^{-1}. $[\alpha]_D^{19}$ -31.4° (*c*0.99, $CHCl_3$). MS *m/e* 306.1461 (M^+, $C_{18}H_{26}S_2$).
9: ^{1}H-NMR ($CDCl_3$) δ; 1.22 (d, 3H, *J*=7.3 Hz), 1.54 (broad s, 3H), 1.69 (broad s, 3H), 1.5-2.1 (m, 3H), 2.35 (s, 3H), 2.67 (sextet, 1H, *J*=7.3 Hz), 5.14 (broad t, 1H, *J*=7 Hz), 7.21 (s, 4H) ppm. IR (film) ν; 2975, 2870, 1516, 1450, 1376, 1110, 1018, 816 cm^{-1}. $[\alpha]_D^{23}$ -46.2° (*c*0.95, $CHCl_3$). MS *m/e* 202.1732 (M^+, $C_{15}H_{22}$).

(Received May 18, 1985)