BREWERS' YEAST-MEDIATED SYNTHESIS OF (1*S*,2*S*)-1-(2-THIENYL)-1,2-PROPANEDIOL AND A STUDY ON THE LIPASE-CATALYZED REGIOSELECTIVE INTRODUCTION OF ACYL PROTECTIVE GROUP TO THE DIOL MOIETY

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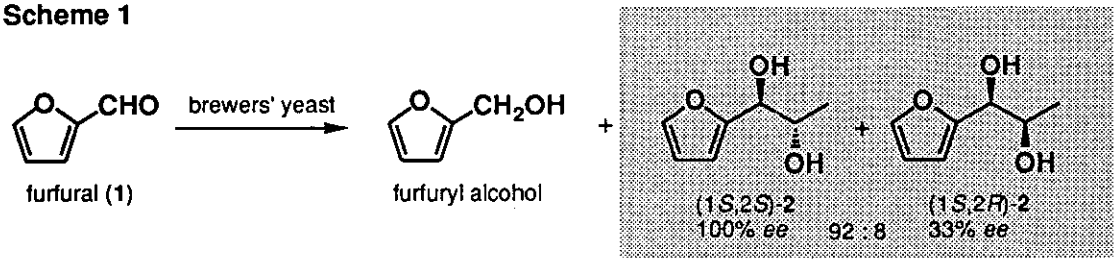
Abstract – Reductive homologation of thiophenecarboxyaldehyde mediated by brewers' yeast and subsequent recrystallization provided (1*S*,2*S*)-1-(2-thienyl)-1,2-propanediol in 29% yield. A *Pseudomonas* lipase-catalyzed acetylation preferentially occurred on the hydroxyl group at C-1 position of the diol.

In our previous paper,[1] we reported a brewers' yeast-mediated reductive bishomologation of furfural (**1**). Along with furfuryl alcohol, (1*S*,2*S*)-1-(2-furyl)-1,2-propanediol (**2**) was obtained in a highly enantioselective manner (Scheme 1).

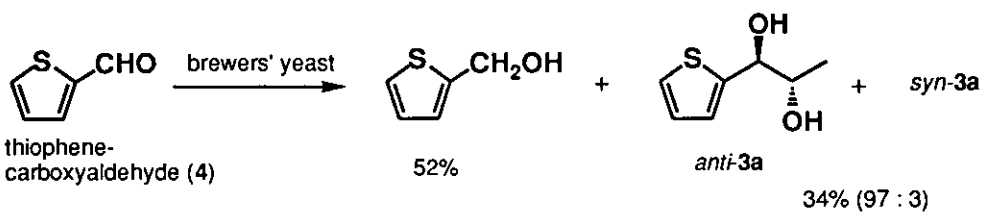
Recent reports on the biochemical transformation[2-5] of thiophene-containing compounds with a substantial synthetic potential[6] prompted us to study the preparation of (1*S*,2*S*)-1-(2-thienyl)-1,2-propanediol (**3a**) from thiophenecarboxyaldehyde (**4**).

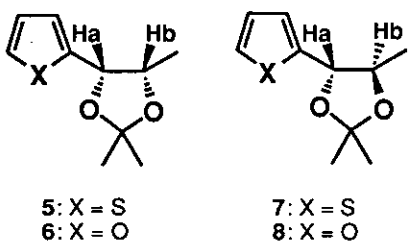
Scheme 1



The incubation of **4** with brewers' yeast[1] gave a mixture of **3a** (34%) and 2-thienylmethanol (52%). The diastereomeric ratio of **3a** was 97 : 3 as judged from its ^{1}H-NMR spectrum. The *anti*-isomer was elucidated to be the major product, by the comparison of coupling constants and NOE enhancement of the corresponding acetonides (**5**) and (**7**) with those of **6** and **8**, whose relative configuration had been unambiguously determined[1] (Scheme 2). The results are listed in Table 1. The major *anti*-isomer was obtained as a pure state by recrystallization of the mixture.

Scheme 2





5: X = S
6: X = O

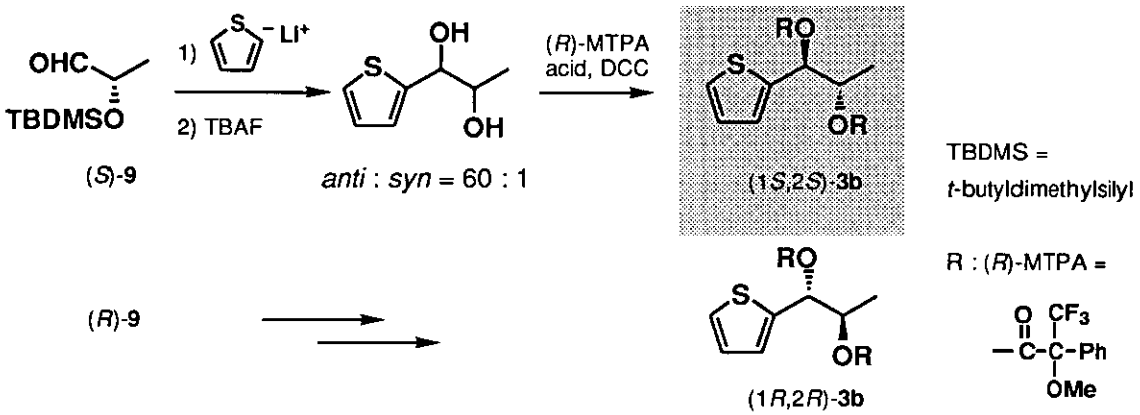
7: X = S
8: X = O

Table 1

	5	**6**	**7**	**8**
J_{ab} (Hz)	6.5	6.3	8.5	8.6
NOE ($H_a \rightarrow H_b$, %)	7.1	7.2	—	—

The next task was the determination of the absolute configuration of the purified isomer. In a similar manner to our previous report,[1] both enantiomers [(1*S*,2*S*) and (1*R*,2*R*) isomer] were prepared from α-siloxyaldehydes ((*S*)-**9** and (*R*)-**9**), respectively. Then, the adducts were converted to the corresponding MTPA esters (**3b**) and analyzed by ^{1}H-NMR (Scheme 3). The results cleanly showed that the absolute configuration of major *anti*-isomer of **3a** was (1*S*,2*S*) and the recrystallized product turned out to be isomerically pure.

Scheme 3



On the other hand, precise determination of the ee and the absolute configuration for *syn*-**3a** was not possible due to some difficulty with the isolation in a pure state. The previous study of brewers' yeast-mediated reductive homologation with benzaldehyde and furfural shows that the e.es of minor *syn*-isomers are as low as 9-33% ee.[1] Accordingly the ee of *syn*-**3a** might be estimated to be not high.

The structure of (*1S,2S*)-**3a** including vicinal glycol system is well coincided with the partial structure of L-rhamnose, a useful optically active starting material in synthetic organic chemistry, in its carbon skelton as well as the stereochemical sense.[7] As pure (1*S*,2*S*)-**3a** became in hand, we then attempted a selective introduction of a protective group on the vicinal glycol system, since a regioselectively protected form would increased its synthetic utility for a chiral synthon. The differentiation of two secondary hydroxyl groups turned out to be difficult by a conventional chemical reaction; for example, benzoylation of **3a** with even a limited amount of benzoic anhydride under mild conditions afforded a mixture of monobenzoates and dibenzoate. We realized that the reactivity of the two hydroxyl groups is very similar toward acylating agent and turned our attention to biocatalyst-mediated selective reaction, especially a *Pseudomonas* lipase-catalyzed acetylation.[8] So far, in many reports, (*S*)-isomers of methylcarbinols have been reported to be unreactive.[9] These characteristics would enable the preferential acetylation of the hydroxyl group on C-1 position, because of the possibly lower reactivity of the hydroxyl group on C-2 position of (1*S*,2*S*)-**3a**.

Scheme 4

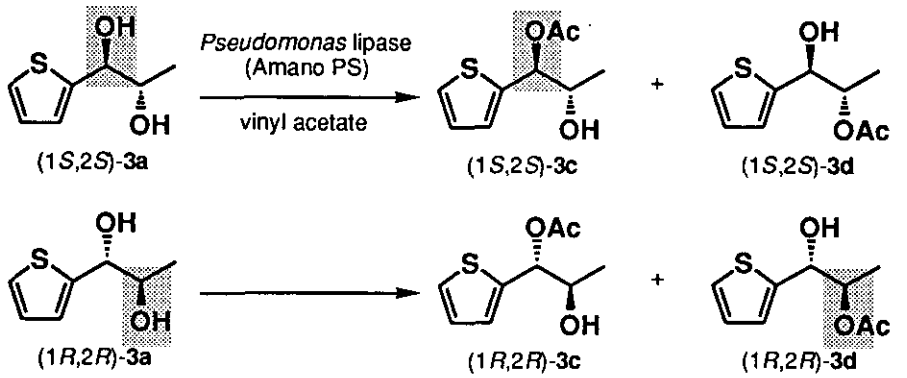


Table 2

substrate	wt of lipase / wt of substrate	reaction time	total Yd of mono-acetates (%)	1-acetate (**3c**) : 2-acetate (**3d**)
(1*S*,2*S*)-**3a**	2.0	5 d	35	4.1 : 1
(1*R*,2*R*)-**3a**	0.5	30 h	80	1 : 5.0

Although the reaction proceeded rather slowly, a preferential acetylation of the hydroxyl group at C-1 position of (1*S*,2*S*)-**3a** took place as expected on treatment with the lipase in vinyl acetate. The ratio of the products (total 35%), 1-acetate (**3c**) to 2-acetate (**3d**) was 4.1 : 1, as judged by ^{1}H-NMR measurement. At this stage, we became interested in the lipase-catalyzed acetylation of the antipodal isomer, which would be useful to examine the stereochemistry-regioselectivity relationship of the reaction.

In contrast to the previous case, when (1*R*,2*R*)-**3a** was used as the substrate, the reaction was very fast and a preferential acetylation of the hydroxyl group at C-2 position (1-acetate (**3c**) : 2-acetate (**3d**) = 1 : 5) of the product (80%) was observed. The both results are summarized in Table 2. The order of reactivity of hydroxyl groups was concluded to be [(2*R*)-OH > (1*R*)-OH > (1*S*)-OH > (2*S*)-OH]. The highest reactivity of (2*R*)-OH of **3a** among four secondary alcohols well coincides with a recently reported result, which had been observed in the case of the lipase-catalyzed regioselective hydrolysis of the acetyl group of ethyl 3-aryl-2,3-diacetoxypropanoates.[10] The decreased regioselectivity and yield of the transesterification on (1*S*,2*S*)-**3a** might also reflect on the bulkyness of the heterocyclic ring in steric hindrance.[10,11]

In conclusion, we have established a short synthesis of enantiomerically and diastereomerically pure (1*S*,2*S*)-1-(2-thienyl)-1,2-propanediol from thiophenecarboxyaldehyde. In addition, the reactivity of the secondary alcohols of the product in the course of *Pseudomonas* lipase-catalyzed acetylation was clarified.

EXPERIMENTAL

Mps were uncorrected. IR spectrum was measured as KBr disc on a Perkin-Elmer 1710 FTIR spectrophotometer. ^{1}H-NMR spectra were measured in $CDCl_3$ with TMS as the internal standard at 400 MHz on a Bruker AM 400 or JEOL JNM α-400 spectrometer. Optical rotations were recorded on a Jasco DIP 360 polarimeter. Mass spectra were measured on a Hitachi M-80B or a VG Auto Spec spectrometer by the EI method.

(1*S*,2*S*)-1-(2-Thienyl)-1,2-Propanediol (3a)

The incubation condition was followed by the previous report.[1] Starting from 4.4 g of **4**, **3a** (2.1 g, 34%) was obtained as an oil; a mixture of *anti* and *syn* isomers in a 97 : 3 ratio. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.13 (*syn*, d, 3H, J = 6.4 Hz), 1.15 (*anti*, d, 3H, J = 6.4 Hz), 3.93 (*syn*, dq, 1H, J = 7.1, 6.4 Hz), 4.07 (*anti*, dq, 1H, J = 4.0, 6.4 Hz), 4.41 (*syn*, d, 1H, J = 7.1 Hz), 4.87 (*anti*, d, 1H, J = 4.0 Hz).

The corresponding acetonides were prepared in a conventional manner: major *cis*-acetonide (**5**) (from *anti*-**3a**) and minor *trans*-acetonide (**7**) (from *syn*-**3a**) were obtained as an inseparable mixture. Measurement of the NMR spectra and a comparison with the spectra of the corresponding acetonides (**6** and **8**) from **2**[1] revealed the relative stereochemistry of **5** and **7**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.99 (**5**, d, 3H, J = 6.4 Hz), 1.32 (**7**, d, 3H, J = 6.0 Hz), 1.44 (**5**, s, 3H), 1.50 (**7**, s, 3H), 1.53 (**7**, s, 3H), 1.64 (**5**, s, 3H), 4.02 (**7**, H-5, dq, 1H, J = 6.0, 8.5 Hz), 4.53 (**5**, H-5, dq, 1H, J = 6.4, 6.5 Hz), 4.73 (**7**, H-4, 1H, d, J = 8.5 Hz), 5.40 (**5**, H-4, d, 1H, J = 6.5 Hz), 6.91 (**5**, broad d, 1H, J = 3.5 Hz), 6.98 (**5**, dd, 1H, J = 3.5, 5.1 Hz), 7.04 (**7**, 1H, broad d, J = 2.5 Hz), 7.26 (**5**, dd, 1H, J = 1.2, 5.1 Hz), 7.30 (**7**, dd, 1H, J = 1.1, 4.9 Hz). MS *m/z* (rel. int.): 198 (M^+, 5%), 183 (M^+–Me, 8%), 154 (M^+–C_2H_4O, 84%), 141 (25%), 125 (50%), 96 (100%), 58 (42%), 43 (64%). It has been reported that $J_{4,5}$ = 8.6 Hz for the *trans*-acetonide (**8**) and $J_{4,5}$ = 6.3 Hz for the *cis*-acetonide (**6**).[1] Irradiation at H-4 in **5** (δ 5.40) enhanced the signal of H-5 (δ

4.53) by 7.1%, while no such enhancement was observed in the case of irradiating H-4 (δ 4.73) in **7**.

Diol (**3a**) solidified in a refrigerator, and recrystallization of the mixture from diisopropyl ether afforded pure *anti*-**3a** as needles, mp 59-60°C in 85% recovery, Anal. Calcd for $C_7H_{10}O_2S$: C, 53.14; H, 6.37. Found: C, 53.17; H, 6.40. $[\alpha]_D^{28}$ –15.6° (*c* 1.36, $CHCl_3$). IR (cm^{-1}): 3270, 1443, 1372, 1346, 1322, 1277, 1235, 1131, 1081, 1066, 992, 924. MS *m/z* (rel. int.): 158 (M^+, 4%), 141 (M^+–OH, 26%), 113 ($C_5H_5OS^+$, 89%), 97 (48%), 85 (100%), 81 (37%), 45 (84%). NMR measurements indicated that the crystal of **3a** was diastereomerically pure; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.15 (d, 3H, *J* = 6.4 Hz), 4.07 (dq, 1H, *J* = 4.0, 6.4 Hz), 4.87 (d, 1H, *J* = 4.0 Hz), 7.00 (dd, 1H, *J* = 3.5, 4.8 Hz) 7.03 (dd, 1H, *J* = 1.3, 3.5 Hz), 7.31 (dd, 1H, *J* = 1.3, 4.8 Hz).

Determination of absolute configuration

In a similar manner as described before,[1] a diastereomeric mixture of **3a** (*anti* : *syn* = 60 : 1) was prepared from aldehyde ((*S*)-**9**) and was subsequently recrystallized to give an authentic sample: mp 59-60°C; $[\alpha]_D^{28}$ –15.6° (*c* 1.06, $CHCl_3$). This was converted to the corresponding (*R*)-MTPA esters ((1*S*,2*S*)-**3b**). In the same manner, (1*R*,2*R*)-**3b** was prepared from (*R*)-**9** *via* (1*R*,2*R*)-**3a**: mp 59-60°C; $[\alpha]_D^{28}$ +15.6° (*c* 1.05, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (1*S*,2*S*)-**3b**: 1.35 (d, 3H, *J* = 6.5 Hz), 3.42 (s, 3H), 3.44 (s, 3H), 5.56 (dq, 1H, *J* = 4.2, 6.5 Hz), 6.04 (d, 1H, *J* = 4.2 Hz), 6.91 (dd, 1H, *J* = 4.0, 5.0 Hz), 6.96 (d, 1H, *J* = 4.0 Hz), 7.25-7.44 (m, 11H); (1*R*,2*R*)-**3b**: 1.17 (d, 3H, *J* = 6.4 Hz), 3.28 (s, 3H), 3.38 (s, 3H), 5.50 (dq, 1H, *J* = 5.5, 6.4 Hz), 6.33 (d, 1H, *J* = 5.5 Hz), 6.98 (dd, 1H, *J* = 3.6, 5.0 Hz), 7.17 (d, 1H, *J* = 3.6 Hz), 7.26-7.34 (m, 11H). By comparing its NMR spectrum with that of an authentic specimen, the sample of **3b** from **3a** obtained by recrystallization of the yeast-fermentation product was determined to be a (1*S*,2*S*)-isomer, and was diastereomerically and enantiomerically pure.

Regioselective acetylation with *Pseudomonas* lipase PS

A mixture of (1*S*,2*S*)-**3a** (20.8 mg), *Pseudomonas* lipase (Amano PS, 40 mg) and vinyl acetate (200 μL) was stirred at 30°C for 5 days. The mixture was filtered with a pad of Celite and the solid residue was washed with ethyl acetate. The filtrate and washings were combined and concentrated in vacuo, and the residue was purified by a preparative thin-layer chromatography (Merck 5744, 20 cm x 10 cm) developed with hexane-ethyl acetate (1 : 1). A mixture of 1-

acetate and 2-acetate in a 4.1 : 1 ratio was obtained (9.3 mg, 35%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.18 (1-acetate, d, 3H, *J* = 6.4 Hz), 1.22 (2-acetate, d, 3H, *J* = 6.4 Hz), 2.08 (2-acetate, s, 3H), 2.10 (1-acetate, s, 3H), 2.51 (2-acetate, d, 1H, OH, *J* = 3.9 Hz), 4.15 (1-acetate, dq, 1H, *J* = 4.9, 6.4 Hz), 5.05 (2-acetate, ddd, 1H, *J* = 1.3, 3.9, 3.9 Hz), 5.19 (2-acetate, dq, 1H, *J* = 3.9, 6.4 Hz), 5.93 (1-acetate, d, 1H, *J* = 4.9 Hz), 6.99 (2-acetate, dd, 1H, *J* =3.4, 4.9 Hz), 7.00 (1-acetate, dd, 1H, *J* = 3.7, 5.1 Hz), 7.02 (2-acetate, ddd, 1H, *J* = 1.3, 1.3, 3.4 Hz), 7.14 (1-acetate, dd, 1H, *J* = 1.2, 3.7 Hz), 7.28 (2-acetate, dd, 1H, *J* = 1.3, 4.9 Hz), 7.32 (1-acetate, dd, 1H, *J* = 1.2, 5.1 Hz). MS *m/z* (rel. int.): 156 (M^+–$COCH_3$, 19%), 140 (M^+–CH_3CO_2H, 38%), 113 ($C_5H_5OS^+$, 100%), 97 (19%), 85 (32%), 43 (91%).

In a similar manner, (1*R*,2*R*)-**3a** (20.2 mg) was treated with Amano PS (10 mg) in vinyl acetate (200 μL) at 30°C for 30 h. Subsequent workup and purification afforded a mixture of 1-acetate and 2-acetate in a 1 : 5 ratio (20.0 mg, 80%).

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