ASYMMETRIC SYNTHESIS OF A CHIRAL NORBORNENE DERIVATIVE BY LIPASE-CATALYZED TRANSESTERIFICATION OF CIS-ENDO-5-NORBORNENE-2,3-DIMETHANOL AND ITS APPLICATION TO THE SYNTHESIS OF AN OPTICALLY ACTIVE TXA_2 ANTAGONIST

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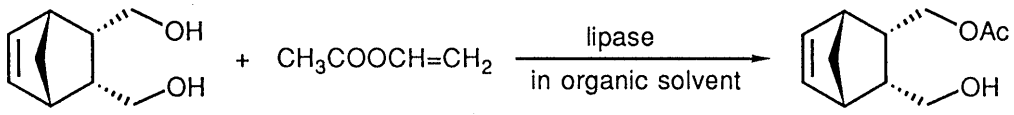
The asymmetric synthesis of chiral cis-endo-5-norbornene-2,3-dimethanol mono acetate by lipase-catalyzed transesterification, and it was used to synthesize an optically active TXA_2 antagonist.

KEYWORDS asymmetric synthesis; lipase; transesterification; cis-endo-5-norbornen-2,3-dimethanol; TXA_2 antagonist

The use of an enzyme to synthesize optically active compounds from prochiral substrates has been well appreciated.[1] In particular, the lipase-catalyzed reaction in organic media is useful because of the convenient procedures for removal of the enzyme and isolation of the product. We have reported the efficient synthesis of chiral 2-O-alkylglycerol and 1,3-propanediol derivatives by lipase-catalyzed transesterification in vinyl acetate.[2] Optically active norbornene derivatives are valuable chiral building blocks for a variety of biologically active compounds and natural products.[3] Zwanenburg reported PLE-catalyzed asymmetric hydrolysis of bicyclic esters. However, cis-endo-5-norbornene-2,3-dicarboxylic acid dimethyl ester did not show any hydrolysis.[4] We now report the asymmetric synthesis of (+)-(2S,3R)-cis-2-(acetoxymethyl)-3-(hydroxymethyl)bicyclo-[2.2.1]-hept-5-ene (2) from meso-cis-endo-5-norbornene-2,3-dimethanol (1) and vinyl acetate by lipase-catalyzed transesterification in organic solvents and its application to the synthesis of an optically pure TXA_2 antagonist (12).[5]



1 2

First, we surveyed several lipases for the transesterification with vinyl acetate.[6] The reaction was generally carried out by stirring a suspension of the meso diol, vinyl acetate, and a crude lipase in CH_2Cl_2 at room temperature.

Although lipase P showed high enantioselectivity for the transesterification of substrates such as 1,3-propanediols, lipase P gave a low optical yield in this case (entry 1 in Table I). Among the lipases tested, it showed the highest enantioselectivity but only moderate conversion to the monoester (entries 8 and 9). We further investigated the effect of solvents on the acylation with lipase GC. The reaction in diethyl ether or without solvent gave satisfactory results as shown in entries 10 and 14.[7] The absolute configuration of (+)-2 was determined by the conversion of (+)-2 into the corresponding MTPA ester.[8]

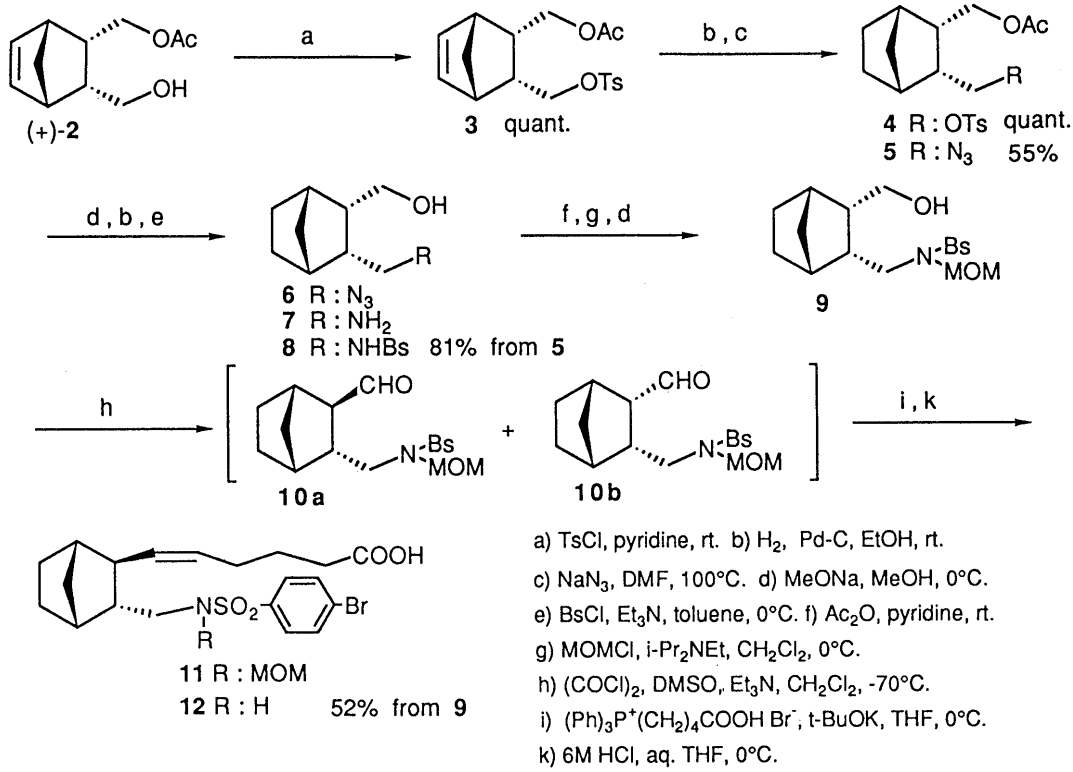
Table I. Lipase-Catalyzed Asymmetric Synthesis of Chiral (+)-(2*S*,3*R*)-*cis*-2-(Acetoxymethyl)-3-(hydroxymethyl)bicyclo[2.2.1]hept-5-ene[a)]

Entry	Lipase	Solvent	Reaction time(day)	Isolated yield(%) Diester	Monoeser	Optical yield[b)] (%ee)
1	P	CH_2Cl_2	3	26	43	33
2	SAM-II	CH_2Cl_2	3	18	37	20
3	LP	CH_2Cl_2	3.5	6	26	27
4	AK	CH_2Cl_2	3	34	51	50
5	MY	CH_2Cl_2	0.25	47	50	11[d)]
6	AY	CH_2Cl_2	0.125	88	11	72[d)]
7	GT	CH_2Cl_2	3	6	29	17
8	GC	CH_2Cl_2	3	0	54	71
9	GC[c)]	CH_2Cl_2	3	12	80	80
10	GC[c)]	$(C_2H_5)_2O$	2	25	72	95
11	GC[c)]	C_6H_6	3	17	75	79
12	GC[c)]	*t*-BuOH	3	0	35	63
13	GC[c)]	$(CH_3)_2CO$	3	3	58	84
14	GC[c)]	———	2	21	74	87

a) All reactions were carried out with substrate (2 mmol), vinylacetate (20 mmol), and lipase (200 mg) at r.t. except as otherwise cited. *b)* Optical yields were determined by HPLC analysis using a column packed with Chiralcel OD (*i*-PrOH / *n*-hexane = 1 / 100) after tosylation of the hydroxy group. *c)* Lipase GC (500 mg). *d)* (-)-(2*S*,3*R*)-*cis*-3-(Acetoxymethyl)-2-(Hydroxymethyl)bicyclo[2.2.1]hept-5-ene.

The utility of (+)-5-norbornene-2,3-dimethanol monoacetate as a chiral building block was demonstrated by the synthesis of an optically active TXA_2 antagonist (12)[5)] (Chart 1).

Treatment of (+)-2 (95%ee) with p-toluenesulfonyl chloride in pyridine followed by recrystallization from petroleum ether gave optically pure 3. The unsaturated tosylate 3 was hydrogenated in the presence of 5% Pd-C to give 2-acetoxy-3-tosyloxynorbornane (4). Compound 4 was treated with sodium azide in DMF to give the azide (5). After deacylation of 5 with sodium methoxide in methanol, hydrogenation of 6 over 5% Pd-C in ethanol gave an amino-alcohol (7). The amino-alcohol reacted with p-bromobenzenesulfonylchloride in the presence of triethylamine in toluene to afford a sulfonamide (8). Because the direct oxidation of 8 gave rise to the formation of O,N-acetal, the oxidation to an aldehyde was carried out after protection of the sulfonamide with chloromethyl methyl ether. Swern oxidation of 9 proceeded smoothly to give a crude aldehyde (10) which was a trans-cis mixture (trans/cis=5/1). When this mixture was treated with (4-carboxybutyl)triphenylphosphonium bromide and potassium t-butoxide in THF, only the trans aldehyde reacted to give 11. Removal of the MOM group by 6M HCl/aq. THF gave 12: $[\alpha]_D^{22}$ +19° (EtOH).[9,10)]



a) TsCl, pyridine, rt. b) H_2, Pd-C, EtOH, rt.
c) NaN_3, DMF, 100°C. d) MeONa, MeOH, 0°C.
e) BsCl, Et_3N, toluene, 0°C. f) Ac_2O, pyridine, rt.
g) MOMCl, i-Pr_2NEt, CH_2Cl_2, 0°C.
h) $(COCl)_2$, $DMSO$, Et_3N, CH_2Cl_2, -70°C.
i) $(Ph)_3P^+(CH_2)_4COOH\ Br^-$, t-BuOK, THF, 0°C.
k) 6M HCl, aq. THF, 0°C.

Chart 1

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6) Lipases were supplied by Amano Pharmaceutical Co. Ltd..
Origin (abbreviation): Pseudomonas sp. (P,SAM-II, AK); Candida Cylindracea (MY); Candida rugosa (AY); Chromobactrium viscosum (LP); Geotrichum candidum (GC).

7) $[\alpha]_D^{22}$ +12.6° (c 1.03, $CHCl_3$) (obtained in entry 10).

8) T. Harada, I. Wada, and A. Oku, J. Org. Chem., 54, 2599 (1989).

9) Recrystallization via the cyclohexylamine salt afforded, after removal of the amine, the optically pure 12, $[\alpha]_D^{22}$ +21.8° (EtOH) [lit.[5], $[\alpha]_D$ +20.4° (EtOH)].

10) Structures of the new compounds obtained here were determined by their spectral data (IR, ^{1}H-NMR, ^{13}C-NMR).

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