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A NEW ACCESS TO CHIRAL AZIRIDINES BY ENZYMATIC TRANSESTERIFICATION OF *MESO*-BIS(ACETOXYMETHYL)AZIRIDINES

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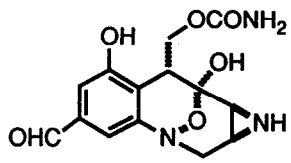
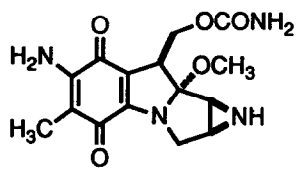
Abstract: (2*R*, 3*S*)-2-Acetoxymethyl-3-hydroxymethylazirizines of high enantiomeric purity were prepared through enzymatic transesterification of *meso*-bis(acetoxymethyl)aziridines.

An antibiotic FR-900482 (**1**), recently isolated and characterized by Fujisawa research group, has been shown to exhibit exceptionally potent anti-tumor activity.[1] Structually related antibiotic, mytomycin C (**2**), has already been used for cancer chemotherapy.[2] These antibiotics are activated in the cells to form interstrand DNA-DNA cross links.[3,4] This is believed to be the origin of the acute cytotoxity. The aziridine moiety in **1** and **2** is suggested to play a key role in the interaction with DNA. From a synthetic standpoint of view, chiral aziridines possessing *cis*-disubstituents are expected to be the most promising starting materials for a total synthsis of these molecules. Recently chiral aziridin **3** was prepared in thirteen steps from L-methionine and used for the synthesis of the core nucleus of **1**.[5] Here we describe a new and convenient method for the synthesis of chiral *cis*-disubstituted aziridines by means of enzymatic transesterification of *meso* derivatives. There have been many papers reported concerning enzymatic hydrolysis of *meso* diesters.[6] To the best of our knowledge, however, enzymatic transformation of *meso*-disubstitued aziridines to chiral ones has never been reported.



1



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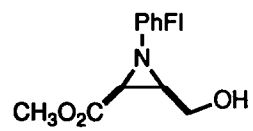


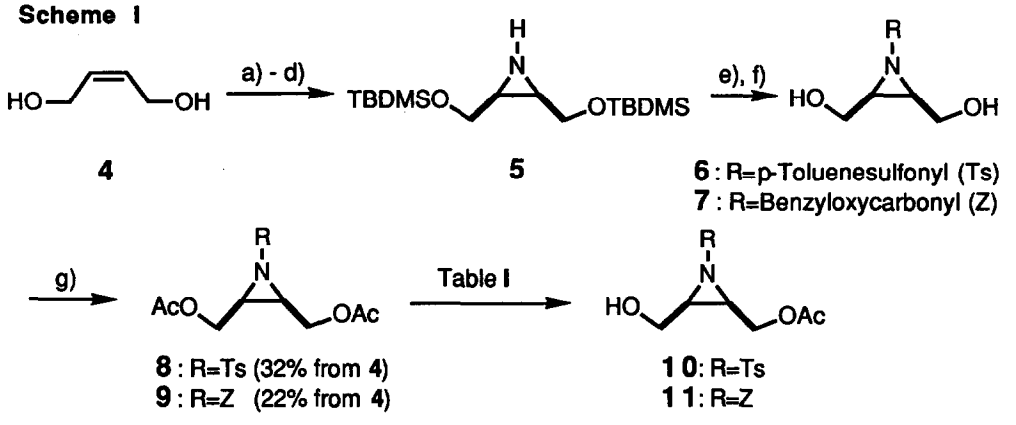
3

PhFl=9-Phenylfluoren-9-yl

Meso azirizine **5** was prepared starting from commercially available *cis*-2-butene-1,4-diol (**4**) (Scheme I). Silylation of **4** was followed by epoxidation and Blum's procedure[7] to give **5**. Protection of the aziridine nitrogen and desilylation affoderd diol **6** and **7**. The cis-relationship between the two hydroxymethyl groups is ununivocally established by an X-ray crystallographic analysis of **6** (Figure I).[8] *Meso*-diacetates **8** and **9** were obtained by acetylation of **6** and **7**. The overall yields of **8** and **9** from **4** were 32% and 22% , respectively.

Taking advantage of enzymatic transesterification in organic solvents,[9] *meso*-diacetates **8** and **9** were treated with ten equivalents of butanol in diisopropyl ether[10] in the presence of enzyme (Table I). After indicated reaction time at 37 °C,[11] the reaction was terminated by removing the enzyme through filtration. Evaporation of the solvent *in vacuo* gave the residue which was purified by SiO_2 preparative TLC. Enantiomeric excess(ee) of the products was determined by the mesurement of 400 MHz ^1H NMR spectra with $Eu(hfc)_3$ or with a combination of (S)-binaphtol and $Eu(hfc)_3$.[12] Among a variety of enzyme screened, Amano P has proved to be highly enantioselective in catalyzing the transesterification (runs 1 and 5). Use of larger amount of Amano P or immobilized Amano P on celite[13] has significantly shorten the reaction time (runs 6 and 7). The absolute configuration of **10** turned out to be (2*R*, 3*S*) by an X-ray crystal structure determination of **12**,[8] mp 96-97 °C, $[\alpha]_D^{20}$ +8.1° (c 0.76, $CHCl_3$), which was obtained by the treatment of **10** with (1*S*)-(-)-camphanic chloride (Figure II). The absolute configuration of N-*benzyloxycarbonyl* aziridine **11** was also determined to be (2*R*, 3*S*) by the chemical correlation with **10**.[14] Interestingly, the major enantiomer obtained in each experiment in runs 1-3 and 5-9 in Table I has the same absolute configuration.

Scheme I



a) $TBDMSCl / NEt_3$ / DMAP, b) MCPBA, c) NaN_3 / NH_4Cl, d) PPh_3, e) RCl, f) Bu_4NF, g) Ac_2O / Py

Table I. Enzymatic Transesterification of **8** and **9** in *n*-BuOH - *i*-Pr_2O.[a)]

Run	Substrate	Enzyme	Time (days)	Product	Yield (%)	ee (%)	Configuration
1	**8**	Amano P[b)]	3	**10**	76	95[h)i)]	(2*R*, 3*S*)
2	**8**	CCL[c)]	4	**10**	56	72[h)]	(2*R*, 3*S*)
3	**8**	PPL[d)]	4	**10**	22	56[h)]	(2*R*, 3*S*)
4	**8**	PLE[e)]	4	**10**	0	-	-
5	**9**	Amano P[b)]	5	**11**	66	98[j)k)]	(2*R*, 3*S*)
6	**9**	Amano P[f)]	6/24	**11**	68	98[j)]	(2*R*, 3*S*)
7	**9**	Amano P[g)]	9/24	**11**	68	97[j)]	(2*R*, 3*S*)
8	**9**	CCL[c)]	5	**11**	14	22[j)]	(2*R*, 3*S*)
9	**9**	PPL[d)]	5	**11**	30	49[j)]	(2*R*, 3*S*)
10	**9**	PLE[e)]	5	**11**	5	-	-

a) All reactions were run at 37 °C. b) Lipase Amano P: 600 units/mmol substrate c) Lipase from *Candida cylinddracea*: 350000 units/mmol substrate d) Porcine pancreatic lipase: 3000 units/mmol substrate e) Pig liver esterase: 500 units/mmol substrate f) 6000 units/mmol substrate g) Immobilized Amano P on celite; 600 units/mmol substrate h) Determined by 400-MHz ^1H NMR with a combination of Eu(hfc)$_3$ (0.25 eq.) and (*S*)-binaphtol (2.0 eq.) i) Mp. 97-99 °C (after recrystallization from ether), $[\alpha]_D^{20}$ -23.8° (c 1.0, $CHCl_3$) j) Determined by 400-MHz ^1H NMR with Eu(hfc)$_3$ (0.6 eq.) k) Colorless oil: $[\alpha]_D^{20}$ -17.8° (c 1.3, $CHCl_3$).

Figure I. X-ray structure of **6**.

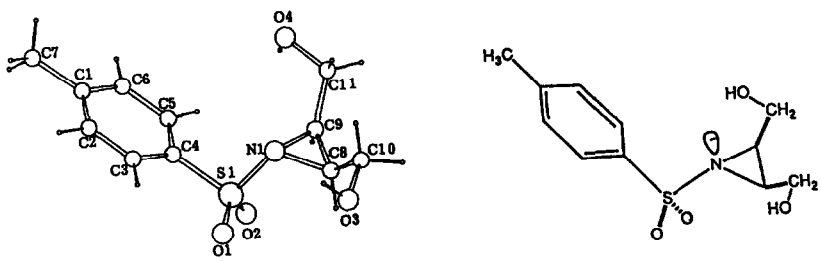
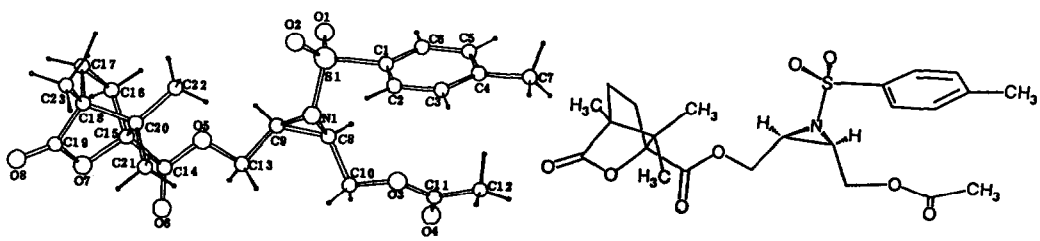


Figure II. X-ray structure of **12**.



In conclusion, an enantioselective method for the preparation of *cis*-disubstituted aziridine was established through enzymatic transesterification of *meso*-derivatives. The present method may provide promising starting materials for the synthesis of **1** and **2**.

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References and Notes

1) Uchida, I,; Takase, S.; Kayakiri, H.; Kiyoto, S.; Hashimoto M. *J. Am. Chem. Soc.*, **1987**, *109*, 4108.
2) Carter, S. K.; Crooke, S. T. *Mitomycin C.; Current Status and New Developments*; Academic Press; New York, **1979**.
3) Masuda, K.; Nakamura, T.; Shimomura, K.; Shibata, T.; Terano, H.; Kohsaka, M. *J. Antibiot.*, **1988**, *41*, 1497.
4) Tomasz, M.; Lipman, R.; McGuinness, B. F.; Nakanishi, K. *J. Am. Chem. Soc.*, **1988**, *110*, 5892.
5) Jones, R. J.; Rapoport, H. *J. Org. Chem.*, **1990**, *55*, 1144.
6) For leading references, see: a) Huang, Fu-C.; Hsu, Lee, L. F.; Mittal, R. S. D.; Ravikumar, P. R.; Chan, J. A.; Sih, C. J.; Caspi, E.; Eck, C. R. *J. Am. Chem. Soc.*, **1975**, *97*, 4144. b) Ito, Y.; Shibata, T.; Arita, M.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.*, **1981**, *103*, 6739. c) Schneider, M.; Engel, N.; Hönicke, P.; Heinemann, G,; Görisch, H. *Angew. Chem. Int. Ed. Engl.*, **1984**, *23*, 67.
7) Ittah, Y.; Sasson, Y.; Shahak, I,; Tsaroom, S.; Blum J. *J. Org. Chem.*, **1978**, *43*, 4271.
8) Crystal data for **6** : $C_{11}H_{15}NO_4S$, space group $P2_1/c$ with a = 11.165 (2), b = 13.149 (2), c = 9.024 (2) Å and D_c = 1.410 g cm^{-3} for Z = 4. Crystal data for **12** : $C_{23}H_{29}NO_8S$, space group $P2_1$ with a = 13.090 (2), b = 6.316 (2), c = 14.917 (3) Å and D_c = 1.305 g cm^{-3} for Z = 2. Bond lengths, bond angles, and atomic coordinates for **6** and **12** have been deposited with the Cambridge Crystallographic Data Center.
9) Klibanov, A. M.; *Acc. Chem. Res.*, **1990**, *23*, 114.
10) Bevinakatti, H. S.; Banerji, A. A.; Newadkar, R. V. *J. Org. Chem.*, **1989**, *54*, 2453.
11) The reactions could be performed also at ambient temperature thougt it requires longer reaction time. For examples, when **8** and **9** were treated with Amano P (600 units/mmol substrate) at ambient temperature, **10** and **11** were obtained in 76% (97% ee) and 68% (97% ee) yield after 7 and 11 days' stirring, respectively.
12) Toda, F.; Mori, K.; Okada, J.; Node, M.; Itoh, A.; Oomine, K.; Fuji, K. *Chem. Lett.*, **1988**, 131.
13) Inagaki, M.; Hiratake, J.; Nishioka, T.; Oda, J. *Agric. Biol. Chem.*, **1989**, *53*, 1879.
14) Tosylate **10** produced through hydrogenolysis (5% Pd-C, H_2) of **11** (93% op) followed by tosylation (TsCl, Py) showed $[\alpha]_D^{25}$ -18.3° (c 1.1, $CHCl_3$) (77% op). The partial racemization is supposed to occur at the stage of tosylation.

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