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Stereoselective Synthesis of (*4S,5R,6S*)-4-(5,6-Epoxy-6-Phenyl)-γ–Lactone.

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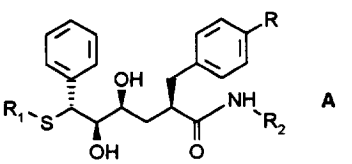
Abstract : A short (7 steps) and efficient (45% overall yield) synthesis of (4S,5R,6S)-4-(5,6-epoxy-6-phenyl)-γ-lactone, a versatile intermediate toward possible HIV-1 protease inhibitors, is described. Two examples of trans-α-benzylation of the lactonic ring followed by a regioselective opening of the epoxide (with thiopropanamide) as well as an opening of the lactone ring with L-valine (2-methoxy-ethyl)-amide are also given.

During work on HIV-1 protease inhibitors[1], we came up with the 4-epoxy-γ-lactone 7 as a common intermediate for the synthesis of dipeptide isosteres of type A. Such dipeptide mimics contain the hydroxyethylene transition-state mimetic, two aryl substituents directed toward the lipophilic pockets, P_1 and P_1', of the HIV-1 aspartic type protease[2] and a sulfur atom able to become oxidized to a sulfoxide or a sulfone functionality that can possibly replace the tetra-coordinated water molecule that bridges the two flaps (via Ile^{50}-HN) of the enzyme to inhibitors[3].



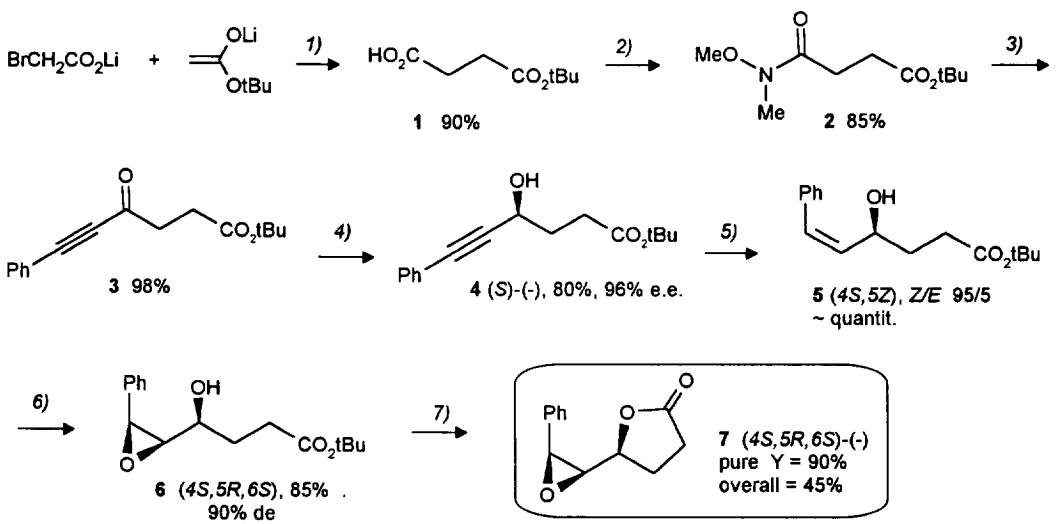
A

We report here an efficient (7 steps and ~45% overall yield), enantio- and diastereostereoselective synthesis of this versatile intermediate 7, Scheme 1, as well as two examples of *trans*-α-benzylation of the lactonic ring, a regioselective opening of the epoxide and an opening of the lactone ring with *L*-valine (2-methoxy-ethyl)-amide.

Results

Synthesis of the 4-epoxy-γ-lactone, **7** : Because the condensation of *tert*-BuOLi and succinic anhydride was known to provide the mono-ester **1** in low yield (30%)[4] the direct mono-esterification of succinic anhydride with *tert*-BuOH (*tert*-BuOH/DMAP/NEt_3 in CH_2Cl_2) was envisaged but the yield was also low (20%) and could not be improved. Therefore the mono ester **1** was finally obtained in 1 step and 90% yield from *tert*-butyl acetate and bromoacetic acid, Scheme 1.

Scheme 1



1) THF/HMPA, -78°C, 2h. *2)* $ClCO_2iBu$, N-Methylpiperidine, CH_2Cl_2 , -10°C ; N-Methylpiperidine, HCl-HN(Me)OMe. *3)* PhC_2MgBr, THF, 65°C. *4) (S)*-Alpine borane, neat, rt. *5)* H_2, 1 atm., Lindlar, quinoline/Toluene, rt. *6)* mCPBA, CH_2Cl_2, rt. *7)* tBuOK 10%, THF, 0°C.

The synthesis of the yne-ketoester **3** was achieved in two steps with a global yield of 83%. To obtain the yne-hydroxyester **4** having high enantiomeric purity and the desired *S* configuration (*cf.* below), the (*S*)-Alpine borane[5] prepared from 97% enantiomerically pure (-)-α-pinene[6] was used and the reaction conducted without solvent[7]. The isolated alcohol **4** (90%) was determined to be 90% enantiomerically pure by ^1H NMR using $Eu(hfc)_3$ and a single crystallization from hexane provided **4** in 80% yield and 96% e.e. Hydrogenation of the triple bond of compound **4** with Lindlar catalyst in toluene gave quantitatively **5** as a 95/5 *Z/E* mixture (as determined from ^1H NMR), which was then used for the next step without further purification.

As expected from the literature results, epoxidation of (*S*)-**5** using mCPBA in CH_2Cl_2 at room temperature gave the *cis* epoxide **6**[8] highly enriched in one diastereomer (95%). Product **6**, which contained about 5% of the second *cis*-isomer and 5% of both *trans*-isomers, was isolated in 85% yield and used without further

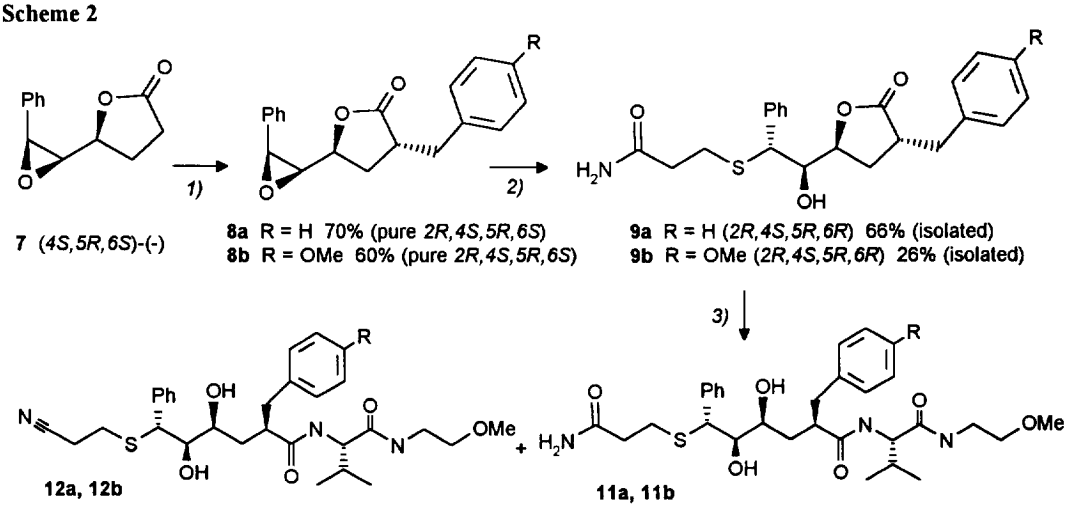
purification for the next step. Cyclisation to the lactone **7** was done using a catalytic amount of tBuOK (10%) in THF at 0°C ; the crude product isolated in 95% yield was then easily purified by crystallization from Et_2O (90% yield)

Pure (4S,5R,6S)-4-(5,6-epoxy-6-phenyl)-γ-lactone 7 was thus obtained in ~45% overall yield from inexpensive commercial starting materials.

Synthesis of dipeptide isostere precursors **9a** *and* **9b** : Alkylations of the epoxylactone **7**, Scheme 2, with Ph-CH_2I and p-$MeOC_6H_4CH_2I$ were performed using LDA in THF at -78 °C and afforded the desired *trans*-disubstituted lactones **8a** and **8b** as major compounds (*trans*/*cis* = 95/5) in satisfactory yields.

The pure (*4S,5R,6S*)-epoxide **8a** was then opened with thiopropanamide, Scheme 2, in the presence of $AlEt_3$. Thiopropanamide was obtained in 2 steps from acrylamide following a known procedure.[9] The best percentage of conversion (75%) was obtained upon addition of a 1/3 mixture of thiopropanamide and $AlEt_3$ to a 1/1 mixture of the lactone **8a** and $AlEt_3$. However the same conditions (not optimized) provided **9b** in only 35% conversion.

Scheme 2



7 (*4S,5R,6S*)-(-)

8a R = H 70% (pure *2R,4S,5R,6S*)
8b R = OMe 60% (pure *2R,4S,5R,6S*)

9a R = H (*2R,4S,5R,6R*) 66% (isolated)
9b R = OMe (*2R,4S,5R,6R*) 26% (isolated)

12a, 12b

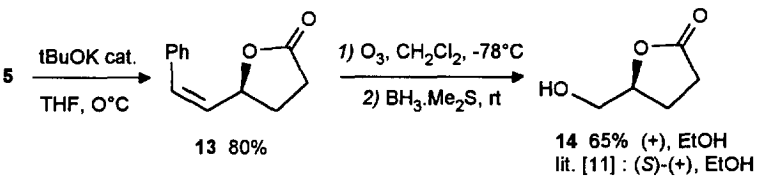
11a, 11b

1) LDA, THF, -78°C ; RCH_2I, THF, -78°C. *2)* $AlEt_3$; HS-CH_2-CH_2-$CONH_2$/ $AlEt_3$ in CH_2Cl_2, -30°C. 3) $AlMe_3$, $CHCl_3$; **10** / $AlMe_3$, $CHCl_3$, 60 °C.

Opening of the lactone ring : The lactones **9a** and **9b** were opened with *L*-valine (2-methoxy-ethyl)-amide **10** to the peptides **11a** and **11b** using $AlMe_3$ as Lewis acid[10], Scheme 2. During this conversion the corresponding nitriles **12a** and **12b** were formed as dehydration products.[11]

Determination of the S-configurations of **4** *and molecular modeling* : The *S*-configuration of compound **4** was determined by chemical correlation as shown on Scheme 3. Compound **5** was converted to the corresponding lactone **13** (80% isolated) using catalytic amount of tBuOK in the THF at 0 °C, which was subsequently transformed into the known (S)-(+) hydroxylactone 14[12] using a two step/one-pot oxydation/reduction reaction.

Scheme 3



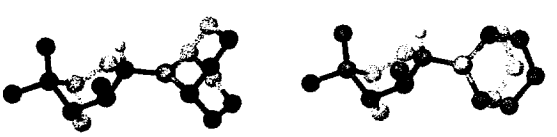
13 80%

14 65% (+), EtOH
lit. [11] : (*S*)-(+), EtOH

It thus appeared that the (*S*)-yne-hydroxyester **4** was obtained from (*S*)-Alpine borane in accord with literature results.[5] A close examination of the model[5] used to predict the configuration of the asymmetric carbon created, prompted us to re-examine it.

(*S*)-Alpine-borane was studied using the AM1 method on the CAChe Work System.[13] After an « optimized search » around the B-Ipc bond three close minima (24.1, 24.0 and 23.9 kcal/mol) were found, among them conformations **AI** (24.1 kcal/mol) and **AII** (23.9 kcal/mol) are shown on Figyre 1. It appeared that the *trans*-staggered conformation **AI** was slightly more stable than the gauche staggered conformation **AII**, but that the LUMO (localized on the boron) was lower for conformation **AII** (1.687 eV) than for conformation **AI** (1.759 eV), which hinted that conformation **AII**, already used by Midland[5] for his model of approach, might well be more reactive toward a carbonyl. One must also note that the boron atom, in both conformations, is Sp2 hybridized, as expected for monomeric trialkyl boranes. Some important geometric parameters are given in Table 1.

Figure 1



AI
H_f = -24.1 kcal/mol
LUMO 1.759 eV

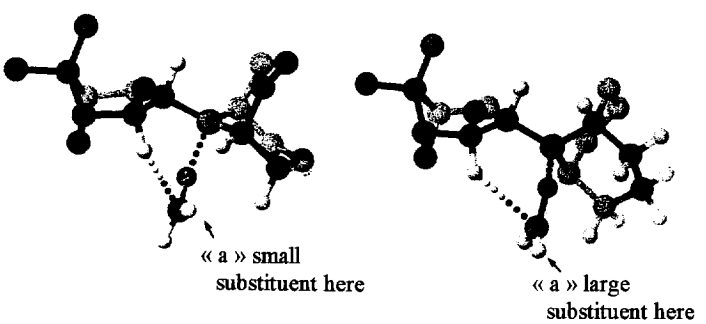
AII
H_f = -23.7 kcal/mol
LUMO 1.687 eV

Both « transition-state » candidates, **AI/CO** and **AII/CO**, were generated by manually « docking » formaldehyde (optimized by AM1) and conformer **AI** and/or **AII**. The oxygen of formaldehyde was approached along the axis of the LUMO in such a way that the β-hydrogen (to be transfered during the reduction step) was directed toward the π system of the Sp2-carbon, then « weak interactions » were introduced between B and O and H and C with distances of 2.0 Å and 2.1 Å respectively. Then, these distances being « locked », **AI/CO** and **AII/CO** were optimized. It is worth noting that, during this optimization process, the boron atom re-hybridized

toward Sp3, as expected, and the conformation around the B-Ipc bond changed in conformer **AII** while it stayed constent in conformer **AI**, Table 1 (apart from the variations due to re-hybridization). In a final step « optimized searchs » were performed on **AI/CO** and **AII/CO,** with B...O and H...C distances being varied respectively between 1.8-2.2 Å and 1.9-2.5 Å. Two « early transition-states » (**TIm$_1$** and **TIIm$_1$**) and two « late transition-states » (**TIm$_2$** and **TIIm$_2$**) are isolated and some important geometrical parameters are given on Table 1. In both cases **TIm** (early and late) was lower in energy than **TIIm** (early and late). These results are in accord with recent results[14] based on SADDLE calculations. It thus appeared that the « transition-state » built from conformer **AI** is the operative one.

A rapid glance at **TIm$_1$** , Figure 2, shows that the diastereoselectivity will be determined by interaction of one of the carbonyl substituents with the cyclo-octyl ring fixed on the boron (and not with the methyl fixed on the pinanyl group as hypothesized in the usual model[5]) and one must reasonably expect the smaller substituent to prefer position « a », *cis* to the cyclo-octyl ring. Therefore, considering that (because of its stick-like shape) the propargyl substituent is smaller than the alkyl, it was to be expected that the *S*-configuration would be formed by this approach, as observed. On the other hand examination of **TIIm1**, Figure 2, shows that the diastereoselectivity is also determined by interaction of one of the carbonyl substituent with the cyclo-octyl ring fixed on the boron but that now the « largest » group must adopt position « a » and therefore the wrong *R*-configuration would be predicted from such a model.

Figure 2



TIm1 **TIIm1**

Determination of the (4S,5R,6S)-configuration of 7 : The (*S*)-configuration at C4 being known, the (*5R,6S*)-configuration of the epoxide ring was then determined using X-ray diffraction analysis of a single crystal of 7, Figure 3.[15]

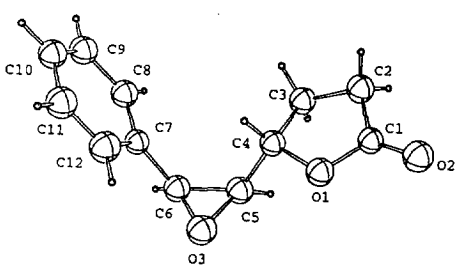
The configuration of (-, in $CHCl_3$)-epoxy-γ-lactone 7 is thus unambiguously determined to be *(4S,5R,6S)*.

Tab!e 1 : Geometrical parameters found for **AI, AII, TIm1, TIm2,TIIm1** and **TIIm2** using MOPAC (AM1) calculations[13].

	AI	**TIm1**[a]	**TIM2**[b]	**AII**	**TIIm1**[a]	**TIIm2**[b]
H_f (kcal/mol)	-24.1	-54.0	-40.9	-23.7	-44.9	-27.3
LUMO (eV)	1.759			1.687		
B-C (Å)	1.556	1.580	1.599	1.560	1.593	1.631
	1.565	1.579	1.583	1.560	1.588	1.584
	1.562	1.578	1.586	1.559	1.583	1.578
B...O(=CH_2) (Å)		1.879	1.730		1.879	1.730
H...C(= O) (Å)		2.500	1.600		2.500	1.600
C-H_β (Å)	1.132	1.134	1.174	1.132	1.135	1.285
H^1-C-B-C^1	+93°	+68°	+56°	+160°	+ 6°	-4°
B...O-C-H		-5°	-40°		+173°	-162°
B...O-C...H_β		+45°	+48°		-82°	-62°
θ_1[c]	2.5°	11°	12°	2°	11°	12°
θ_2[d]		0°	4°		0°	5°

a) "Early" transition-state ; b) « late » transition state. c) θ_1 : planarity of the Boron atom. d) θ_2 : planarity of the carbonyl of the formaldehyde.

Figure 3



Ortep plot of one molecule of **7** showing the labeling used. Elipsoids are scaled to enclose 50% of electronic density.

C4-O1-C1-C2 = -0.89° ; C12-C7-C6-O3 = -20.85° ; C6-C5-C4-O1 = +141.06°

Conclusion.

The target molecule, (*4S,5R,6S*) -7, was synthesized in 7 steps and high overall yield (~45%) from inexpensive and commercially available *tert*-butyl acetate and bromo acetic acid. Pure (*2R,4S,5R,6R*)-**9a** was then easily obtained in 2 steps and 46% yield. The lactone ring was opened with *L*-valine (2-methoxy-ethyl)-amide **10** in the presence of $AlMe_3$ to the peptide mimetics **11a** and **11b**. It is worth noting that this synthesis

will allow the introduction of various substituents in positions 2 and 6 and will give access to the other enantiomer (*2S,4R,5S,6S*) of compounds **9**.

We would like to thank Dr. T. Winkler for NMR- and Mr. S. Moss for IR-analysis and Mr. F. Raschdorf for mass spectroscopy.

Experimental

For ^1H (200 MHz when not specified) and ^{13}C (50 MHz) NMR spectra, δ in ppm are referenced to TMS, Δν and J are in Hertz, and the sign of J is not given. Melting points are uncorrected. All starting materials were commercially available research-grade chemicals purchased from Aldrich or Fluka and used without further purification. THF was distilled after refluxing over Na/benzophenone and Et_2O was distilled from $LiAlH_4$. Diisopropylamine was dried over NaOH and distilled under argon prior to use. All reactions were run under argon. Silica gel 60 F_{254} was used for TLC, and the spots were detected with UV. Flash chromatography was performed using silica gel 70-330 mesh from Merck. The X-ray diffraction experimentals are provided as Supplementary material. Semiempirical studies were carried out on a CAChe Worksystem from Oxford Molecular using AM1.

Mono-*tert*-Butylsuccinate 1 To a solution of diisopropylamine (2.0 g, 20 mmol) in THF (20 ml) at -78°C was added dropwise a 1.5 M solution of nBuLi in hexane (12.9 ml, 20 mmol), and the solution was stirred for 30 min at -78°C. *tert*-Butylacetate (2.32 g, 20 mmol) was added and the mixture was stirred for 20 min. Separately bromoacetic acid (2.78 g, 20 mmol) was added to a suspension of lithium hydride (0.19 g, 24 mmol) in THF (20 ml) at 0°C. HMPT (3.58 g, 20 mol) was added and the solution was transferred *via* canula to the ester enolate solution at -78°C. After stirring at -78°C for 2 h, a 1N HCl (60 ml) solution was added and the mixture was allowed to reach rt. The organic layer was decanted, and the aqueous phase was extracted with Et_2O (3 x 40 ml). The combined organic layers were washed with brine (100 ml) and dried over $MgSO_4$. After concentration of the solution, the crude material was purified by flash chromatography (Et_2O) to give a white solid (3.06 g, 88%) : M.p. 49-50°C; IR (CH_2Cl_2) 2920, 1700 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 10.75 (s, 1H), 2.55 (m, 4H), 1.42 (s, 9H) ; ^{13}C NMR ($CDCl_3$) δ 178.7, 171.5, 81.1, 30.1, 29.3, 28.1. Anal. calc. for $C_8H_{14}O_4$ (174.19) : C, 55.17 ; H, 8.04. Found : C, 55.00 ; H, 7.83.

N-Methoxy-N-methylamido-*tert*-butylsuccinate 2. To a solution of acid **1** (5.0 g, 28.7 mmol) in CH_2Cl_2 (150 ml) at -5°C was added successively N-methylpiperidine (3.5 ml, 28.7 mmol) and isobutylchloroformate (3.71 ml, 31.0 mmol). After stirring for 2 min, a solution of N-methylpiperidine (3.76 ml, 31.0 mmol) and methoxymethylamine chlorohydrate (3.08 g, 31.0 mmol) in CH_2Cl_2 (50 ml) was added quickly. After stirring for 1 h at -5°C and 2 h at rt, a 10% HCl solution (100 ml) was added and the mixture was allowed to reach rt. The organic layer was decanted, and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 ml). The combined organic layers were washed with brine (100 ml) and dried over $MgSO_4$. After concentration of the solution, the crude material was purified by flash chromatography (Et_2O/hexane = 40/60) to give a colorless oil (5.35 g,

85%) : TLC (Et_2O/Hexane = 40/60) R_f=0.21 ; IR (CCl_4) 1700, 1650 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 3.69 (s, 3H), 3.16 (s, 3H), 2.62 (m, 4H), 1.42 (s, 9H) ; ^{13}C NMR ($CDCl_3$) δ 172.2, 171.4, 79.4, 60.5, 29.5, 27.8, 26.7. Anal. calc. for $C_{10}H_{19}O_4N$ (217.26) : C, 55.29 ; H, 8.75. Found : C, 55.09 ; H, 8.72.

***tert*-Butyl 4-oxo-6-phenyl-5,6-hexynoate 3.** A 1M solution of ethylmagnesium bromide (18 ml, 18 mmol) in Et_2O was added dropwise to a solution of phenylacetylene (1,98 ml, 18 mmol) in THF (20 ml) at 0°C. After stirring at rt for 20 min, this solution was transferred *via* canula to a solution of amide **2** (3.55 g, 16.35 mmol) in THF (100 ml) at 0°C. The temperature was rised to 65°C for 30 min. After cooling to rt the mixture was poured into a 1M solution of NaH_2PO_4 (100 ml). The organic layer was decanted, and the aqueous phase was extracted with Et_2O (100 ml). The combined organic layers were washed with a 1M solution of NaH_2PO_4 (100 ml), with brine (100 ml) and dried over $MgSO_4$ to give a yellow powder (4.14 g, 98%). : TLC (Et_2O/Hexane = 50/50) R_f=0.67 ; M.p. 46-48°C ; IR (CH_2Cl_2) 2200, 1715 , 1660 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 7.59-7.28 (m, 5H), 2.94 (t, 2H), 2.62 (t, 2H), 1.44 (s, 9H) ; ^{13}C NMR ($CDCl_3$) δ 185.9, 171.3, 133.1, 130.8, 128.7, 120.0, 91.2, 87.5, 81.0, 40.3, 29.5, 28.1. Anal. calc. for $C_{16}H_{18}O_3$ (258.30) : C, 74.41 ; H, 6.97. Found : C, 74.38 ; H, 7.13.

***(-)-(S)-tert*-butyl 4-Hydroxy-6-phenyl-5,6-hexynoate 4.** (-)-α-Pinene 97% ee (10.32 g, 75.7 mmol) was added to a 0.5 M solution of 9-BBN in THF (134.76 ml, 67.3 mmol). The mixture was refluxed for 4 h, then was concentrated and the excess α-pinene was removed under vacuum (0.1 mmHg) at 45°C. The crude oil obtained (S-Alpine-borane) was cooled down to 0°C and **3** (12.80 g, 49.6 mmol) was added with a spatula. After stirring for 12 h, freshly distilled propionaldehyde (4.0 g, 67.3 mmol) was added. The stirring was maintained for 1h. The excess propionaldehyde was removed under vacuum (16 mmHg) and the α-pinene was distilled out (0.1 mmHg) at 45°C. The crude residue was dissolved in THF (40 ml, cooled down to 0°C and a 3 M aqueous solution of NaOH (25 ml) was added dropwise, followed by a 30% aqueous solution of H_2O_2 (25 ml). The mixture was stirred for 2 h at 40°C. The organic layer was decanted, and the aqueous phase was extracted with Et_2O (3 x 80 ml). The combined organic layers were washed with brine (100 ml) and dried over $MgSO_4$. After concentration of the solution, the crude material was purified by flash chromatography (Et_2O/hexane = 20/80) 80%, 90% ee. After crystallization in cold hexane, **4** was obtained as colorless crystals (9.02 g, 70%, 96% ee) : TLC (Et_2O/Hexane = 40/60) R_f=0.26 ; M.p. 47-49°C ; $[\alpha]_D$ = -10 (c = 1, $CHCl_3$) ; IR ($CHCl_3$) 1690 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 7.50-7.25 (m, 5H), 4.70 (q, J = 5.5, 1H), 2.54 (d, J = 5.5, 1H), 2.54 (m, 2H), 2.09 (m, 2H), 1.45 (s, 9H) ; ^{13}C NMR ($CDCl_3$) δ. 173.1, 131.5, 128.2, 128.1, 122.5, 89.4, 84.9, 80.6, 61.8, 32.6, 31.3, 27.9. Anal. calc. for $C_{16}H_{20}O_3$ (260.32) : C, 73.81 ; H, 7.74. Found : C, 74.03 ; H, 7.77.

***(-)-(S)-tert*-butyl *cis*-4-hydroxy-6-phenyl-5,6-hexenoate 5.** A solution of alcohol **4** (2.1 g, 8 mmol) in toluene (50 ml) was added to a suspension of Lindlar catalyst (0.42 g) in a 72/25 mixture of toluene/chinoline as solvent (100 ml), then H_2 (1 atm) was introduced. After 1 h, the mixture was filtered on Celite 545. The filtrate was washed with 10% HCl aqueous solution (2 x 150 ml), with brine (100 ml) and dried over $MgSO_4$. After concentration of the solution, the crude material was purified by flash chromatography (Et_2O/hexane = 40/60)

to give a colorless oil (2.1 g, ~100%) : TLC (Et_2O/Hexane = 40/60) R_f=0.15 ; $[\alpha]_D$ = -9 (c = 1.25, $CHCl_3$) ; ^1H NMR ($CDCl_3$) δ 7.34-7.24 (m, 5H), 6.53 (d, J_{cis} = 11.5, 1H), 5.65 (dd, J_{cis} = 11.5, ^3J = 9.5, 1H), 4.58 (m, 1H), 2.44 (d, J = 3.5, 1H), 2.36 (t, J = 7.5, 2H) 1.89 (m, 2H), 1.36 (s, 9H) ; ^{13}C NMR ($CDCl_3$) δ. 173.4, 136.6, 134.0, 131.3, 128.8, 128.4, 127.3, 80.6, 67.2, 32.6, 31.8, 28.1.Anal. calc. for $C_{16}H_{22}O_3$ (262.33) : C, 73.28 ; H, 8.39. Found : C, 73.16 ; H, 8.58.

***(4S,5R,6S)-tert*-butyl 5,6-Epoxy-4-hydroxy-6-phenyl hexanoate 6.** A solution of mCPBA (4.7 g, 19.2 mmol) in CH_2Cl_2 (100 ml) was added to a stirred solution of **5** (4.22 g, 16 mmol) in CH_2Cl_2 (200 ml) at rt. After over night stirring, the mixture was poured in a saturated Na_2SO_3 solution (400 ml). The aqueous phase was extracted with CH_2Cl_2 (2x100 ml). The combined organic layers were washed with brine (200 ml), dried over $MgSO_4$ and evaporated. The white powder obtained (4.95g, 82%) after purification by flash chromatography (Et_2O/Hexane = 40/60) was contaminated by 6% of the second diastereomer. TLC (Et_2O/Hexane = 40/60) R_f=0.20 ; IR ($CHCl_3$) 3550, 1700 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 7.40-7.24 (m, 5H), 4.19 (d, J = 4, 1H), 3.15 (m, 2H), 2.43 (d, J = 3, 1H), 2.15 (m, 2H), 1.66 (m, 2H), 1.35 (s, 9H) ; ^{13}C NMR ($CDCl_3$) δ.172.8, 134.8, 128.4, 128.0, 126.1, 80.5, 68.8, 62.5, 57.7, 31.2, 28.2, 28.0. Anal. calc. for $C_{16}H_{22}O_4$ (278.34) : C, 69.03 ; H, 7.90. Found : C, 69.20 ; H, 8.04.

***(-)-(4S,5R,6S)*-4-(5,6-epoxy-6-phenyl)-γ-lactone 7.** A catalytic amount of tBuOK (180 mg, 10%) was added to a stirred solution of **6** (4.5 g, 16.18 mmol) in THF (150 ml) at 0°C. After stirring for 30 min, the mixture was poured in a 10% HCl solution (200 ml). The aqueous phase was extracted with Et_2O (3 x 250 ml). The combined organic layers were washed with brine (300 ml), dried over $MgSO_4$ and evaporated. Recrystallization from Et_2O led to pure **7**. The mother liquors were purified by flash chromatography (Et_2O/Hexane = 60/40) to give a second crop of **7**. Total yield : 2.9 g (90%) : TLC (Et_2O/Hexane = 60/40) R_f=0.17 ; M.p. 85-87°C ; $[\alpha]_D$ = -79 (c = 1, $CHCl_3$) ; IR ($CHCl_3$) 2980, 1760 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 7.35 (s, 5H), 4.20 (d, J = 4.5, 1H), 3.98 (q, J = 8.5, 1H), 3.30 (dd, J = 4.5, 8.5, 1H), 2.42 (m, 2H), 1.90 (m, 2H) ; ^{13}C NMR ($CDCl_3$). δ 176.6, 134.1, 128.6, 128.3, 126.0, 79.5, 59.7, 55.4, 28.0, 23.8. Anal. calc. for $C_{12}H_{12}O_3$ (204.22) : C, 70.59 ; H, 5.89. Found : C, 70.20 ; H, 6.12.

***(-)-(2R,4S,5R,6S)*-2-Benzyl-4-(5,6-epoxy-6-phenyl)-γ-lactone 8a.** To a solution of diisopropylamine (1.08 g, 10.67 mmol) in THF (20 ml) at -78°C was added a 1.5 M solution of nBuLi in hexane (7.06 ml, 10.67 mmol) dropwise, and the solution was stirred for 30 min at -78°C. A solution of **7** (1.98 g, 9.71 mmol) in THF (80 ml) was then added. After stirring for 20 min at -78°C, freshly prepared benzyl iodide (2.54 g, 11.64 mmol) was added dropwise. The stirring was maintained at -78°C for 30 min before pouring the mixture in a 1N HCl solution (60 ml). The organic layer was decanted, and the aqueous phase was extracted with CH_2Cl_2 (2 x 200 ml). The combined organic layers were washed with brine (200 ml) and dried over $MgSO_4$. After concentration, ^1H NMR of the crude product showed a 90% d.e. Purification by flash chromatography (Et_2O/hexane = 50/50) led to pure **8a** as a single diastereomer (1.97 g, 70%) : TLC (Et_2O/Hexane = 50/50) R_f=0.21 ; colorless needles

: M.p. 106-109°C ; $[\alpha]_D$ = -40 (c = 1, $CHCl_3$); IR ($CHCl_3$) 1760 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 7.40-7.15 (m, 8H), 7.00-6.90 (m, 2H), 4.13 (d, J = 4.5, 1H), 3.65 (q, J = 8, 1H), 3.22 (dd, J = 4.5, 8, 1H), 2.82 (AB of ABX, J_{AB} = 13, J_{AX} = 4, J_{BX} = 8.5, Δν = 83, 2H), 2.87 (m, 1H), 1.92 (m, 1H), 1.64 (m, 1H) ; ^{13}C NMR ($CDCl_3$) δ 178.1, 137.5, 134.0, 128.9, 128.8, 128.6, 128.2, 127.0, 126.0, 77.7, 59.5, 55.5, 41.0, 36.3, 28.9. Anal. calc. for $C_{19}H_{18}O_3$ (294.33) : C, 77.55 ; H, 6.12. Found : C, 77.62 ; H, 6.40.

***(-)-(2R,4S,5R,6S)*- 2-(4-methoxybenzyl)-4-(5,6-epoxy-6-phenyl)-γ-lactone 8b.** As described above, 7 (1.20 g, 5.91 mmol) was reacted with LDA (5.61 mmol) before addition of 4-methoxybenzyl iodide (1.46 g, 5.91 mmol). The crude product (d.e = 90% based on ^1H NMR) was purified by flash chromatography (Et_2O/toluene = 5/95) to give **8b** as a single diastereomer (1.65 g, 60%) : TLC (Et_2O/Toluene = 5/95) R_f=0.24 ; white powder : M.p. 84-86°C ; $[\alpha]_D$ = -24 (c = 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.37-7.22 (m, 5H), 6.86-6.68 (AA'BB', 4H), 4.12 (d, J = 4.5, 1H), 3.78 (s, 3H), 3.60 (q, J = 8, 1H), 3.21 (dd, J = 4.5, 8, 1H), 2.75 (m, 3H), 1.94 (ddd, J = 7, 9, 13, 1H), 1.65 (ddd, J = 7, 9, 13, 1H) ; ^{13}C NMR ($CDCl_3$) δ 178.3, 158.5, 134.1, 129.9, 129.3, 128.6, 128.2, 126.0, 114.2, 77.8, 59.5, 55.5, 55.3, 41.1, 35.5, 28.8. Anal. calc. for $C_{20}H_{20}O_4$ (324.36) : C, 74.05 ; H, 6.21. Found : C, 74.09 ; H, 6.27.

***(-)-(2R,4S,5R,6R)*-2-Benzyl-4-[5-hydroxy-6-phenyl-6'-(3-thiopropanamide)]-γ-lactone 9a.** A 1M solution of $AlEt_3$ (6.1 ml, 6.1 mmol) in hexane was added to a suspension of **9** (0.22 g, 2 mmol) in CH_2Cl_2 (10 ml). After Stirring for 30 min a solution of **8a** (0.46 g, 1.58 mmol) and $AlEt_3$ (1.6, 1.6 ml) in anhydrous CH_2Cl_2 (5 ml) at -30°C was then added dropwise. After stirring for 3 h at -30°C, the mixture was allowed to warm up to 0°C. A saturated solution of sodium tartrate (10 ml) was added and the mixture was vigorously stirred for 1 h. The organic layer was decanted, and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 ml). The combined organic layers were washed with brine (40 ml) and dried over $MgSO_4$. Purification by flash chromatography ($CHCl_3$/EtOAc/MeOH = 60/35/5) led to pure **9a** as a white powder (0.415 g, 66%) : TLC ($CHCl_3$/EtOAc/MeOH = 60/35/5) R_f=0.14 ; M.p. 45-50°C ; $[\alpha]_D$ = -109 (c = 1, $CHCl_3$); IR ($CHCl_3$) 3500, 3400, 1760, 1670, 1590 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 7.31-7.08 (m, 10H), 6.06 (br s, 2H), 4.10 (d, J = 4 , 1H), 4.06 (d, J = 10, 1H), 3.93 (br d, J = 8.5, 1H), 3.72 (ddd, J = 10, 4, 1, 1H), 3.25 (m, 1H), 3.12 (dd, A of ABX, J_{AB} = 13, J_{AX} = 4.5, 1H), 2.66 (dd, B of ABX, J_{AB} = 13, J_{BX} = 9, 1H), 2.60 (AA'BB', 4H), 2.20 (m, 1H), 1.75 (m, 1H).; ^{13}C NMR ($CDCl_3$) δ 180.0, 174.8, 139.5, 138.4, 129.1, 129.0, 128.6, 128.4, 127.9, 126.7, 77.0, 76.8, 54.3, 40.9, 36.9, 35.3, 30.1, 27.1. Anal. calc. for $C_{22}H_{24}O_4NS$ (398.48) : C, 66.33 ; H, 6.03 ; N, 3.5. Found : C, 66.20 ; H, 6.43 ; N, 3.4.

***(-)-(2R,4S,5R,6R)*-2-(4-methoxybenzyl)-4-[5-Hydroxy-6-phenyl-6'-(3-thiopropanamide)]-γ-lactone 9b.** As described above, a 1M solution of $AlEt_3$ in hexane (3.05 ml, 3.05 mmol) was added to a suspension of **9** (0.12 g, 1.11 mmol) in CH_2Cl_2. A solution of **8b** (0.33 g, 1.0 mmol) and $AlEt_3$ (1 ml, 1mmol) in CH_2Cl_2 (5 ml) at -30°C was then added dropwise. After work up and purification by flash chromatography ($CHCl_3$/EtOAc/MeOH = 60/35/5), **9b** was obtained as a white powder (0.11 g, 26%). : TLC

($CHCl_3$/EtOAc/MeOH = 60/35/5) R_f=0.11 ; M.p. 77-79°C ; $[\alpha]_D$ = -75 (c = 1, $CHCl_3$); IR ($CHCl_3$) 3500, 3400, 1755, 1670, 1600 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 7.27 (m, 5H), 6.90 (AA'BB', 4H), 6.13 (d, 2H), 4.79 (s, 1H), 4.60 (d, J = 10, 1H), 3.92 (br d, J = 8 , 1H), 3.72 (s, 3H), 3.70 (dd, J = 10, 1, 1H), 3.18 (m, 1H), 3.04 (dd, A of ABX, J_{AB} = 14 , J_{AX} = 5, 1H), 2.85-2.32 (m, including B of ABX, 5H), 2.20 (ddd, J = 12.5, 4, 1, 1H), 1.88 (dt, J = 12.5, 8, 8, 1H) ; ^{13}C NMR ($CDCl_3$) δ 180.0, 174.3, 158.4, 139.4, 130.2, 130.0, 129.0, 128.4, 127.9, 114.0, 76.8, 55.3, 54.4, 41.1, 36.0, 35.2, 30.0, 27.1. Anal. calc. for $C_{23}H_{27}O_5NS$ (429.51) : C, 64.31 ; H, 6.33 ; Found : C, 64.09 ; H, 6.87.

Synthesis of ***L*-valine (2-methoxy-ethyl)-amide 10**.

Cbz-*L*-valine (2-methoxy-ethyl)-amide: To a solution of Cbz-*L*-valine (1000 g, 3.98 mol) in dichloromethane (4000 mL) was added dropwise isobutyl chloroformate (554.2 g, 4.06 mol) at -10 °C, followed by N-methylmorpholine (402.5 g, 3.98 mol). After stirring for 30 min at -10 °C, 2-methoxy-ethylamine (346.8 g, 4.62 mol) was added. The mixture was stirred for 2 h at ambient temperature and then partitioned between dichloromethane (1 L) and water (8 L). The aqueous layer was separated and re-extracted with dichloromethane (1 L). The organic phases were washed with 1N NaOH (8 L), 3x water (4 L) and brine (4 L), dried (Na_2SO_4), and concentrated *in vacuo*. Vigorous stirring in hexane (5 L) and filtration gave 1167 g (95 %) of Cbz-*L*-valine (2-methoxy-ethyl)-amide: M.p. 129-130 °C; ^1H-NMR ($CDCl_3$) δ 7.35 (m, 5H), 6.21 (sb, 1H), 5.40 (db, J=8, 1H), 5.11 (s, 2H), 3.97 (dd, J=8, 7, 1H), 3.44 (sb, 4H), 3.33 (s, 3H), 2.11 (oct, J=7, 1H), 0.96 and 0.92 (2d, J=7, 6H). ***L*-valine (2-methoxy-ethyl)-amide 10**. A suspension of Cbz-*L*-valine (2-methoxy-ethyl)-amide (1164 g, 3.775 mol) in methanol (5 L) was hydrogenated in the presence of Pd/C 10 % (100 g). Filtration and concentration gave 655 g (99 %) of **10** as an oil: ^1H-NMR ($CDCl_3$) δ 7.5 (sb, 1H), 3.45 (m, 4H), 3.35 (s, 3H), 3.22 (m, 1H), 2.28 (m, 1H), 1.25 (sb, 2H), 0.97 and 0.82 (2d, J=7, 6H); Anal. calc. for $C_8H_{18}N_2O_2$ (174.24) : C, 55.15; H, 10.41; N, 16.08. Found : C, 54.8 ; H, 10.5; N, 15.8.

***(2R,4S,5R,6R)*-6-(2-Carbamoyl-ethylsulfanyl)-4,5-dihydroxy-2-benzyl-6-phenyl-hexanoic acid [*(1S)*-1-(2-methoxy-ethylcarbamoyl)-2-methyl-propyl]-amide (11a)**. A solution of lactone **9a** (159.8 mg, 0.40 mmol) in 1,1,1-trichlorethane (266 µL) and trimethylaluminium (2 M solution in toluene; 600 µL, 1.20 mmol) was stirred for 1 h at room temperature (argon). In a second vessel, 2 M trimethylaluminium in toluene (960 µL, 1.92 mmol) was added to *L*-valine (2-methoxy-ethyl)-amide **10** (167 mg, 0.96 mmol) in 240 µL of 1,1,1-trichlorethane (argon). The reaction mixture was heated to 60 °C for 1 h and then cooled to room temperature. This solution was transferred *via syringe* to the first vessel and rinsed with 0.2 ml of 1,1,1-trichlorethane. The resulting mixture was heated for 10 h to 60 °C, cooled to 0 °C, and finally protonated with 534 µL of acetic acid. The slurry formed was diluted with water and ethyl acetate, and the precipitate dissolved by addition of a 10 % solution of citric acid. The aqueous phase was saturated with NaCl, separated, and re-extracted three times with ethyl acetate. The organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Chromatography (SiO_2, THF/CH_2Cl_2/toluene 1:1:1 → EtOAc → EtOAc/EtOH 9:1) yielded 57 mg (25

%) **11a** together with 48 mg (22%) of **12a** (from dehydration). **11a** : TLC (EtOAc/EtOH 9/1) R_f=0.21; ^{1}H-NMR (500 MHz, CD_3OD) δ 7.30 (m, 4H), 7.21 (m, 3H), 7.12 (m, 3H), 4.15 (d, J=9, 1H), 3.90 (d, J=8, 1H), 3.64 (dd, J=9, 2, 1H), 3.35 (m, 2H), 3.31 (s, 3H), 3.22 (m, 3H), 2.79 (m, 2H), 2.58 (m, 2H), 2.50 (m, 1H), 2.37 (t, J=7.5, 2H), 1.78 (m, 2H), 1.70 (m, 1H), 0.71 (d, J=7, 3H), 0.64 (d, J=7, 3H); FAB MS $(M+1)^+$=574.

12a : ***(2R,4S,5R,6R)*-6-(2-Cyano-ethylsulfanyl)-4,5-dihydroxy-2-benzyl-6-phenyl-hexanoic acid [*(1S)*-1-(2-methoxy-ethylcarbamoyl)-2-methyl-propyl]-amide,** TLC (THF/CH_2Cl_2/toluene 2:2:1) R_f=0.42; IR (KBr)] 3420bs, 3312bs, 2959m, 2927m, 2250w, 1646s, 1615s, 701m cm^{-1} ; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.4-7.1 (m, 8H), 7.05 (d, J=8, 2H), 6.16 (d, J=8, 1H), 5.93 (t, J=6, 1H), 4.14 (d, J=9, 1H), 4.03 (m, 1H), 3.63 (db, J=9, 1H), 3.4-3.3 (m, 6H), 3.34 (s, 3H), 3.09 (sb, 1H), 2.88 (dd, J=13, 8, 1H), 2.70 (m, 1H), 2.64 (m, 3H), 2.42 (t, J=7, 2H), 1.96 (oct, J=7, 1H), 1.85 (m, 1H), 1.72 (m, 1H), 0.75 (d, J=7, 3H), 0.71 (d, J=7, 3H); FAB MS $(M+1)^+$=556.

***(2R,4S,5R,6R)*-6-(2-Carbamoyl-ethylsulfanyl)-4,5-dihydroxy-2-(4-methoxy-benzyl)-6-phenyl-hexanoic acid [*(1S)*-1-(2-methoxy-ethylcarbamoyl)-2-methyl-propyl]-amide 11b** As described above, a solution prepared from *L*-valine (2-methoxy-ethyl)-amide **10** (260 mg, 1.49 mmol) and trimethylaluminium (2 M in toluene; 1.49 ml, 2.98 mmol) in 1,1,1-trichlorethane (373 µL) was added *via syringe* to a solution of lactone **9b** (267 mg, 0.621 mmol) and trimethylaluminium (932 µL , 1.86 mmol) in 1,1,1-trichlorethane (413 µL). After rinsing with 0.3 ml of 1,1,1-trichlorethane, the mixture was heated to 60 °C for 9 h, cooled to room temperature, and diluted with 3 mL of dichloromethane. Protonation at 0 °C by a solution of 828 µL of acetic acid in 1 mL of dichloromethane, aqueous work-up and chromatography (SiO_2, EtOAc/toluene 7:1 → EtOAc → EtOAc/EtOH 19:1 → EtOAc/EtOH 10:1) yielded 68 mg (18 %) **11b** together with 112 mg (31 %) **12b** (from dehydration). **11b** : TLC (EtOAc/EtOH 10:1) R_f=0.14; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.3 (m, 5H), 7.03 (m, 2H), 6.75 (m, 2H), 7.0, 6.5, 6.23, 6.05, 5.97, 5.80 and 5.24 (b, 4 HNCO), 4.22 and 4.19 (2d, J=9, 1H), 3.97 (dd, J=7, 9, 1H), 3.87 (m, 1H), 3.75 (s, 3H), 3.67 and 4.33 (2m, 1H), 3.4-3.2 (m, 5H), 3.31 (s, 3H), 2.95-2.55 (m, 6H), 2.44 (m, 1H), 1.93 (m, 1H), 1.85 (m, 1H), 1.78 (s, 1H), 1.73 (m, 1H), 0.67 and 0.62 (2d, J=7, 3H), 0.58 and 0.55 (2d, J=7, 3H); FAB MS $(M+1)^+$=604.

12b : ***(2R,4S,5R,6R)*-6-(2-Cyano-ethylsulfanyl)-4,5-dihydroxy-2-(4-methoxy-benzyl)-6-phenyl-hexanoic acid [*(1S)*-1-(2-methoxy-ethylcarbamoyl)-2-methyl-propyl]-amide**, TLC (EtOAc/toluene 7:1) R_f=0.19; IR (KBr) 3410bs, 3317bs, 2961m, 2932m, 2251w, 1647s, 1614s, 1512s, 1248s, 1115m, 1034m, 704m cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 5H), 6.95 (d, J=9, 2H), 6.76 (d, J=9, 2H), 6.24 (d, J=9, 1H), 5.97 (t, J=5, 1H), 4.15 (d, J=9, 1H), 4.04 (dd, J=6, 8, 1H), 3.77 (s, 3H), 3.63 (d, J=9, 1H), 3.4-3.3 (m, 5H), 3.33 (s, 3H), 3.14 (sb, 2H), 2.81 (m, 1H), 2.63 (m, 4H), 2.42 (t, J=7.5, 2H), 1.96 (m, 1H), 1.83 (m, 1H), 1.71 (m, 1H), 0.75 (d, J=7, 3H), 0.72 (d, J=7, 3H); FAB MS $(M+1)^+$=586.

***(+)-(4S,Z)*-γ-lactone 13**. A catalytic amount of tBuOK (100 mg, 10%) was added to a stirred solution of **5** (2.76 g, 10.5 mmol) in THF (50 ml) at 0°C. After 30 min, the mixture was poured on 10% HCl solution (100 ml). The aqueous phase was extracted with Et_2O (3 x 150 ml). The combined organic layers were washed with brine (200 ml), dried over $MgSO_4$ and evaporated. Purification by flash chromatography (Et_2O/Hexane = 40/60) led to pure **13** as a white powder : 1.58 g (80%) : TLC (Et_2O/Hexane = 40/60) R_f=0.24 ; M.p. 45-47°C ; $[\alpha]_D$ = + 227 (c = 1, $CHCl_3$) ; IR ($CHCl_3$) 1760 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 7.38-7.25 (m, 5H), 6.80 (d, J = 11.5, 1H), 5.72 (d, J = 11.5, 9, 1H), 5.30 (q, J = 6, 1H), 2.68-1.81 (m, 4H) ; ^{13}C NMR ($CDCl_3$). δ 177.0, 135.7, 134.7, 129.0, 128.8, 128.0, 126.3, 76.8, 37.4, 29.0. Anal. calc. for $C_{12}H_{12}O_2$ (188.22) : C, 76.56 ; H, 6.42. Found : C, 76.70 ; H, 6.38.

(+)-(*S*)-4-Hydroxymethyl-γ-lactone 14. Ozone was bubbled for 15 min through a solution of **12** (0.2 g, 1.06 mmol) in CH_2Cl_2 (10 ml) at -78°C. The excess of ozone was removed with argon at rt and BH_3-Me_2S (0.32 ml, 3.18 mmol) was then added slowly. After over night stirring, a 5% HCl solution (0.5 ml) was added carefully. After vigorous stirring for 1 h, solid $NaHCO_3$ was added until the pH of the solution became basic. The mixture was dried over $MgSO_4$ and filtered. After concentration of the solution and purification by chromatography (Et_2O/hexane = 50/50), pure **14** was obtained as a colorless liquid (79 mg, 65%) whose NMR spectra was in accord with the literature [11] : $[\alpha]_D$ = + 27 (c = 2.66, EtOH) (lit. $[\alpha]_D$ = + 31 (c = 2.66, EtOH) ; ^1H NMR ($CDCl_3$) δ 4.66 (m, 1H), 4.06-3.55 (m, 3H), 2.8-2 (m, 4H).

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