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New enantiodivergent procedure for the syntheses of chiral α-substituted serines from α-alkyl-α-aminomalonates utilizing enzymatic hydrolysis

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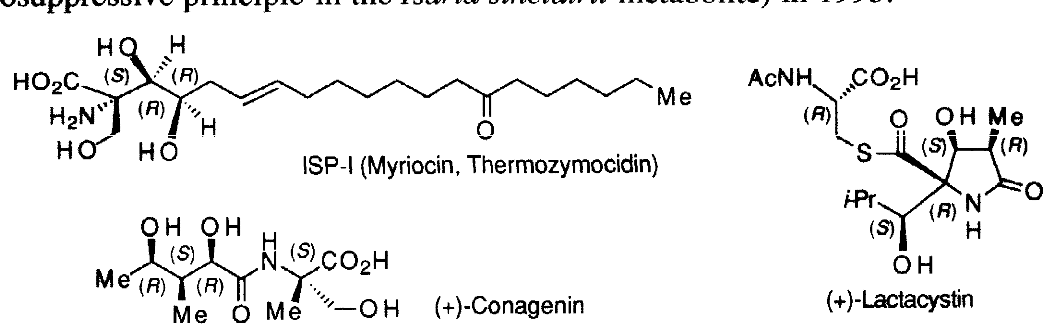
Abstract

Porcine liver esterase (PLE)- or rabbit liver esterase (RLE)-catalyzed hydrolysis of the pro-*S* ester group of diethyl α-alkyl-α-(benzyloxycarbonylamino)malonates **2a-c** afforded (*R*)-ethyl α-alkyl-α-(benzyloxycarbonylamino)malonates **3a-c** each in excellent enantiomeric excess. Enantiodivergent reductions of these acid esters **3a-c** readily furnished both the corresponding enantiomeric α-substituted serines (*R*)- and (*S*)-**5a-c**.

Keywords: amino acids and derivatives; asymmetric synthesis; enzymes and enzyme reactions; reduction

α-Substituted α-amino acids moieties have been found in natural products, and a number of synthetic methods for them have been developed.[1] Particularly, the synthesis of α-substituted serines has been of major interest in recent years. Natural products such as ISP-I,[2,3] (+)-lactacystin,[4,5] and (+)-conagenin[6,7] bearing the chiral α-substituted serine moiety have attracted our attention because of their biological activities. As part of our own contribution to this area, we achieved an asymmetric total synthesis of ISP-I (a potent immunosuppressive principle in the *Isaria sinclairii* metabolite) in 1995.[8,9]



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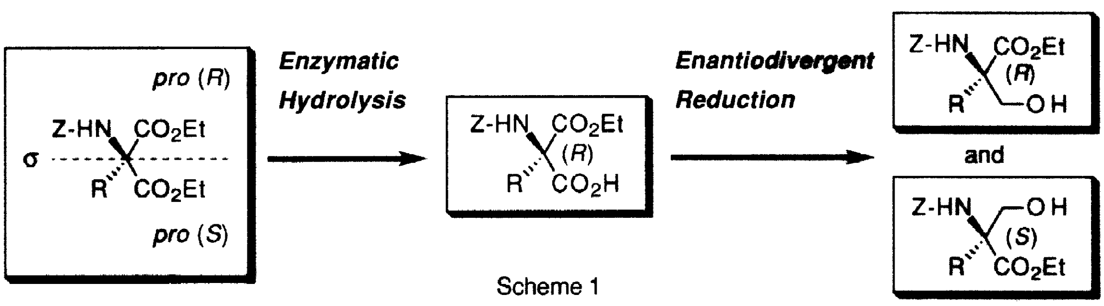
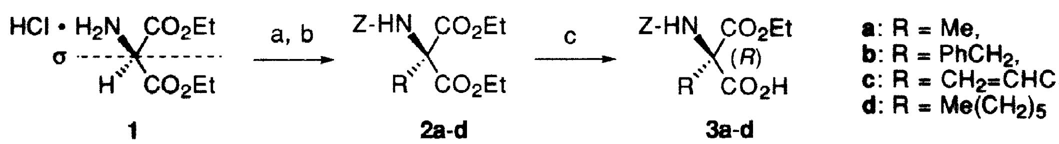
Herein we wish to describe a new elaborated procedure for enantiodivergent construction of chiral α-substituted serines as shown in Scheme 1. σ-Symmetric prochiral diethyl α-aminomalonate **1** was protected by treatment with benzyloxycarbonyl (Z) chloride in the presence of $NaHCO_3$ in 97% yield followed by alkylation using alkyl halides and sodium hydride to afford α-alkyl-α-(Z-amino)malonates **2a-d** in 77 - 83% yields (Scheme 2). Their enantioselective enzymatic hydrolyses with porcine liver esterase (PLE) [Sigma, suspension in 3.2 M $(NH_4)_2SO_4$ solution, pH 8] or rabbit liver esterase (RLE) [Sigma, crystalline suspension in 3.2 M $(NH_4)_2SO_4$, 0.01 M Tris, pH 8.5] were undertaken as follows. The diesters **2a-d** were dissolved in 1/15M phosphate buffer solution (pH 7.0) and MeCN (10 : 1). After adding enzyme (PLE or RLE), the mixture was stirred at room temperature (ca. 23 °C) for the required time. The reaction mixture was treated with 5% HCl and then extracted with AcOEt. After evaporation of the extract *in vacuo*, the residue was purified on a silica gel column with CH_2Cl_2-MeOH as the eluent to give the corresponding carboxylic acid esters **3a-c** as a colorless oil. The enantiomeric excess (ee) values of **3a-c** were determined to be 97, 95, and 90%, respectively, by exploiting HPLC equipped with a chiral column after methylation of **3a-c** with diazomethane (Table 1, entries 1, 3, and 6). Unfortunately, the enzymatic hydrolysis of **2d** only gave a trace amount of acid ester **3d** employing PLE or RLE. All results are summarized in Table 1.



Scheme 1



Scheme 2 a) Z-Cl / $NaHCO_3$ / H_2O - Et_2O / rt, b) NaH / RBr or RI / THF / rt or 50 °C, c) esterase / 1/15M phosphate buffer (pH 7.0) - MeCN / rt

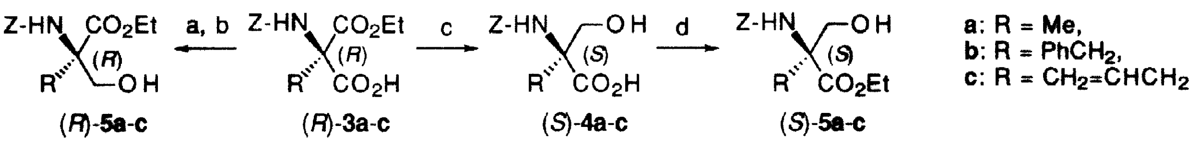
The absolute configuration of acid ester **3a** was determined to be *R* by its chemical conversion to the known compound[10] and in comparison of the specific rotation with the literature value[10] as shown in Scheme 3. Namely, reduction of **3a** with $LiBH_4$ in Et_2O under reflux gave (*S*)-Z-α-methylserine [(*S*)-**4a**], which was submitted to hydrogenolytic debenzyloxycarbonylation to obtain (*S*)-α-methylserine {$[\alpha]_D^{28}$ +5.4 (*c* 0.85, H_2O), lit.[10] $[\alpha]_D^{22}$ +6.5 (*c* 1.01, H_2O)}, a fragment of (+)-conagenin.[6,7] The absolute configurations of acid esters **3b,c** were similarly determined to be *R* by their chemical conversions to the known compounds.[11] These enantioselectivities in the PLE-catalyzed hydrolysis may be explained in accordance with the Jones active-site model by regarding the Z-amino group as accommodating to a large hydrophobic pocket of the PLE active-site.[12,13]

Table 1
Esterase-catalyzed hydrolysis of diethyl α-alkyl-α-(Z-amino)malonates **2a-d**

Entry	Substrate	Esterase (units/mmol) a)	Time	Product	Yield (%)	Ee (%) b)
1	**2a**	PLE (800)	12 h	**3a**	96	97
2	**2a**	PLE (400)	13 h	**3a**	97	96
3	**2b**	PLE (800)	3 d	**3b**	86	95
4	**2b**	PLE (400)	12 d	**3b**	80	92
5	**2c**	PLE (400)	2 d	**3c**	90	60
6	**2c**	RLE (200)	10 d	**3c**	83	90
7	**2d**	PLE (400)	3 d	**3d**	6	— c)
8	**2d**	RLE (200)	3 d	**3d**	12	— c)

a) PLE: porcine liver esterase, RLE: rabbit liver esterase. b) HPLC analysis (CHIRALCEL OD) after methylation of acid esters **3a-c** with diazomethane. c) Not determined.

Enantiodivergent transformation of (*R*)-**3a-c** to (*R*)- or (*S*)-α-alkylserine derivatives **5a-c** was performed as shown in Scheme 3.[14,15] Fluorination of (*R*)-**3a-c** [(*R*)-**3a**: 96% ee, (*R*)-**3b**: 92% ee, (*R*)-**3c**: 90% ee] with cyanuric fluoride[16] in the presence of pyridine, followed by reduction of the resultant acyl fluorides with $NaBH_4$ in THF, then addition of MeOH, gave the corresponding (*R*)-Z-α-alkylserine ethyl esters **5a-c** in 72-84% overall yields. On the other hand, reduction of (*R*)-**3a-c** [(*R*)-**3a**: 96% ee, (*R*)-**3b**: 92% ee, (*R*)-**3c**: 90% ee] with $LiBH_4$ in Et_2O afforded the corresponding (*S*)-Z-α-alkylserines **4a-c** in 31-56% yields. Esterification of **4a-c** gave the (*S*)-Z-α-alkylserine ethyl esters **5a-c** in 53-74% yields, respectively. The ee values of (*R*)- and (*S*)-**5a-c** were confirmed to be almost the same as those of the corresponding acid esters (*R*)-**3a-c** as shown in Table 2.



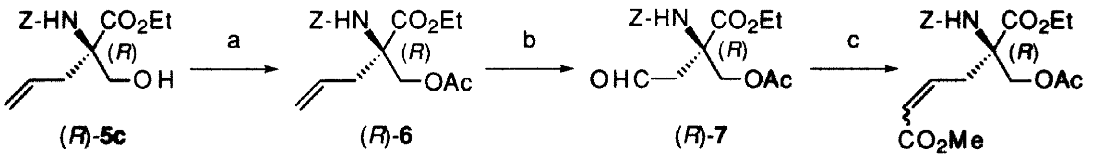
Scheme 3 a) cyanuric fluoride / pyridine /CH_2Cl_2 / 0 °C, b) $NaBH_4$ / MeOH / 0 °C, c) $LiBH_4$ / Et_2O / reflux, d) EtI / K_2CO_3 / acetone / reflux

Table 2
Enantiomeric excess and specific rotation of Z-α-alkylserine ethyl esters **5a-c**

	(*R*)-enantiomer		(*S*)-enantiomer	
	Ee (%) a)	$[\alpha]_D^{26}$ ($CHCl_3$)	Ee (%) a)	$[\alpha]_D^{26}$ ($CHCl_3$)
5a [from (*R*)-**3a** (96% ee)]	97	-2.7 (*c* 1.04)	96	+3.0 (*c* 1.24)
5b [from (*R*)-**3b** (92% ee)]	93	+51.1 (*c* 1.65) b)	92	-52.0 (*c* 1.27) c)
5c [from (*R*)-**3c** (90% ee)]	91	-3.0 (*c* 1.03) b)	90	+3.6 (*c* 0.39)

a) HPLC analysis (CHIRALCEL OD or CHIRALPAK AD). b) 27 °C. c) 25 °C.

Among chiral α-substituted serines **5a-c**, Z-α-allylserine ethyl ester **5c** can be useful for the further α-substituted serine syntheses based on the chemical modification of the double bond. Scheme 4 illustrates a chemical conversion of (*R*)-**5c** to α-substituted serine derivatives (*R*)-**7** and (*R*)-**8**. (*R*)-**5c** was protected by treatment with AcCl in the presence of pyridine in 88% yield. Ozonolysis with (*R*)-**6** furnished (*R*)-**7** (100% yield), which was submitted to the Horner-Wadsworth-Emmons reaction with methyl bis(trifluoroethyl)phosphonate to give α,β-unsaturatd esters (*R*)-**8** in 77% yield (*E* : *Z* = 1 : 9).[17] Further synthetic applications of this convenient approach to various chiral α-substituted serines are currently being under study.



(*R*)-**5c** (*R*)-**6** (*R*)-**7** (*R*)-**8**

Scheme 4 a) AcCl / pyridine / CH_2Cl_2 / 0 °C, b) O_3 /CH_2Cl_2 -MeOH / rt, c) NaH / $(CF_3CH_2O)_2POCH_2CO_2Me$ / THF / rt

References and notes

[1] Wirth T. Angew. Chem. Int. Ed. Engl. 1997;36:225-277 and references cited therein.

[2] Fujita T, Inoue K, Yamamoto S, Ikumoto T, Sasaki S, Toyama R, Chiba K, Hoshino Y, Okumoto T. J. Antibiotics 1994;47:208-215.

[3] Fujita T, Inoue K, Yamamoto S, Ikumoto T, Sasaki S, Toyama R, Yoneta M, Chiba K, Hoshino Y, Okumoto T. J. Antibiotics 1994;47:216-224.

[4] Omura S, Fujimoto T, Otoguro K, Matsuzaki K, Moriguchi R, Tanaka H, Sasaki Y. J. Antibiotics 1991;44:113-116.

[5] Omura S, Matsuzaki K, Fujimoto T, Kosuge K, Furuya T, Fujita S, Nakagawa A. J. Antibiotics 1991;44:117-118.

[6] Yamashita T, Iijima M, Nakamura H, Isshiki K, Naganawa H, Hattori S, Hamada M, Ishizuka M, Takeuchi T. J. Antibiotics 1991;44:557-559.

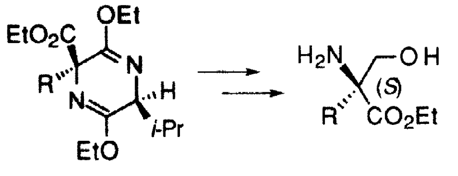
[7] Kawatsu M, Yamashita T, Ishizuka M, Takeuchi T. J. Antibiotics 1995;48:222-225.

[8] Sano S, Kobayashi Y, Kondo T, Takebayashi M, Maruyama S, Fujita T, Nagao Y. Tetrahedron Lett. 1995;36:2097-2100.

[9] Sano S, Liu X-K, Takebayashi M, Kobayashi Y, Tabata K, Shiro M, Nagao Y. Tetrahedron Lett. 1995;36:4101-4104.

[10] Moon S-H, Ohfune Y. J. Am. Chem. Soc. 1994;116:7405-7406.

[11] Decarbobenzoxylation of acid esters **5b** and **5c** afforded α-alkylserine ethyl esters **9b** {$[\alpha]_D^{24}$ -4.3 (*c* 0.41, MeOH)} and **9c** {$[\alpha]_D^{22}$ +2.3 (*c* 1.02, MeOH)}. The absolute configurations of these two compounds were determined to be *R* in comparison of their specific rotations with those of (*S*)-**9b,c**. Details of asymmetric syntheses of (*S*)-**9b,c** will be published as part of a forthcoming paper.



(*S*)-**9b**: R = $PhCH_2$, $[\alpha]_D^{24}$ +4.5 ° (*c* 0.69, MeOH)
(*S*)-**9c**: R = CH_2=$CHCH_2$, $[\alpha]_D^{21}$ -2.2 ° (*c* 0.46, MeOH)

[12] Toone EJ, Werth MJ, Jones JB. J. Am. Chem. Soc. 1990;112:4946-4952.

[13] Breznik M, Kikelj D. Tetrahedron: Asymmetry 1997;8:425-434.

[14] Canet J-L, Fadel A, Salaün J. J. Org. Chem. 1992;57:3463-3473.

[15] Fadel A, Garcia-Argote S. Tetrahedron: Asymmetry 1996;7:1159-1166.

[16] Kokotos G, Noula C. J. Org. Chem. 1996;61:6994-6996.

[17] Diastereomer ratios were confirmed by ^1H NMR analysis (200 MHz, $CDCl_3$).