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Enzymatic desymmetrization of 2-amino-2-methyl-1,3-propanediol: asymmetric synthesis of (*S*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinal and (4*R*)-methyl-4-[2-(thiophen-2-yl)ethyl]oxazolidin-2-one

Takashi Tsuji, Yukiko Iio, Toshiyasu Takemoto and Takahide Nishi*

Medicinal Chemistry Research Laboratories, Sankyo Co., Ltd, 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan

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Abstract—We report herein, the novel enzymatic desymmetrization of 2-*tert*-butoxycarbonylamino-2-methyl-1,3-propanediol **1**. This method makes it possible to prepare (*S*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinal **3**, which is a chiral building block for the synthesis of a variety of α-substituted alanine derivatives. Moreover, optically active (4*R*)-methyl-4-[2-(thiophen-2-yl)ethyl]oxazolidin-2-one **4**, one of the key intermediates in the synthesis of a novel immunosuppressant, has been prepared by this methodology.

1. Introduction

In recent years, a great deal of attention has been focused on the synthesis of α,α-disubstituted α-amino acids with a view to design and synthesize short chain peptides for the purpose of enhanced properties and beneficial physiological effects.[1] Moreover, α,α-disubstituted α-amino acids themselves are known as powerful enzyme inhibitors.[2] Chiral *N*-Boc-*N*,*O*-isopropylidene-α-methylserinal **3**, for example, is known to be a potential building block for the synthesis of enantiomerically pure α-substituted alanines.[3] Additionally, α,α-disubstituted α-amino alcohols, are also recognized as significant components of biologically active compounds.[4] (4*R*)-Methyl-4-[2-(thiophen-2-yl)ethyl]oxazolidin-2-one **4** is one of the key intermediates in the synthesis of a novel immunosuppressant bearing the α,α-disubstituted α-amino alcohol moiety.[5] Accordingly, the synthetic importance as well as biological interest for the construction of optically active quaternary carbon centers has been recognized.[6] In this context and as a part of our research program, we have been interested in the study and development of the methodology for the synthesis of **3** and **4**.

2. Results and discussion

Among a number of synthetic methods to achieve this aim, the enzymatic desymmetrization of achiral 2-amino-2-methyl-1,3-propanediol leading to the enantiomerically enriched monoester was considered attractive. Desymmetrization reactions have the advantage over conventional kinetic resolution reactions in the terms of the potential ability to achieve high enantiomeric excess (ee) and also obtain up to 100% conversion. Although many successful examples of similar desymmetrizations of 2-monosubstituted 1,3-propanediols have already been reported,[7] to the best of our knowledge, there are only a few examples of such desymmetrization methods applied to prochiral compounds bearing a quarternary carbon center.[8] In this regard, we first focused our attention on the enzymatic desymmetrization of 2-amino-2-methyl-1,3-propanediol bearing a quarternary carbon center for the synthesis of (*S*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinal **3** and (4*R*)-methyl-4-[2-(thiophen-2-yl)ethyl]oxazolidin-2-one **4** (Scheme 1).

2-*t*-Butoxycarbonylamino-2-methyl-1,3-propanediol **1**[9] was selected as a substrate to set up the experimental conditions for the lipase-catalyzed desymmetrization using vinyl *n*-hexanoate as an acylating agent in *i*-Pr_2O at ambient temperature. As shown in Table 1, from among the numerous commercial lipases screened, immobilized lipase from *Pseudomonas* sp. (TOYOBO) clearly showed the best result (88% yield, 89% ee, entry

* Corresponding author. Tel.: +81 3 3492 3131; fax: +81 3 5436 8563; e-mail: takahi@shina.sankyo.co.jp

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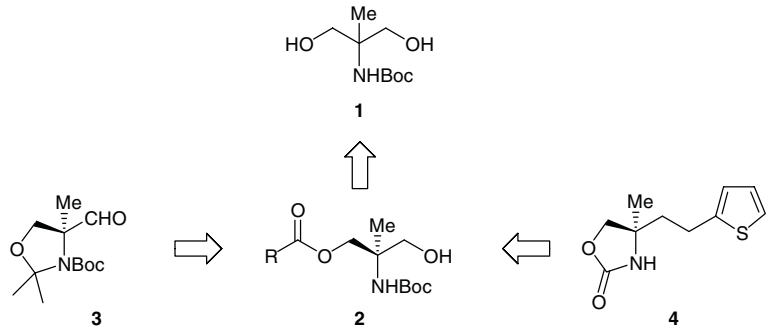


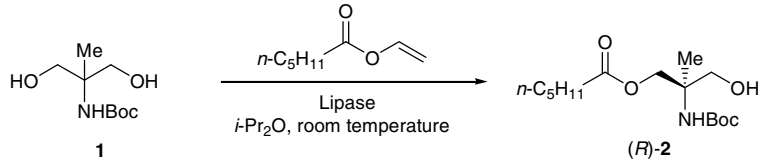
Scheme 1.

1).[10] Other lipases gave relatively moderate yields and ee. It is noteworthy that when lipases from *Rhizopus arrhizus* and *Mucor javanicus* were used for this reaction, there was a preference to yield (*S*)-**2** with the opposite configuration, though the ee was moderate (entries 7 and 8). The ee of (*R*)-**2** could be determined by chiral HPLC analysis [column, ChiralCel OF (4.6$\phi \times 250$ mm); eluent, 70:30 *n*-hexane–2-propanol mixture; flow rate, 0.5 mL/min; t_R of (*S*)-isomer, 8.2 min; t_R of (*R*)-isomer, 10.5 min].

Immobilized lipase from *Pseudomonas* sp. was chosen for further optimization of this reaction. To increase enantioselectivity, we examined various combinations of acylating reagents and solvents (Table 2). Although several solvents were examined for the reaction, no drastic solvent effects in terms of yields or ee were observed. The best yield was obtained in the case of CH_2Cl_2 as the solvent used, but the ee was not very high (entry 7). Amongst all the solvents examined, *i*-Pr_2O and *t*-BuOMe gave the highest ee (entries 2 and 3). Acylating reagents were also explored. Yields and ee values varied according to the length of the vinyl ester side chain. Consequently, it was found that using vinyl *n*-hexanoate provided the best result (entry 2). Acylating reagents having either a shorter or longer alkanoyl group than that of the *n*-hexanoyl group, gave poor results (entries 9–13).

Having determined the optimal conditions for the lipase-catalyzed desymmetrization of **1**, we sought to apply this method to the synthesis of (*S*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinal **3** (Scheme 2). Recently, several studies on the synthesis of **3** have been reported, but the procedures often required many steps.[11] The hydroxyl group of (*R*)-**2** was protected with *tert*-butyldiphenylsilyl chloride (TBDPSCl) and the subsequent hydrolysis of the ester group was achieved by treatment with 1 M NaOH solution resulting in 84% yield over two steps. The acetonide formation of **5** took place with the use of 2,2-dimethoxypropane in CH_2Cl_2 with boron trifluoride etherate as a catalyst. Subsequent treatment with tetrabutylammonium fluoride (TBAF) gave alcohol **6** in 73% yield over two steps. Finally, the oxidation of alcohol **6** under Swern conditions was completed to give the required (*S*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinal **3** in 96% yield.[12] As a result, **3** was prepared in 61% overall yield from compound (*R*)-**2** in only five steps.

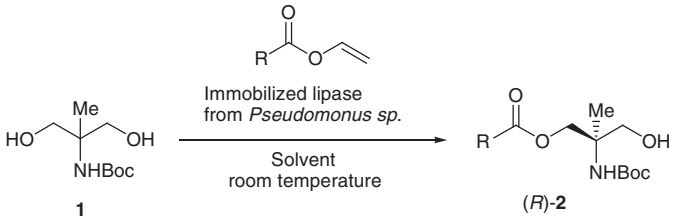
Table 1.



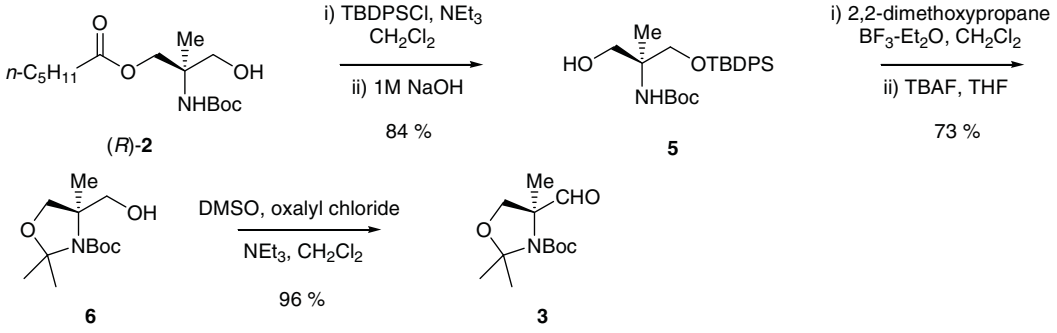
Entry	Lipase	Yield (%)	% ee of (*R*)-**2**
1	Immobilized lipase from *Pseudomonas* sp.[a]	88	89
2	Lipase, immobilized on cellulose from *Pseudomonas* sp.[b]	89	84
3	Lipase from *Chromobacterium viscosum*[c]	45	35
4	Lipase from hog pancreas[c]	32	35
5	Lipase from *Penicillium roquefortl*[c]	17	58
6	Lipase AK 'Amano' 20[d]	32	20
7	Lipase from *Rhizopus arrhizus*[c]	45	51 (*S*)
8	Lipase from *Mucor javanicus*[c]	24	37 (*S*)

[a] Lipase from TOYOBO.
[b] Lipase from Sigma.
[c] Lipase from Fluka.
[d] Lipase from AMANO.

Table 2.

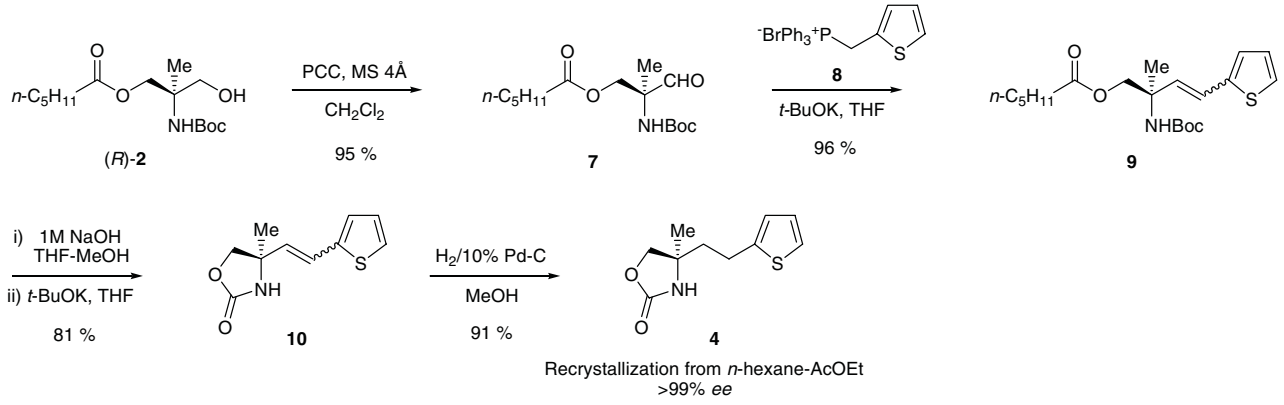


Entry	R	Solvent	Yield (%)	% ee of (*R*)-**2**
1	n-C_5H_{11}	—	83	77
2	n-C_5H_{11}	i-Pr_2O	88	89
3	n-C_5H_{11}	t-BuOMe	84	89
4	n-C_5H_{11}	n-Hexane	82	86
5	n-C_5H_{11}	Toluene	87	81
6	n-C_5H_{11}	Et_2O	89	79
7	n-C_5H_{11}	CH_2Cl_2	95	78
8	n-C_5H_{11}	THF	78	77
9	CH_3	i-Pr_2O	43	62
10	n-C_3H_7	i-Pr_2O	52	72
11	n-C_7H_{15}	i-Pr_2O	86	82
12	n-C_9H_{19}	i-Pr_2O	60	71
13	$(CH_3)_3C$	i-Pr_2O	69	53



Scheme 2.

In the course of our studies to synthesize a novel immunosuppressant, (4*R*)-methyl-4-[2-(thiophen-2-yl)ethyl]-oxazolidin-2-one **4** was recognized as one of the key intermediates.[5] Compound (*R*)-**2** was converted to enantiomerically pure **4** as follows: after oxidation of the primary alcohol with PCC in CH_2Cl_2, Wittig condensation with phosphonium salt **8** was performed in the presence of *t*-BuOK in THF at 0 °C to give **9** in good yield. Deprotection of the ester group of **9** followed by treatment with *t*-BuOK in THF provided **10** in 81% yield.



Scheme 3.

4 was then obtained in 91% yield by treating **10** with 10% Pd–C in MeOH under a hydrogen atmosphere. The desired enantiomerically pure **4** was obtained by single recrystallization from *n*-hexane and AcOEt to increase the ee to >99% {$[\alpha]_D^{25} = +7.8$ (*c* 2.0, $CHCl_3$)}. The ee value of **4** was determined by chiral HPLC analysis [column, ChiralCel OD-H (4.6$\phi \times 250$ mm); eluent, 60:40 *n*-hexane–2-propanol mixture; flow rate, 0.5 mL/min; t_R of (*S*)-isomer, 16.8 min; t_R of (*R*)-isomer, 17.6 min] (Scheme 3).

3. Conclusion

In conclusion, we have demonstrated the enzymatic desymmetrization of 2-amino-2-methyl-1,3-propanediol. Using this enzymatic reaction, an efficient and practical method for the preparation of (*S*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinal **3** and (4*R*)-methyl-4-[2-(thiophen-2-yl)ethyl]oxazolidin-2-one **4** has been achieved.

References

1. (a) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517; (b) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645.
2. Koert, U. *Nachr. Chem. Technol. Lab.* **1995**, *43*, 347.
3. (a) Obrecht, D.; Altorfer, M.; Lehmann, C.; Schonholzer, P.; Muller, K. *J. Org. Chem.* **1996**, *61*, 4080; (b) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1999**, *10*, 4653.
4. For example: (a) Hinterding, K.; Albert, R.; Cottens, S. *Tetrahedron Lett.* **2002**, *43*, 8095; (b) Hinterding, K.; Cottens, S.; Albert, R.; Zecri, F.; Buehlmayer, P.; Spanka, C.; Brinkmann, V.; Nussbaumer, P.; Ettmayer, P.; Hoegenauer, K.; Gray, N.; Pan, S. *Synthesis* **2003**, 1667.
5. Nishi, T.; Takemoto, T.; Shimozato, T.; Nara, F. U.S. Patent 6,723,745, 2004; Sankyo Co., Ltd.
6. (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037; (b) Ohfune, Y.; Horikawa, M. *J. Synth. Org. Chem.* **1997**, *55*, 982.
7. (a) Faber, K.; Riva, S. *Synthesis* **1992**, 895; (b) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071; (c) Theil, F. *Chem. Rev.* **1995**, *95*, 2203; (d) Nakamura, K.; Hirose, Y. *J. Synth. Org. Chem., Jpn.* **1995**, *53*, 668; (e) Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769; (f) Ogasawara, K. *J. Synth. Org. Chem., Jpn.* **1999**, *57*, 957; (g) Yokomatsu, T.; Minowa, T.; Murano, T.; Shibuya, S. *Tetrahedron* **1998**, *54*, 9341; (h) Neri, C.; Williams, J. M. J. *Tetrahedron: Asymmetry* **2002**, *13*, 2197; (i) Neri, C.; Williams, J. M. *J. Adv. Synth. Catal.* **2003**, *345*, 835; (j) Batovska, D. I.; Tsubota, S.; Kato, Y.; Asano, Y.; Ubukata, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3551, and references cited therein.
8. (a) Fadel, A.; Arzel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 283; (b) Akai, S.; Naka, T.; Takebe, Y.; Kita, Y. *Tetrahedron Lett.* **1997**, *38*, 4243; (c) Guanti, G.; Narisano, E.; Riva, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1859; (d) Alexandre, F.-R.; Huet, F. *Tetrahedron: Asymmetry* **1998**, *9*, 2301, and references cited therein.
9. Compound **1** was synthesized from commercially available 2-amino-2-methyl-1,3-propanediol by treatment with Boc_2O in CH_2Cl_2 at room temperature in 90% yield.
10. Typical enzymatic desymmetrization procedure: 2-*t*-Butoxycarbonylamino-2-methyl-1,3-propanediol **1** (200 mg, 0.97 mmol) was dissolved in *i*-Pr_2O (2 mL), and vinyl *n*-hexanoate (0.16 mL, 1.02 mmol) and lipase [immobilized lipase from *Pseudomonas* sp. (TOYOBO; 0.67 U/mg)] (20 mg) then added followed by stirring for 3 h at room temperature. After the insoluble substances in the reaction mixture were removed by filtration, the filtrate was concentrated, and the residue purified by flash silica gel column chromatography (eluent, *n*-hexane–AcOEt = 10:1–7:3) to give (*R*)-**2** (260 mg, 88% yield) as a colorless oil. The absolute configuration of (*R*)-**2** was determined by the comparison of the specific rotation with that of the known compound, (2*R*)-*t*-butoxycarbonylamino-2-methyl-3-buten-1-ol, which can be easily synthesized from (*R*)-**2** as described in Ref. 3b. For (*R*)-**2**: $[\alpha]_D^{24} = -1.1$ (*c* 0.81, MeOH) (89% ee); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.89 (1H, br s), 4.24 (1H, d, $J = 11.2$ Hz), 4.19 (1H, d, $J = 11.2$ Hz), 3.66–3.54 (2H, m), 2.36 (2H, t, $J = 7.4$ Hz), 1.69–1.57 (2H, m), 1.44 (9H, s), 1.39–1.22 (4H, m), 1.25 (3H, s), 0.90 (3H, t, $J = 6.6$ Hz). This procedure was also applied for other reaction conditions including other lipases, acylating agents, and solvents. Usually, the reactions were carried out until the starting materials disappeared or when the reactions did not proceed any further.
11. (a) Avenoza, A.; Cativiela, C.; Corzana, F.; Pergrina, J. M.; Zurbano, M. M. *J. Org. Chem.* **1999**, *64*, 8220; (b) Avenoza, A.; Cativiela, C.; Corzana, F.; Pergrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2195; (c) Avenoza, A.; Cativiela, C.; Corzana, F.; Pergrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2001**, *12*, 949.
12. The absolute stereochemistry of **3** was determined to be *S* by comparison of the specific rotation with that of the reported compound as described in Ref. 11a.