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A route to enantiomerically pure 5-(2′-hydroxyethyl)cyclopent-2-en-1-ol and its absolute configuration by Mosher esters

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ABSTRACT

The (±)-5-(2′-hydroxyethyl)cyclopent-2-en-1-ol **1** was prepared in a one-pot procedure, and was resolved using lipase AK and vinyl acetate with high ee. This provides a readily available chiral synthon for the synthesis of a wide variety of biologically interesting molecules. Further, the absolute configuration of diol **1** was confirmed directly by the Mosher ester method.

1. Introduction

We have prepared 5-(2′-hydroxyethyl)cyclopent-2-en-1-ol **1** as a precursor for conformationally restricted insect pheromone analogues **2**[1] (Fig. 1). Other compounds for which diol **1** could serve as a precursor include (Fig. 1) antiviral nucleoside analogues and *cis*-3,5-disubstituted cyclopentenes **3a**[2] and **3b**,[3] iridoid lactones[4] **3c** and **3d** and the spirodiketone unit of a fredericamycin A analogue **3e**.[5] The closely related hemiacetal **4a** and lactone **4b** are important precursors for prostaglandin A_2 and J_2, **5a** and **5b**.[6] The enantiomer of **4b** (R = Br or $OP(O)(OPh)_2$) has been used to synthesize jasmonoids such as **5c**.[7]

The enantiomerically pure diol **1** is an attractive chiral synthon for the synthesis of carbocyclic nucleosides that are structural analogues of natural and synthetic nucleosides, where the endocyclic oxygen atom is replaced by a methylene group. Naturally occurring carbocyclic nucleosides such as aristeromycin **6**[8] and neplanocine **7**[9] (Fig. 2) exhibit powerful antitumor and antiviral activities. The synthetic analogues such as carbovir **8** and carbocyclic-ddA **9** show high activities against HIV and hepatitis B virus.[10] Efficient enantioselective syntheses of carbovir analogues using diol **1** as an important intermediate have been reported by Olivo et al.[2a]

Three protocols have previously been employed to synthesize the racemic diol **1** (Scheme 1). First,[2a,11] the diol **1** was obtained via a hetero-Diels Alder reaction between cyclopentadiene **10** and glyoxylic acid. The initial adduct rearranges to provide lactone **11**, which is then reduced in a three-step procedure. This strategy involves relatively tedious work-up and purification procedures. Furthermore, relatively long reaction sequences are required. In a second strategy,[2c] cyclization of **12** was accomplished by Larock's procedure,[12] followed by reduction of **13** to afford diol **1**. However, an expensive palladium reagent was used in this protocol. Thirdly,[13] Meinwald rearrangement of 2,5-norbornadiene **14**, followed by a mild acid-catalyzed hydrolysis and hydride reduction in a one-pot operation gave the desired diol **1**.

In a previous attempt to prepare optically active diols of **1**, the lactone precursor **11** was resolved with either *Pseudomonas fluorescens* lipase or Amano lipase PS.[2a,14] The absolute configuration of (−)-(1*S*,5*R*)-**1** was deduced indirectly (Scheme 2). The initial absolute configuration can be traced back to (−)-aristeromycin **6**, in which the absolute configuration was established by X-ray analysis.[15] The absolute configuration of **16** was assigned by the correlation with **15**,[16] which is an intermediate to the total synthesis of (−)-aristeromycin **6**.[17] (−)-(1*S*,4*S*)-Carbovir **8** was synthesized from **16** in seven steps.[18] The absolute configuration of (−)-(1*S*,4*R*,5*S*)-**11a** was correlated with (−)-(1*S*,4*S*)-carbovir by several chemical transformations.[14] Since optically active (−)-(1*S*,5*R*)-**1** was obtained from (−)-(1*S*,4*R*,5*S*)-**11a**, its absolute configuration was correlated. However, in that work,[2a,14] a lower specific rotation for (−)-**1** was reported than the rotation we have observed. More importantly, due to a typographical error, they named compound (−)-**1** as '(1*R*,5*R*)'. Their structure of (−)-**1** as drawn does not agree with our assignment.

Herein, we report a method to enantiomerically pure diols (+)-**1** and (−)-**1** by enzymatic kinetic resolution, in which racemic **1** was obtained in a more economical, shorter and more efficient approach (route 3) when compared with routes 1 and 2. In this strategy, the required racemic **1** was synthesized from 2,5-norbornadiene **14** (route 3) in a one-pot operation. Furthermore, the absolute configuration of diol **1** was revisited directly by the Mosher ester method.

2. Results and discussion

2.1. Preparation of diol (±)-1

As mentioned above, three protocols are available to synthesize (±) dio1 **1**. First, strategy **1** was attempted (Scheme 3).[11] The

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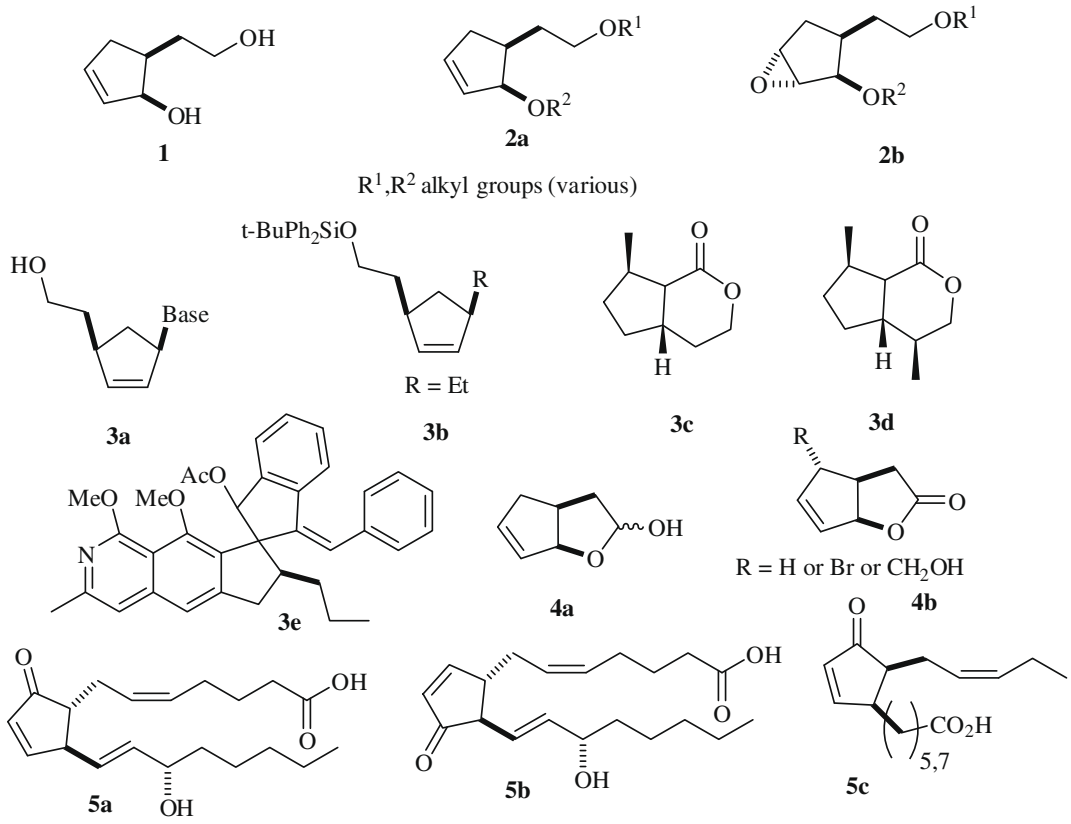


Figure 1. Potential examples using enantiomerically pure **1** as chiral synthon.

synthesis was started from hydroxylactone **11**, which was obtained by the water-promoted reaction of glyoxylic acid with cyclopentadiene. The reaction selectively gave a *cis*-adduct with a 2:1 ratio of *endo* **11a** to *exo* **11b** isomers. The hydroxylactones **11a** and **11b** were converted to racemic diol **1** in three steps. Initially, hydroxylactone **11** was reacted with mesyl chloride to the corresponding *endo*- and *exo*-mesylated products **15a** and **15b**, followed by a bromination reaction with lithium bromide to give bromolactone **16** in THF at reflux for 30 h. Close monitoring of the reaction by GC showed that the rate of bromination of *endo* mesyl isomer **15a** was faster than that of the *exo* isomer **15b**. The *endo* isomer required 4–6 h, whereas the *exo* isomer needed 30 h to achieve complete conversion. It was also observed that, upon bromination, the *endo* to *exo* ratio was inverted, indicating a S_N2 mechanism. Finally, (±) dio1 **1** was obtained by treating bromolactones **16a** and **16b** with $LiAlH_4$ in THF at reflux for 24 h. The overall yield of this sequence of reactions was 43% (relative to cyclopentadiene), and the procedures required more than 5 days (mainly because the hetero Diels–Alder reaction takes 3 days). Overall ca. 20 L of various solvents was required for the production of 1 mol of diol product.

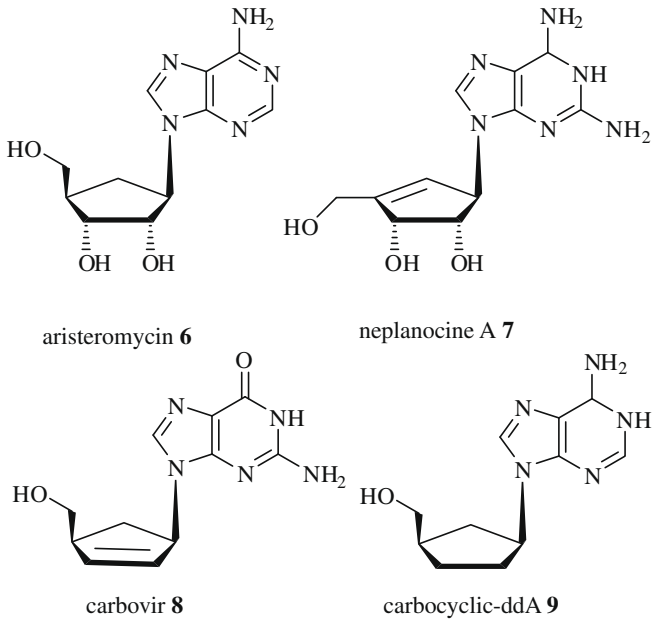
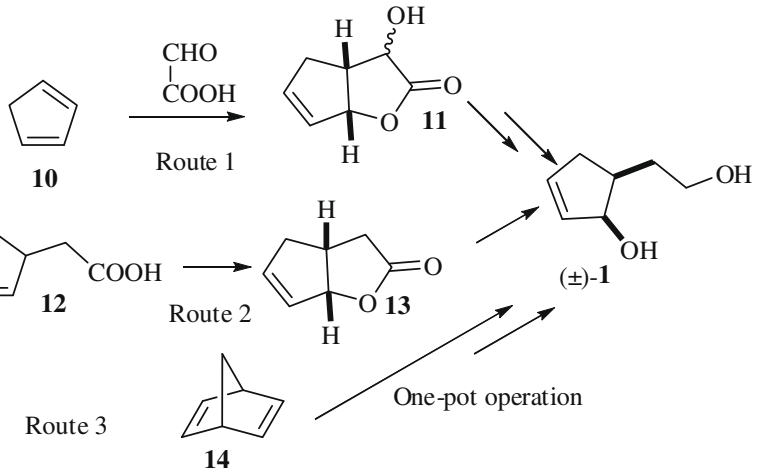


Figure 2. Examples of carbocyclic nucleosides.

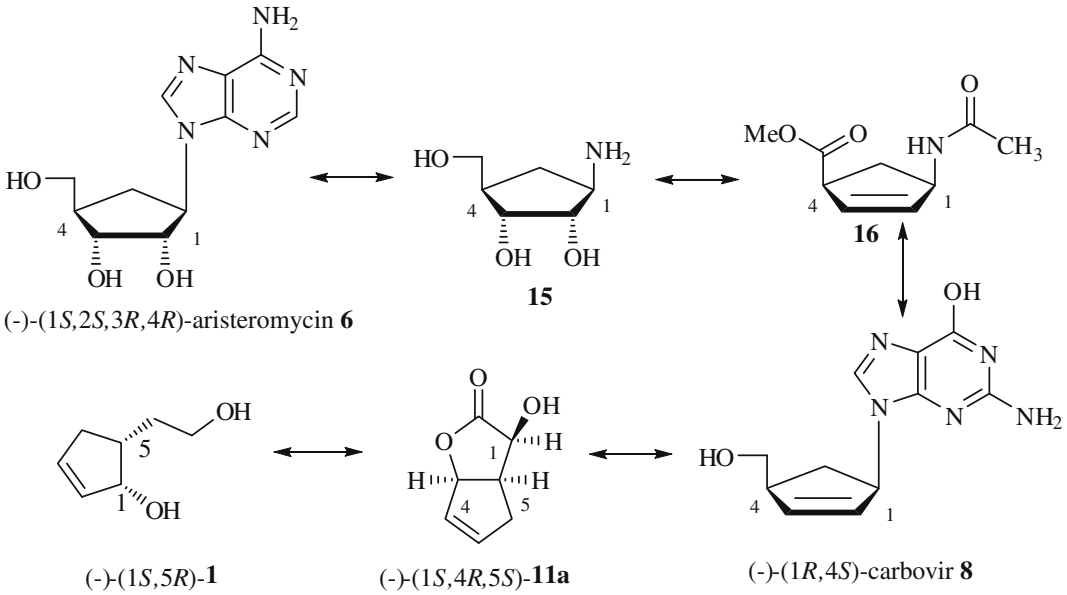
Alternatively, the required racemic **1** was synthesized from 2,5-norbornadiene **14**[13a] (Scheme 4) in a one-pot operation. Presumably, Meinwald rearrangement of the peracid oxidation of **14** gave an equilibrium mixture of bicyclic aldehyde **17** and the bicyclic enol ether **18**. Oxalic acid catalyzed hydrolysis of the mixture afforded the lactol **19**. Subsequent sodium borohydride reduction in water–acetonitrile yielded (±)-**1** in 60% overall yield. Compared to the above synthetic method for previous racemic diol **1**, the current protocol is more efficient and attractive. First, by avoiding the use of cyclopentadiene as a starting material it eliminates the tedious pyrolytic cracking of dicyclopentadiene to cyclopentadiene and the subsequent distillation procedure. Second, the 18 h and one-pot reaction sequence in the current protocol is advantageous over the greater than day-long and multiple reaction sequence, in that it only requires 5 L of solvents for the production of 1 mol of diol.

2.2. Resolution of diol (±)-1

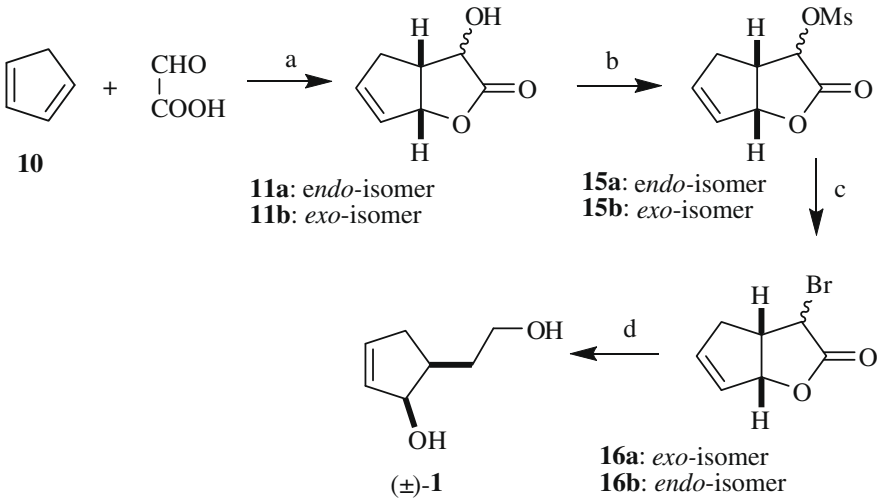
The racemic diol **1** was resolved by the biocatalytic esterification with neat vinyl acetate. The enzymatic resolution gave the



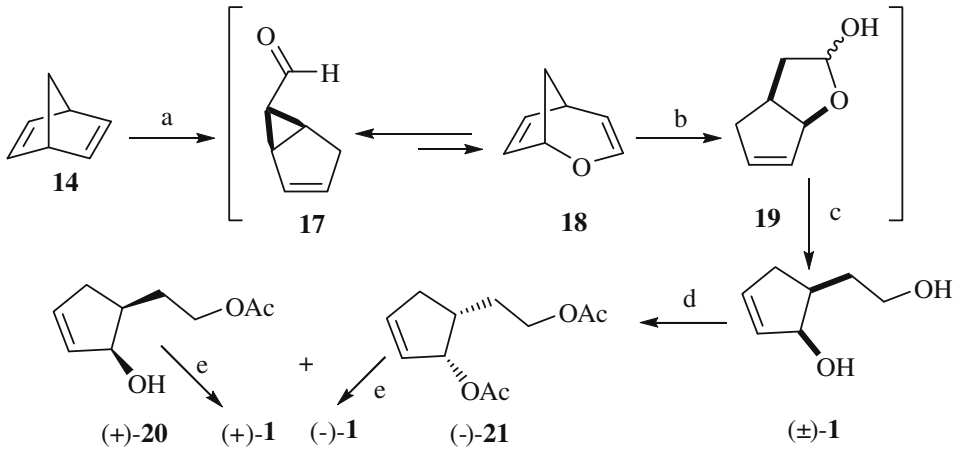
Scheme 1. Three protocols for the synthesis of diol (±)-**1**.



Scheme 2. Establishment of the absolute configuration of (−)-(1*S*,5*R*)-**1**. The double headed arrows denote correlations of absolute configuration.



Scheme 3. (Route 1) Reagents and conditions: (a) H_2O, rt, 3 d; (b) MsCl, triethylemine, DCM, 0 °C, 4 h; (c) LiBr, THF, reflux, 30 h; (d) $LiAlH_4$, THF, reflux, 24 h.



Scheme 4. (Route 3) Reagents and conditions: (a) anhydrous Na_2CO_3, 32% peracetic acid, DCM, rt, 2 h; (b) 5.0 mol % oxalic acid, H_2O, rt, 12 h; (c) $NaBH_4$, CH_3CN, rt, 4 h; (d) NaOH, MeOH, rt, 24 h (see Table 1).

monoacetate for one enantiomer and the diacetate for the other. Five commercially available lipases (porcine pancreatic lipase, *Candida rugusa* lipase, Lipase AY 30, *Pseudomonas cepacia* lipase and Lipase AK) were tested for the acetylation of racemic **1** to the corresponding esters (+)-**20**, and (−)-**21** (see Scheme 4 and Table 1). The resolution was carried at room temperature in neat vinyl acetate, the mono- and di-acetate product ratio was consistent with the higher reactivity and low enantioselectivity of lipases towards less hindered primary alcohols. The reaction was monitored by GC, and the enantiomeric excess of diacetate (−)-**21** was determined by chiral GC (Table 1). For all the lipases tested, the formation of monoacetate **20** was found to be very fast (100% conversion in 30 min) and regioselective, but not at all enantioselective. This observation is consistent with the higher reactivity and low enantioselectivity of lipases towards less hindered alcohol nucleophiles.[19] The diacetylation of diol **1** with lipases all showed moderate to high enantioselectivity (see Table 1). This result is consistent with many studies, in which secondary alcohols have been resolved by lipases successfully.[20] Lipase AK was chosen for the enantiomeric resolution of racemic **1**, because it was the fastest enzyme with the highest enantioselectivity for the acetylation of the secondary alcohol moiety. Porcine pancreatic lipase also had high enantioselectivity, but reacted slowly. Interestingly, the pattern of *E* values reported here for *P. cepacia* and *C. rugosa* lipase was similar to patterns observed for the resolution of 2-subtituted cyclopentanols: high *E* values (over 50) for *P. cepacia* lipase and low *E* values (1.4) for *C. rugosa* lipase.[20g] Reactions were stopped at 50% conversion of monoacetate **20**. Compounds (+)-**20** ($[\alpha]_D^{20} = +68.4$ (*c* 1.6, $CHCl_3$)) and (−)-**21** ($[\alpha]_D^{20} = -206.9$ (*c* 1.6, $CHCl_3$)) were separated by flash chromatography and was hydrolyzed separately by NaOH in MeOH, to afford the corresponding diols; (+)-**1** ($[\alpha]_D^{20} = +90.0$ (*c* 0.003, $CHCl_3$)) and (−)-**1** ($[\alpha]_D^{20} = -90.2$ (*c* 0.006, $CHCl_3$)).

2.3. Determination of the absolute configuration of diol 1 by primary and secondary alcohol Mosher ester

In previous studies,[2a,14] the racemic lactonol **11** was resolved with a lipase and then reduced, to give (1*S*,5*R*)-(−)-**1**, with $[\alpha]_D^{25} = -80.7$. The establishment of absolute configuration was based on selected chemical transformations. In our study, the same tentative assignment could be made by considering the enantioselectivity of lipase, according to an empirical rule for predicting which enantiomer reacts faster during the resolution of secondary alcohols.[20a,b,d,f,h] However, a few exceptions to this rule have been reported.[20b,h]

Table 1
Lipase-catalyzed kinetic resolution of (±)-**1** with vinyl acetate as acyl donor

Enzyme	Time (h)	Conversion rate[a] (%)	Selectivity		% ee of (+)-**20**[d]	% ee of (−)-**21**[e]	*E*[f]
			Monoacetate (+)-**20**[b]	Diacetate (−)-**21**[b]			
Porcine pancreatic lipase	4	94.6	100	ND[c]	0	NA[c]	—
	24	100	73.8	26.2	36	99.9	200
Candida regusa	4	100	88.0	12.0	7	51.5	3
	24	100	48.5	51.5	71	66.4	10
Lipase AY 30	4	100	>99	Trace	<1	99.9	>200
	24	100	45.5	54.5	85	70.6	15
Pseudomonas cepacia	4	100	33.0	67.0	>99	86.4	78
	24	100	18.3	81.7	99	86.4	70
Lipase AK	4	100	74.6	25.4	34	100	>200
	24	100	36.0	64.0	99	88.8[g]	97

[a] Reaction conditions: Diol **1** (20 mg, 0.16 mmol), lipase (20 mg), vinyl acetate (0.5 mL, neat solution), at room temperature. The value refers to the percentage of racemic diol **1** converted to the monoacetate and diacetate.
[b] Analysis of product samples was done by GC, DB5 column.
[c] ND = not detected, NA = not applicable.
[d] Calculated from ee or (−)-**21** and percentage of mono and diacetate.
[e] From GC analysis of (−)-**21** samples on a CycloSil-B column.
[f] Calculated according to literature.[20f]
[g] The ee can be enriched over 95% by further resolution.

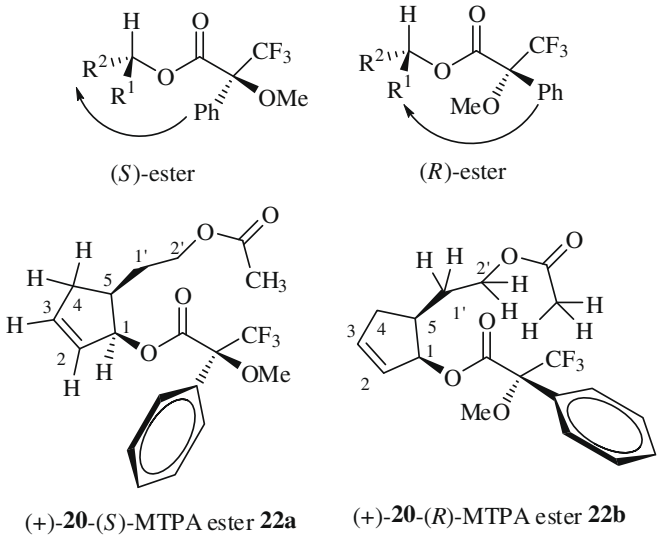


Figure 3. Dominant conformers of MTPA esters.

With the optically active diol **1** in hand, we decided to revisit its absolute configuration with the Mosher ester method. The absolute configuration of (+)-**20** at the secondary carbinol stereogenic centre was determined by analysis of the diastereomeric Mosher esters. This method involves derivatization of the secondary alcohol of (+)-**20** with each of the enatiomeric pair (*S*)-(−)-MTPA and (*R*)-(+)-MTPA (α-methoxy-α-trifluoromethylphenylaceticacid), affording two diastereoisomeric esters [(*S*)- and (*R*)-ester, respectively]. The success of the following NMR analysis relies on the empirically based conformation for the esters that is shown in Figure 3.[21] The major conformation is the one in which the ester adopts the *s-trans* (antiperiplanar) arrangement about the O–CO bond and a *syn*-coplanar (0° dihedral angle) arrangement between the CF_3 group and carbinol methane proton with respect to the carbonyl group.[21] The phenyl group of MTPA is known to impose an anisotropic effect above or below the aromatic ring, resulting in an upfield chemical shift in the NMR spectrum for the spatially proximal protons. Protons residing within group R^2 of the (*S*)-ester are relatively more shielded and thus upfield (Fig. 3). The same applies for the proton residing within group R^1 of the (*R*)-ester. The sign of $\Delta\delta(SR) = \delta_H(S) - \delta_H(R)$ for protons residing within group R^1 will thus be positive and for protons in group R^2 negative, leading to the determination of the absolute configuration of the secondary carbinol centre.

Table 2
Analysis of chemical shift differences for Mosher esters **22a** and **22b**

No.	δ-*S*-ester (ppm)	δ-*R*-ester (ppm)	$\Delta\delta^{SR}$ ($=\delta_S - \delta_R$) ppm	Hz (600 MHz)
H-1	5.69	5.72	−0.03	−18
H-2	6.17	6.23	−0.06	−36
H-3	6.00	6.04	−0.04	−24
H-4	2.47	2.49	−0.02	−12
	2.15	2.19	−0.04	−24
H-5	2.40	2.40	0.00	0
H-1′	1.90	1.75	+0.15	+90
	1.73	1.61	+0.12	+72
H-2′	4.07	3.97	+0.10	+60
$-COCH_3$	2.03	2.02	+0.01	+6

The (*S*)- and (*R*)-MTPA-esters **22a** and **22b** (Fig. 3) for (+)-**20** were prepared using coupling reagents EDCI and DMAP. ^{1}H NMR analysis of two diastereomers (*S*)-(+)-**20**-MTPA-ester **22a** and (*R*)-(+)-**20**-MTPA-ester **22b** was performed (see Table 2 for details). Positive $\Delta\delta_H(SR)$ values for H-1′, H-2′ and $COCH_3$ indicate aryl-shielding of the side chain moiety in the (*R*)-ester. In contrast, negative $\Delta\delta_H(SR)$ values for H-1, H-2, H-3 and H-4 imply aryl-shielding of the five-membered ring moiety in the (*S*)-ester. This result establishes the absolute configuration of (+)-**20** as (1*R*,5*S*)-(+)-**20**.

When diols (+)-**1** and (−)-**1** were esterified with (*S*)-(−)-MTPA-Cl, we found that only the primary alcohol group esterifies, giving diastereomers (*R*)-((+)-1)-MTPA-ester **23a** and (*R*)-((−)-1)-MTPA-ester **23b** (see Fig. 4 for structures, **23b** is the enantiomer of **23b′**). This places the MTPA moiety three atoms away from the stereogenic centre and, interestingly, significant chemical shift differences between those two diastereomers can be observed (see Table

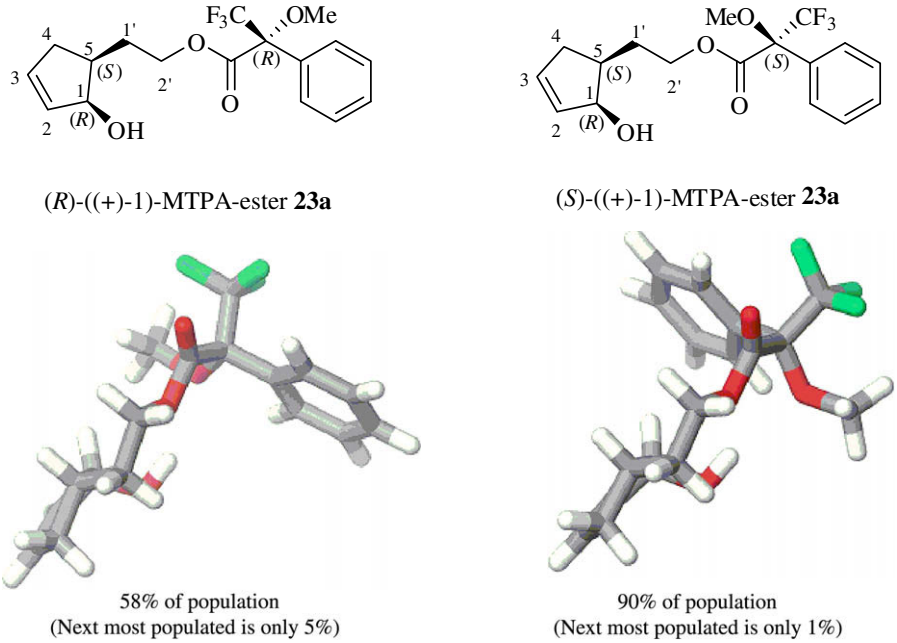


Figure 4. Major conformers of **23a** and **23b′** obtained by a molecular mechanic conformational search with MMFF force field.

Table 3
NMR data for primary MTPA esters of **(+)-1** and (−)-**1**, compounds **23a** and **23b**

No.	(*R*)-((+)-1)-MTPA-ester, **23a**	(*R*)-((−)-1)-MTPA-ester, **23b**	$\Delta\delta^{(+)(-)}$ (=$\delta_+ - \delta_-$) (ppm)
H-1	4.56	4.44	+0.12
H-2	6.02	6.00	+0.02
H-3	5.90	5.87	+0.03
H-4	2.37	2.36	+0.01
	2.12[a]	2.08[a]	+0.04
H-5	2.02–2.06[a]	2.04[a]	N/A
H-1′	2.10[b]	2.11	−0.01
	1.84	1.83	+0.01
H-2′	4.47	4.45[b]	+0.02
	4.39	4.41[b]	−0.02

[a] Splitting patterns can not be resolved.
[b] Overlapping signals.

3). As seen in Table 3, the H-1 in **23a** is strongly deshielded (0.12 ppm), compared to the H-1 in **23b**. The vinylic protons (H-2 and H-3) in **23a** are slightly deshielded (0.02–0.03 ppm), compared to the vinylic protons in **23b**. This observation also implies absolute configurations of **(+)-1** and (−)-**1** as (1*R*,5*S*)-(+)-**1** and (1*S*,5*R*)-(−)-**1**. Furthermore, two major conformer structures for **23a** and **23b′** were obtained from a molecular mechanics conformational search with the MMFF force field[22] (Fig. 4). The energies (from which the populations were calculated) were taken from single point B3LYP/6-31G**, gas calculations on the MMFF geometries.[23] The key structural feature seems to be a hydrogen bond between the OH and ester oxygen and/or the oxygen of the OMe group. According to this model, even though the MTPA is not directly attached to one of the stereogenic centres, the internal hydrogen bond in those two diastereomers appears to provide sufficient rigidity to place H-1, H-2 and H-3 in a defined position, relative to the phenyl group shielding cone.

3. Conclusions

In conclusion, an efficient and facile protocol to diols (+)-**1** and (−)-**1** is now readily available with high ee. This strategy provides attractive potential chiral synthons for the synthesis of a wide variety of biologically interesting molecules. The absolute configuration of diol **1** was confirmed by the Mosher ester method. Interestingly, the chemical shift differences between two MTPA ester diastereomers can still be observed when the MTPA moiety was placed three atoms away from the stereogenic centre, because an internal H-bond provided some rigidity for the molecule.

4. Experimental

4.1. General

Commercial grade solvents were distilled under nitrogen prior to use and reagents were used without further purification with the following exceptions: triethylamine was distilled and stored over NaOH. CH_2Cl_2 was distilled over $CaCl_2$ and stored over molecular sieves 3 Å. Dried THF was obtained from a MBRAUN LTS 350 solvent purification system. GC was run on a Hewlett Packard 5890 using a SPB column (Supelco, 30 m, 0.25 mm i.d., 0.25 μm film), programmed 100 °C (5 min), 10 °C/min, 200 °C (4.0 min), 15 °C/min, 250 °C (14.0 min). The gas chromatographic data on the DB-5 column are reported as retention indices (RI). The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker 500 and 600 MHz spectrometers. Enantiomer compositions were analyzed on a Varian 3400 gas chromatography, equipped with a Cyclo-Sil B column (J & W, 30 m, 0.25 mm i.d., 0.25 μm film), programmed isothermally at 140 °C and 25 psi head pressure. GC–mass spectra were recorded on a Varian Saturn 2000 MS coupled to a CP 300 GC, equipped with a SPB-5 GC column (same type as above), programmed as above. Mass spectra were acquired in EI mode [2 μscans (0.55 s/scan), emission current (30 μamp), scanning single ion storage SIS (49–375 m/z)]. Infrared spectra (IR) were recorded on a Perkin Elmer 599B IR spectrophotometer using NaCl plates. HRMS was recorded on a 6210 Series Time-of-Flight LC/MS System.

4.2. Preparation of optically active diol 1 and its MTPA derivatives

4.2.1. 3-Hydroxy-3,3a,4,6a-tetrahydro-cyclopenta-β-furan-2-one 11a and 11b

Glyoxylic acid 3.3 g (44.5 mmol) was dissolved in 19.8 mL of water, giving a 2.25 M solution. To this solution, freshly distilled cyclopentadiene (1.24 mL, 15.1 mmol) was added. The reaction mixture was stirred vigorously at room temperature for 3–4 days. After completion of the reaction, the mixture was extracted with *n*-heptane (3 × 15 mL), and then the aqueous layer was saturated with NaCl. The aq layer was further extracted with ethyl acetate (8 × 20 mL). The combined organic layers were concentrated to 50 mL under vacuum and cooled to 0 °C. The organic layer was washed with cold saturated sodium bicarbonate (2 × 20 mL). The separated aqueous layer was extracted further with ethyl acetate (3 × 20 mL). The combined organic layer (ethyl acetate layers only) was dried over Na_2SO_4, filtered and evaporated under vacuum to give a yellow oil (1.35 g of **11a** and **11b**, 2:1, 60%). The heptane layer contained the cyclopentadiene dimer. Isomers **11a** and **11b** were separated by flash chromatography (silica gel, ether/hexane, 9:1) to yield a light yellow syrup. Data for **11a** and **11b** were consistent with the literature.[11b] Compound **11a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 (m, 1H), 5.87 (m, 1H), 5.51 (m, 1H), 4.13 (d, J = 6.0 Hz, 1H), 3.6–4.0 (br s, 1H,), 3.02 (dd, J = 1.5, 7.5 Hz, 1H), 2.74 (ddd, J = 2.0, 7.5, 17.5 Hz, 1H), 2.56 (ddd, J = 2.0, 4.0, 17.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 137.1, 129.6, 87.7, 74.6, 44.4, 36.9; MS *m/z* (relative intensity): 141 (M^++H, 32%), 140 (M^+, 9%), 123 (100%), 95 (61%), 67 (72%); GC-RI: 1268. Compound **11b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.2 (dd, J = 2.5, 6.0 Hz, 1H), 5.87 (dd, J = 2.5, 6.0 Hz, 1H), 5.29 (td, J = 2.17, 6.0 Hz, 1H), 4.3–4.7 (d, J = 9.4 Hz, 1H), 3.6–4.0 (s, 1H), 3.2 (tt, J = 6.5, 9.5 Hz, 1H), 2.7 (ddd, J = 2.5, 6, 18 Hz, 1H), 2.4 (ddd, J = 2.0, 9.5, 18 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.16, 141.5, 127.7, 86.9, 69.4, 40.8, 31.1; MS *m/z* (relative intensity): 141 (M^++H, 40%), 140 (M^+, 9%), 123 (100%) GC-RI: 1255.

4.2.2. 2-Oxo-3,3a,4,6a-tetrahydro-2*H*-cyclopenta-β-furan-3-yl-ester 15a and 15b

A solution of **11a** and **11b** (2.5 g, 18 mmol) and triethylamine (3.75 mL, 26.9 mmol) in dry CH_2Cl_2 (200 mL) was stirred at 0 °C. To this cooled mixture, methanesulfonyl chloride (2.5 mL, 32 mmol) was added dropwise with stirring. The mixture was reacted for 4 h, after which the reaction was quenched with water (10 mL). Saturated $NaHCO_3$ (50 mL) and brine were added to the biphasic reaction mixture, until the pH was neutral. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The collected residue was purified by flash chromatography (silica gel, hexane/EtOAc, 8:2) to give **15a** and **15b** (2:1) as a colorless syrup (3.6 g, 92%). Compound **15a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.12–6.16 (m, 1H), 5.91–5.94 (m, 1H), 5.60–5.62 (d, J = 7.7 Hz, 1H), 4.94–4.96 (d, J = 7.0 Hz, 1H), 3.26–3.30 (m, 1H), 2.76–2.81 (m, 1H), 3.26 (s, 3H), 2.66–2.70 9 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 137.3, 129.4, 87.8, 80.5, 43.1, 39.9, 36.2; MS *m/z* (relative intensity): 219 (M^++H, 100%), 218 (M^+, 25%), 123 (34%), 78 (77%);

GC-RI: 1694. Compound **15b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20–6.22 (td, J = 2.3, 5.6 Hz, 1H), 5.88–5.90 (td, J = 2.3, 7.8 Hz, 1H), 5.45–5.47 (d, J = 9.5 Hz, 1H), 5.35–5.37 (td, J = 2.1, 6.4 Hz, 1H), 3.29–3.36 (m, 1H), 3.22 (s, 3H), 2.62–2.69 (dtd, J = 2.0, 4.7, 18.3 Hz, 1H), 2.50–2.57 (tdd, J = 2.2, 9.1, 18.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 141.1, 127.7, 87.0, 75.5, 39.7, 39.6, 32.1; MS m/z (relative intensity): 219 (M^++H, 100%), 218 (M^+, 31%), 123 (31%), 78 (79%); GC-RI: 1663.

4.2.3. 3-Bromo-3,3a,4,6a-tetrahydro-cyclopenta-β-furan-2-one 16a and 16b

A solution of mesyl lactone **15a** and **15b** (4.2 g, 19.3 mmol) in 100 mL of dry THF and LiBr (4.5 g, 51.8 mmol) was stirred at reflux for 24 h. The solution was filtered and mixed with water (50 mL), and was extracted with ethyl acetate (4 × 75 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 8.5:1.5) to afford a mixture of **16a** and **16b** (1:2) as a dark red colored syrup (3.4 g, 88%). Data for **16a** and **16b** were consistent with the literature.[11c] Compound **16a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20–6.22 (m, 1H), 5.95–6.0 (td, J = 2.2, 8.0 Hz, 1H), 5.38–5.44 (td, J = 2.0, 6.6 Hz, 1H), 4.83 (d, J = 9.3 Hz, 1H), 3.30–3.36 (m, 1H), 2.78–2.83 (m, 1H), 2.62–2.68 (tdd, J = 2.2, 8.8, 17.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 137.6, 129.0, 87.7, 56.9, 47.0, 37.0; MS m/z (relative intensity): 205 (M^+ (^{81}Br), 100%), 203 (M^+(^{79}Br), 88%), 185 (13%), 171 (30%), 143 (27%), 123 (68%), 105 (91%), 79 (39%); GC-RI: 1433. Compound **16b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.12–6.15 (m, 1H), 5.9–6.0 (ddd, J = 2.0, 3.9, 7.5 Hz, 1H), 5.56–5.57 (d, J = 6.8 Hz, 1H), 4.25 (d, J = 4.0 Hz, 1H), 3.28–3.33 (m, 1H), 2.80–2.86 (m, 1H), 2.38–2.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 138.3, 128.7, 88.1, 47.6, 43.7, 37.5; MS m/z (relative intensity): 205 (M^+ (^{81}Br), 51%), 203 (M^+ (^{79}Br), 60%),171 (25%), 143 (19%), 123 (100%), 105 (47%), 79 (51%); GC-RI: 1496.

4.2.4. (±)-*cis*-5-(2-Hydroxy-ethyl)cyclopent-2-enol 1

A solution of bromolactones **16a** and **16b** (1.9 g, 9.32 mmol) in dry THF (100 mL) was added dropwise to a solution of $LiAlH_4$ (900 mg, 23.7 mmol) in dry THF (50 mL) at 0 °C. The mixture was stirred at reflux for 20–24 h. Diethyl ether saturated with water (25 mL) was added dropwise with vigorous stirring, followed by water (4 mL), at a rate that caused gentle reflux. This procedure resulted in formation of a gray precipitate. The mixture was stirred at reflux for 1 h and then allowed to stand for 15 min. The supernatant liquid was decanted and filtered through Celite filter agent. Tetrahydrofuran (50 mL) and water (2 mL) were added to the precipitate. The suspension was stirred at reflux for 1 h, and then the hot mixture was filtered through Celite and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, hexane/ethyl acetate, 1:1) to afford compound **1** as a colorless oil (1.0 g, 89%). Data for **1** were consistent with the literature.[2c] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95–5.96 (dd, J = 2.7, 5.8 Hz, 1H), 5.82–5.84 (dd, J = 1.9, 5.6 Hz, 1H), 4.60–4.62 (td, J = 1.9, 6.3 Hz, 1H), 3.81 (s, 2H, -OH), 3.70–3.75 (td, J = 5.2, 10.4 Hz, 1H), 3.58–3.63 (td, J = 4.4, 9.2 Hz, 1H), 2.34–2.38 (tdd, J = 1.8, 7.1, 15.8 Hz, 1H), 2.12–2.17 (m, 1H), 2.05–2.12 (m, 1H), 1.80–1.88 (m, 1H), 1.63–1.69 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.5, 132.8, 76.5, 62.2, 41.5, 37.6, 31.8; MS m/z (relative intensity): 1: 127 (M^+–H, 5%), 111 (100%), 93 (100%), 81 (27%), 67 (44%). GC-RI: 1189.

4.2.5. One-pot operation for the synthesis of (±)-*cis*-5-(2-hydroxy-ethyl)cyclopent-2-enol 1

To a rapidly stirred suspension of anhydrous Na_2CO_3 in a solution of 2,5-norbornadiene **14** (7.5 g, 81 mmol) and DCM (50 mL) was added 32% peracetic acid (9.7 g, 41 mmol) which had been previously treated with 0.2 g of sodium acetate to neutralize any sulfuric acid present. The addition was carried out at rt. After the reaction mixture was allowed to stir for an additional 4 h, the reaction mixture was filtered, and the filter cake was washed with a few portions of DCM. The solvent and excess starting material **14** were evaporated to give 4.7 g of residue. The residue was added to 200 mL of water and then oxalic acid (0.27 g, 2.2 mmol). After being stirred for 15 h at rt, 250 mL of acetonitrile was added to the reaction mixture. Sodium borohydride (2.5 g, 65.3 mmol) was then added in several portions over 5–10 min. After the reaction mixture was stirred for 4 h, the resulting mixture was concentrated to remove organic solvent. The remaining aqueous solution was saturated with NaCl and extracted with chloroform 4–6 times. The combined organic solvent was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, hexane/ethyl acetate, 1:1) to afford compound **1** as a colorless oil (3.2 g, 60% overall yield). The NMR data for **1** were consistent with the data shown in Section 4.2.4.

4.2.6. (+)-*cis*-5-(2-Acetyloxy-ethyl)cyclopent-2-enol 20 and acetyloxy-(−)-*cis*-5-(2-acetyloxy-ethyl)cyclopent-2-enol 21

Diol (±)-**1**(100 mg, 0.78 mmol) was dissolved in 3.0 mL (32.5 mmol) of vinyl acetate and then Lypase AK (80 mg) was added to it. The suspension was stirred at room temperature for 24 h. The reaction mixture was filtered and concentrated and then purified by flash chromatography (silica gel, ethyl acetate/hexane, 1:4) to afford pure compounds **20** (62 mg, 93.4% yield for 50% conversion) and **21** (51 mg, 61.6% yield for 50% conversion). Compound **20**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03(m, 1H), 5.92 (m, 1H), 4.60 (m, 1H), 4.18 (m, 2H), 2.41 (m, 1H), 2.09–2.18 (m, 2H) (2.05 (s, 3H), 1.99 (dddd, J = 7.0, 7.0, 7.0, 13.7 Hz, 1H), 1.77 (dddd, J = 6.6, 6.6, 6.6, 14.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 134.0, 132.9, 129.9, 64.12, 39.2, 36.6, 27.9, 20.9. $[\alpha]_D^{20} = +68.4$ (c 0.002, $CHCl_3$). Compound **21**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07 (m, 1H), 5.83 (td, J = 2.3, 8.1 Hz, 1H), 5.56 (td, J = 2.1, 6.7 Hz, 1H), 4.06 (m, 2H), 2.44 (dddd, J = 7.1, 7.1, 7.2, 16.5 Hz, 1H), 2.32 (dddd, J = 7.1, 7.1, 7.2, 14.4 Hz, 1H), 2.15 (m, 1H), 2.01 (s, 3H), 2.00 (s, 3H), 1.88 (dddd, J = 7.0, 7.0, 7.0, 13.7 Hz, 1H), 1.67 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.09, 170.8, 137.6, 129.5, 79.2, 63.5, 38.1, 37.0, 28.0, 21.1, 20.9; $[\alpha]_D^{20} = -206.9$ (c 0.002, $CHCl_3$).

4.2.7. (1*R*,5*S*)-(+)-5-(2′-Hydroxyethyl)cyclopent-2-en-1-ol (+)-1 and (1*S*,5*R*)-(−)-5-(2′-hydroxyethyl)cyclopent-2-en-1-ol (−)-1

Compound **20** (217 mg, 1.28 mmol) was dissolved in 5 mL of MeOH. Then 2.5 mL of 10% NaOH was added and stirred at room temperature for 20 h. After 20 h, the reaction mixture was diluted with chloroform. The organic layer was washed with sat. NH_4Cl (3 × 20 mL) and brine (2 × 20 mL). Then the organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was then purified by flash chromatography (silica gel, ethyl acetate/hexane, 1:1) to yield 156 mg of pure (+)-**1**. Yield = 95.7%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.00–6.02 (dd, J = 2.7, 5.8 Hz, 1H), 5.88–5.90 (dd, J = 1.9, 5.6 Hz, 1H), 4.67 (m, 1H), 3.81–3.84 (td, J = 5.2, 10.4 Hz, 1H), 3.67–3.71 (td, J = 4.4, 9.2 Hz, 1H), 2.81 (br s, 2H, –OH), 2.39–2.43 (tdd, J = 1.8, 7.1, 15.8 Hz, 1H), 2.18–2.23 (m, 1H), 2.10–2.17 (m, 1H), 1.88–1.94 (m, 1H), 1.70–1.75 (m, 1H). $[\alpha]_D^{20} = +90.0$ (c 0.003, $CDCl_3$) Procedure for the synthesis of (+)-**1** was repeated with compound **21** (400 mg, 2.35 mmol) and yielded (−)-**1** in 95.0% yield (286 mg). $[\alpha]_D^{20} = -90.2$ (c 0.006, $CDCl_3$).

4.2.8. Mosher esters of (+)-20, (+)-1 and (−)-1

Compounds **22a** and **22b**: A solution of (*S*)-(−)-MTPA (82 mg, 0.35 mmol) or (*R*)-(+)-MTPA (82 mg, 0.35 mmol) in 3 mL of DCM was cooled to 0 °C for 10 min. To this solution was added **(+)-20** (50 mg, 0.29 mmol) followed by EDCI (111 mg, 0.58 mmol) and DMAP (11 mg, 0.09 mmol). The mixture was allowed to warm to rt and stir overnight. Four milliliters of saturated NH_4Cl solution

were added, and the organic phase was separated. The aqueous phase was extracted with 3 × 10 mL of diethyl ether and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, hexanes/ethyl acetate 5:1) to afford compounds **22a** (60 mg, 50%) and **22b** (62 mg, 50%), respectively, as colourless oils. Compound **22a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.39 (m, 3H), 6.17 (m, 1H), 6.00 (m 1H), 5.69 (m, 1H), 4.07 (m, 2H), 3.48 (br s, 3H), 2.47 (m, 1H), 2.40 (dddd, J = 7.2, 7.2, 7.2, 14.4 Hz, 1H), 2.15 (m, 1H), 2.03 (s, 3H), 1.90 (dddd, J = 7.2, 7.2, 7.2, 13.9 Hz, 1H), 1.73 (dddd, J = 7.2, 7.2, 7.2, 13.9 Hz 1H); HRMS calcd for $C_{19}H_{21}O_5F_3Na$: 409.1238, found: 409.1233. Compound **22b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.38 (m, 3H), 6.23 (m, 1H), 6.04 (m 1H), 5.72 (m, 1H), 3.97 (m, 2H), 3.53 (br q, J = 1.2 Hz, 3H), 2.49 (dddd, J = 1.2, 3.0, 7.2, 16.8 Hz, 1H), 2.40 (dddd, J = 7.2, 7.2, 7.2, 14.7 Hz, 1H), 2.19 (m, 1H), 2.02 (s, 3H), 1.75 (dddd, J = 7.2, 7.2, 7.2, 13.8 Hz, 1H), 1.61 (dddd, J = 6.6, 6.6, 6.6, 14.7 Hz, 1H).

Compounds **23a** and **23b**: Compound (+)-**1** or (−)-**1** (20 mg, 0.16 mmol) was dissolved in 0.2 mL of pyridine and then DMAP (4 mg, 0.3 mmol) was added and reaction mixture was stirred for 5 min at 0 °C. (*S*)-(+)-MTPA-Cl (30 μL, 0.16 mmol) was then added and stirring was continued at 0 °C for 4 h. After 4 h, the reaction was quenched with water and diluted with EtOAc. The reaction mixture was the washed with 1 M HCl, 1 M NaOH and brine. The organic layer was then dried over Na_2SO_4 and concentrated. The residue was then purified by flash chromatography (silica gel, ethyl acetate/hexane, 1:10) to yield compounds **23a** (14.9 mg, 27%) and **23b** (13.6 mg, 25%), respectively. Compound **23a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.40 (m, 3H), 6.02 (m, 1H), 5.90 (m, 1H), 4.56 (br s, 1H), 4.47 (ddd, J = 6.1, 6.5, 10.9 Hz, 1H), 4.39 (ddd, J = 6.4, 6.8, 10.9 Hz, 1H), 3.55 (br d, J = 1.2 Hz, 3H), 2.37 (m, J = 1.8, 6.5, 7.2, 10.0 Hz, 1H), 2.12 (m, 1H), 2.10 (m, 1H), 2.04 (m, 1H), 1.84 (m, 1H); IR ν_{max} 3402.36, 3063.90, 2956.21, 2925.44, 2849.24, 1747.45, 1451.90, 1268.29, 1169.67, 1123.52, 1019.27, 911.75, 799.82, 765.9, 719.6; HRMS calcd for $C_{17}H_{19}O_4F_3Na$: 367.1133, found: 367.1127. Compound **23b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.41 (m, 3H), 6.00 (m, 1H), 5.87 (m, 1H), 4.45 (td, J = 6.0, 10.8 Hz, 1H), 4.41 (td, J = 6.4, 10.8 Hz, 1H), 3.56 (br d, J = 1.2 Hz, 3H), 2.36 (m, 1H), 2.11 (m, 1H), 2.04 (m, 1H), 1.83 (m, 1H). IR ν_{max} 3446.15, 3123.07, 3015.38, 2984.61, 2907.69, 1747.03, 1272.10, 1169.38, 1123.34, 1018.89, 911.50, 765.45, 719.77.

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