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Asymmetric Epoxidation of Allylic Alcohol by the Modified Sharpless Reagent

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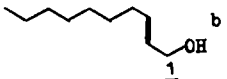
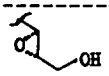
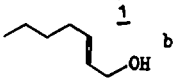
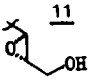
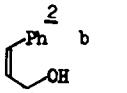
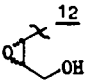
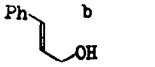
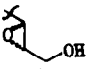
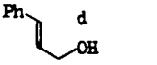
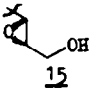
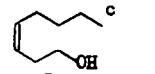
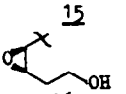
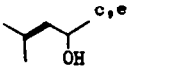
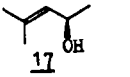
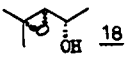
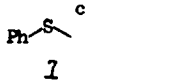
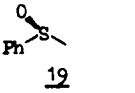
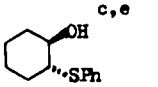
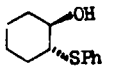
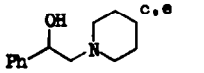
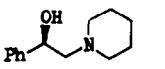
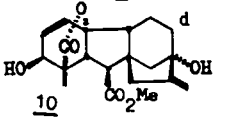
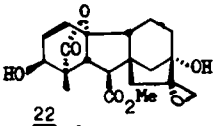
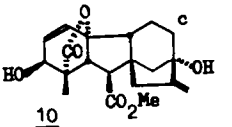
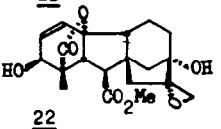
Abtract: The modified Sharpless reagent can be applied to the epoxidation of various allylic alcohols just as the Sharpless reagent does, but the reaction time was greatly reduced. Methyl gibberellate 10, which failed to give the normal epoxidation product on treatment with Sharpless reagent, readily yielded the corresponding epoxy derivative 22 when the modified Sharpless reagent was used.

The asymmetric epoxidation of allylic alcohols by using Sharpless reagent [$Ti(OiPr)_4$, (+)- or (-)-diethyl tartrate(DET) and tert-butyl hydroperoxide(TBHP)][1] has been widely used in the syntheses of chiral natural products.[2] A drawback of this epoxidation is that a rather long reaction time is usually required, sometimes up to several weeks. So its application was limited to some extent.[3] Recently we have reported that the addition of a catalytic amount of calcium hydride and silica gel to the Sharpless reagent can dramatically reduce the reaction time.[4] In order to extend the scope of the modified method, we further investigated the asymmetric epoxidation of various substrates, as shown in Table 1.

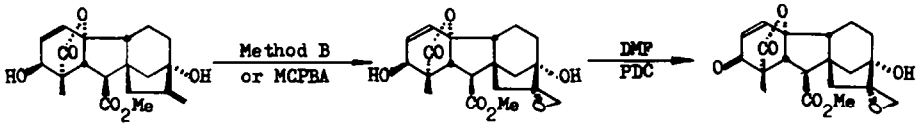
The time reducing effect of the modified Sharpless reagent on the asymmetric epoxidation of aliphatic allylic alcohols are most attractive. For example, the epoxidation of the aliphatic allylic E-alcohols 1 and 2 shown in Table 1 was completed within one hour, while epoxidation by using Sharpless reagent usually needs many hours.[4] The reaction time of Z-cinnamyl alcohol 3 was much longer than that of E-cinnamyl alcohol.[4] Since the epoxidation reaction was usually incomplete in case of E- or Z-cinnamyl alcohols, the chemical yield is often poor. Furthermore, during the epoxidation of cinnamyl alcohols the epoxy opened product would increase on prolonged reaction time. In the epoxida-

Table 1: Asymmetric epoxidation of allylic alcohols by Sharpless reagent and modified Sharpless reagent

Entry	Allylic alcohols	Mothod[a]	Time(h)	Epoxy alcohols	yield(%)	[α]	ee%
1	 1	B	1	 11	71	-27.2°	95
2	 2	B	1	 12	76	-29.7°	95
3	 3	A	120	 13	56	-30.7°	85[5]
		B	48		50	-30.0°	85
4	 4	A	1.2	 14	44	-51.7°	95[5]
		B	0.75		54	-49.5°	89[19]
5	 5	B	0.75	 15	60	+51.2°	92
6	 6	A	144	 16	50	+4.8°	60
		B	24		60	+4.6°	60
7	 7	B	6	 17	25	-4.3°	94
				 18	24	-2.6°	96
8	 7	C	12	 19	90	+132°	91[6]
		D	5		90	+12.5°	9
9	 8	C		 20		+40.8°	20[7]
		D	6		48	+4.3°	2.1
10	 9	E	2	 21	37	-51.2°	97[8]
		F	0.5		30	-26.7°	51
11	 10	A	30d	 22	5		
		B	30h		81		80
12	 10	A	30d	 22	0		
		B	96h		71		75

a.Method A: Epoxidation using Sharpless reagent[$Ti(OiPr)_4$:DET=1:1.2][1]; Method B: Addition of 5-10 mol% of CaH_2 and 10-15 mol% silica gel to the Sharpless reagent[4]; Method C: Modified method of Kagan[6]; Method D: Addition of 5-10 mol% of CaH_2 and 10-15mol% of silica gel to the Kagan system; Method E: Sharpless method [$Ti(OiPr)_4$:DIPT=1:2][8]; Method F: Addition of 5-10 mol% of CaH_2 and 10-15 mol% silica gel to Sharpless system[$Ti(OiPr)_4$:DIPT=1:2]. b. L-(+)-diethyltartrate was used. c. D-(-)-DIPT was used. d. L-(+)-DIPT was used. e. Kinetic resolution.

tion of the homoallylic alcohol 5, similar chemical and optical yields were obtained in comparison with Sharpless method[9], but the reaction time was greatly reduced. In kinetic resolution[10] of racemic allylic alcohol 6, the steric hindrance in β-carbon seemed to be of no influence and the reaction time was also reduced. The modified Sharpless reagent could reduce the oxidation time of sulfide 7 to the chiral sulfoxide 19 with excellent chemical yield, but the optical yield was much lower than that obtained by Kagan's modified method[6]. Compared with the results of Sharpless Method[7,8], lower optical yield was also observed from the kinetic resolution of racemic β-thioalcohol 8 and β-aminoalcohol 9. Our experiment with the natural product methyl gibberellate 10 turned out to be quite interesting. In the epoxidation of 10 using Sharpless reagent, the starting material was not completely consumed even after 30 days, while epoxidation could be accomplished within 30 hours in 80% yield by our modified reagent and the reaction was regiospecific, that is, the epoxidation takes place only on the tertiary allylic alcohol moiety, not on the secondary allylic alcohol one. The extraordinary epoxidation on the tertiary allylic alcohol moiety[11] which has greater steric hindrance, might result from the smaller steric hindrance at $C_{16,17}$ double bond in 10. To confirm the site of this epoxidation, 22 was oxidized with PDC, and the expected compound of α,β-unsaturated ketone 23 was indeed obtained (Scheme 1). The epoxidation of 10 using the modified Sharpless reagent



10 22 23

with L-(+)-DIPT or D-(-)-DIPT as ligand give the same product 22, which was coincident with that obtained from epoxidation with MCPBA. This suggests that the attacking direction of the "peroxide" on the double bond was determined by the steric hindrance of double bond rather than by the structure of the Ti(IV) complex. In addition , on treatment with the Sharpless reagent 10 afforded a less polar product, in which neither epoxy nor methylcarbonyl group exists. Similar disappointing results[12] have been reported from epoxidation of allylic alcohols containing the terminal ester group with the Sharpless reagent. On the contrary, the ester group in 10 survived epoxidation by our modified Sharpless reagent as shown in Table 1 (Entry 11 and 12).

Experimental

All m.ps were uncorrected. All reactions were carried out under dry nitrogen. All additions were made by syringes. Reactions were monitored by using thin layer chromatography (tlc). The silica gel used in epoxidation and for flash chromatography was silica gel H (10-40μ) which was produced by Qingdao Chemical Plant, China. IR spectra were measured on a Shimadzu 440 spectrometer. ^{1}H-NMR spectra were recorded on Varian EM-360A (60MHz) spectrometer, using TMS as internal standard. MS spectra were conducted on a Finnigan 4021 GS-MS instrument. The optical rotations were measured on a Autopol spectrometer III automatic polarimeter. Elemental analyses were performed by Analytical Department of this Institute. Dichloromethane (A.R) was distilled from calcium hydride. Diethyl tartrate (DET) was prepared from tartaric acid and diisopropyl tartrate (DIPT) was obtained from Aldrich Chemical Co.. Titanium(IV) isopropoxide was distilled under reduced pressure and stored under inert atmosphere. 85% tert-butyl hydroperoxide (TBHP) was obtained from Merk-Schuchardt Co., which was further purified according to the literature.[13] Calcium hydride was obtained from Fluka-Garantie Co..

All substrates were prepared by ourselves, except for (E)-3-phenyl-2-propen-1-ol 4. (E)-2-Decen-1-ol 1 was prepared from coupling of heptyl bromide with dilithium propargyloxide followed by reduction with lithium aluminium hydride.[14] Preparation of (E)-2-hepten-1-ol 2 is the same as described for 1. (Z)-3-Phenyl-2-propen-1-ol 3 was prepared from bromobenzene by Pd-catalyzed coupling with propargyl alcohol,[15] followed by hydrogenation with P-2Ni. (Z)-3-Octen-1-ol 5 was prepared from coupling of dilithium 3-butynoxide with butyl bromide, followed by hydrogenation with P-2Ni.[16] (±)-4-Methyl-3-penten-2-ol 6 was prepared from methylmagnesium iodide and 3-methyl 2-buten-1-al. Methyl phenyl sulfide 7 was prepared from the reaction of phenylthiol with methyl iodide.[17] (±)-Trans-2-phenylthio cyclohexane 8 was prepared from the epoxidation of cyclohexene with MCPBA followed by addition of sodium benzenethiolate. (±)-1-Phenyl-2-(1-piperidyl)-ethanol 9 was prepared from the epoxidation of phenylethene with MCPBA followed by addition of piperidylmagnesium bromide.[18] Methyl gibberellate 10 was prepared from the esterification of gibberellic acid (GA_3) with CH_2N_2.

Preparation and analysis of Mosher's ester

To a solution of 100 μL of pyridine and 20 mg of a purified alcohol in 1 mL of CCl_4 in a 5 mL of Sharp-bottomed flask was added 1 mL of the solution of (50 mg/mL) of (+)-α-methoxy-β-(trifluoromethyl)phenylacetyl chloride

(MTPA chloride).[19] After a few seconds, pyridinium chloride precipitated. After standing at room temp. for 24 h, the reaction mixture was poured into water. The organic layer was washed successively with 5% HCl solution, 1 M NaOH solution, water, and brine. After being dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure. The crude product was purified on the preparative thin layer chromatography. The purified Mosher's ester was analyzed on ^{19}F-NMR spectra or on GC.

(2S,3S)-2,3-Epoxydecan-1-ol 11

To a mixture of 1.5 mL (5 mmol) of $Ti(OiPr)_4$, 20 mg (0.5 mmol) of CaH_2 and 30 mg of silica gel in 30 mL of dry CH_2Cl_2 was injected 0.9 mL (6 mmol) of L-(+)-diethyl tartrate (DET) via syringe under N_2 at -20 °C. After 10 min (E)-2-decen-1-ol 1 (630 mg, 5 mmol) was injected. The reaction mixture was stirred for another 10 min. 1.1 mL (10 mmol) of anhydrous TBHP (9.45 M) was then injected at -40 °C. After 1 h, 12 mL of 10% aqueous tartaric acid solution was added at -20 °C. Stirring was continued at room temp. until the aqueous layer became clear. After separation and concentration in vacuum, the residue was diluted with 30 mL of diethyl ether, and then 12 mL of 1 M NaOH solution was added, and stirred at 0 °C for 30 min. After separation, the organic layer was washed successively with 5% aq. HCl solution, water, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuum followed by purification using flash column chromatography on silica gel (Petroleum ether-ethyl acetate 85:15) afforded 470 mg of a colourless liquid 11 in 71% yield. $[\alpha]_D^{15}$-27.2° (c, 0.2, $CHCl_3$) [lit[15] $[\alpha]_D$-27° (c, 1.3, $CHCl_3$)] IR (thin film) νmax 3300 (OH), 1250 (epoxy) cm^{-1}; ^{1}H-NMR (CCl_4) δ: 0.85(3H, t, J=6Hz, CH_3), 1.26 [10H, br, $(CH_2)_5$], 1.41(2H, m, CH_2-C-O), 2.03(1H, s, OH), 2.80 (2H, m, epoxy), 3.63 (2H, m, HO-CH_2) ppm; MS m/z: 173 (M^++1, 29%), 155 (M^+-OH, 23%), 127 ($C_7H_{15}CO$, 1%), 137 (155-H_2O, 99%), 97 (C_7H_{15}, 3%), 95 (97%), 81 (100%).

(2S,3S)-2,3-Epoxyheptan-1-ol 12

(E)-2-Hepten-1-ol 2 (520 mg, 5 mmol) was subjected to epoxidation with a system of $Ti(OiPr)_4$ (1.5 mL, 5 mmol), 20 mg of CaH_2, 30 mg of silica gel, L-(+)-DET (0.9 mL, 6 mmol) and TBHP (1.1 mL, 10 mmol) in 30 mL of CH_2Cl_2. The reaction mixture was stirred at -40 °C for 1 h. After working up with 10% aq. tartaric acid solution, evaporation of the solvent in vacuum provided a slightly yellow oil, which was treated with 1 M aq. NaOH solution in diethyl ether for 30 min[1]. The organic layer was separated, and washed successively with 5% aq. HCl solution, water, and brine, and dried over Na_2SO_4.

Removal of the solvent in vacuum followed by purification with flash column chromatography on silica gel gave 450 mg of a colourless liquid 12 in 76% yield. $[\alpha]_D^{15}$-29.9° (c, 0.64, $CHCl_3$) [lit[15] $[\alpha]_D$-29.7° (c, 2.0, $CHCl_3$)]; IR (thin film) νmax: 3400 (OH), 1240 (epoxy), 800 cm^{-1}; ^{1}H-NMR (CCl_4) δ: 0.85 (3H, t, J=6Hz, CH_3), 1.26 [4H, br, $(CH_2)_2$], 1.4 (2H, br, CH_2-C-O), 2.03 (1H, m, OH), 2.8 (2H, m, epoxy), 3.6 (2H, m, CH_2-O) ppm. MS m/z 131 (M^++1, 20%), 113 (M^+-17, 6.7%), 95 (113-H_2O, 100%), 67 (82%), 57 (C_4H_9,33%).

(2S,3R)-2,3-Epoxy-3-phenylpropan-1-ol 13

The epoxidation as described for 11 was performed in this case at -40 °C for 4 h on 1.64 g (12 mmol) of (Z)-3-phenylpropen-1-ol 3 in 100 mL of CH_2Cl_2 using 3.4 g (12 mmol) of $Ti(OiPr)_4$, 2.96 g (14.4 mmol) of L-(+)-DET, 40 mg of CaH_2, 60 mg of silica gel, and 3.1 mL (24 mmol) of TBHP (7.78 M). After 4 h the reaction was quenched with 40 mL of acetone containing 7 mL of water.[10] Stirring was continued at room temp. until the reaction solution became clear. The solution was diluted with diethyl ether, and washed successively with 5% aq. HCl solution, water, and brine. The extract was dried over anhydrous Na_2SO_4, and concentrated to dryness under reduced pressure to give the crude product which after purification by flash column chromatography on silica gel (cyclohexane-ethyl acetate 85:15) afforded 920 mg of a colourless oil 13 in 50% yield (90% ee by analysis of the ester derived from (+)-MTPA chloride), $[\alpha]_D^{20}$-30° (c, 0.30, $CHCl_3$) [lit[15] $[\alpha]_D$-30.7° (c, 1.5, $CHCl_3$)]. IR (thin film) νmax: 3400 (OH), 1600, 1500 (C_6H_5), 1260 (epoxy), 1050 (C-O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.18 (1H, br, OH), 3.30 (3H, m, CH_2-O, epoxy), 3.98 (1H, d, epoxy) 7.23 (5H, br, C_6H_5) ppm; MS m/z 151 (M^++1, 4%), 149 (M^+-1, 3%), 133 (M^+-17, 100%), 119 (M^+-CH_3O, 27%), 105 (64%), 91 (90%), 74 (47%). found: C, 71.98; H, 6.71. Calc. for $C_9H_8O_2$: C, 71.80; H, 6.61.

(2S,3S)-2,3-Epoxy-3-phenylpropan-1-ol 14

The reaction as described for 13 was carried out in this case at -40 °C on 1.34 g (10 mmol) of (E)-3-phenyl-2-propen-1-ol 4 in 80 mL of CH_2Cl_2 using 2.84 g (10 mmol) of $Ti(OiPr)_4$, 2.52 g (12 mmol) of L-(+)-DET, 40 mg of CaH_2, 60 mg of silica gel, and 2.6 mL (20 mmol) of TBHP (7.78 M). After 0.75 h working up in the way as described above for 13, purification by flash column chromatography on silica gel (cyclohexane-acetone 85:15) and recrystallization from cyclohexane-acetone afforded colourless crystals 14 810 mg, 54% yield, 95% ee by analysis of the ester derived from (+)-MTPA chloride). m.p 51-52 °C (lit[21] 51.5-53 °C). $[\alpha]_D^{13}$-51.7° (c, 1.2, $CHCl_3$) [lit[21] $[\alpha]_D^{25}$-49.5° (c, 2.4, $CHCl_3$). IR νmax: 3350 (OH), 1600 (C_6H_5), 1260 (epoxy), 1050 (C-O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) : 2.47 (1H, br, OH), 3.0 (1H, m,

epoxy), 3.72 (3H, m, CH_2-O, epoxy), 7.15 (5H, br, C_6H_5) ppm; MS m/z 150 (m^+, 5%), 133 (M^+-17, 12%), 120 (M^+-CH_2O, 32%), 91 (66%), 79 (56%), 42 (100%). Found: C, 71.90; H, 6.69. Calc. for $C_9H_8O_2$: C, 71.98; H, 6.71.

(2R,3R)-2,3-Epoxy-3-phenylpropan-1-ol 15

The reaction as described for 14 was carried out in this case using D-(-)-diisopropyl tartrate (DIPT) instead of L-(+)-DET. After working up as described for 14, 900 mg of colourless crystals 15 were obtained in 60% yield (95% ee by analysis of the ester derived from (+)-MTPA chloride). m.p 51-52 °C. $[\alpha]_D^{13}$+51.2° (c, 2.6, $CHCl_3$). IR (KCl) νmax: 3350 (OH), 1600 (C_6H_5), 1260 (epoxy), 1050 (C-O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 2.45 (1H, br, OH), 3.0 (1H, m, epoxy), 3.70 (3H, m, CH_2-O, epoxy), 7.20 (5H, br, C_6H_5) ppm; MS m/z 150 (M^+, 7%), 133 (M^+-17, 15%), 120 (M^+-CH_2O, 20%), 42 (100%).

(3R,4S)-3,4-Epoxyoctan-1-ol 16

A mixture of 240 mg (1.67 mmol) of (Z)-3-octen-1-ol 5, 0.59 mL (2.0 mmol) of $Ti(OiPr)_4$, 0.49 mL (2.4 mmol) of L-(+)-DIPT, 10 mg of CaH_2, 20 mg of silica gel in 15 mL of dry CH_2Cl_2 was stirred at -20 °C under nitrogen. After 10 min, 0.52 mL (4 mmol) of TBHP (7.78 M) was added. The reaction mixture was stored at -40 °C for 48 h followed by treatment with 6 mL of 10% aq. tartaric acid solution. Working up in the usual way gave a colourless liquid 16 (155 mg, in 60% yield, in 60% ee by analysis of the ester derived from (+)-MTPA chloride). $[\alpha]_D^{24}$+4.6° (c, 1.8, EtOH). IR (thin film) νmax: 3300 (OH), 1260 (epoxy), 1050 (C-O), 720 cm^{-1}; ^{1}H-NMR (CCl_4) δ: 0.86 (3H, t, J=4Hz, CH_3), 1.21 [6H, m, $(CH_2)_3$], 1.69 (2H, m, CH_2-C-O), 2.80 (2H, m, epoxy), 3.73 (1H, s, OH), 3.60 (2H, t, J=6Hz, CH_2-O) ppm; MS m/z: 145 (M^++1, 9%), 127 (M^+-17, 64%), 115 (M^+-CHO, 27%), 99 (M^+-C_4H_5O, 45%), 85 (M^+-C_3H_7O, 18%), 57 (C_4H_9, 100%).

Kinetic resolution of (±)-4-methyl-3-penten-2-ol 6

The kinetic resolution reaction of 6 was performed by using 1.28 mL (8.6 mmol) of $Ti(OiPr)_4$, 1.08 mL (10 mmol) of L-(+)-DIPT, 860 mg (8.6 mmol) of (±)-4-methyl-3-penten-2-ol 6, 40 mg of CaH_2, 60 mg of silica gel and 0.66 mL (0.6 eq., 7.78 M) of TBHP. After the reaction mixture being stored at -40 °C for 6 h, the reaction was quenched with 3 mL of water at room temp. After 60 min of vigorous stirring at room temp, the reaction mixture was filtered through silica gel (100-200 mesh). The organic phase was separated and the water phase extracted with ether. The combined ether phase was washed successively with 5% HCl solution, water, and brine. After being dried over Na_2SO_4, evaporation of the solvent afforded a crude mixture,

which was separated by flash column chromatography on silica gel. From the petroleum ether-ethyl acetate (92.5:7.5) elutate, 214 mg of a colourless liquid 17 in 25.4% yield was obtained. $[\alpha]_D^{29}$-4.3° (c, 0.79, EtOH), [lit[21] $[\alpha]_D^{22}$-4.2° (c, 5.51, EtOH)]; IR (thin film) νmax 3400 (OH), 1620 (C=C), 1375 [C(CH_3)$_2$] cm^{-1} ^{1}H-NMR (CCl_4) δ: 1.10 (3H, d, J=6Hz, CH_3), 1.65 (6H, s, 2xCH_3), 3.14 (1H, s, OH), 4.37 (1H, dd, J=6Hz, J=8Hz, CH-O), 5.12 (1H, d, J=8Hz, =CH) ppm; MS m/z: 100 (M^+, 100%), 83 (M^+-17, 15%). The petroleum ether-ethyl acetate (85:15) elutate gave 210 mg of a colourless liquid 18 in 24% yield. $[\alpha]_D^{29}$-2.6° (c, 1.39, EtOH). IR (thin film) νmax: 3400 (OH), 1375 [C(CH_3)$_2$], 1250 (epoxy), 1060 (C-O) cm^{-1}; ^{1}H-NMR δ: 1.10 (3H, d, J=6Hz, CH_3), 1.24 (6H, s, 2xCH_3), 2.06 (1H, s, OH), 2.92 (1H, d, J=8Hz, epoxy), 3.46 (1H, m, CH-O) ppm; MS m/z: 116 (M^+, 5%), 72 (M^+-C_2H_5O, 30%), 45 (C_2H_5O, 60%), 59 (C_3H_7O, 100%).

(+)-Methyl phenyl sulfoxide 19

To a mixtue of 0.79 mL (2.5 mmol) of Ti(OiPr)$_4$, 1.32 mL (5.0 mmol) of L-(+)-DIPT, 20 mg of CaH_2, and 30 mg of silica gel in 30 mL of dry CH_2Cl_2 was added 0.05 ml of H_2O by a microsyringe at room temp. under nitrogen. After stirring for 30 min at room temp., 310 mg (2.5 mmol) of methyl phenyl sulfide 7 was added. The reaction mixture was cooled to -20 °C and 0.7 mL (5 mmol) of TBHP (7.78 M) was added. After 5 h working up as Kagan's procedure[6] gave the crude product which, on flash column chromatography on silica gel (cyclohexane-acetone 1:1), afforded 300 mg of a slightly yellow oil 19 in 90% yield. $[\alpha]_D^{28}$+12.5° (c, 1.1, CH_2Cl_2) [lit[6] $[\alpha]_D$+130° (c, 0.65, CH_2Cl_2)]; IR (thin film) νmax: 3100 (C_6H_5), 1210 (S=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ: 2.70 (3H, s, CH_3), 7.54 (5H, br, C_6H_5) ppm; MS m/z: 140 (M^+, 8%), 139 (M^+-1, 10%), 125 (M^+-15, 10%), 124 (m^+-16, 90%), 123 (M^+-17, 100%), 77 (C_6H_5, 16%).

Kinetic resolution of (±)-trans-2-phenylthiocyclohexanol 8

The reaction was performed on a 2.4 mmol scale using 0.79 mL (2.5 mmol) of Ti(OiPr)$_4$, 1.32 mL (5.0 mmol) of L-(+)-DIPT, 0.05 mL of water, 15 mg of CaH_2, 30 mg of silica gel and 0.28 mL (1.3 mmol, 0.6eq.) of TBHP (7.78 M). After 6 h (60% conversion), working up as described above for 19 provided 240 mg of a yellowish oil 20 in 45% yield. $[\alpha]_D^{28}$+4.3° (c, 2.32, CH_2Cl_2) [lit[7] $[\alpha]_D$+20°], IR (thin film) νmax: 3400 (OH), 1590 (C_6H_5), 1420, 1250, 1100, 1060 (C-O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.21 [4H, m, (CH_2)$_2$], 1.66-1.97 (4H, m, O-C-CH_2, S-C-CH_2), 2.65 (1H, dt, J=6Hz, J=4Hz, S-CH), 3.10 (1H, dt, J=6Hz, J=6Hz, O-CH), 3.24 (1H, s, OH), 7.25 (5H, br, C_6H_5) ppm; MS m/z: 208 (M^+, 20%), 190 (M^+-18, 11%), 138 ($C_6H_5SC_2H_5$, 100%), 109 (C_6H_5S, 50%).

Kinetic resolution of (±)-1-phenyl-2-(1-piperidyl)ethanol 9

In a 100 mL of round bottomed flask (flashed with nitrogen) was charged with 30 mL of dichloromethane, 15 mg of CaH_2, 30 mg of silica gel, 1.49 mL (5.0 mmol) of $Ti(OiPr)_4$, 0.63 mL (2.8 mmol) of L-(+)-DIPT, 500 mg (2.5 mmol) of (±)-1-phenyl-2-(1-piperidyl)ethanol 9. The resulted mixture was stirred for 30 min at room temp. The mixture was cooled to -20 °C and 0.193 mL (0.6 eq.) of TBHP was added. The reaction mixture was stored at -20 °C for 30 min. Work up[8] yielded 150 mg of (-)-1-phenyl-2-(1-piperidyl)ethanol 21 as a solid in 30% yield. $[\ ]_D^{29}$-26.7° (c, 0.6, EtOH) [lit[8] $[\ ]_D^{20}$-51.2° (c, 1.12, EtOH)]; IR (KCl) max: 3400, 3200 (OH), 3085, 3060, 3000, 2940, 2850, 1605 (C_6H_5), 1340, 1320 (N-C), 1280, 1160, 1060, 900, 870, 760, 705 cm^{-1} ^{1}H-NMR ($CDCl_3$) : 1.48-1.61 [6H, m, $(CH_2)_3$], 2.29-2.52 [4H, m, $N(CH_2)_2$], 3.46 (2H, m, N-CH_2-C-O), 3.93 (1H, s, OH), 4.63 (1H, t, J=6Hz, CH-O), 7.13 (5H, br, C_6H_5) ppm; MS m/z: 206 (M^++1, 20%), 188 (M^+-17, 13%), 174 (M^+-31, 38%), 128 (M^+-C_6H_5, 1%), 99 (M^+-C_7H_6O, 100%), 84 ($C_5H_{10}N$, 2%).

Methyl (16S)-16,17-epoxygibberellate 22

The epoxidation reaction was carried out in the same way as 11: 350 mg (0.95 mmol) of methyl gibberellate 10, 0.66 mL (2.0 mmol) of $Ti(OiPr)_4$, 0.56 mL (2.4 mmol) of L-(+)-DIPT, 15 mg of CaH_2, 30 mg of silica gel, and 0.28 mL (2.0 mmol) of TBHP (7.78 M) were used. After 4 days at -20 °C work-up in the usual way afforded 250 mg of crystals 22 (from cyclohexane-acetone) in 71% yield. m.p 236 °C (decomp.). $[\ ]_D^{29}$+69.8° (c, 0.256, EtOH), IR (KCl) max: 3500 (OH), 1775 (lactone), 1710 (ester), 1660 (C=C), 1380, 1250 (epoxy), 1040 (C-O), 940, 890 (cis-CH=CH) cm^{-1} ^{1}H-NMR (CD_3COCD_3) : 1.27 (3H, s, CH_3), 2.83 (2H, s, epoxy), 3.66 (3H, s, CO_2CH_3), 3.98 (1H, d, J=3Hz, 3-H), 5.83 (1H, dd, J=3Hz, J=12.5Hz, 2-H), 6.33 (1H, d, J=12.5Hz,1-H) ppm; MS m/z: 376 (M^+, 18%), 359 (M^+-17, 9%), 344 (M^+-30, 26%), 287 (M^+-$C_6H_{11}O$, 100%), 256 (51%), 241 (47%), 169 (52%), 155 (54%). Found: C, 64.04, H, 6.39. Calc. for $C_{20}H_{24}O_7$: C, 63.84, H, 6.38.

The epoxidation of 10 using D-(-)-DIPT

350 mg (0.95 mmol) of methyl gibberellate 10 was epoxidized as described above, in this case using D-(-)-DIPT. After 30 h, workup provided 300 mg of crystals in 81% yield. m.p 235-236 °C (decomp.). The m.p of this compound was not depressed on mixing with the product obtained from the above experiment.

The oxidation of methyl (16S)-16,17-epoxygibberellate 22

To a solution of 10 mg of 22 in 1 mL of dry DMF was added 20 mg of PDC. The reaction mixture was stirred at room temp. for 2 h, which was poured into 20 mL of ethyl acetate. The organic layer was washed successively with 5% HCl

solution, water, and brine. After being dried over Na_2SO_4. Concentration of the extracts under reduced pressure afforded 8 mg of a solid 23 in 80% yield. IR (KCl) max: 3400 (OH), 1770 (lactone), 1710 (ester), 1690 (C=C-C=O), 1640 (C=C), 1250 (epoxy) cm^{-1}; ^{1}H-NMR ($CDCl_3$) : 1.27 (3H, s, CH_3), 2.83 (2H, s, epoxy), 3.70 (3H, s, ester), 5.98 (1H, d, J=10Hz, 2-H), 6.72 (1H, d, J=10Hz, 1-H).

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