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The Preparation of Optically Active 2-Cyclopenten-1,4-Diol Derivatives from Furfuryl Alcohol

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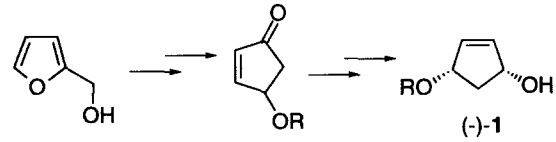
Abstract: The preparation and enzymatic resolution of several *cis*-mono-4-*O*-protected-2-cyclopenten-1,4-diols are described. The process starts with inexpensive furfuryl alcohol and lends itself to the preparation of multigram quantities of various protected, optically active 2-cyclopenten-1,4-diol derivatives. Stereoselective reduction of 4-*O*-protected-2-cyclopentenone to the *cis*-mono-*O*-protected-2-cyclopenten-1,4-diol using $LiAlH_4$/LiI or Red-Al®/NaI is described. Subsequent pancreatin-promoted, stereoselective acylation was conducted on these *cis*-(+/-)-mono-*O*-protected-cyclopenten-1,4-diols to afford the corresponding alcohols and acetates in moderate to excellent enantioselectivities.

INTRODUCTION

Although, there has been a tremendous effort put forth to prepare optically active *cis*-2-cyclopenten-1,4-diol derivatives, many of these methods employ numerous steps, expensive reagents, complicated reaction apparatus, and/or cyclopentadiene.[1] Whereas, all of the inconveniences[2] attributed to these routes are not impossible to overcome in large-scale preparation of such materials, one would prefer to avoid them. There have been several useful approaches toward both *cis* and *trans* optically active 2-cyclopenten-1,4-diols.[3] Additionally, methods to prepare optically active 4-hydroxy or 4-*O*-protected-2-cyclopentenone have been described.[4] The utility of such optically active *cis*-cyclopenten-1,4-diol derivatives has been borne out in the synthesis of carbocyclic nucleosides,[5] prostaglandins,[6] and other natural products.[7] During the course of a study directed toward the large-scale preparation of optically active carbocyclic nucleosides, we had a need to prepare large (multi-kilo) quantities of optically active *cis*-2-cyclopenten-1,4-diol **1** (Scheme 1). Herein, we detail the

Scheme 1



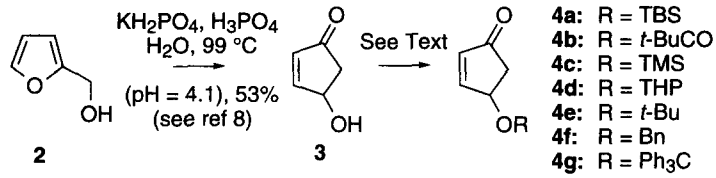
stereoselective conversion of furfuryl alcohol into optically active *cis*-2-cyclopenten-1,4-diol derivatives. The key steps to the process are (1) stereoselective reduction of 4-*O*-protected 2-cyclopentenones, and (2) enzyme-promoted, stereoselective acylation of the mono-*O*-protected-*cis*-cyclopenten-1,4-diol.

RESULTS AND DISCUSSION

Preparation and Stereoselective Reduction of Enones

Following the procedure reported by Nanni *et al.*,[8] furfuryl alcohol (**2**) was converted into 4-hydroxy-2-cyclopentenone (**3**) in 53% yield. Several 4-*O*-protected cyclopentenones were prepared to determine the effect of the protecting group on the stereoselective, ketone reduction (Scheme 2). The *O*-protected hydroxy enones **4a-c** were prepared in 74, 80 and 62% yield, respectively, by reaction of hydroxy enone **3** with RCl (R= TBS, *t*-BuCO and TMS), Et_3N and DMAP (cat) in THF or MeCN at rt. The tetrahydropyranyl (THP) protected enone **4d** was prepared in 76% yield by reaction of hydroxy enone **3** with dihydropyran (DHP) and pyridinium *p*-toluenesulfonate (PPTs, cat) in THF. The *t*-BuO and BnO enones **4e,f** were prepared in 40 and 30% yield, respectively, by reaction of hydroxy enone **3** with the respective trichloroacetimidates and $BF_3{\bullet}OEt_2$ (cat) in CH_2Cl_2/*c*-hexane.[9] *O*-Trityl protected enone **4g** was prepared in 36% yield by reaction of hydroxy enone **3** with Ph_3CCl[10] and DBU in CH_2Cl_2.

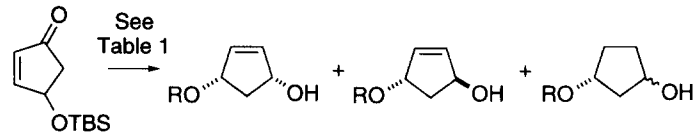
Scheme 2



A reduction survey was conducted on enone **4a**, employing the *t*-butyldimethylsilyl (TBS) protecting group. The products and ratios from the reduction of enone **4a** were determined by comparison to authentic samples,[11] GC, and GC/MS analysis of the crude reaction mixtures.[12] Some results of this investigation are shown in Scheme 3 and Table 1. Reduction using $LiAlH_4$ in Et_2O at -78 °C (entry 1) gave an excellent ratio of *cis/trans* products but provided significant amounts of conjugate reduction products. $LiAlH_4$/LiI[13] in Et_2O at -20 °C gave an excellent *cis/trans* ratio, and the weak Lewis acid suppressed conjugate reduction (entry 2). Using THF instead of ether at -78 °C or TBME (*t*-butyl methyl ether) at -20 °C gave a 2:2:1 or 9:1:1 ratio of products, respectively. This solvent trend is precedented.[14a,b] Due to the observation that all of the LiI did not dissolve, the amount utilized was curtailed to a catalytic amount. In addition, we discovered that a mixed solvent system, TBME/PhMe 1:2, proved to be very similar to Et_2O and provided excellent *cis* selectivity (entry 3). Serendipitously, we observed an improvement in the *cis/trans*/1,4+1,2-reduction product from 24/1/trace to 35/1/trace when the starting ketone **4a** was contaminated with 20-25 mol% of TBSOH (*t*-butyldimethylsilanol; entry 4).[15] Increasing the amount of silanol to an equivalent molar ratio with $LiAlH_4$ gave slightly diminished selectivity (28/1/trace) under similar conditions. We do not know what new species is involved but have consistently observed an improved ratio. Interestingly, the reduction did not occur at rt when PhMe was employed as solvent, perhaps due to the insolubility of the reducing agent under these conditions. Using LiBr, $ZnCl_2$ or $MgBr_2$ with $LiAlH_4$ in solutions of enone **4a** containing 20 mol% TBSOH proved inferior.[16] We have also tried the addition of TBSOH (20 mol%) to another 4-*O*-protected cyclopentenone and a decrease in

cis/trans/conjugate reduction product ratio was observed (*vida infra*). Some insight as to what role silanol may be playing can be seen when the reducing agent is Red-Al® [$Na^+(MeOCH_2CH_2O)_2H_2Al^-$] with NaI (or LiI, entry

Scheme 3



4a **5a** **6a** **7a**

Table 1: Reduction of Enone **4a**.

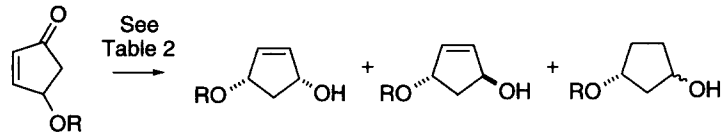
Entry	Conditions: Reagents (eq), Solvent(s), Temp °C	Yield %	Ratio **5a/6a/7a**
1	$LiAlH_4$ (1), Et_2O, -78	70	40/1/4
2	$LiAlH_4$ (1), LiI (5), Et_2O, -20	74	25/1/trace
3	$LiAlH_4$ (0.5), LiI (0.5), PhMe/TBME (2:1), -30	79	24/1/trace
4	$LiAlH_4$ (0.5), LiI (0.5), TBSOH (0.2-0.25), PhMe/TBME (2:1), -30	74	35/1/trace
5	Red-Al® (0.67), NaI (0.5), PhMe/TBME (2:1), -30	71	32/1/trace
6	Dibal-H (1), PhMe, -40	72	9/1/0
7	$NaBH_4$ (0.5), $CeCl_3$ (2), MeOH, -20	93	8/1/0
8	$LiAl(OMe)_3H$ (2.5), THF, -20 to rt	44	20/1/2*

*This was determined to be a 2:1 mixture of 3-TBSO-cyclopentanone:**7a** via GC and GC/MS.

5). This result suggests that the silanol is modifying the reducing agent (adding bulk and perhaps increasing solubility), but why the silanol can be used in catalytic amounts is not fully understood. Dibal-H in PhMe gave modest selectivity at -40 °C; notably, the conjugate reduction product was not detected (GC, ^1H NMR; entry 6). Luche reduction[17] in MeOH gave adequate selectivities (8:1) and minimized conjugate reduction (entry 7). Reduction of ketone **4a** using $LiAl(OMe)_3H$ in THF[14c] provided inferior selectivity (entry 8).

Concurrent with the reduction studies on **4a**, the reduction of enones **3**, and **4b-f** were examined. Our best results are summarized in Scheme 4 and Table 2. Luche reduction of hydroxy enone **3** did work in modest selectivity (7/1/1, **5h/6h/7h**) and in 68% yield (Table 2, entry 1).[18] Pivalate **4b** was reduced under Luche[17] conditions to provide a marginally selective **5b/6b** ratio (Scheme 4; Table 2, entry 2). Reduction of pivalate **4b** using $LiAlH_4$/LiI conditions reduced the ester and gave poor selectivities. Similarly, the TMS ether **4c** afforded

Scheme 4



3: R = H	**5h**	**6h**	**7h**
4b: R = *t*-BuCO	**5b**	**6b**	**7b**
4c: R = TMS	**5c**	**6c**	**7c**
4d: R = THP	**5d**	**6d**	**7d**
4e: R = *t*-Bu	**5e**	**6e**	**7e**
4f: R = Bn	**5f**	**6f**	**7f**
4g: R = Ph_3C	**5g**	**6g**	**7g**

Table 2: Reduction of Enones **3, 4b-g.**

Entry	R	Conditions: Reagents (eq), Solvent(s), Temp °C	Yield %	Ratio **5/6/7**
1	H	$NaBH_4$ (1), $CeCl_3$ (1), MeOH/THF (1:1), 0 to rt	68	7/1/1
2	*t*-BuCO	$NaBH_4$ (1), $CeCl_3$ (1), MeOH, -20	98	3/1/0
3	TMS	$LiAlH_4$ (1), LiI (5), PhMe/TBME (5:1), -20	99	7/1/trace*
4	THP	$LiAlH_4$ (0.5), LiI (2), PhMe/TBME (2:1), -20	73	11/1/trace
5	THP	$LiAlH_4$ (0.5), LiI (2), TBSOH (0.2), PhMe/TBME (2:1), -20 to 0	72	9/1/trace
6	*t*-Bu	$LiAlH_4$ (0.5), LiI (2), PhMe/TBME (2:1), -20	42	9/1/trace
7	Bn	$LiAlH_4$ (0.5), LiI (2), Et_2O, -40	34	7/1/1
8	Ph_3C	$LiAlH_4$ (0.5), LiI (2), PhMe/TBME (4:1), -20 to 15	95	30/1/trace

*Deprotection occurred during the reaction and work-up. The ratio represents that of diols **5h/6h/7h**.

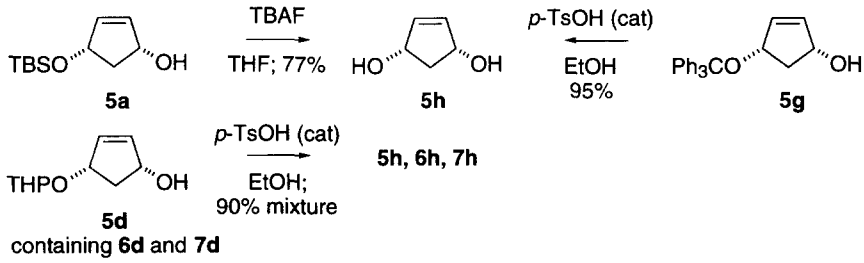
modest selectivities using $LiAlH_4$/LiI conditions (entry 3). The decrease in selectivity is probably due to the less bulky protecting group as well as partial loss of the protecting group during the course of the reaction.

THP, *t*-Bu, Bn and Ph_3C protected hydroxy enones **4d-g** (Scheme 4; entries 4-8, Table 2) were reduced using the $LiAlH_4$/LiI conditions. Reaction of THP protected hydroxy enone **4d** without the addition of TBSOH gave slightly better selectivity than when silanol was added (compare entries 4 and 5). This may in part be due to the increased temperature which was necessary to promote the reaction in <24 h. The reduction of the *t*-Bu protected hydroxy enone **4e** was superior to the Bn protected enone **4f** in *cis* selectivity and in yield (entries 6 and 7). Reduction of the Ph_3C protected hydroxy enone **4g** was comparable to that observed in the TBS case (entry 8). Enones **4a** and **4g** were shown to be the best substrates for the selective reduction to the *cis*-diol derivatives **5a** and **5g**, respectively, using $LiAlH_4$/LiI or Red-Al®/NaI.

*The Conversion of Diol Derivatives **5a,d** and **g** into cis-2-Cyclopenten-1,4-diol*

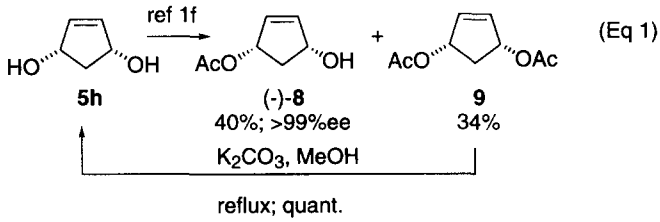
Cleavage of silyl ether **5a** with tetra-*n*-butylammonium fluoride (TBAF) in THF at rt provided diol **5h** in 77% yield (Scheme 5). Cleavage of the THP ether mixture, obtained from the reduction of ketone **4d**, using PPTs (cat) in EtOH gave an analogous mixture of diols (*cis/trans*/1,4- + 1,2-reduction products; GC) as the starting material (22/2/1) in 90% yield. Mono-tritylated *cis*-diol **5g** was converted into the *cis*-diol **5h** using *p*-TsOH in EtOH at 50-55 °C in a quantitative yield.

Scheme 5



*Desymmetrization of cis-Diol **5h***

We then desymmetrized *cis*-diol **5h** using conditions as reported by Theil *et al.*[1e,f] and obtained a 34% yield of bis-acylated diol **9** (Eq 1). This bis-acylated diol **9** could easily be separated from the desired mono-



acetate by chromatography and could be recycled quantitatively by ester saponification. Recrystallization of (-)-**8** gave a 40% yield of the desired mono-acetate (-)-**8** in >99% optical purity. Nevertheless, an improved process was sought. Attempts to utilize *Mucor sp.* as reported by Theil *et al.*[1e,f] did not work in our hands as described.

We began to consider alternatives toward making the enzyme step better. We realized, as had Theil *et al.*,[19] that diols typically exhibit poor solubility in aprotic, nonpolar organic solvents, and that such solvents are good for enzymatic reactions. We noted that pancreatin-promoted desymmetrization of diol **5h** in THF was typically dark brown. We surmised that pancreatin is either partly degraded or is partly soluble, because after filtration of the enzyme reaction mixture through celite, subsequent concentration of the resulting filtrate gave precipitants. In addition for the desymmetrization of diol **5h**, the *first acylation* is not very selective (2:1), while the *second acylation is highly enantioselective*.

Resolution of cis-Monoprotected-2-Cyclopenten-1,4-diols

Pancreatin-promoted resolution[20] of (+/-)-TBS ether **5a** in a few solvents provided enriched (-)-**10** and enriched (-)-**11** in 46-48% and 44-48% yield respectively, and in good optical purities (Scheme 6; Table 3, entries 1-3). The results of using Lyphozyme IM and Sp 435 in TBME are also reported and gave inferior yields to the pancreatin-promoted reaction. From the results reported in Table 3, it is obvious that pancreatin in TBME is the enzyme/solvent combination of choice for the enantioselective acylation of (+/-)-TBS ether **5a**.

Scheme 6

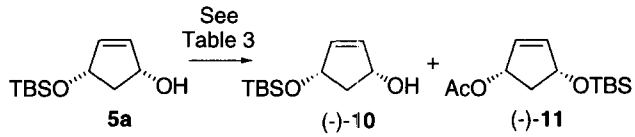


Table 3: Enzymatic Resolution of mono-TBSO-cyclopentenol **5a**.

Entry	Enzyme (wt. eq)	Conditions: Solvent, Reagents* (eq), Time (h)	%Yield (-)-**10** (%ee)	%Yield (-)-**11** (%ee)
1	Pancreatin (3)	THF, VA (5), Et_3N (0.7), 26	46 (96)	48 (98)
2	Pancreatin (3)	TBME, VA (5), Et_3N (0.7), 7	47 (98)	48 (98)
3	Pancreatin (3)	*c*-Hex, VA (5), Et_3N (0.7), 2	48 (97)	44 (98)
4	Lyphozyme IM (3)	TBME, VA (4), 5	39 (98)	37 (94)
5	Sp435 (0.3)	TBME, IA (3), 5.5	33 (98)	53 (57)

*All reactions were run at rt. VA= vinyl acetate; IA= isopropenyl acetate. Optical purity was assessed by GC chiral column analysis of acetates (-)-**11** and (+)-**27**. Absolute configurations of (-)-**10** and (-)-**11** were assigned by comparison to literature rotation values[1q,r,v,4f] and were confirmed by preparation of authentic samples followed by GC chiral column analysis.[21]

The less polar solvents, TBME or cyclohexane, improved the selectivity and increased the rate of the reaction in comparison to THF.[22] The (+/-)-TBS ether **5a** is a more soluble substrate than diol **5h** in solvents less polar than THF, and is suitable for selective acylation using pancreatin. We thought that this was a remarkable improvement because *each isomer resulting from the resolution can be used to prepare the same enantioenriched carbocyclic nucleoside.*

We also wanted to test the generality of this enzymatic acylation. Therefore, other mono-*O*-protected *cis*-2-cyclopenten-1,4-diols were subjected to pancreatin resolution conditions. These results are summarized in Table 4 and Scheme 7. Pancreatin resolves other (+/-)-*cis*-monoprotected-2-cyclopenten-1,4-diols; however,

Scheme 7

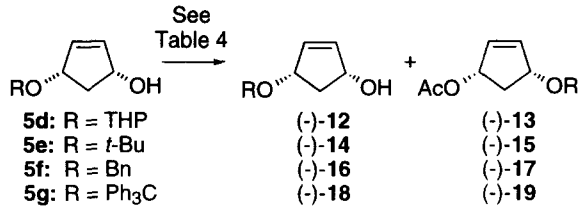
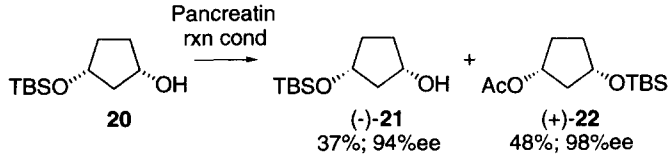


Table 4: Pancreatin Resolution of *cis*-Monoprotected-Cyclopenten-1,4-diols **6d-g**.

Entry	R	ReactionTime (h)*	%Yield Alcohol (%ee)	%Yield Acetate (%ee)
1	THP	7	50 (94)	45 (91)
2	*t*-Bu	17	40 (98)	51 (76)
3	Bn	4	20 (98)	74 (30)
4	Ph_3C	24	100 (0)	no acylation

*All reactions were run using pancreatin (3 wt. eq) and vinyl acetate (5 eq) in TBME at rt. Optical purities of (-)-**12** and (-)-**13** were assessed by conversion to mono-acetates and GC chiral col. analysis. Optical purities of *t*-Bu alcohols (-)-**14** and (+)-**25** as well as their acetates could be assessed by GC chiral column analysis. The optical purity of Bn derivatives were assessed as their acetates (-)-**17** and (+)-**29**. The absolute configurations of (-)-**12**, (-)-**13**, (-)-**16** and (-)-**17** were assigned on the basis of literature rotations.[1q,r,v] The absolute configuration of (-)-**14** and (-)-**15** were assigned by analogy to the series reported herein.

we found it to be less selective with ethers **5d-f** than with silyl ether **5a**. Quite interestingly, the enzyme does not distinguish stereocenters outside the cyclopentenyl ring system, as evidenced by the THP ether which gave a 1:1 diastereomeric mixture of alcohol (-)-**12** and acetate (-)-**13** (entry 1). Mono-protected *cis*-diols (+/-)-**5e** and **5f**[23] underwent pancreatin-promoted asymmetric acylation in >90% yield with excellent optical purities of the alcohols, and moderate to poor optical purities of the acetates (entries 2 and 3). The Ph_3C group is apparently too large to fit into the enzyme; no acylation resulted (Table 4; entry 4). In addition, (+/-)-*cis*-mono-TBS-protected cyclopentan-1,3-diol **20** underwent pancreatin-promoted asymmetric acylation with good optical purity of both alcohol (-)-**21** and acetate (+)-**22** and in satisfactory yield (Eq 2).

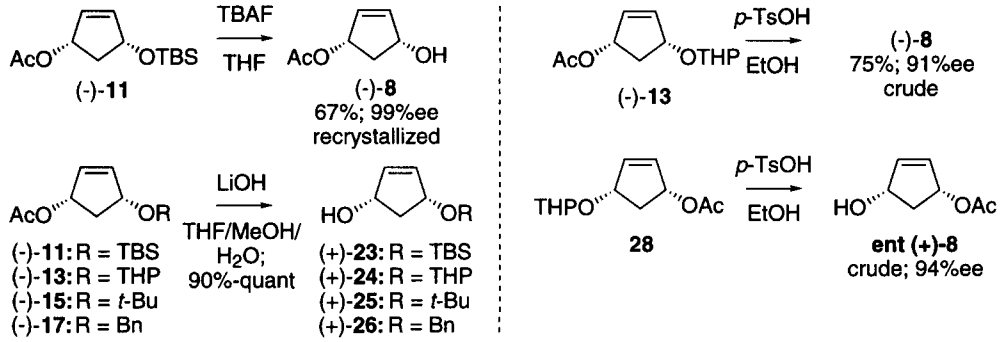


Ether Cleavage and Acetate Hydrolysis

Silyl ether cleavage of enriched (-)-**11** (Scheme 8) using TBAF provided enriched acetate (-)-**8** in 67% yield.[24] THP ether cleavage of (-)-**13** was accomplished using *p*-TsOH (cat) to provide (-)-**8**, which was used

to assess optical purity via GC chiral column analysis (Scheme 8). The optical purity of alcohol (-)-**12** was assessed by acylation to form **28** followed by THP removal and analysis of the resulting enantioenriched mono-acetate (+)-**ent-8** (Scheme 9 for preparation of acetate derivatives; Scheme 8 for THP cleavage). Saponification of enantioenriched acetates (-)-**11**, (-)-**13**, (-)-**15** and (-)-**17** provided optically enriched alcohols (+)-**23-26** respectively in >90% yield (Scheme 8).

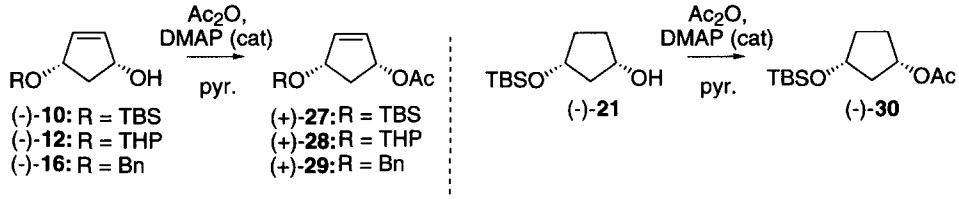
Scheme 8



Acetate Formation to Assess Optical Purity

Although, we were unable to assess the optical purity of alcohols (-)-**10**, (-)-**12**, (-)-**16** and (-)-**21** directly, the optical purities of the alcohols resulting from enzymatic acylation were assessed by preparation of the acetates (+)-**27**, (+)-**29** and (-)-**30** and GC chiral column analysis. Enantiomers of both alcohol (-)-**14** and its acetate (-)-**15** were adequately separated by GC chiral column, which was the method used to assess optical purities. The preparation of the acetates was accomplished using Ac_2O/pyridine with catalytic DMAP and is shown in Scheme 9. The optical purities thus obtained are reported in Tables 3, 4 and Eq 2.

Scheme 9



CONCLUSION

In conclusion, we have demonstrated the conversion of furfuryl alcohol into optically active-mono-protected *cis*-2-cyclopenten-1,4-diols in good yield and excellent optical purity. We have shown that LiI/$LiAlH_4$ with or without TBSOH and Red-Al®/NaI in TBME/PhMe 1:2 gave excellent stereoselectivity in the conversion

of various 4-*O*-protected cyclopentenones into *cis*-2-cyclopenten-1,4-diol derivatives. Subsequent resolution of these cyclopenten-1,4-diol derivatives in TBME with pancreatin gave modest to excellent optical purities of both the alcohols and acetates. For the best case (TBSO-enone **4a**), furfuryl alcohol was converted into (-)-**10** and (-)-**11** in 26% overall yield (13% each) and four chemical steps. Selective deprotection of (-)-**11** affords monoacetate (-)-**8**. Both (-)-**10** and (-)-**8** contain the same "handedness" and can be used to prepare analogous optically-active carbocyclic nucleosides, prostaglandins and other natural products.

EXPERIMENTAL

General

Melting points were obtained on a Thomas Hoover melting point apparatus and are uncorrected. Optical rotations were recorded on a Jasco model DIP 360. IR spectra were recorded on a Mattson Galaxy Series 5000 FTIR. NMR spectra were recorded on a Varian XL-300, Bruker Ace 300 or Gemini 300 at 300 MHz (^{1}H), at 75 MHz (^{13}C), and chemical shifts are recorded in ppm relative to TMS standard. Mass spectra were obtained on a Finnigan SSQ 7000 spectrometer. GC standard conditions (method A): linear velocity (He) = 30 cm/sec; column, HP-5 cross linked, 5% PH ME silicone, 30 m x 0.32 mm; injection port, 200 °C; detector, 275 °C; oven (gradient), 100 °C (10 min), increase 10 °C/min to 200 °C (hold 5 min). GC chiral column (method B): linear velocity (H_2) = 80 mL/min; column, Chiraldex® β-PH 10 m x 0.25 mm id, 0.125 μm film, (ASTEC); injection port, 200 °C; detector, 220 °C; oven, 80 °C. GC chiral column (method C): CDX-β, linear velocity (He) = 80 cm/sec; column, 10 m x 0.25 mm id, 0.25 μm film (J & W Scientific); injector, 200 °C; detector, 220 °C; oven, 100 °C.

(+/-)-4-Hydroxy-2-cyclopentenone (3)

A solution of furfuryl alcohol (**2**, 125 g, 1.27 mol) in H_2O (3.7 L) was treated with KH_2PO_4 (6.3 g, 46.3 mmol). The solution was adjusted to pH = 4.1 (pH meter) with H_3PO_4, then heated to 99 °C for 40 h. The cooled solution was washed with CH_2Cl_2 (2 x 500 mL). The combined organic layers were extracted with H_2O (2 x 500 mL), and the H_2O layers combined and evaporated (70 °C, 20 mmHg) to give a red oil. The red oil was dissolved in CH_2Cl_2 (1 L), dried ($MgSO_4$), filtered and the filtrate evaporated *in vacuo* (40 °C, 20 mmHg) to give **3** as a dark red oil, 66.5 g, 53%. t_R (method A) = 4.55 min; ^{1}H NMR ($CDCl_3$) 7.61 (dd, 1H, J = 5.6, 4.8 Hz), 6.20 (d, 1H, J = 5.6 Hz), 5.0 (m, 1H), 3.6 [s(broad), 1H], 2.75 (dd, 1H, J = 18.5, 3.2 Hz). 2.26 (dd, 1H, J = 18.5, 6.0 Hz); ^{13}C NMR ($CDCl_3$) 207.4, 164.0, 134.7, 70.1, 44.1; IR (neat) ν_{max} 3387, 2974, 1711 cm^{-1}; EIMS m/e (% relative intensity) 98 (M^+, 100). Anal calcd. for $C_5H_6O_2 \bullet 0.16\ H_2O$ (116.79): C, 59.47; H, 6.30. Found: C, 59.56; H, 6.52.

(+/-)-4-*t*-Butyldimethylsilyloxy-2-cyclopentenone (4a)

A solution of 4-hydroxy-2-cyclopentenone (**3**, 191 g, 1.95 mol) and Et_3N (430 mL, 3.09 mol), in THF (1 L, anhyd.) was treated with DMAP (4.90 g, 40.0 mmol). The solution was cooled to 0 °C and treated portionwise with *t*-butyldimethylsilyl chloride (278 g, 1.84 mol) to keep the temperature at or below 10 °C (10 min). The resulting mixture was stirred at rt overnight, then poured into aqueous HCl (0.5N, 1 L). The phases were separated, and the aqueous phase was extracted with heptane (2 x 1 L). The organic phases were combined,

washed sequentially with aqueous HCl (0.5N, 2 x 500 mL), 5% $NaHCO_3$ (1 x 500 mL), brine (1 x 500 mL), dried ($MgSO_4$), filtered, and the filtrate evaporated (40 °C, 20 mmHg) to give 325 g of crude 4-*t*-butyldimethylsilyloxy-2-cyclopentenone (**4a**). To remove TBSOH down to levels of about 2% (total area, GC), the crude mixture was azeotroped with PhMe (2 x 500 mL; 50 °C, 15 mmHg). When azeotropic removal of TBSOH was not done, distillation gave the desired product **4a** contaminated with 0.22-0.20 mol% TBSOH (17-19 area %, GC); which if carried into the $LiAlH_4$/LiI reduction gave the desired selectivity. Purification by Kugelrohr distillation (bp 70-80 °C, 1 mmHg) provided 282 g of enone **4a** as a light yellow oil, 72% yield. R_f = 0.55, 20% EtOAc/hex; t_R (method A) = 14.97 min; ^{1}H NMR ($CDCl_3$) 7.48 (dd, 1H, *J* = 5.7, 2.4 Hz), 6.20 (d, 1H, *J* = 5.7 Hz), 4.9 (m, 1H), 2.72 (dd, 1H, *J* = 2.3, 18.2 Hz). 2.25 (dd, 1H, *J* = 18.2, 6.0 Hz), 0.88 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$) 206.4, 163.8, 134.4, 70.8, 44.9, 25.7, 18.0, -4.47, -4.75; IR (neat) ν_{max} 2957, 2931, 2887, 1725 cm^{-1}; EIMS m/e (% relative intensity) 212 (M^+, 5), 155 (M^+-C_4H_9, 100). Anal calcd. for $C_{11}H_{20}O_2Si$ (212.37): C, 62.21; H, 9.51. Found: C, 62.39; H, 9.50.

(+/-)-4-Pivaloyloxy-2-cyclopentenone (4b)

A solution of 4-hydroxy-2-cyclopentenone (**3**, 20.0 g, 0.204 mol) and Et_3N (45.0 mL, 0.323 mol) in THF (100 mL, anhydrous) was treated with DMAP (0.50 g, 4.10 mmol). The solution was cooled to 0 °C and treated with pivaloyl chloride (24.0 mL, 0.195 mol). The resulting mixture was stirred at rt overnight, then poured into water (500 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (2 x 250 mL). The organic phases were combined, washed sequentially with aqueous HCl (0.5N, 2 x 100 mL), 5% $NaHCO_3$ (1 x 100 mL), and brine (1 x 100 mL), then dried ($MgSO_4$), treated with activated charcoal, filtered and evaporated (40 °C, 20 mmHg) to give crude 4-pivaloyloxy-2-cyclopentenone (**4b**). Purification by Kugelrohr distillation (b.p. 40-80 °C, 1 mmHg) provided 4-pivaloyloxy-2-cyclopentenone (**4b**) as a colorless oil, 22.0 g, 62% yield. t_R (method A) = 12.46 min; ^{1}H NMR ($CDCl_3$) 7.58 (dd, 1H, *J* = 5.6, 2.4 Hz), 6.34 (d, 1H, *J* = 5.6 Hz), 5.8 (m, 1H), 2.84 (dd, 1H, *J* = 18.7, 6.5 Hz), 2.29 (dd, 1H, *J* = 18.7, 2.3 Hz), 1.22 (s, 9H); ^{13}C NMR ($CDCl_3$) 205.0, 178.0, 159.1, 136.9, 71.8, 41.0, 38.7, 27.0; IR (neat) ν_{max} 3550, 2976, 1728 cm^{-1}; CIMS (CH_4) m/e (% relative intensity) 183 (MH^+, 100). Anal calcd. for $C_{10}H_{14}O_3$ (182.22): C, 65.92; H, 7.74. Found: C, 65.89; H, 7.95.

(+/-)-4-Trimethylsilyloxy-2-cyclopentenone (4c)

A solution of 4-hydroxy-2-cyclopentenone (**3**, 5.09 g, 0.052 mol) and Et_3N (10.5 mL, 0.075 mol) in THF (50 mL, anhydrous) was treated with DMAP (0.10 g, 0.82 mmol). The solution was cooled to 0 °C and treated dropwise with trimethylsilyl chloride (6.10 mL, 0.048 mmol). The resulting mixture was stirred at rt overnight then poured into water (100 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (100 mL). The organic layers were combined, washed sequentially with aqueous NH_4Cl (2 x 100 mL), and with brine (100 mL), dried ($MgSO_4$), filtered and evaporated (40 °C, 20 mmHg) to give 6.57 g of crude 4-trimethylsilyloxy-2-cyclopentenone (**4c**), 80% yield. t_R (method A) = 7.02 min; ^{1}H NMR ($CDCl_3$) 7.46 (dd, 1H, *J* = 5.7, 2.3 Hz), 6.18 (d, 1H, *J* = 5.7 Hz), 4.9 (m, 1H), 2.70 (dd, 1H, *J* = 18.2, 6.0 Hz), 2.23 (dd, 1H, *J* = 18.2, 2.3 Hz), 0.17 (s, 9H); ^{13}C NMR ($CDCl_3$) 206.2, 163.6, 134.5, 70.4, 44.7, -0.048; IR (neat) ν_{max}

2958, 2901, 1719 cm^{-1}; CIMS (CH_4) m/e (% relative intensity) 171 (MH^+, 100). Anal calcd. for $C_8H_{14}O_2Si$ (170.28): C, 56.43; H, 8.29. Found: C, 56.07; H, 7.91.

4R*S*-4-(2'R*-Tetrahydropyranyloxy)-2-cyclopentenone (4d)

A solution of 4-hydroxy-2-cyclopentenone (**3**, 1.41 g, 14.4 mmol) in THF (24 mL) was treated with DHP (2 mL,21.9 mmol, 1.5 eq) and PPTs (500 mg, 2 mmol, 0.14 eq) then stirred at rt for 18 h. The resulting reaction mixture was diluted with EtOAc (25 mL) and washed with 1/2 sat'd brine (2 x 30 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The resulting crude brown oil was purified by SiO_2 plug filtration (25 g, 33% EtOAc/hex, 310 mL). Isolated **4d** as a yellow oil, 2.00 g, 76% yield. R_f = 0.25, 50% EtOAc /hex; t_R (method A) = 17.4, 17.6 min; ^1H NMR ($CDCl_3$) 7.46 (2 x dd, 1H, *J* = 16.3, 5.7 Hz), 6.2 (m, 1H), 4.9 (m, 1H), 4.80 (d appt, 1H, *J* = 23.8, 2.9 Hz), 3.9 (m, 1H), 3.6 (m, 1H), 2.73 (2 x dd, 1H, *J* = 18.4, 6.2 Hz), 2.35 (2 x d, 1H, *J* = 18.4 Hz), 1.8 (m, 2H), 1.6 (m, 4H); IR (neat) ν_{max} 2944, 1723, 1348, 1202, 1182, 1152, 1128 cm^{-1}; CIMS (CH_4) m/e (% relative intensity) 183 (MH^+, 28), 85 (100).

(+/-)-4-*t*-Butyloxy-2-cyclopentenone (4e)

A solution of 4-hydroxy-2-cyclopentenone (**3**, 1.15 g, 11.7mmol) in CH_2Cl_2 was cooled to 3 °C and treated sequentially with *t*-butyl trichloroacetimidate (4.2 mL, 23.7 mmol, 2 eq) and $BF_3 \bullet OEt_2$ (0.15 mL, 0.1 eq). The resulting reaction mixture was stirred at 3-10 °C for 2 h then allowed to warm to rt with stirring for 22 h. The reaction mixture was treated with $NaHCO_3$ (250 mg), filtered and evaporated *in vacuo*. The crude oil was chromatographed on SiO_2 [39 g, 3 x 7 cm; 20% EtOAc/hexane (600 mL)] to provide **4e** as a yellow oil, 355 mg, 40 % yield. t_R (method A)= 8.07 min; R_f = 0.42, 33% EtOAc/hex; ^1H NMR ($CDCl_3$) 7.44 (dd, 1H, *J* = 2.4, 5.4 Hz), 6.2 (d, 1H, *J* = 5.4 Hz), 4.8 (m, 1H), 2.68 (dd, 1H, *J* = 5.8, 18 Hz), 2.25 (d, 1H, *J* = 18 Hz), 1.27 (s, 9H); IR (neat) ν_{max} 2976, 2936, 1721, 1368, 1352, 1188, 1103, 1161 cm^{-1}; CIMS (CH_4) m/e (% relative intensity) 155 (MH^+, 22), 99 (100).

(+/-)-4-Benzyloxy-2-cyclopentenone (4f)

Prepared in a similar fashion to **4e** only using benzyl trichloroacetimidate. Hydroxy enone **3** (1.29 g, 13.1 mmol), gave crude **4f**. Crude **4f** was purified via SiO_2 plug filtration (55 g SiO_2, 4.5 x 5.5 cm; 10% EtOAc/hexane-20% EtOAc/hexane) and gave 747 mg, 30% of **4f** as a colorless oil. For **4f**: R_f = 0.17, 20% EtOAc/hex; t_R (method A) = 20.3 min; ^1H NMR ($CDCl_3$) 7.61 (d, 1H, *J* = 5.8 Hz), 7.4 (m, 5H), 6.25 (d, 1H, *J* = 5.8 Hz), 4.4-4.6 (m, 3H), 2.69 (dd, 1H, *J* = 5.9, 18.2 Hz), 2.38 (d, 1H, *J* = 18.2 Hz); IR (neat) ν_{max} 3030, 2928, 1719, 1350, 1107, 1071 cm^{-1}; CIMS (CH_4) m/e (% relative intensity) 189 (MH^+, 52), 91 (100).

(+/-)-4-Trityloxy-2-cyclopentenone (4g)

A solution of Ph_3CCl (3.44 g, 12.3 mmol, 1.2 eq) in CH_2Cl_2 (20 mL) was treated sequentially with DBU (2.2 mL, 14.7 mmol, 1.4 eq) and **3** (1.01 g, 10.0 mmol; in CH_2Cl_2 5 mL). The resulting reaction darkened and was stirred for 3 d at rt then poured into ice H_2O (25 mL). The phases were separated and the resulting organic phase washed again with H_2O (25 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo* (rt, 15 mmHg) to give a black foam. Purification via chromatography on SiO_2 (40 g, 4 x 7 cm, gradient elution,

10-20% EtOAc/hex) gave 1.26 g, 36% yield of **4g** as a pale yellow oil which solidified on standing. R_f = 0.22, 10% EtOAc/hex; ^{1}H NMR ($CDCl_3$) 7.5 (m, 6H), 7.3 (m, 9H), 6.85 (dd, 1H, *J* = 1.7, 5.8 Hz), 6.05 (d, 1H, *J* = 5.8 Hz), 4.8 (m, 1H), 2.1 (m, 2H); ^{13}C NMR ($CDCl_3$) 206.6, 162.9, 144.3, 135.2, 128.8, 128.4, 127.7, 88.2, 73.1, 43.4; IR (KBr) ν_{max} 3061, 1719, 1491, 1449, 1352, 1181, 1107, 1053 cm^{-1}; CIMS (NH_3) m/e (% relative intensity) 340 (M^+, 64), 243 (100). FABHRMS (MNBA/PEG) m/e 341.1559 ($C_{24}H_{20}O_2$ requires 341.1542).

(+/-)-*cis*-4-*t*-Butyldimethylsilyloxy-2-cyclopentenol (5a)

$LiAlH_4$/LiI/TBSOH Method

A slurry of $LiAlH_4$ (500 mg, 13 mmol, 0.65 eq) and LiI (1.4 g, 10 mmol, 0.5 eq) in PhMe (42 mL) under N_2 was cooled to -30 °C and treated dropwise (30 min) with a solution of 4-*t*-butyldimethylsilyloxy-2-cyclopentenone **4a** (4.3 g, 0.020 mmol) and TBSOH (600 mg, 4.5 mmol, 0.23 eq) in TBME (21 mL). The mixture was stirred at -25 to -30 °C for 23 h (normally 5-8 h) then treated with sat'd aqueous NH_4Cl and filtered. The phases were separated, and the aqueous phase was extracted with PhMe (2 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification via vacuum distillation through a 14 cm, packed glass bead (0.5 mm) column at 65-68 °C (0.4 mmHg; alternatively, Kugelrohr distillation has been used with similar results) gave 3.2 g of **5a** in 74% yield and a 35/1/trace ratio of diastereomers by GC.

Red-Al®/NaI Method

A slurry of NaI (1.30 g, 8.7 mmol, 0.5 eq) in PhMe (31 mL) was cooled to -30 °C and treated with Red-Al® (3.4 mL, 11.6 mmol, 0.67 eq). The resulting reaction mixture was then treated dropwise (over 30 min) with a solution of enone **4a** (3.67 g, 17.3 mmol) in TBME (17 mL) and stirred at -30 to -25 °C for 5 h. Work-up as described above, followed by Kugelrohr distillation (70 °C, 0.5 mmHg) gave 2.65 g, 71% yield of **5a** which was determined to be a 32/1/trace mixture of diastereomers. For **5a**: R_f = 0.20, 20% EtOAc/hex; t_R (method A) = 13.95 min; ^{1}H NMR ($CDCl_3$) 5.93 (dt, 1H, *J* = 5.5, 1.7 Hz), 5.84 (dt, 1H, *J* = 5.5, 1.6 Hz), 4.6 (m, 1H), 4.5 (m, 1H), 2.8 [s(broad), 1H], 2.69 (dt, 1H, *J* = 13.8, 7.1 Hz), 1.52 (dt, 1H, *J* = 13.8, 4.7 Hz), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$) 136.7, 135.6, 75.1, 75.0, 44.5, 25.9, 18.1, -4.41, -4.43; IR (neat) ν_{max} 3373, 2957, 2932 cm^{-1}; EIMS m/e (% relative intensity) 157 (M^+-C_4H_9, 100). Anal calcd. for $C_{11}H_{22}O_2Si$ (214.38): C, 61.63; H, 10.34. Found: C, 61.41; H, 10.18.
Although both reduction methods proved to be analogous for enone **4a** and because there was no need to add TBSOH to the reduction mixture of enone **4a** (see preparation of **4a**), the $LiAlH_4$/LiI method was preferred.

(+/-)-*cis*-4-Pivaloyloxy-2-cyclopentenol (5b)

A stirred solution of 4-pivaloyloxy-2-cyclopentenone (**4b**, 1.00 g, 5.49 mmol) in methanol (25 mL) was treated with $CeCl_3$ (2.10 g, 5.64 mmol). The mixture was cooled to -20 °C and treated with $NaBH_4$ (210 mg, 5.56 mmol). After stirring overnight at -20 °C, the reaction was quenched by the slow addition of saturated aqueous NH_4Cl (50 mL). The resulting suspension was diluted with water, then extracted with Et_2O (2 x 50 mL). The organic phases were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated (40 °C, 20

mmHg) to provide a 3/1 mixture of **5b/6b** as a colorless oil, 1.0 g, 99% yield. For major isomer **5b**: t_R (method A) = 12.5 min; ^{1}H NMR ($CDCl_3$) 6.1 (m, 1H), 5.9 (m, 1H), 5.5 (m, 1H), 4.7 (m, 1H), 2.86 (dt, 1H, *J* = 14.4, 7.3 Hz), 2.50 [s(broad), 1H], 1.61 (dt, 1H, *J* = 14.4, 4.2 Hz), 1.20 (s, 9H); ^{13}C NMR ($CDCl_3$) 178.3, 138.2, 132.6, 76.9, 74.8, 40.6, 38.5, 27.1; IR (neat) ν_{max} 3423, 2976, 1726 cm^{-1}; CIMS (CH_4) m/e 185 (MH^+, 5), 167 (MH^+-H_2O, 100).

(+/-)-*cis*-4-(2'R*-Tetrahydropyranyloxy)-2-cyclopentenol (5d)

A slurry of $LiAlH_4$ (220 mg, 5.8 mmol, 0.49 eq) and LiI (3.2 g, 24 mmol, 2.0 eq) in TBME (6 mL)/ PhMe (16 mL) was cooled to -15 °C, and a solution of ketone **4d** (2.179 g, 11.97 mmol) in TBME (2 mL) /PhMe (2 mL) was added dropwise (40 min; -20 to -13 °C). The resulting reaction mixture was stirred for 30 min then NaOH (1N, 5 mL) was added slowly. The slurry was filtered, phases separated and the aqueous phase extracted with EtOAc (2 x 10 mL). The organic phases were combined, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The resulting crude oil was chromatographed on SiO_2 (30 g, 2 x 6.5 cm; 50% EtOAc/hex, 400 mL) to provide 1.62 g, 73 % yield which proved to be 22/2/1 mixture (GC) of **5d/6d/7d**. For **5d**: t_R (method A)= 16.8, 16.9 min; R_f = 0.17, 33 % EtOAc/hex; ^{1}H NMR ($CDCl_3$) 6.1 (m, 2H), 4.7 (m, 1H), 4.6 (m, 2H), 3.9 (m, 1H), 3.5 (m, 1H), 2.7 (m, 1H), 1.4-2.0 (m, 8H); ^{13}C NMR ($CDCl_3$) 137.2, 137.1, 134.8, 133.6, 98.3, 97.8, 79.7, 79.5, 74.7, 74.5, 62.6, 62.5, 42.0, 41.1, 31.1, 30.9, 25.4, 19.6, 19.5; IR (neat) ν_{max} 3410, 2942, 1020 cm^{-1}; CIMS (CH_4) m/e (% relative intensity) 183 (MH^+, 7), 167 (MH^+-H_2O, 40), 85 (100).

(+/-)-*cis*-4-*t*-Butyloxy-2-cyclopentenol (5e)

A slurry of $LiAlH_4$ (55 mg, 1.4 mmol, 0.52 eq) and LiI (1.65 g, 5.76 mmol, 2.0 eq) in TBME (2 mL)/ PhMe (3 mL) was cooled to -15 °C and treated dropwise with a solution of ketone **4e** (430 mg, 2.79 mmol) in PhMe (1 mL, 5 min). The resulting reaction mixture was stirred for 2 h at -20 to -12 °C. The cold bath was removed and the reaction mixture allowed to warm to rt with stirring for 30 min. The reaction mixture was treated sequentially with NaOH (1N, 1 mL) and TBME (10 mL) and then filtered. Phases were separated , the aqueous phase extracted with TBME (15 mL). The organic phases were combined, dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by SiO_2 chromatography (30 g, 2.5 x 7 cm; 33% EtOAc/hex) provided 183 mg of a yellow oil, 42% yield. GC analysis showed a 9/1/trace ratio of **5e/6e/7e**. For **5e**: t_R (method A)= 6.63 min; R_f = 0.21, 33% EtOAc/hex; ^{1}H NMR ($CDCl_3$) 5.9 (m, 1H), 5.8 (m, 1H), 4.6 (m, 1H), 4.5 (m, 1H), 2.7 (m, 1H), 2.0 (d, 1H, *J* = 9.6 Hz), 1.5 (d appt, 1H, *J* = 4.5, 14 Hz), 1.2 (s, 9H); ^{13}C NMR ($CDCl_3$) 136.6, 136.0, 75.5, 74.4, 74.0, 44.6, 28.7; IR (neat) ν_{max} 3395, 2974, 2934, 1068 cm^{-1}; CIMS (CH_4) m/e (% relative intensity) 157 (MH^+, 18), 139 (MH^+-H_2O, 57), 83 (100).

(+/-)-*cis*-4-Benzyloxy-2-cyclopentenol (5f)

A solution of $LiAlH_4$ (45 mg, 1.2 mmol) and LiI (451 mg, 3.37 mmol) in Et_2O (4 mL) was cooled to -30 °C and treated dropwise with a solution of 4-benzyloxy-2-cyclopentenone **4f** (444 mg, 2.36 mmol) in Et_2O (1 mL, 5 min; -32 to -26 °C). The resulting reaction mixture was stirred for 1.5 h at -25 °C, treated with NaOH (1N, 1 mL) and allowed to warm to rt. The mixture was filtered and filtrate extracted with EtOAc (2 x 10 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo*. GC analysis showed a 7/1/1 ratio of

5f/6f/7f. Purification via SiO_2 chromatography (25g, 5.5 x 2.5 cm, gradient elution 20%-33% EtOAc/hex) gave a pale yellow oil, 151 mg, 34% yield. For **5f**: t_R (method A)= 19.9 min; R_f = 0.28, 33% EtOAc/hex; ^{1}H NMR ($CDCl_3$) 7.3 (m, 5H), 6.05 (appt, 2H, *J* = 7 Hz), 4.6 (m, 1H), 4.56 (dd, 2H, *J* = 11.7, 17 Hz), 4.44 (dd, 1H, *J* = 4, 6.8 Hz), 2.7 (m, 1H), 1.67 (d appt, 1H, *J* = 4, 14 Hz); ^{13}C NMR ($CDCl_3$) 138.6, 137.4, 134.5, 128.7, 128.1, 127.9, 81.7, 75.3, 71.3, 41.3; IR (neat) ν_{max} 3387, 3063, 2935, 2863, 1072 cm^{-1}; CIMS (CH_4) m/e (% relative intensity) 173 (MH^+-H_2O, 38), 91 (100). Anal calcd. for $C_{12}H_{14}O_2$ (190.24): C, 75.77; H, 7.41. Found: C, 75.61; H, 7.78.

Due to the poor yields obtained for the formation of ketone **4f** and subsequent reduction to form **5f**, **5f** was alternatively prepared by mono-*O*-alkylation of *cis*-diol **5h** with benzylbromide.[23]

(+/-)-*cis*-4-Trityloxy-2-cyclopentenol (5g)

A slurry of enone **4g** (1.03 g, 3.03 mmol) in PhMe (8 mL) was cooled to -20 °C and treated sequentially with $LiAlH_4$ (76 mg, 2.0 mmol, 0.66 eq), LiI (1.06 g, 7.9 mmol, 2.6 eq), and dropwise with TBME (2 mL; 5 min). The resulting reaction was stirred for 1 h at -20 °C, 0.5 h at -20 to 0 °C, 4 h at 0 to 15 °C. NaOH (1N, 2 mL) was added slowly, the reaction filtered, and the solids were washed with TBME (20 mL). The phases were separated, organic phase dried ($MgSO_4$), filtered, and evaporated *in vacuo* (55 °C, 15 mmHg). Purification via flash chromatography on SiO_2 (40 g, 4 x 7 cm; 20% EtOAc/hex) gave **5g**, 980 mg, 95% yield, as a white foam. For **5g**: R_f = 0.13, 20% EtOAc/hex; ^{1}H NMR ($CDCl_3$) 7.5 (m, 6H), 7.3 (m, 9H), 5.79 (d, 1H, *J* = 5.5 Hz), 5.14 (d, 1H, *J* = 5.5 Hz), 4.5 (m, 1H), 4.4 (m, 1H), 2.2 (m, 1H), 1.42 (d appt, 1H, *J* = 4.7, 13.8 Hz); ^{13}C NMR ($CDCl_3$) 145.1, 136.2, 135.9, 129.0, 128.1, 127.3, 87.7, 77.4, 74.9, 43.2; IR (KBr) ν_{max} 3422, 3057, 1024 cm^{-1}; CIMS (NH_3) m/e (% relative intensity) 342 (M^+, 26), 243 (100). FABHRMS (MNBA/PEG) m/e 343.1717 ($C_{24}H_{22}O_2$ requires 343.1698).

cis-2-Cyclopentenyl-1,4-diol (5h)

Synthesized from (+/-)-cis-4-t-butyldimethylsilyloxy-2-cyclopentenol (5a)

A solution of *cis*-4-*t*-butyldimethylsilyloxy-2-cyclopentenol (**5a**, 50 g, 0.233 mol) in THF (250 mL) at rt was treated sequentially with Et_3N (5.00 mL, 0.036 mol) and TBAF (250 mL, 1M in THF, 0.25 mol). After stirring for 3 h, the solution was concentrated (40 °C, 20 mmHg) and the residue chromatographed on SiO_2 (100 x 160 mm), eluting with 10% acetone in EtOAc. The resulting solid was recrystallized from $CHCl_3$ to provide **5h** as white needles,[25] 18.0 g, 77% yield. Mp 57-58 °C; R_f = 0.25, 10% acetone/EtOAc; t_R (method A) = 3.71 min; ^{1}H NMR ($CDCl_3$) 6.01 (s, 2H), 4.6 (m, 2H), 4.02 (d, 2H, *J* = 7.3 Hz), 2.73 (dt, 1H, *J* = 14.5, 7.3 Hz), 1.57 (dt, 1H, *J* = 14.5, 3.4 Hz); IR (KBr) ν_{max} 3402, 3391, 3364 cm^{-1}; CIMS (CH_4) m/e (% relative intensity) 83 (MH^+- H_2O, 100). Anal calcd. for $C_5H_8O_2$ (100.12): C, 59.98; H, 8.05. Found: C, 59.79; H, 8.36.

Synthesized from cis-2-cyclopentenyl-1,4-diacetate (9)

A solution of *cis*-2-cyclopentenyl-1,4-diacetate **9** (74.0 g, 0.402 mol) in methanol (200 mL) was treated with K_2CO_3 (110 g, 0.797 mol) and refluxed for 2 h. The mixture was diluted with THF (1 L), filtered, and concentrated (40 °C, 20 mmHg) to afford **5h** as an oily solid, 40 g, quantitative yield. The material gave analogous analytical data to the above reported diol.

Synthesized from (+/-)-cis-4-Trityloxy-2-cyclopentenol ***5g***

A solution of trityl alcohol **5g** (200 mg, 0.58 mmol) in EtOH (2 mL) was treated with *p*-TsOH (20 mg) and stirred at 55 °C for 8 h. The resulting reaction mixture was concentrated *in vacuo* (55 °C, 15 mmHg) and purified on SiO_2 as previously reported to provide diol **5h**, 58 mg, quantitative yield. GC analysis showed a 30/1/trace mixture of *cis/trans*/1,4-+1,2-reduction products. This diol had similar analytical data as above.

(1*R*,4*S*)-(-)-4-Acetoxy-2-cyclopentenol (8)

*From TBAF Deprotection of (-)-**11***

A solution of enriched silyl ether (-)-**11** (150 g, 587 mmol) in THF (500 mL) and Et_3N (8 mL, 0.1 eq) was treated with a solution of TBAF (1M in THF, 600 mL, 600 mmol, 1.02 eq) and stirred for 2 h at rt. The resulting reaction mixture was treated with H_2O (32 mL, 1.78 mol, 3 eq), stirred for 20 min then evaporated *in vacuo* (20 mm Hg, rt). The residue was purified by plug chromatography on SiO_2 [750 g, 20% EtOAc/heptane (10 L); 50% EtOAc/heptane (20 L)] to provide 74 g of a yellow solid enriched (-)-**8**. Recrystallization from TBME/heptane (400 mL/450 mL) provided 55.5 g, 67% yield (4 crops; 41g, 9.5 g, 3 g, 2 g). For enriched (-)-**8**: mp 46-48 °C; $[\alpha]_D^{20}$ = -69.6° (c = 1.03, $CHCl_3$); R_f = 0.13, 33% EtOAc/hex; t_R (method A) = 6.74 min; t_R (method B) = 13.1 min; ^1H NMR ($CDCl_3$) 6.1 (m, 1H), 6.0 (m, 1H), 5.5 (m, 1H), 4.8 (m, 1H), 2.83 (dt, 1H, *J* = 14.5, 7.3 Hz), 2.22 (d, 1H, *J* = 7.8 Hz), 2.08 (s, 3 H), 1.6 (dt, 1H, *J* = 14.5, 3.8 Hz); ^{13}C NMR ($CDCl_3$) 170.8, 138.5, 132.5, 76.6, 74.8, 40.5, 21.2; IR (KBr) ν_{max} 3385, 3327, 1726 cm^{-1}; CIMS (CH_4) m/e (% relative intensity) 143 (MH^+, 10), 125 (MH^+- H_2O, 52), 83 (MH^+- AcOH, 100). Anal calcd. for $C_7H_{10}O_3$ (142.16): C, 59.15; H, 7.09. Found: C, 59.10; H, 7.01.

*THP Removal to Assess Optical Purity of (-)-**13***

Enriched (-)-acetate THP ether (-)-**13** (192 mg, 0.85 mmol) was dissolved in EtOH (1.5 mL), treated with *p*-TsOH (11.7 mg) and stirred for 2 h at rt. Carbonate or bicarbonate (excess) was added, and solvent evaporated *in vacuo* (rt, 15 mmHg). The crude colorless oil was chromatographed on SiO_2 [3 g, 1.5 x 3 cm, 33% EtOAc/hex (80 mL)] to provide 90 mg, 75% yield of enriched mono-acetate (-)-**8**. Analysis of optical purity by GC chiral column: t_R (method B) = 13.1 min (major) and 13.5 min (minor); 91%ee.

(1*S*,4*R*)-(+)-4-Acetoxy-2-cyclopentenol (ent-8)

*Acylation of THP Alcohol (-)-**12** Followed by THP Removal to Assess Optical Purity of (-)-**12***

Enriched (-)-THP alcohol **12** (292mg, 1.59 mmol) was dissolved in pyridine (2.8 mL), treated sequentially with Ac_2O (0.39 mL) and DMAP (16 mg), and stirred at rt for 16 h. The resulting reaction mixture was evaporated to dryness, diluted with EtOAc (10 mL), washed sequentially with HCl 1/2 sat'd brine (0.5M; 2 x 10 mL), $NaHCO_3$ sat'd solution (10 mL) then brine (10 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude oil **28** was converted into mono-acetate (+)-**ent-8** in an analogous fashion to enriched (-)-**13**. (+)-**ent-8** was obtained 147 mg, 65% overall yield as a white solid which was >94%ee; t_R (method B) = 13.5 min.

(1*R*,4*S*)-(-)-4-*t*-Butyldimethylsilyloxy-2-cyclopentenol (10)

General procedure for the resolution of *cis*-mono-*O*-protected 2-cyclopenten-1,4-diols: Alcohol (+/-)-**5a** (25.4 g, 119 mmol) in TBME (150 mL) was treated sequentially with Et_3N (11.3 mL, 81 mmol, 0.68 eq), pancreatin (75 g, 3 wt eq; Sigma 8xUHP) and vinyl acetate (55 mL, 600 mmol, 5 eq) and stirred for 6-8 h at rt. The resulting slurry was filtered and concentrated *in vacuo*. Purification by plug filtration on SiO_2 [600 g, 8 x 14 cm; 5% EtOAc/hex (2 L), 10% EtOAc/hex (2 L), 20% EtOAc/hex (2 L)] gave 14.66 g, 48% yield of acetate (-)-**11** (98%ee using GC Method C) and 11.83 g, 47% yield of alcohol (-)-**10** (98%ee as determined by conversion to acetate derivative (+)-**27** and GC chiral column analysis). For enriched (-)-**10**: spectroscopically identical to (+/-)-**5a**; $[\alpha]_D^{20}$ = -21.2° (c = 0.89, $CHCl_3$). Anal calcd. for $C_{11}H_{22}O_2Si$ (214.38): C, 61.63; H, 10.34. Found: C, 61.80; H, 10.40. This material could not be separated by GC chiral columns described in this report. Therefore, acetate derivative (+)-**27** was prepared to assess the optical purity.

(1*S*,4*R*)-(-)-4-*t*-Butyldimethylsilyloxy-2-cyclopentenyl acetate (11)

Isolated from the pancreatin reaction of (+/-)-**5a**. For enriched (-)-**11**: spectral data analogous to (+)-**27**; $[\alpha]_D^{20}$ = -0.6° (c = 1.00, $CHCl_3$); t_R (method C) = 19.2 min and proved to be 98%ee.

(1*R*,4*S*)-(-)-4-(2'*R-Tetrahydropyranyloxy)-2-cyclopentenol (12)**

Following the general enzyme procedure: (+/-)-alcohol **5d** (1.091, 5.92 mmol) was stirred for 7 h at rt. Work-up and chromatography on SiO_2 (30 g, 3 x 6.5 cm; 10% EtOAc/hex, 200 mL; 20% EtOAc/hex, 300 mL) gave enriched acetate (-)-**13** 601 mg, 45 % yield, along with enriched alcohol (-)-**12** 560 mg, 50% yield. Isolated (-)-**12** was spectroscopically identical to (+/-)-**5d**. For enriched (-)-**12**: $[\alpha]_D^{20}$ = -9.9° (c = 1.06, $CHCl_3$). This material was determined to be 94%ee by conversion to its acetate derivative (+)-**ent-8** and subsequent GC chiral column analysis. Anal calcd. for $C_{11}H_{16}O_3 \bullet 0.13\ H_2O$ (186.58): C, 64.38; H, 8.78. Found: C, 64.32; H, 8.97.

(1*S*,4*R*)-(-)-4-(2'*R-Tetrahydropyranyloxy)-2-cyclopentenyl acetate (13)**

Isolated from enzyme resolution of (+/-)-**5d**. For enriched (-)-**13**: $[\alpha]_D^{20}$ = -19.8° (c = 1.00, $CHCl_3$); t_R (method A)= 19.7 min; ^1H NMR ($CDCl_3$) 6.1 (m, 1H), 5.9 (m, 1H), 5.5 (m, 1H), 4.7 (m, 2H), 3.9 (m, 2H), 3.5 (m, 1H), 2.1 and 2.05 (s, 3H), 1.5-1.9 (m, 7H); ^{13}C NMR ($CDCl_3$) 171.1, 137.8, 136.3, 132.9, 132.5, 98.8, 98.5, 79.6, 79.3, 77.0, 76.8, 62.9, 62.8, 38.9, 37.9, 31.2, 31.1, 25.7, 21.4, 19.9, 19.8; IR (neat) ν_{max} 2944, 2872, 1736, 1364, 1078, 1020 cm^{-1}; CIMS m/e (% relative intensity) 227 (MH^+, 5), 167 (MH^+- AcOH, 41), 125 (MH^+-$C_5H_{10}O_2$, 25), 85 (100). This material was determined to be 91%ee by conversion to enriched mono-acetate (-)-**8** by THP removal and analysis by GC chiral column. Anal calcd. for $C_{12}H_{18}O_4$ (226.27): C, 63.70; H, 8.01. Found: C, 63.42; H, 8.09.

(1*R*,4*S*)-(-)-4-*t*-Butyloxy-2-cyclopentenol (14)

(+/-)-Cyclopentenol **5e** (485 mg, 3.1 mmol) was subjected to the pancreatin reaction conditions with stirring for 17 h at rt to provide enriched (-)-**14**, 194 mg as a pale yellow oil in 40% yield, along with enriched

acetate (-)-**15** in 51% yield. For (-)-**14**: $[\alpha]_D^{20}$ = -17.2° (c = 1.09, $CHCl_3$); t_R (method C)= 5.6 min. By GC chiral column the other enantiomer (+)-**25** was not detected [GC, t_R (Method C) = 4.7 min, 98%ee]. This material provided identical spectral data to (+/-)-**5e**. Anal calcd. for $C_9H_{16}O_2$ (156.23): C, 69.19; H, 10.32. Found: C, 69.07; H, 10.37.

(1*S*,4*R*)-(-)-4-*t*-Butyloxy-2-cyclopentenyl acetate (15)

Isolated from enzyme resolution of (+/-)-**5e**. For enriched (-)-**15**: $[\alpha]_D^{20}$ = -10.9° (c = 0.98, $CHCl_3$); t_R (method C)= 8.7 min (major), 8.4 min (minor); ^{1}H NMR ($CDCl_3$) 5.94 (d, 1H, *J* = 5.5 Hz), 5.89 (d, 1H, *J* = 5.5 Hz), 5.46 (appt, 1H, *J* = 5.5 Hz), 4.52 (appt, 1H, *J* = 5.5 Hz), 2.8 (m, 1H), 2.00 (s, 3H), 1.60 (d appt, 1H, *J* = 4.8, 14 Hz), 1.22 (s, 9H); ^{13}C NMR ($CDCl_3$) 171.2, 138.6, 131.6, 77.4, 77.2, 41.0, 28.7, 28.6, 21.4; IR (neat) ν_{max} 2976, 1738, 1364, 1242 cm^{-1}; CIMS (CH_4) m/e (% relative intensity) 199 (MH^+, 4), 139 (MH^+-AcOH, 70), 83 (100). Anal calcd. for $C_{11}H_{18}O_3$ (198.12): C, 66.64; H, 9.15. Found: C, 67.11; H, 9.03. The enantiomeric purity of this material was analyzed by GC chiral column and determined to be 76%ee (88/12 mixture).

(1*R*,4*S*)-(-)-4-Benzyloxy-2-cyclopentenol (16)

Following the general enzyme procedure: (+/-)-**5f** (623 mg, 3.28 mmol) after 4 h at rt, work-up and chromatography gave alcohol (-)-**16** in 20% yield and 98%ee, along with enriched acetate (-)-**17** in 74% yield and 30%ee. The optical purity of enriched (-)-**16** was determined by the preparation of its acetate derivative and GC chiral column analysis. For enriched (-)-**16**: $[\alpha]_D^{20}$ = -16.2° (c = 0.72, $CHCl_3$); 98%ee by GC chiral column analysis of acetate (+)-**29** (no enantiomer (-)-**17** detected).

(1*S*,4*R*)-(-)-4-Benzyloxy-2-cyclopentenyl acetate (17)

Isolated from the enzyme resolution of (+/-)-**5f**. Determined to be 35/65 mixture of enantiomers (+)-**29**/(-)-**17**, 30% ee. For enriched (-)-**17**: $[\alpha]_D^{20}$ = -5.2° (c = 0.97, $CHCl_3$); t_R (method C; col. temp =132 °C) = 31.5 min (major), 30.7 min (minor); t_R (method A)= 22.4 min; ^{1}H NMR ($CDCl_3$) 7.3 (m, 5H), 6.13 (d, 1H, *J* = 5 Hz), 5.99 (d, 1H, *J* = 5 Hz), 5.5 (m, 1H), 4.59 (d, 1H, *J* = 11.8 Hz), 4.54 (d, 1H, *J* = 11.8 Hz), 4.5 (m, 1H), 2.78 (d appt, 1H, *J* = 7.2, 14.3 Hz), 2.05 (s, 3H), 1.76 (d appt, 1H, *J* = 4.4, 14.3 Hz); ^{13}C NMR ($CDCl_3$) 171.1, 138.5, 136.4, 133.1, 128.7, 128, 127.9, 81.4, 77.1, 71.2, 37.8, 21.4; IR (neat) ν_{max} 2938, 1734, 1454, 1366, 1069, 1026 cm^{-1}; CIMS (CH_4) m/e (% relative intensity) 233 (MH^+, 5), 173 (MH^+-AcOH, 70), 91 (100). Anal calcd. for $C_{14}H_{16}O_3$ (232.28): C, 72.40; H, 6.94. Found: C, 72.60; H, 7.08.

(1*S*,3*R*)-(-)-3-*t*-Butyldimethylsilyloxycyclopentanol (21)

Following the general enzyme procedure: (+/-)-alcohol **20**[11] (2.12 g, 9.8 mmol) for 27 h at rt gave after work-up and chromatography on SiO_2 [55g, 6 x 8 cm; gradient elution hexane (300 mL), 5% EtOAc/hex (500 mL)] 1.23 g of enriched acetate (+)-**22**, 48% yield (GC chiral column analysis showed 98%ee) and enriched alcohol (-)-**21**, 771 mg, 37% yield (GC chiral column analysis of acetate derivative (-)-**30** showed 94%ee). For (-)-**21**: $[\alpha]_D^{20}$ = -3.7° (c = 1.20, $CHCl_3$); R_f = 0.2, 20% EtOAc/hex; t_R (method A)= 14.22 min; t_R (method C)= 8.9 min; ^{1}H NMR ($CDCl_3$) 4.4 (m, 1H), 4.3 (m, 1H), 3.03 (d, 1H, *J* = 10.5 Hz), 1.9-1.6 (m, 6H), 0.89 (s,

9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) 74.9, 74.1, 44.4, 34.2, 34.1, 25.8, 17.9, -4.9, -5.0; IR (neat) ν_{max} 3405, 2957, 2932, 1038, 1026 cm^{-1}; CIMS (CH_4) m/e (% relative intensity) 217 (MH^+, 81), 199 (MH^+-H_2O, 37), 67 (100). Anal calcd. for $C_{11}H_{24}O_2Si$ (216.40): C, 61.06; H, 11.18. Found: C, 61.32; H, 11.13. This enantiomer and its antipode could not be separated using GC chiral columns described in this report. The optical purity of this material was determined by the preparation of its acetate derivative (-)-**30** and GC chiral column analysis.

(1*R*,3*S*)-(+)-3-*t*-Butyldimethylsilyloxycyclopentanyl acetate (22)

Obtained from enzymatic acylation of (+/-)-**20**. For enriched acetate (+)-**22**: $[\alpha]_D^{20}$ = +7.0° (c = 1.12, $CHCl_3$); t_R (method C)= 19.2 min. Anal calcd. for $C_{13}H_{26}O_3Si$ (258.40): C, 60.42; H, 10.14. Found: C, 60.70; H, 10.51. All other spectral data was analogous to acetate (-)-**30**.

(1*S*,4*R*)-(+)-4-*t*-Butyldimethylsilyloxy-2-cyclopentenol (23)

Representative procedure for the hydrolysis of esters **11**, **13**, **15**, and **17**: A solution of enriched acetate (-)-**11** (600 mg, 2.3 mmol) in THF/MeOH/H_2O (2.7 mL:0.9 mL:0.9 mL) was treated with LiOH•H_2O (105 mg, 1.1 eq) and stirred at rt for 3 h. The resulting reaction mixture was diluted with H_2O (10 mL) and extracted with TBME (3 x 15 mL). The organic phases were combined, dried ($MgSO_4$), filtered, and evaporated *in vacuo*. Purification by SiO_2 plug filtration (3 g, 0.5 x 4.5 cm; 20% EtOAc/hexane) gave 452 mg, quantitative yield. For enriched alcohol (+)-**23**: $[\alpha]_D^{20}$ = +21.8° (c = 1.02, $CHCl_3$). All other analytical data was analogous to (-)-**10** and (+/-)-**5a**.

(1*S*,4*R*)-(+)-4-(2'*R-Tetrahydropyranyloxy)-2-cyclopentenol (24)**

Using general hydrolysis procedure: **13** (106 mg, 0.47 mmol) gave 80 mg of (+)-THP alcohol **24** in 93% yield. For enriched (+)-**24**: $[\alpha]_D^{20}$ = +9.9° (c = 0.98, $CHCl_3$). This material was determined to be 91%ee by analysis of its acetate derivative (-)-**8**, and subsequent GC chiral column analysis.

(1*S*,4*R*)-(+)-4-*t*-Butyloxy-2-cyclopentenol (25)

Enriched acetate (-)-**15** (90 mg, 0.45 mmol) was subjected to standard hydrolysis conditions as previously described and chromatographed on SiO_2 (2 g, 1.5 x 2.5 cm, 40% Et_2O in hexane) to provide a pale yellow oil, 71 mg, quantitative yield. For enriched (+)-**25**: $[\alpha]_D^{20}$ = +14.6° (c = 1.03, $CHCl_3$); t_R (method C)= 4.7 min (major), 5.6 min (minor), 76%ee. All other spectral data was analogous to (+/-)- **5e** and (-)-**14**.

(1*S*,4*R*)-(+)-4-Benzyloxy-2-cyclopentenol (26)

Using general hydrolysis conditions: enriched acetate (-)-**17** (158 mg, 0.68 mmol) gave 120 mg, 93% yield of enriched alcohol (+)-**26**. For enriched acetate (+)-**26**: $[\alpha]_D^{20}$ = +5.0° (c = 0.94, $CHCl_3$). Anal calcd. for $C_{12}H_{14}O_2$•0.12 H_2O (216.19): C, 74.80; H, 7.51. Found: C, 74.91; H, 7.46.

(1*R*,4*S*)-(+)-4-*t*-Butyldimethylsilyloxy-2-cyclopentenyl acetate (27)

Representative procedure for the preparation of acetates **27-30** from optically active mono-*O*-protected diols **10**, **12**, **16** and **21**: (-)-TBS ether (**5a**, 1 g, 4.67 mmol) was dissolved in pyridine (20 mL), then treated with Ac_2O (2 mL) and stirred overnight at rt. The resulting crude reaction mixture was diluted with Et_2O (100 mL) and washed sequentially with HCl (3N; 3 x 100 mL), sat'd $NaHCO_3$ (100 mL) and brine (100 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo* to provide 1 g, 98% of crude yellow oil. For enriched (+)-**27**: R_f = 0.5, 5% EtOAc/hex; $[\alpha]_D^{20}$ = +0.4° (c = 1.00, $CHCl_3$); t_R (method C) = 18.3 min; 99.1:0.9, 98.2% ee; t_R (method A) = 17.47 min. ^{1}H NMR ($CDCl_3$) 6.0 (m, 1H), 5.9 (m, 1H), 5.5 (m, 1H), 4.7 (m, 1H), 2.8 (m, 1H), 2.05 (s, 3H), 1.6 (m, 1H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$) 170.8, 138.8, 131.1, 76.9, 74.8, 41.1, 25.8, 21.1, 18.1, -4.7, -4.6; IR (neat) ν_{max} 2955, 2932, 1739, 1369, 1240, 1049 cm^{-1}; CIMS m/e (% relative intensity) 256 (MH^+, 7), 197 (MH^+-AcOH, 100). Anal calcd. for $C_{13}H_{24}O_3Si$ (256.42): C, 60.90; H, 9.43. Found: C, 60.41; H, 9.41.

(1*R*,4*S*)-(+)-4-Benzyloxy-2-cyclopentenyl acetate (29)

Following the general acylation procedure: enriched alcohol (-)-**16** (48 mg, 0.25 mmol) gave 55 mg, 94% yield of enriched acetate (+)-**29**. For enriched (+)-**29**: $[\alpha]_D^{20}$ = +11.8° (c = 0.98, $CHCl_3$); t_R (method C; col. temp =132 °C)= 30.7 min (only detected isomer). All other spectral data analogous to (-)-**17**. Anal calcd. for $C_{14}H_{16}O_3$ (232.28): C, 72.39; H, 6.94. Found: C, 72.80; H, 7.12.

(1*S*,3*R*)-(-)-3-*t*-Butyldimethylsilyloxycyclopentanyl acetate (30)

Following the standard acylation conditions: enriched alcohol (-)-**21** (209 mg, 2.5 mmol) gave acetate (-)-**30** in quantitative yield (crude) after work-up. Analysis of the crude material by GC chiral column showed a 97/3 ratio of enantiomers. For enriched acetate (-)-**30**: $[\alpha]_D^{20}$ = -6.6° (c = 0.99, $CHCl_3$); t_R (method A)= 17.5 min; t_R (method C)= 18.4 min; ^{1}H NMR ($CDCl_3$) 5.0 (m, 1H), 4.2 (m, 1H), 2.2 (m, 1H), 2.02 (s, 3H), 1.9 (m, 2H), 1.7 (m, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$) 171.3, 75.0, 72.7, 42.3, 34.3, 30.5, 26.0, 21.5, 18.3, -4.5; IR (neat) ν_{max} 2957, 2932, 1740, 1250, 1045 cm^{-1}; CIMS m/e (% relative intensity) 259 ($M+H^+$, 100).

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2. a) Starting with cyclopentadiene, cracking of the dimer (which we wanted to avoid) is required; some re-dimerization takes place. b) $^1O_2$ reaction with cyclopentadiene has been demonstrated on a 100 g scale (ref 1b) but further scale-up would be problematic. In the past, we also had problems with easily removing the reducing agent and by-products even on laboratory scale. c) Epoxidation of cyclopentadiene gives the mono-epoxide which is not stable and slowly forms cyclopent-3-enone (see 2a). See: Deardorff, D. R.; Myles, D. C. and MacFerrin K. D. *Tetrahedron Lett.* **1985**, *26*, 5615. d) Bromination and subsequent acetoxylation of cyclopentadiene (ref 3) in our hands was nonselective. A 1:1 mixture of *cis*:*trans* acetates was obtained.

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7. For a recent example of this see: Knight, S. D.; Overman, L. E. and Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776-5788.

8. a) Nanni, M.; Ta-machi, H. and Moriyama-shi Japanese Patent Disclosure Bulletin #57-62236, April 15, 1982. Compound **3** stains almost all surfaces, including skin. Care should be taken to keep the material in the flask.

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11. Reduction of (+/-)-**5a** with Ni_2B catalyst/H_2 in MeOH provides (+/-)-**20**. A similar procedure was used to prepare authentic samples of 3-TBSO-cyclopentanone from **4a**. For the preparation of Ni_2B SC-1 see: Belisle, C. M.; Young, Y. M. and Singaram, B. *Tetrahedron Lett.* **1994**, *35*, 5595-5598.

For 3-TBSO-cyclopentanone: t_R (method A)= 14.7 min; ^1H NMR ($CDCl_3$) 4.5 (m, 1H), 2.3 (m, 2H), 2.2-1.9 (m, 4H), 0.85 (s, 9H), 0.050 (s, 3H), 0.040 (s, 3H); ^{13}C NMR ($CDCl_3$) 217.8, 70.4, 48.5, 35.8, 33.0, 25.9, 18.2, -4.6, -4.7.

(+/-)-*Trans*-mono-TBS-cyclopenten-1,4-diol was isolated via flash chromatography after Dibal-H reduction of the ketone **4a** at 0 °C. For **6a**: t_R (method A)= 14.9 min; ^1H NMR ($CDCl_3$) 5.9 (m, 2H), 5.1 (m, 1H), 5.0 (m, 1H), 2.1 (m, 2H), 0.90 (s, 9H), 0.090 (s, 6H); ^{13}C NMR ($CDCl_3$) 138.3, 135.5, 76.6, 76.2, 44.4, 25.9, 18.2, -4.7.

A 15/85 mixture of *cis/trans* cyclopentan-1,3-diol (**7h**) was prepared by reaction of BH_3 with cyclopentadiene. We thank Syncom for supplying us with this material. This mixture was monosilylated[23] to give authentic samples of **7a**. For **7a**: t_R (method A)=13.8 min (*cis*), 14.3 min (*trans*).

12. Because some impurities overlapped and to confirm ratios of products in the TBS series, another analytical method was developed for GC and GC/MS conditions. DB-Wax (15 m x 0.32 mm id.) 0.25 μm; linear velocity (He) = 23 cm/sec; injection port, 200 °C; detector, 240 °C; oven (gradient), 100 °C (40 min), 10 °C/min to 140 °C (hold 20 min). Under these conditions the following retention times were obtained: 3-TBSO-cyclopentanone, t_R = 10.8 min; *cis*-**7a**, t_R = 12.3 min; **4a**, t_R = 16.1 min; *trans*-**7a**, t_R = 22.7 min; **5a**, t_R = 28.2 min; **6a**, t_R = 38.9 min.

13. a) Mori, Y. and Suzuki, M. *Tetrahedron Lett.* **1989**, *30*, 4383-4386. b) *ibid.*; 4387-4390.

14. a) Brown, H. C. and Hess, H. M. *J. Org. Chem.* **1969**, *34*, 2206-2209. b) Brown, H. C. and Weissman, P. M. *J. Am. Chem. Soc.* **1965**, *87*, 5614-5620. c) Brown, H. C. and Deck, H. R. *J. Am. Chem. Soc.* **1965**, *87*, 5620-5625. d) Reduction of cyclopentenone with 9-BBN has been reported, and we did not try this on our substrates. Brown, H. C. and Krishnamurthy, S. *J. Org. Chem.* **1975**, *40*, 1864-1865.

15. We initially set a goal of 20:1 *cis*:*trans* selectivity. After having difficulty in the separation of many *cis* and *trans* mono-protected alcohols chromatographically, and discovering that the enzyme did not resolve the *trans* mono-protected alcohols, and therefore contaminated the optically active alcohols, we had a desire to attain very high *cis*-selectivity in the reduction.

16. With LiBr, *cis/trans* selectivity (**5a/6a**) was 15/1. With $ZnCl_2$ or $MgBr_2$ *cis/trans* selectivity was >25/1, but the amount of conjugate reduction product **7a** increased significantly.

17. a) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226-2227. b) Luche, J.-L. and Gemal A. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454-5459.

18. Attempts to reduce enone **3** under a range of reducing conditions with reagents that have been reported to be selective (>25:1) for the preparation of *cis*- or *trans*-1,3-diols (for *cis*, Et_2BOMe, $NaBH_4$[a,b] or for *trans*, $NaBH(OAc)_3$[c,d]) from β-hydroxy ketones were not useful in this system. We were unable to extract the water soluble diol from the worked-up reaction mixture or unable to degrade the presumably formed borate

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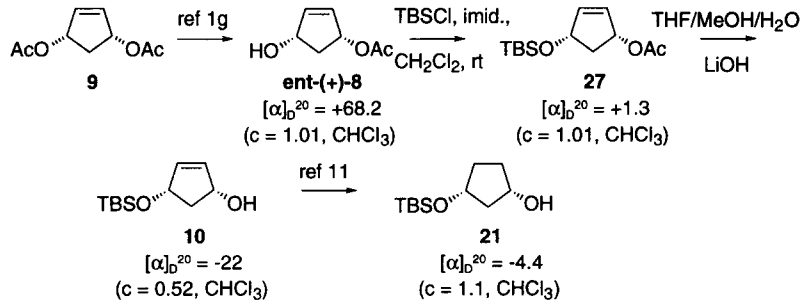
19. Theil, F.; Weidner, J.; Ballschuh, S.; Kunath, A. and Schick, H. *J. Org. Chem.* **1994**, *59*, 388-393.

20. An initial communication on the resolution of **5a** has appeared: Curran, T. T. and Hay, D. A. *Tetrahedron: Asymmetry* **1996**, *7*, 2791-2792.

21. Authenic samples were prepared as follows:



9

ent-(+)-8
$[\alpha]_D^{20}$ = +68.2
(c = 1.01, $CHCl_3$)

27
$[\alpha]_D^{20}$ = +1.3
(c = 1.01, $CHCl_3$)

10
$[\alpha]_D^{20}$ = -22
(c = 0.52, $CHCl_3$)

21
$[\alpha]_D^{20}$ = -4.4
(c = 1.1, $CHCl_3$)

22. For general comments on organic solvents used in enzymatic reactions see: Kvittingen, L. *Tetrahedron* **1994**, *50*, 8253-8274.

23. For monoprotection of diols: a) Rapoport, H. and Castellino, A. J. *J. Org. Chem.* **1986**, *51*, 1006-1011. b) Roush, W. R.; Straub, J. A. and VanNieuwenhze, M. S. *J. Org. Chem.* **1991**, *56*, 1636-1648. c) Additionally, reaction of diol **5h** under phase-transfer conditions [Bu_4NHSO_4 (cat) in NaOH (1.5 eq), H_2O, PhMe and BnBr at reflux] also provided monoprotected diol in >50% yield.

24. Acetyl migration has been observed in sugars: Franke, F. and Guthrie, R. D. *Aust. J. Chem.* **1977**, *30*, 639; Franke, F. and Guthrie, R. D. *Aust. J. Chem.* **1977**, *31*, 1285. On small scale (10-35 g) we did not observe acetyl migration or racemization. On larger scale (100 g), acetyl migration was observed and was easily diminished by the addition of water.

25. Diol **5h** is hygroscopic and will oil out if not kept in an inert, anhydrous atmosphere.

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