Palladium-Catalyzed Ring Opening of Isoprene Monoxide with Nitrogen Nucleophiles – Asymmetric Synthesis of Branched Amino Sugars

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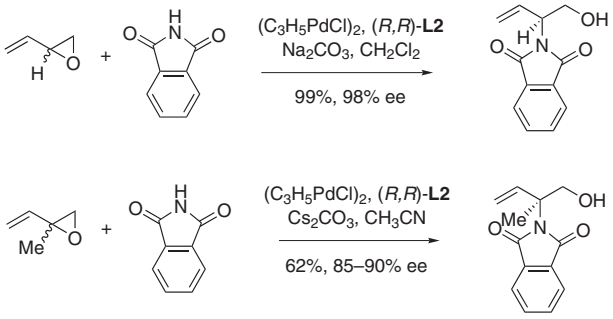
Received 24 May 2005

This paper is dedicated to Professor Steven Ley, scholar, educator, and scientific statesman, in honor of his 60th birthday.

Abstract: The Pd-catalyzed regio- and enantioselective ring opening of isoprene monoxide with primary amines as pronucleophiles is developed with good yield and enantioselectivity, constructing a quaternary stereocenter enantioselectively. This methodology was used as the chirality inducing key step in the asymmetric synthesis of vancosamine derivative **19**. The synthesis was achieved in 9 total steps and 28.6% overall yield.

Key words: palladium catalysis, enantioselectivity, quaternary stereocenter, asymmetric synthesis, amino sugar

Palladium-catalyzed dynamic kinetic asymmetric transformation (DYKAT) on vinyl epoxide type substrates showcases the efficiency by which the ligands developed in these laboratories exercise control of the chemo-, regio-, and enantioselectivities in the asymmetric allylic alkylation (AAA) reactions. A series of nucleophiles, such as alcohols,[1] carbonates,[2] imides,[3] carbodiimides,[4] and stabilized carbon nucleophiles,[5] have been employed in the reaction. In the previous reported Pd-catalyzed ring opening of vinyl epoxides with nitrogen nucleophiles,[3] while the reaction between butadiene monoxide and phthalimide affords excellent yield and enantioselectivity, isoprene monoxide proved to be a more challenging substrate presumably because a quaternary stereocenter is generated in the reaction (Scheme 1). Envisioning that sterically less demanding primary amines might ameliorate some of the issues in such a case encouraged us to examine the use of benzylamines and other sterically less demanding nitrogen nucleophiles.



Scheme 1 Pd-catalyzed ring opening of vinyl epoxides with phthalimide

Optimization of the Palladium-Catalyzed Ring Opening of Isoprene Monoxide with Nitrogen Nucleophiles

Table 1 summarizes the series of nitrogen nucleophiles that were screened for the Pd-catalyzed asymmetric ring opening of isoprene monoxide and the results. The chiral ligands used in the reaction are shown in Figure 1.

Among the nitrogen nucleophiles, benzylamine ($BnNH_2$, Table 1, entry 5) and *p*-methoxybenzylamine ($PMBNH_2$, Table 1, entry 6) gave the best results in terms of both yield and enantioselectivity. Although the reaction yield with benzylamine was slightly higher, the PMB group would be a better protecting group on nitrogen since its deprotection was easier and more versatile. The further optimization of $PMBNH_2$ addition is shown in Table 2. The results indicate that decreasing the catalyst loading and increasing the reaction concentration at the same time improved the reaction yield, while the enantioselectivity slightly dropped. The rationalization of this dependency is illustrated in Scheme 2. The full equilibration between the diastereomeric intermediates **I-1** and **I-2** is the prerequisite for the high enantioselectivity of the DYKAT reaction. At higher concentration and lower catalyst loading, the relatively high concentration of the amine nucleophile

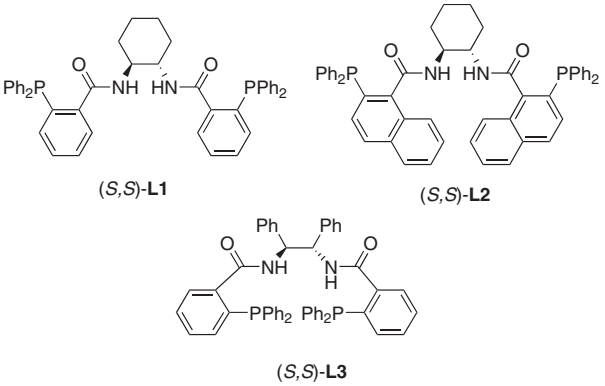
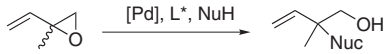


Figure 1 Chiral ligands used in the Pd-catalyzed DYKAT reaction

SYNTHESIS 2005, No. 19, pp 3335–3345
Advanced online publication: 25.10.2005
DOI: 10.1055/s-2005-918443; Art ID: C04605SS

Table 1 Pd-Catalyzed Ring Opening of Isoprene Monoxide with Nitrogen Nucleophiles



	Nucleophile	Conditions[a]	Yield (%)	ee (%)
1	phthalamide	Pd(II), **L2**, MeCN, 10% Cs_2CO_3	62	85–90%
2	$HN(CHO)_2$	Pd(0), **L1**, CH_2Cl_2, 10% Cs_2CO_3	4	–
3	$HN(Boc)_2$	Pd(II), **L1**, CH_2Cl_2, 10% Cs_2CO_3	5	–
4	H_2NCbz	Pd(0), **L1**, CH_2Cl_2	0	–
5	$BnNH_2$	Pd(II), **L3**, CH_2Cl_2, 5% Et_3N	83	94[b]
6	$PMBNH_2$	Pd(0), **L1**, CH_2Cl_2, 40 °C	74	94[b]
7	2,4-$(MeO)_2C_6H_3CH_2NH_2$	Pd(0), **L1**, CH_2Cl_2	67	74.5[b]
8	Bn_2NH	Pd(II), **L3**, CH_2Cl_2, 5% Et_3N	0	–
9	$(PMB)_2NH$	Pd(0), **L1**, CH_2Cl_2	0	–
10	$BnONH_2$·HCl	Pd(0), **L1**, CH_2Cl_2, Et_3N	0	–
11	$NaNO_2$	Pd(0), **L1**, CH_2Cl_2–H_2O, Et_3N·HCl	30	0
12	$TMSN_3$	Pd(0), **L1**, CH_2Cl_2	70	ND[c]

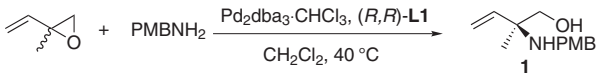
[a] Pd source: Pd(0): $Pd_2(dba)_3$·$CHCl_3$; Pd(II): $[(\eta^3\text{-}C_3H_5)PdCl]_2$. 2 mol% Pd and 3 mol% ligand were used in all cases. Reactions were carried out using concentrations of 0.1–0.2 M at r.t. unless otherwise indicated.
[b] Determined by chiral HPLC after protecting the initial product with a *N*-Cbz group.
[c] Not determined. The 1,2-adduct slowly transforms to the 1,4-adduct at r.t.

compared to the active species **I-1** and **I-2** results in a faster nucleophilic addition and possibly incomplete equilibration between **I-1** and **I-2**, which is responsible for the lower enantioselectivity. On the other hand, at low concentration and high catalyst loading, since the nucleophilic addition is not fast enough, other side reactions of the active species become competitive, such as the 1,2-hydride migration to form the aldehyde byproduct **2**.

This ring-opening reaction was easy to scale up without affecting the yield and enantioselectivity (Table 2, entries 3 and 5). The conditions in entry 5 were used for the large-scale preparation of compound **1**.

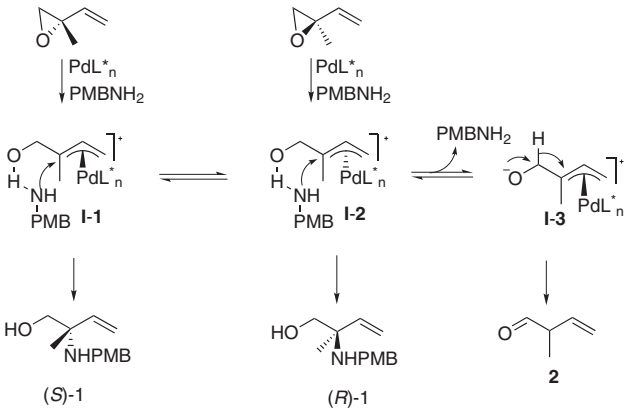
The absolute configuration of the 1,2-adduct **1** was determined by transforming it to known derivatives **3**, **4**, and **6**, as shown in Scheme 3. Table 3 lists their measured and literature reported optical rotation values. All three optical rotations clearly indicated that compound **1**, prepared using the (*R*,*R*)-**L1** ligand, has an *S* configuration in accordance with the prediction of the working model of the chiral ligand.[6]

Table 2 Optimization of the Palladium-Catalyzed Ring Opening of Isoprene Monoxide with *p*-Methoxybenzylamine[a]

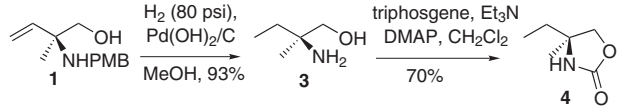


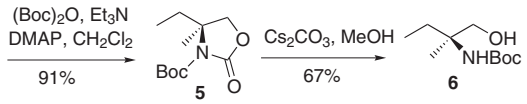
Entry	Catalyst loading (mol%)	Concentration (M)	Scale (mmol)	Reaction time (h)	Yield (%)	ee[b] (%)
1	1.0	0.2	0.5	4	74	94
2	0.5	0.4	1.0	5	76	93
3	0.5	0.4	10	6.5	80	93
4	0.25	0.8	2.0	22	86	90
5	0.25	0.8	20	24	85	89.5
6	0.125	1.33	2.0	45	87	81.5

[a] The molar ratio of (Pd/**L1**) is 1:1.5. The molar ratio of the two starting materials is 1:1.
[b] Determined by chiral HPLC after *N*-Cbz protection.



Scheme 2 Rationalization of the dependency of the reaction yield and enantioselectivity on the concentration and catalyst loading

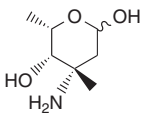




Scheme 3 Determination of the absolute configuration of the 1,2-adduct **1**

Asymmetric Synthesis of the L-Vancosamine Derivative

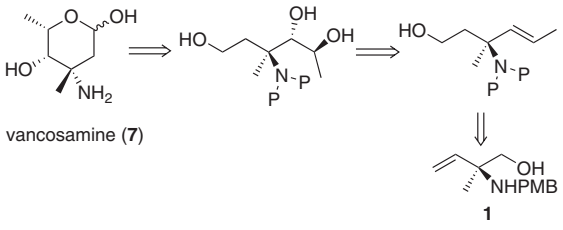
Partially deoxygenated branched amino sugars are important components of several classes of natural products with significant antibiotic and anticancer activities. In particular, L-vancosamine (**7**) (Figure 2) is a carbohydrate component of the glycopeptide antibiotic vancomycin[9] and glycosidic antibiotic sopraviridin.[10] Vancomycin has been demonstrated to be an important drug for use against antibiotic-resistant infections caused by Gram-positive bacteria,[11] while sopraviridin is active against Gram-positive bacteria, acid-fast bacteria, and trichophyton, but highly toxic with hemolytic activity. Synthetically, the structure of vancosamine is a challenge to synthetic chemists because of the Me–C–NH_2 branch at the 3-position. Tremendous efforts have been devoted to the synthesis of vancosamine and its derivatives from either carbohydrate or noncarbohydrate starting materials. Three racemic syntheses[12] and more than 13 asymmetric syntheses[13] of vancosamine and its derivatives have been reported. In almost all the asymmetric syntheses, enantiopure chiral compounds were employed as the starting materials and the quaternary stereocenter was introduced at a later stage by a diastereoselective process. The only exception is the synthesis of Fronza,[13h] in which an enzyme-catalyzed reaction was used to synthesize the enantiopure intermediate in low yield. Using the Pd-catalyzed ring opening of isoprene monoxide with $PMBNH_2$, we could synthesize the vancosamine derivative starting from racemic isoprene monoxide via DYKAT.



L-vancosamine (**7**)

Figure 2 Structure of L-vancosamine

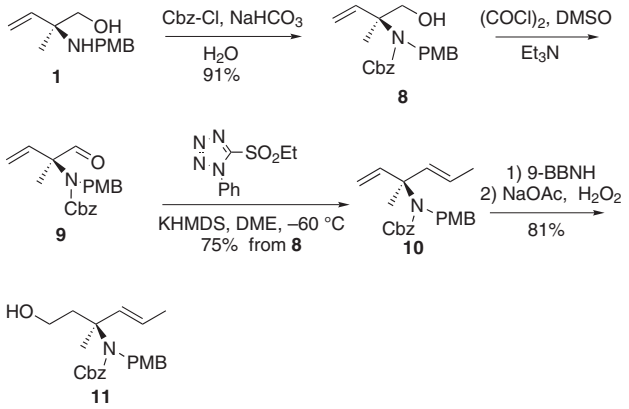
The retrosynthetic analysis for the asymmetric synthesis of L-vancosamine is shown in Scheme 4. Since the direct Moffatt–Swern oxidation of the initial 1,2-adduct **1** was problematic, the secondary amine in **1** was further protected by a Cbz group. While the Cbz protection in tetrahydrofuran solvent resulted in a slow reaction and significant amount of doubly protected product, in aqueous conditions the reaction proceeded smoothly and gave the N-protected product **8** in excellent yield (see Scheme 5). The alcohol **8** was transformed smoothly into the aldehyde **9** by a Moffatt–Swern oxidation, and this compound was olefinated by a modified Julia olefination to afford the diene **10** with complete geometric selectivity for the *E* isomer. The diene **10** was chemoselectively hydroborated and oxidized to the primary alcohol **11** efficiently.



Scheme 4 Retrosynthetic analysis

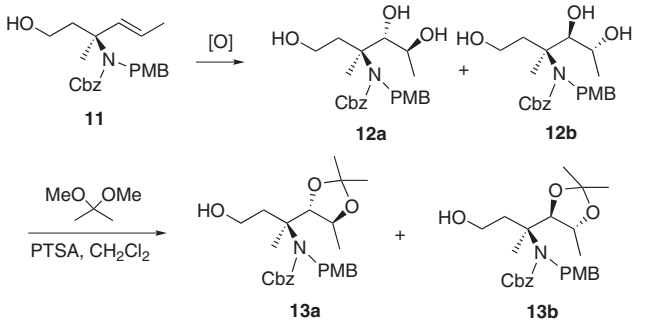
Table 3 Comparison of the Measured and Literature-Reported Optical Rotation Values

	3	4	6
$[\alpha]_D$ (measured)	–2.58 (*c* 6.1, EtOH)	–1.44 (*c* 7.3, EtOH)	–3.87 (*c* 2.2, MeOH)
$[\alpha]_D$ (lit.)	+1.2 (*c* 7.21, EtOH) (46% ee, *R*-isomer)	+1.0 (*c* 5.92, EtOH) (46% ee, *R*-isomer)	+4.1 (*c* 1.00, MeOH) (*R*-isomer)
Ref.	7	7	8



Scheme 5 Synthesis of intermediate **11**

The diastereoselective dihydroxylation of **11** was a challenging problem (see Scheme 6 and Table 4). Because of the steric hindrance of the adjacent quaternary center and the sensitivity of the molecule toward oxidation, many dihydroxylation conditions failed to provide the desired product. Among the conditions screened, osmium(VIII) oxide/*N*-methylmorpholine *N*-oxide (OsO_4/NMO) in a mixed solvent of acetone and water was the best oxidation system. Careful control of the reaction conditions gave the desired triol **12** as the only product. After the protection of the 1,2-diol in **12** as an acetonide, the diastereomers **13a** and **13b** were easily separable by column chromatography on silica gel, giving a diastereomeric ratio of 1.2:1 and isolated yield of 93% over the two steps (Table 4, entry 1). When DABCO (1.5 equiv) was used as an additive, the diastereoselectivity was improved to 2:1 (Table 4, entry 2). Catalyst-controlled stereoselectivity using the Sharpless AD reaction failed. It should be noted that this diastereoselectivity is among the best obtained to date in the dihydroxylations of similar intermediates in other vancosamine syntheses.[13a,c]



Scheme 6 Dihydroxylation of **11**

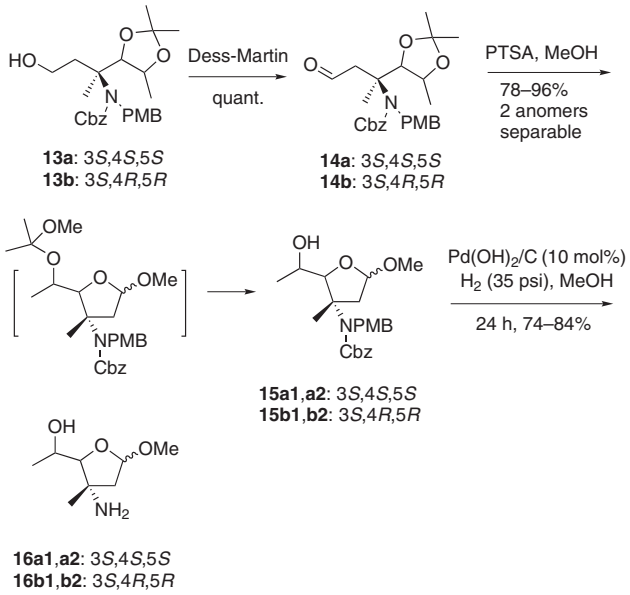
The pure acetonides **13a** and **13b** were oxidized to the corresponding aldehydes **14a** and **14b**, respectively, by Dess–Martin periodinane in nearly quantitative yield (Scheme 7). Acidic deprotection of the acetonide with 10 mol% *p*-toluenesulfonic acid in methanol gave the cyclized products **15** as a 1:1 mixture of the two anomers, easily separable by column chromatography on silica gel. Instead of the thermodynamically more stable pyran sugars, the furan sugars were actually obtained. The rationale was as follows: the deprotection of the acetonide from the 1,2-diol proceeded in a stepwise fashion, with the sterically more hindered hydroxy group preferentially deprotected. This hydroxy group attacked the aldehyde to form the furan sugar products without further isomerization. Under hydrogenolysis conditions, the Cbz and PMB groups were removed successively in one pot, to afford the furanoid amino sugar **16** in good yields.

It was suggested that a stronger acid in the deprotection–cyclization step is required to force the equilibration between the furan and pyran sugars. As shown in Scheme 8, under prolonged treatment with 0.7 M hydrogen chloride in methanol, the furan sugars **15b1** and **15b2** as well as their precursor **14b**, derived from the minor diastereomer

Table 4 Dihydroxylation of **11**

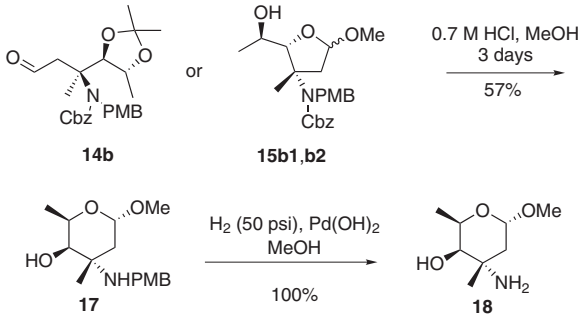
Entry	Conditions	Outcome
1	OsO_4, NMO, acetone–H_2O, 0 °C to r.t.	**12** [93%;[a] ratio (**13a/13b**) 1.2:1]
2	OsO_4, NMO, DABCO, acetone–H_2O, 0 °C to r.t.	**12** [90%;[a] ratio (**13a/13b**) 2:1]
3	OsO_4, NMO, CH_2Cl_2–H_2O, r.t.	starting material + Cbz-NH-PMB
4	OsO_4, Me_3NO, acetone–H_2O, r.t.	complex mixture
5	OsO_4, Me_3NO, CH_2Cl_2–H_2O, r.t.	complex mixture and starting material
6	AD-mix-α or AD-mix-β	<5% conversion
7	K_2OsO_4, $K_3Fe(CN)_6$, K_2CO_3	**12** (1:1 dr) with byproducts
8	OsO_4, $K_3Fe(CN)_6$, K_2CO_3, DABCO	complex mixture
9	$RuCl_3$, $NaIO_4$, EtOAc–MeCN, 0 °C	decomposition
10	$KMnO_4$, 18-crown-6, acetone–benzene	starting material + Cbz-NH-PMB

Yield of **13** after the protection of the 1,2-diol with acetonide.



Scheme 7 Lactol cyclization under kinetic conditions

in the dihydroxylation step, were transformed to the pyran sugar **17**, a 4,5-di-*epi*-vancosamine derivative, as a single diastereomer. The Cbz group was removed in situ during the reaction. The relative configuration of **17** was confirmed by single crystal X-ray analysis (Figure 3). Compound **17** was finally transformed to the amino sugar **18** in quantitative yield by hydrogenolysis.



Scheme 8 Lactol equilibration of a 4,5-di-*epi*-vancosamine derivative

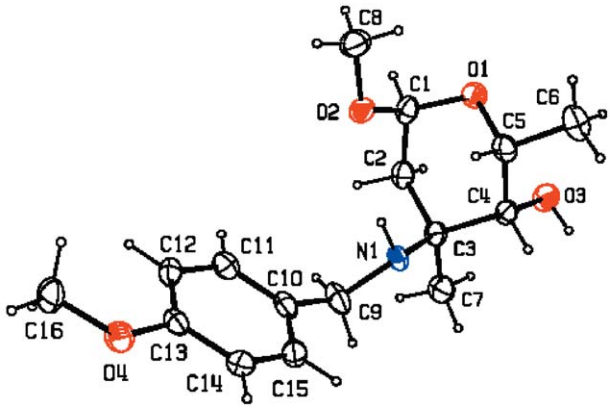
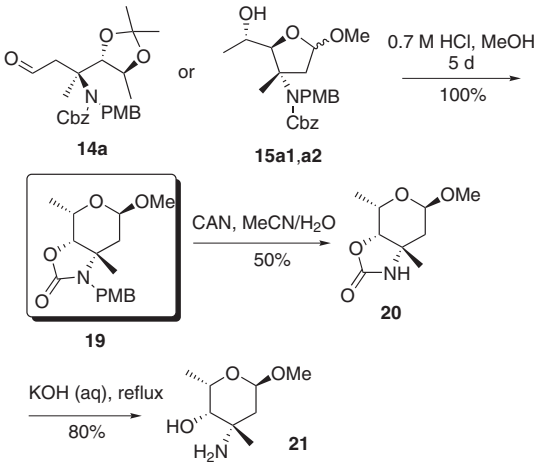


Figure 3 X-ray analysis of the relative configuration of **17**

The furan sugars **15a1** and **15a2** or their precursor **14a**, derived from the major diastereomer in the dihydroxylation step, were also transformed to the corresponding pyran sugar completely when stirred with 0.7 M hydrogen chloride in methanol at room temperature. The cyclic carbamate was formed from the partial deprotection of Cbz group during the reaction (Scheme 9). Both anomers of **19** were initially observed, while longer reaction time allowed further equilibration to give the more stable α-anomer as the sole product, which was a derivative of L-vancosamine. Compound **19** was further transformed to a known derivative of vancosamine **21** {$[\alpha]_D^{24}$ –105.12 (*c* 0.1, MeOH), lit. $[\alpha]_D$ –132 (*c* 1.4, MeOH)[13g] or $[\alpha]_D$ –118 (*c* 0.09, MeOH)[9b]} by oxidative cleavage of the PMB group and hydrolysis of the carbamate. The ^{1}H NMR data of **21** also matched with those reported in the literature.[13g]



Scheme 9 Lactol equilibration of L-vancosamine derivative

Palladium-catalyzed asymmetric ring opening of isoprene monoxide with nitrogen nucleophiles was further investigated. The scope of nitrogen nucleophiles used was extended to primary amines, such as benzylamine and *p*-methoxybenzylamine, with high yields and enantioselectivities obtained in the reaction. A quaternary stereocenter is generated in a highly enantioselective fashion. The ring opening of isoprene monoxide by *p*-methoxybenzylamine was used as a key step in the asymmetric synthesis of L-vancosamine derivative **19**. Compound **19** was synthesized in 9 total steps and 28.6% overall yield from racemic isoprene monoxide. It is the first asymmetric synthesis of the vancosamine derivative using a nonenzyme-catalyzed enantioselective reaction as the source of chirality. However, the modest diastereoselectivity in the dihydroxylation of **11** calls for the development of new methodologies for more efficient dihydroxylation of olefins.

All reactions were performed in oven-dried glassware, under an atmosphere of dry argon. Solvents were dried and distilled using standard procedures. Dichloromethane, 1,2-dichloroethane, acetonitrile, pyridine, and triethylamine were distilled from calcium hydride; tetrahydrofuran, diethyl ether, and toluene were distilled from sodium/benzophenone, while benzene was distilled from

sodium metal. Petroleum ether (PE) used had the boiling range 36–60 °C.

NMR spectra were recorded using a Varian Gemini 300 (300 MHz for ^{1}H NMR, 75 MHz for ^{13}C NMR) or Unity Inova 500 (500 MHz for ^{1}H NMR, 125 MHz for ^{13}C NMR) spectrometer using TMS (0.00 ppm), residue $CHCl_3$ (7.26 ppm) and $CDCl_3$ (77.0 ppm) as the internal standard. IR spectra were recorded on liquid films (NaCl plates) employing a Perkin-Elmer Paragon 500 FTIR spectrophotometer. Optical rotations were measured in a Jasco DIP-360 digital polarimeter in 5-cm cells at r.t. Elemental analyses were obtained from M-H-W Laboratories, Phoenix, Arizona. Mass spectra were obtained from the Mass Spectrometry Facility at the School of Pharmacy, UCSF, California, 94143-0446.

Chiral HPLC was performed on a Thermo Separation Products Spectra Series P100 HPLC using Chiralpak OD columns with detection at 254 nm. Chiral gas–liquid chromatography was performed on a HP 6890 capillary gas chromatograph using a 30 m × 0.252 mm J&W Cyclosil B column, with a split ratio of ~80:1 and 1.0 mL·min^{-1} He as the carrier gas.

Tris(dibenzylideneacetone)dipalladium–chloroform complex (Pd_2dba_3·$CHCl_3$) was prepared according to the method described by Ukai et. al.[14]

(*S*)-2-(4-Methoxybenzyl)amino-2-methylbut-3-en-1-ol (1)

Specific reaction details are given in Table 5. To an oven-dried, round-bottom flask were added Pd_2dba_3·$CHCl_3$, (*R*,*R*)-**L1**, and a stirbar. The flask was then placed under reduced pressure (vacuum pump) for 10 s and refilled with Ar; this purging procedure was repeated five times to ensure no oxygen remained in the reaction vessel. After being placed under an Ar atmosphere, freshly distilled CH_2Cl_2 was added and the resulting dark purple solution was stirred at r.t. for 10 min until it turned a deep orange color. During this time, neat $PMBNH_2$ was added. Finally, 2-methyl-2-vinyloxirane was added to the mixture and the solution turned bright yellow. The solution was heated to 40 °C and stirring was continued for the time indicated in Table 2, at which point the orange color returned. The solvent was removed in vacuo. The crude product was purified by flash chromatography (PE–EtOAc 2:1, with 5 vol% Et_3N) on silica gel to afford the desired product **1** as a colorless oil. The enantioselectivity was determined in the form of **8** after the *N*-Cbz protection of **1**.

$[\alpha]_D^{22}$ –17.84 (*c* 0.98, $CHCl_3$) (93% ee).

R_f = 0.43 (hexanes–EtOAc–Et_2NH, 1:1:0.1).

IR (film): 3301, 3081, 2933, 2883, 1612, 1513, 1464, 1301, 1248, 1177, 1036, 921 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.7 Hz, 2 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 5.85 (dd, *J* = 10.9, 17.7 Hz, 1 H), 5.24 (d, *J* = 11.0 Hz, 1 H), 5.17 (d, *J* = 17.7 Hz, 1 H), 3.80 (s, 3 H), 3.59 (d, *J* = 12.1 Hz, 1 H), 3.56 (d, *J* = 12.0 Hz, 1 H), 3.44 (d, *J* = 10.5 Hz, 1 H), 3.40 (d, *J* = 10.5 Hz, 1 H), 1.24 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.58, 141.98, 132.62, 129.36, 114.75, 113.78, 68.07, 58.38, 55.21, 46.10, 20.86.

HRMS (EI): *m*/*z* calcd for $C_{12}H_{16}NO$ (M^+ – OCH_3): 190.1232; found 190.1236.

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65. Found: C, 70.78; H, 8.40.

(*R*)-2-Benzylamino-2-methylbut-3-en-1-ol

Following the above procedure, 2-(*R*)-benzylamino-2-methylbut-3-en-1-ol was synthesized with the following quantities of reagents and solvent: $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (0.91 mg, 2.5 μmol), (*S*,*S*)-**L3** (5.2 mg, 7.5 μmol), CH_2Cl_2 (2 mL), $BnNH_2$ (21.4 mg, 22 μL, 0.2 mmol), Et_3N (1.0 mg, 1.3 μL, 0.01 mmol), and isoprene monoxide (17 mg, 19 μL, 0.2 mmol). The reaction was complete in 2 h at r.t. and the crude product was purified by flash chromatography (silica gel, PE–EtOAc 2:1, with 5% Et_3N) to afford the desired compound as a colorless oil in 94% ee (determined after *N*-Cbz protection); yield: 32 mg (83%).

$[\alpha]_D^{22}$ +12.54 (*c* 1.01, CH_2Cl_2).

IR (film): 3330, 1456, 1048, 921 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.23 (m, 5 H), 5.84 (dd, *J* = 10.9, 17.4 Hz, 1 H), 5.23 (dd, *J* = 1.0, 11.0 Hz, 1 H), 5.17 (dd, *J* = 0.9, 17.4 Hz, 1 H), 3.62 (dd, *J* = 2.9, 12.3 Hz, 2 H), 3.41 (dd, *J* = 4.8, 15.3 Hz, 2 H), 2.20 (br s, NH, OH), 1.23 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.1, 140.7, 128.4, 127.0, 114.8, 68.1, 58.5, 46.8, 21.1.

HRMS (EI): *m*/*z* calcd for $C_{11}H_{14}N$ (M^+ – OCH_3): 160.1126; found: 160.1127.

(*S*)-2-Amino-2-methylbutan-1-ol (3)

A mixture of (*S*)-**1** (90% ee) (200 mg, 0.904 mmol) and $Pd(OH)_2$/C (20 wt% with 50 wt% H_2O, 127 mg, 0.090 mmol) in MeOH (10 mL) was stirred under 80 psi H_2 at r.t. for 20 h. After filtration and removal of the solvent in vacuo, the residue was redissolved in Et_2O

Table 5 Reaction Details for the Pd-Catalyzed Ring Opening of Isoprene Monoxide with $PMBNH_2$

Entry	2-Methyl-2-vinyloxirane	$PMBNH_2$	Pd_2dba_3·$CHCl_3$	(*R*,*R*)-**L1**	CH_2Cl_2	Yield	ee (%)
1	42 mg, 0.50 mmol	69 mg, 0.50 mmol	5.2 mg, 5.0 μmol	10.4 mg, 15.0 μmol	2.5 mL	82 mg (74%)	94
2	84 mg, 1.0 mmol	137 mg, 1.0 mmol	5.2 mg, 5.0 μmol	10.4 mg, 15.0 μmol	2.5 mL	168 mg (76%)	93
3	840 mg, 10.0 mmol	1.38 g, 10.0 mmol	52 mg, 0.050 mmol	104 mg, 0.150 mmol	25 mL	1.775 g (80%)	93
4	168 mg, 2.0 mmol	274 mg, 2.0 mmol	5.2 mg, 5.0 μmol	10.4 mg, 15.0 μmol	2.5 mL	379 mg (86%)	90
5	1.68 g, 20.0 mmol	2.74 g, 20.0 mmol	52 mg, 0.050 mmol	104 mg, 0.150 mmol	25 mL	3.760 g (85%)	89.5
6	168 mg, 2.0 mmol	274 mg, 2.0 mmol	2.6 mg, 2.5 μmol	5.2 mg, 7.5 μmol	1.5 mL	387 mg (87%)	81.5

and dried (Na_2SO_4), and the solvent was removed in vacuo to afford 87 mg of **3** (93%) along with some 4-methylanisole. The mixture can be carried on for the next step directly. To remove 4-methylanisole, the mixture was dissolved in 5% aq $NaHSO_4$ and extracted with Et_2O. The aqueous layer was basified with 1 M NaOH, saturated with K_2CO_3, and then extracted with EtOAc. The organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo to afford pure **3**.

$[\alpha]_D^{24}$ –2.58 (*c* 6.1, EtOH) {lit.[7] $[\alpha]_D^{15}$ +1.2 (*c* 7.21, EtOH) (46% ee, *R*-isomer)}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.33 (d, *J* = 10.4 Hz, 1 H), 3.28 (d, *J* = 10.4 Hz, 1 H), 1.45 (dq, *J* = 7.6, 13.7 Hz, 1 H), 1.37 (dq, *J* = 7.6, 13.8 Hz, 1 H), 1.03 (s, 3 H), 0.90 (t, *J* = 7.6 Hz, 3 H).

(*S*)-4-Ethyl-4-methyloxazolidin-2-one (4)

To a solution of **3** (84 mg, 0.814 mmol) and DMAP (1 mg, 0.081 mmol) in CH_2Cl_2 (24 mL) were added Et_3N (205 mg, 0.28 mL, 2.03 mmol) and triphosgene (82 mg, 0.276 mmol). The solution was stirred at r.t. for 2 h and solvent was removed in vacuo. The residue was purified by flash chromatography (silica gel, PE–EtOAc 1:1) to afford known compound **4**; yield: 74 mg (70%).

$[\alpha]_D^{23}$ –1.44 (*c* 7.3, EtOH) {lit.[7] $[\alpha]_D^{12}$ +1.0 (*c* 5.92, EtOH) (46% ee, *R*-isomer)}.

IR (film): 3286, 1743, 1483, 1462, 1399, 1273, 1197, 1039, 945, 772 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.08 (br s, 1 H), 4.15 (d, *J* = 8.5 Hz, 1 H), 4.05 (d, *J* = 8.4 Hz, 1 H), 1.62 (q, *J* = 7.6 Hz, 1 H), 1.34 (s, 3 H), 0.96 (t, *J* = 7.5 Hz, 3 H).

***tert*-Butyl (*S*)-[1-(Hydroxymethyl)-1-methylpropyl]carbamate (6)**

To a solution of **4** (74 mg, 0.57 mmol) and DMAP (14 mg, 0.11 mmol) in CH_2Cl_2 were added Et_3N (115 mg, 0.16 mL, 1.14 mmol) and $(Boc)_2O$ (188 mg, 0.855 mmol) at 0 °C. The solution was warmed to r.t., stirred overnight, quenched with sat. aq $NaHCO_3$, and extracted with EtOAc. The organic layers were washed with brine and dried (Na_2SO_4). After removal of the solvent, the crude product was purified by flash chromatography (silica gel, PE–EtOAc 5:1) to afford **5**; yield: 120 mg (91%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.08 (d, *J* = 8.7 Hz, 1 H), 3.89 (d, *J* = 8.7 Hz, 1 H), 2.07 (m, 1 H), 1.65 (m, 1 H), 1.55 (s, 9 H), 1.51 (s, 3 H), 0.91 (t, *J* = 7.4 Hz, 3 H).

A solution of **5** (37 mg, 0.161 mmol) and Cs_2CO_3 (54 mg, 0.166 mmol) in MeOH (2 mL) was stirred at r.t. for 1 d and quenched with H_2O. After extracting with EtOAc, the organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed and the crude product was purified by flash chromatography (silica gel, PE–EtOAc 5:1 → 2:1) to afford known compound **6**; yield: 22 mg (67%).

$[\alpha]_D^{23}$ –3.87 (*c* 2.2, MeOH) {lit.[8] $[\alpha]_D^{25}$ +4.1 (*c* 1.00, MeOH)}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.63 (br s, 1 H), 3.65 (d, *J* = 11.5 Hz, 1 H), 3.59 (d, *J* = 11.5 Hz, 1 H), 1.70–1.78 (m, 1 H), 1.52–1.60 (m, 1 H), 1.43 (s, 9 H), 1.15 (s, 3 H), 0.90 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.28, 79.76, 69.48, 57.05, 29.00, 28.30, 21.95, 7.79.

(*S*)-2-[(Benzyloxycarbonyl)(4-methoxybenzyl)amino]-2-methylbut-3-en-1-ol (8)

A suspension of (*S*)-2-(4-methoxybenzyl)amino-2-methylbut-3-en-1-ol **1** (3.76 g, 17.0 mmol), benzyl chloroformate (3.48 g, 2.91 mL, 20.4 mmol), and $NaHCO_3$ (3.85 g, 45.9 mmol) in H_2O (24 mL) was stirred at r.t. for 4 h. The mixture was diluted with H_2O and extracted with EtOAc, and the organic layers were dried ($MgSO_4$). After removal of the solvent in vacuo, the crude product was purified by flash chromatography (silica gel, PE–EtOAc 5:1 → 2:1) to afford the desired product **8** as a colorless oil; yield: 5.48 g (91%).

HPLC (Chiralcel OD, heptane–*i*-PrOH 90:10, 1.0 mL·min^{-1}, 254 nm): 9.62 min (*R*-isomer), 12.16 min (*S*-isomer).

$[\alpha]_D^{26}$ –20.97 (*c* 1.30, $CHCl_3$) (93% ee).

R_f = 0.15 (hexanes–EtOAc, 4:1).

IR (film): 3447, 3032, 2953, 2835, 2360, 1684, 1613, 1586, 1513, 1458, 1398, 1352 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22–7.32 (m, 3 H), 7.08–7.20 (m, 2 H), 7.08 (d, *J* = 8.4 Hz, 2 H), 6.81 (d, *J* = 8.5 Hz, 2 H), 5.96 (dd, *J* = 11.0, 17.4 Hz, 1 H), 5.16 (d, *J* = 10.7 Hz, 1 H), 5.15 (d, *J* = 17.5 Hz, 1 H), 5.10 (s, 2 H), 4.49 (d, *J* = 16.7 Hz, 1 H), 4.44 (d, *J* = 16.7 Hz, 1 H), 3.91 (dd, *J* = 5.7, 11.5 Hz, 1 H), 3.80 (s, 3 H), 3.76 (dd, *J* = 7.7, 11.4 Hz, 1 H), 1.36 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.28, 156.99, 140.84, 136.17, 131.70, 128.37, 127.90, 127.83, 127.33, 114.45, 113.71, 69.33, 67.26, 65.97, 55.24, 48.99, 20.32.

HRMS (EI): *m*/*z* calcd for $C_{21}H_{25}NO_4$ (M^+): 355.1783; found: 355.1781.

Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09. Found: C, 70.74; H, 6.86.

(*S*)-2-[(Benzyloxycarbonyl)(4-methoxybenzyl)amino]-2-methylbut-3-enal (9)

Oxalyl chloride (1.28 g, 0.885 mL, 10.1 mmol) was added dropwise to a solution of DMSO (1.58 g, 1.44 mL, 20.2 mmol) in dry CH_2Cl_2 (15 mL) at –60 °C. After 30 min, **8** (1.545 g, 4.35 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The solution was stirred between –60 and –40 °C for 1.5 h and then cooled to –60 °C. Triethylamine (2.33 g, 3.2 mL, 23 mmol) was added and the cold bath was removed. After warming to r.t., Et_2O (30 mL) was added and the mixture was filtered. Then, H_2O was added and the mixture was extracted with Et_2O. The organic layers were washed with brine and dried ($MgSO_4$). Crude product 1.617 g (>100%) was obtained and directly used for the next step. For analytical purposes, some crude product was purified by flash chromatography (silica gel, PE–EtOAc 4:1 → 2:1 → 1:1) to afford the desired product **9** as a colorless oil.

R_f = 0.38 (hexanes–EtOAc, 4:1).

IR (film): 2994, 2956, 2836, 2368, 2339, 1734, 1684, 1613, 1514, 1354 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.39 (s, 1 H), 7.15–7.47 (m, 5 H), 7.16 (d, *J* = 8 Hz, 2 H), 6.83 (d, *J* = 8 Hz, 2 H), 5.87 (dd, *J* = 11, 18 Hz, 1 H), 5.35 (d, *J* = 11 Hz, 1 H), 5.25 (d, *J* = 18 Hz, 1 H), 5.18 (s, 2 H), 4.46 (AB, 2 H), 3.80 (s, 3 H), 1.38 (s, 3 H).

Because of hindered rotation of the carbamate bond, the carbon spectrum was very complex.

HRMS (EI): *m*/*z* calcd for $C_{21}H_{23}NO_4$ (M^+): 353.1627; found 353.1625.

Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.36; H, 6.56. Found: C, 71.52; H, 6.80.

(*S*)-3-[(Benzyloxycarbonyl)(4-methoxybenzyl)amino]-3-methylhexa-1,4*E*-diene (10)

A solution of 0.5 M KHMDS in toluene (14.6 mL, 7.3 mmol) was added dropwise over a period of 45 min to a solution of **9** (1.617 g crude, directly from above reaction, 4.35 mmol) and 5-ethylsulfonyl-1-phenyl-1*H*-tetrazole (1.55 g, 6.53 mmol) in dry DME (65 mL) at –60 °C under Ar. The mixture was stirred for 20 min before H_2O (20 mL) was added. The cold bath was removed and the mixture was slowly allowed to reach ambient temperature. The mixture was extracted with Et_2O and the combined organic layers were

washed with brine and dried ($MgSO_4$). After removal of the solvent in vacuo, the crude product was purified by flash chromatography (silica gel, PE–EtOAc 19:1) to afford the desired product **10** as a colorless oil; yield: 1.195 g (75% from **8**).

$[\alpha]_D^{23}$ +5.75 (*c* 1.26, $CHCl_3$).

R_f = 0.52 (hexanes–EtOAc, 4:1).

IR (film): 2937, 1702, 1612, 1512, 1395, 1350, 1240, 1174 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.21–7.38 (m, 5 H), 7.13 (d, *J* = 8.5 Hz, 2 H), 6.82 (d, *J* = 8.5 Hz, 2 H), 5.99 (dd, *J* = 10.5, 17.6 Hz, 1 H), 5.57 (d, *J* = 15.9 Hz, 1 H), 5.46 (dq, *J* = 6.1, 15.6 Hz, 1 H), 5.12 (s, 2 H), 5.01 (d, *J* = 11.2 Hz, 1 H), 5.00 (d, *J* = 17.3 Hz, 1 H), 4.51 (s, 2 H), 3.80 (s, 3 H), 1.64 (d, *J* = 5.9 Hz, 3 H), 1.53 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.24, 156.34, 143.22, 136.73, 135.08, 132.48, 128.26, 127.85, 127.69, 123.79, 113.61, 111.67, 66.81, 63.80, 55.21, 48.78, 23.38, 17.77.

Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.67; H, 7.48; N, 3.90.

(*S*)-3-[(Benzyloxycarbonyl)(4-methoxybenzyl)amino]-3-methylhex-4*E*-en-1-ol (11)

A solution of 9-BBN-H (244 mg, 2.01 mmol) in THF (3 mL) was added slowly to a solution of **10** (488 mg, 1.34 mmol) in THF (1.5 mL) at 0 °C and the mixture was heated at 60 °C for 2.5 h. Cooling to 0 °C again, 3.0 M aq NaOAc (1.34 mL, 4.0 mmol) and 30% H_2O_2 (1.21 mL, 10.7 mmol) were added and the mixture was stirred at r.t. for 10 min and then at 60 °C for 1 h. After cooling to r.t., the mixture was extracted with Et_2O. The combined organic layers were washed with brine and dried ($MgSO_4$). After removal of the solvent in vacuo, the crude product was purified by flash chromatography (silica gel, PE–EtOAc 3:1 → 2:1) to afford the desired product **11** as a colorless oil; yield: 415 mg (81%).

$[\alpha]_D^{23}$ –1.75 (*c* 1.20, $CHCl_3$).

R_f = 0.47 (hexanes–EtOAc, 1:1).

IR (film): 3449, 2937, 2836, 1698, 1612, 1513, 1454, 1397, 1247 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.36 (m, 5 H), 7.10 (d, *J* = 8.8 Hz, 2 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 5.60 (d, *J* = 15.9 Hz, 1 H), 5.48 (dq, *J* = 5.9, 15.7 Hz, 1 H), 5.13 (s, 2 H), 4.55 (d, *J* = 16.4 Hz, 1 H), 4.42 (d, *J* = 16.4 Hz, 1 H), 3.80 (s, 3 H), 3.60 (m, 2 H), 2.26 (m, 2 H), 1.63 (d, *J* = 5.9 Hz, 3 H), 1.44 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.24, 156.54, 136.62, 136.28, 132.35, 128.34, 127.82, 123.40, 113.63, 66.86, 61.91, 59.53, 55.17, 48.86, 41.89, 24.37, 17.78.

Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 71.92; H, 7.69; N, 3.57.

Benzyl [(1*S*)-3-Hydroxy-1-methyl-1-(2,2,5-trimethyl[1,3]dioxolan-4-yl)propyl](4-methoxybenzyl)carbamate (13a and 13b)

A solution of 4% OsO_4 in H_2O (0.11 mL, 0.017 mmol) was added to a solution of **11** (129 mg, 0.336 mmol), NMO (59 mg, 0.504 mmol), and DABCO (56 mg, 0.504 mmol) in acetone (2.4 mL) and H_2O (0.6 mL) at 0 °C. The solution was stirred at r.t. overnight before sat. $NaHSO_3$ (0.4 mL) was added and the mixture stirred for a further 10 min. The mixture was diluted with brine and extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$), and the solvent was removed in vacuo to afford a 2:1 mixture of triol **12a/12b**. The mixture was dissolved in acetone (1.6 mL) and PTSA·H_2O (3.0 mg, 0.016 mmol) and 2,2-dimethoxypropane (66 mg, 78 μL, 0.63 mmol) were added. The mixture was stirred at ambient temperature overnight before quenching with sat. $NaHCO_3$. The aqueous layer was extracted with EtOAc and the combined organic layers were dried ($MgSO_4$). The two diastereomeric acetonides were isolated by flash chromatography (silica gel, PE–EtOAc 2:1).

***First eluted acetonide* 13a**

Colorless oil.

Yield: 92 mg (60%).

$[\alpha]_D^{23}$ +23.11 (*c* 1.05, $CHCl_3$).

R_f = 0.45 (hexanes–EtOAc, 1:1).

IR (film): 3477, 2984, 2935, 1697, 1612, 1513, 1247, 1043 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.38 (m, 5 H), 7.13 (d, *J* = 8.4 Hz, 2 H), 6.82 (d, *J* = 8.6 Hz, 2 H), 5.19 (d, *J* = 12.2 Hz, 1 H), 5.13 (d, *J* = 12.2 Hz, 1 H), 4.76 (d, *J* = 16.6 Hz, 1 H), 4.57 (d, *J* = 7.8 Hz, 1 H), 4.37 (d, *J* = 16.6 Hz, 1 H), 3.84–3.96 (m, 1 H), 3.80 (s, 3 H), 3.58 (q, *J* = 5.9 Hz, 2 H), 2.39 (dt, *J* = 5.6, 14.4 Hz, 1 H), 2.26 (dt, *J* = 6.6, 14.4 Hz, 1 H), 1.59 (s, 3 H), 1.36 (s, 3 H), 1.35 (s, 3 H), 1.13 (d, *J* = 6.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.51, 156.47, 136.20, 131.75, 128.42, 128.30, 128.19, 128.13, 113.77, 107.90, 84.09, 73.34, 67.31, 62.73, 59.04, 55.17, 48.98, 41.20, 27.30, 26.84, 20.08, 19.16.

Anal. Calcd for $C_{26}H_{35}NO_6$: C, 68.25; H, 7.71; N, 3.06. Found: C, 68.45; H, 7.67; N, 3.07.

***Second eluted acetonide* 13b**

Colorless oil.

Yield: 46 mg (30%).

$[\alpha]_D^{25}$ +39.23 (*c* 1.28, $CHCl_3$).

R_f = 0.33 (hexanes–EtOAc, 1:1).

IR (film): 3474, 2985, 2835, 1695, 1613, 1513, 1395 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.36 (m, 5 H), 7.17 (d, *J* = 8.8 Hz, 2 H), 6.82 (d, *J* = 8.5 Hz, 2 H), 5.18 (d, *J* = 12.5 Hz, 1 H), 5.12 (d, *J* = 12.7 Hz, 1 H), 4.85 (d, *J* = 17.1 Hz, 1 H), 4.39 (d, *J* = 7.8 Hz, 1 H), 4.36 (d, *J* = 17.1 Hz, 1 H), 3.82–3.96 (m, 1 H), 3.79 (s, 3 H), 3.46–3.63 (m, 2 H), 2.80–2.96 (m, 1 H), 1.58–1.76 (m, 1 H), 1.39 (s, 3 H), 1.38 (s, 3 H), 1.33 (s, 3 H), 1.31 (d, *J* = 5.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.24, 156.54, 136.51, 132.64, 128.35, 127.87, 127.72, 113.63, 107.60, 85.32, 73.13, 66.90, 61.95, 59.01, 55.16, 49.35, 39.30, 27.36, 26.93, 20.26, 20.07.

Anal. Calcd for $C_{26}H_{35}NO_6$: C, 68.25; H, 7.71; N, 3.06. Found: C, 68.07; H, 7.66; N, 3.04.

Benzyl (4-Methoxybenzyl)((1*S*)-1-methyl-3-oxo-1-{(4*S*,5*S*)-2,2,5-trimethyl[1,3]dioxolan-4-yl}propyl)carbamate (14a, from the First Eluted Acetonide 13a)

Dess–Martin periodinane (177 mg, 0.42 mmol) was added to a solution of the first eluted acetonide **13a** (128 mg, 0.28 mmol) in CH_2Cl_2 (3 mL) and the mixture was stirred at ambient temperature for 15 min before the entire mixture was transferred to a flash column and eluted (hexanes–EtOAc, 4:1) to afford **14a** as a colorless oil; yield: 124 mg (97%).

R_f = 0.60 (hexanes–EtOAc, 1:1).

IR (film): 2985, 2935, 1717, 1694, 1623, 1512, 1247 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.64 (t, *J* = 2.5 Hz, 1 H). 7.24–7.40 (m, 5 H), 7.10 (d, *J* = 8.8 Hz, 2 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 5.19 (d, *J* = 12.0 Hz, 1 H), 5.14 (d, *J* = 12.0 Hz, 1 H), 4.84 (d, *J* = 16.6 Hz, 1 H), 4.49 (d, *J* = 7.6 Hz, 1 H), 4.48 (d, *J* = 16.6 Hz, 1 H), 3.76–3.92 (m, 1 H), 3.79 (s, 3 H), 3.24 (dd, *J* = 2.2, 16.4 Hz, 1 H), 2.96 (dd, *J* = 2.3, 16.0 Hz, 1 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 1.33 (s, 3 H), 1.11 (d, *J* = 5.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.05, 158.66, 156.21, 136.05, 131.30, 128.48, 128.26, 128.21, 128.14, 113.91, 108.37, 83.36, 73.13, 67.49, 61.68, 55.19, 50.61, 48.91, 27.31, 26.71, 20.34, 20.02.

Anal. Calcd for $C_{26}H_{33}NO_6$: C, 68.55; H, 7.30; N, 3.07. Found: C, 68.56; H, 7.18; N, 3.08.

Benzyl (4-Methoxybenzyl)((1*S*)-1-methyl-3-oxo-1-{(4*R*,5R)-2,2,5-trimethyl[1,3]dioxolan-4-yl}propyl]carbamate (14b, from the Second Eluted Acetonide 13b)

Dess–Martin periodinane (101 mg, 0.24 mmol) was added to a solution of the second eluted acetonide **13b** (72 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) and the mixture was stirred at ambient temperature for 15 min before the entire mixture was transferred to a flash column and eluted (hexanes–EtOAc 4:1) to afford **14b** as a colorless oil; yield: 70 mg (98%).

$[\alpha]_D^{28}$ +24.50 (*c* 0.96, $CHCl_3$).

R_f = 0.49 (hexanes–EtOAc, 2:1).

IR (film): 2986, 2935, 1722, 1694, 1613, 1514, 1247 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.62 (t, *J* = 2.4 Hz, 1 H), 7.20–7.36 (m, 5 H), 7.13 (d, *J* = 8.8 Hz, 2 H), 6.82 (d, *J* = 8.5 Hz, 2 H), 5.16 (d, *J* = 12.5 Hz, 1 H), 5.10 (d, *J* = 12.5 Hz, 1 H), 4.78 (d, *J* = 17.1 Hz, 1 H), 4.47 (d, *J* = 17.1 Hz, 1 H), 4.29 (d, *J* = 8.1 Hz, 1 H), 3.90–4.00 (m, 1 H), 3.79 (s, 3 H), 3.72–3.82 (m, 1 H), 2.22 (dd, *J* = 2.7, 15.6 Hz, 1 H), 1.49 (s, 3 H), 1.37 (s, 3 H), 1.36 (s, 3 H), 1.24 (d, *J* = 5.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.95, 21.64, 26.80, 27.33, 48.74, 49.16, 55.19, 60.77, 67.23, 72.96, 84.91, 107.97, 113.73, 127.84, 127.99, 128.39, 131.73, 136.17, 156.33, 158.40, 200.53.

Anal. Calcd for $C_{26}H_{33}NO_6$: C, 68.55; H, 7.30; N, 3.07. Found: C, 68.56; H, 7.18; N, 3.08.

(*S*)-1-{(2*S*,3*S*)-3-[(Benzyloxycarbonyl)(4-methoxybenzyl)amino]-5-methoxy-3-methyltetrahydrofuran-2-yl}ethanol (15a1 and 15a2)

To the solution of **14a** (509 mg, 1.12 mmol) in MeOH (10 mL) was added PTSA·H_2O (41 mg, 0.22 mmol). The mixture was stirred overnight and quenched with sat. aq $NaHCO_3$. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine and dried ($MgSO_4$). The two anomers were isolated by flash chromatography (silica gel, PE–EtOAc 3:1).

***First eluted anomer* 15a1**

Colorless oil.

Yield: 150 mg (31%).

$[\alpha]_D^{25}$ –35.08 (*c* 10.2, $CHCl_3$).

IR (film): 3463, 1694, 1613, 1514, 1456, 1397, 1357, 1297, 1248, 1190, 1146, 1098, 1046, 970, 912, 841, 776, 738, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25–7.35 (m, 5 H), 7.13 (d, *J* = 8.5 Hz, 2 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 5.17 (d, *J* = 12.5 Hz, 1 H), 5.12 (d, *J* = 12.5 Hz, 1 H), 4.60 (t, *J* = 5.2 Hz, 1 H), 4.56 (d, *J* = 9.8 Hz, 2 H), 3.81–3.89 (m, 1 H), 3.79 (s, 3 H), 3.36 (s, 3 H), 3.02 (d, *J* = 11.2 Hz, 1 H), 2.81 (dd, *J* = 6.1, 15.4 Hz, 1 H), 1.93 (dd, *J* = 4.9, 15.4 Hz, 1 H), 1.62 (s, 3 H), 1.18 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.55, 156.23, 136.30, 128.42, 127.98, 127.88, 127.36, 113.95, 105.06, 89.76, 69.26, 67.10, 65.80, 55.69, 55.20, 48.43, 44.30, 21.52, 20.36.

Anal. Calcd for $C_{24}H_{31}NO_6$: C, 67.11; H, 7.27; N, 3.26. Found: C, 66.84; H, 7.15; N, 3.24.

***Second eluted anomer* 15a2**

Colorless oil.

Yield: 225 mg (47%).

$[\alpha]_D^{25}$ +8.36 (*c* 4.26, $CHCl_3$).

IR (film): 3493, 1685, 1514, 1399, 1247, 1041 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.34 (m, 5 H), 7.14 (d, *J* = 8.5 Hz, 2 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 5.20 (d, *J* = 12.5 Hz, 1 H), 5.13 (d, *J* = 12.2 Hz, 1 H), 5.01 (dd, *J* = 1.0, 5.4 Hz, 1 H), 4.92 (d, *J* = 17.5 Hz, 1 H), 4.59 (d, *J* = 17.1 Hz, 1 H), 4.30 (s, 1 H), 4.06–4.16 (m, 1 H), 3.79 (s, 3 H), 3.37 (s, 3 H), 2.70 (dd, *J* = 1.0, 14.7 Hz, 1 H), 1.89 (d, *J* = 10.0 Hz, 1 H), 1.79 (dd, *J* = 5.4, 14.9 Hz, 1 H), 1.41 (s, 3 H), 1.18 (br s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.45, 156.35, 136.36, 131.19, 128.44, 128.16, 128.09, 128.01, 113.78, 103.22, 88.97, 67.19, 66.49, 65.98, 55.21, 54.84, 48.56, 44.67, 22.94, 22.14.

Anal. Calcd for $C_{24}H_{31}NO_6$ + 3 wt% CH_2Cl_2: C, 65.52; H, 7.12; N, 3.16. Found: C, 65.80; H, 6.85; N, 3.26.

(*R*)-1-{(2*R*,3*S*)-3-[(Benzyloxycarbonyl)(4-methoxybenzyl)amino]-5-methoxy-3-methyltetrahydrofuran-2-yl}ethanol (15b1 and 15b2)

To the solution of **14b** (403 mg, 0.885 mmol) in MeOH (9 mL) was added PTSA·H_2O (34 mg, 0.18 mmol). The mixture was stirred overnight and quenched with sat. aq $NaHCO_3$. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine and dried ($MgSO_4$). The two anomers were isolated by flash chromatography (silica gel, PE–EtOAc 4:1 → 3:1).

***First eluted anomer* 15b1**

Colorless oil.

Yield: 163 mg (43%).

$[\alpha]_D^{24}$ –20.29 (*c* 4.3, $CHCl_3$).

IR (film): 3484, 1693, 1612, 1514, 1460, 1400, 1365, 1300, 1248, 1175, 1144, 1104, 1031, 1002, 950 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.16–7.38 (m, 7 H), 6.82 (d, *J* = 8.3 Hz, 2 H), 5.14 (AB, 2 H), 4.97 (br s, 1 H), 4.84 (d, *J* = 16.2 Hz, 1 H), 4.39 (d, *J* = 16.5 Hz, 1 H), 4.33 (s, 1 H), 3.77–3.86 (m, 1 H), 3.79 (s, 3 H), 3.45 (s, 3 H), 2.84 (d, *J* = 12.0 Hz, 1 H), 2.59 (d, *J* = 8.7 Hz, 1 H), 1.99 (dd, *J* = 6.1, 12.7 Hz, 1 H), 1.32 (s, 3 H), 1.21 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.58, 156.10, 136.70, 130.82, 128.51, 128.50, 127.94, 127.78, 113.69, 104.23, 89.75, 67.19, 66.03, 65.70, 55.92, 55.19, 49.54, 43.25, 21.57, 21.03.

Anal. Calcd for $C_{24}H_{31}NO_6$: C, 67.11; H, 7.27; N, 3.26. Found: C, 66.91; H, 7.12; N, 3.25.

***Second eluted anomer* 15b2**

Colorless oil.

Yield: 200 mg (53%).

$[\alpha]_D^{24}$ –53.40 (*c* 4.1, $CHCl_3$).

IR (film): 3498, 1692, 1613, 1514, 1460, 1401, 1358, 1298, 1245, 1200, 1175, 1142, 1111, 1062, 1039, 1006 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.38 (m, 5 H), 7.20 (d, *J* = 8.1 Hz, 2 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 5.19 (d, *J* = 12.3 Hz, 1 H), 5.15 (d, *J* = 12.2 Hz, 1 H), 5.03 (d, *J* = 6.7 Hz, 1 H), 4.60 (d, *J* = 16.5 Hz, 1 H), 4.49 (d, *J* = 16.1 Hz, 1 H), 4.18 (br s, 1 H), 3.78–3.88 (m, 1 H), 3.78 (s, 3 H), 3.34 (s, 3 H), 2.79 (dd, *J* = 6.8, 12.1 Hz, 1 H), 1.73 (d, *J* = 12.2 Hz, 1 H), 1.52 (s, 3 H), 1.10 (br s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.15, 158.70, 156.50, 136.05, 131.37, 128.52, 128.36, 128.21, 114.00, 104.41, 90.71, 67.55, 66.56, 65.39, 55.40, 55.20, 49.63, 43.57, 21.03 (2 C).

Anal. Calcd for $C_{24}H_{31}NO_6$: C, 67.11; H, 7.27; N, 3.26. Found: C, 66.90; H, 7.14; N, 3.25.

1-[(3S)-3-Amino-5-methoxy-3-methyltetrahydrofuran-2-yl]ethanol (16)

The solution of **15** in MeOH (0.05 M) with $Pd(OH)_2/C$ (20 wt% on dry base, <50 wt% H_2O, 0.20 equiv) was stirred under 35 psi H_2 for 24 h. The mixture was filtered (washed with MeOH) and the solvent was removed in vacuo. The crude product was purified by flash chromatography (silica gel, EtOAc–MeOH–Et_3N 100:5:10) to afford the desired product **16** as a white wax-like solid.

16a2: Following the above procedure, compound **15a2** was converted into **16a2** with the following quantities of reagents and solvent: **15a2** (42 mg, 0.098 mmol), $Pd(OH)_2/C$ (20 wt% on dry base, <50 wt% H_2O, 14 mg, 9.8 μmol), and MeOH (2.0 mL) under 35 psi H_2. The reaction was complete in 20 h and the crude product was purified by flash chromatography (silica gel, EtOAc–MeOH–Et_3N 100:5:10) to afford the desired compound **16a2**; yield: 14 mg (82%).

$[\alpha]_D^{24}$ +132.03 (*c* 1.37, $CHCl_3$).

IR (film): 3354 (br), 1648, 1602, 1450, 1381, 1199, 1147, 1098, 1034, 997, 923, 869, 842 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.02 (dd, *J* = 2.0, 5.5 Hz, 1 H), 3.81 (dq, *J* = 4.4, 6.3 Hz, 1 H), 3.61 (d, *J* = 4.3 Hz, 1 H), 3.39 (s, 3 H), 2.16 (dd, *J* = 5.6, 13.3 Hz, 1 H), 1.89 (br s, 3 H), 1.86 (dd, *J* = 2.1, 13.4 Hz, 1 H), 1.26 (d, *J* = 6.5 Hz, 3 H), 1.25 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 103.94, 90.72, 66.63, 58.08, 55.09, 49.75, 23.46, 20.60.

16b1: Following the above procedure, compound **15b1** was converted into **16b1** with the following quantities of reagents and solvent: **15b1** (43 mg, 0.100 mmol), $Pd(OH)_2/C$ (20 wt% on dry base, <50 wt% H_2O, 14 mg, 0.010 mmol), and MeOH (2.0 mL) under 35 psi H_2. The reaction was complete in 25 h and the crude product was purified by flash chromatography (silica gel, EtOAc–MeOH–Et_3N 100:5:10) to afford the desired compound **16b1**; yield: 13 mg (74%).

$[\alpha]_D^{24}$ +55.66 (*c* 1.3, $CHCl_3$).

IR (film): 3375, 1598, 1439, 1377, 1203, 1140, 1095, 1027, 996, 924 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.02 (dd, *J* = 1.9, 5.9 Hz, 1 H), 4.00 (dq, *J* = 2.3, 6.6 Hz, 1 H), 3.43 (s, 3 H), 3.42 (d, *J* = 2.4 Hz, 1 H), 2.43 (br s, 3 H), 2.16 (dd, *J* = 5.9, 13.4 Hz, 1 H), 1.93 (dd, *J* = 1.9, 13.5 Hz, 1 H), 1.28 (s, 3 H), 1.27 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 104.04, 89.24, 66.13, 58.26, 55.18, 49.17, 27.29, 20.39.

16b2: Following the above procedure, compound **15b2** was converted into **16b2** with the following quantities of reagents and solvent: **15b2** (38 mg, 0.088 mmol), $Pd(OH)_2/C$ (20 wt% on dry base, <50 wt% H_2O, 12 mg, 8.8 μmol), and MeOH (1.7 mL) under 35 psi H_2. The reaction was complete in 27 h and the crude product was purified by flash chromatography (silica gel, EtOAc–MeOH–Et_3N 100:5:10) to afford the desired compound **16b2**; yield: 13 mg (84%).

$[\alpha]_D^{24}$ –116.81 (*c* 1.3, $CHCl_3$).

IR (film): 3362 (br), 1438, 1376, 1206, 1143, 1103, 1032, 974 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.14 (dd, *J* = 3.3, 5.7 Hz, 1 H), 4.05 (dq, *J* = 2.0, 6.5 Hz, 1 H), 3.44 (d, *J* = 2.0 Hz, 1 H), 3.39 (s, 3 H), 2.32 (br s, 3 H), 2.11 (dd, *J* = 5.7, 13.8 Hz, 1 H), 1.96 (dd, *J* = 3.3, 13.7 Hz, 1 H), 1.34 (s, 3 H), 1.31 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 102.95, 85.50, 65.51, 59.20, 55.24, 50.85, 26.52, 20.40.

Anal. Calcd for $C_8H_{17}NO_3$: C, 54.84; H, 9.78; N, 7.99. Found: C, 55.04; H, 10.00; N, 8.15.

(2*R*,3*R*,4*S*,6*S*)-6-Methoxy-4-(4-methoxybenzylamino)-2,4-dimethyltetrahydropyran-3-ol (17)

Acetyl chloride (110 mg, 0.1 mL, 1.41 mmol) was added to MeOH (2 mL). After stirring for 15 min, the solution was added to **14b** (46 mg, 0.101 mmol). The solution was stirred for 2.5 d and quenched with sat. aq $NaHCO_3$. After extraction with EtOAc, the organic layers were washed with brine and dried (Na_2SO_4). After removal of the solvent, the crude product was purified by flash chromatography (silica gel, PE–EtOAc 2:1, with 5 vol% Et_3N) to afford the desired product **17** as a single diastereomer; yield: 17 mg (57%).

$[\alpha]_D^{24}$ = +100.73 (*c* 1.2, $CHCl_3$).

IR (film): 3432, 3344, 1513, 1457, 1247, 1176, 1155, 1117, 1045, 997, 780 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.9 Hz, 2 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 4.74 (d, *J* = 4.2 Hz, 1 H), 4.21 (q, *J* = 6.6 Hz, 1 H), 3.80 (s, 3 H), 3.73 (d, *J* = 11.6 Hz, 1 H), 3.58 (d, *J* = 11.6 Hz, 1 H), 3.33 (s, 3 H), 3.27 (d, *J* = 7.2 Hz, 1 H), 1.87 (d, *J* = 14.8 Hz, 1 H), 1.79 (br d, *J* = 8.8 Hz, 1 H), 1.70 (dd, *J* = 4.4, 14.6 Hz, 1 H), 1.23 (d, *J* = 6.5 Hz, 3 H), 1.22 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.47, 133.34, 129.35, 113.79, 99.23, 73.44, 62.03, 55.26, 55.14, 54.21, 45.79, 33.10, 23.11, 17.13.

(2*R*,3*R*,4*S*,6*S*)-4-Amino-6-methoxy-2,4-dimethyltetrahydropyran-3-ol (18)

A solution of **17** (32 mg, 0.108 mmol) and suspension of $Pd(OH)_2/C$ (20 wt%, with 50 wt% H_2O, 15 mg, 0.011 mmol) in MeOH (2 mL) was stirred under 50 psi H_2 at r.t. for 20 h. After filtration and removal of the solvent in vacuo, the residue was purified by flash chromatography (silica gel, EtOAc–MeOH–Et_3N 100:5:10) to afford the desired product **18**; yield: 20 mg (100%).

$[\alpha]_D^{25}$ +127.27 (*c* 0.9, MeOH).

IR (film): 3366, 1122, 1050, 997 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.74 (d, *J* = 4.4 Hz, 1 H), 4.26 (q, *J* = 6.6 Hz, 1 H), 3.35 (s, 3 H), 3.01 (s, 1 H), 1.93 (br s, 3 H), 1.85 (dd, *J* = 4.4, 14.4 Hz, 1 H), 1.54 (d, *J* = 14.4 Hz, 1 H), 1.25 (d, *J* = 6.6 Hz, 3 H), 1.15 (s, 3 H).

^1H NMR (500 MHz, $CDCl_3$ with stoichiometric TMSCl and D_2O): δ = 4.83 (d, *J* = 3.3 Hz, 1 H), 4.04 (q, *J* = 6.1 Hz, 1 H), 3.63 (s, 1 H), 3.40 (s, 3 H), 2.04 (dd, *J* = 3.8, 14.9 Hz, 1 H), 1.78 (d, *J* = 14.8 Hz, 1 H), 1.46 (s, 3 H), 1.31 (d, *J* = 6.3 Hz, 3 H).

^1H NMR (500 MHz, pyridine-d_5): δ = 4.85 (d, *J* = 3.9 Hz, 1 H), 4.47 (q, *J* = 6.6 Hz, 1 H), 3.32 (s, 3 H), 3.29 (s, 1 H), 2.19 (dd, *J* = 4.4, 13.9 Hz, 1 H), 1.69 (d, *J* = 13.9 Hz, 1 H), 1.48 (d, *J* = 6.5 Hz, 3 H), 1.40 (s, 3 H).

^1H NMR (500 MHz, MeOH-d_4): δ = 4.72 (d, *J* = 3.5 Hz, 1 H), 4.13 (q, *J* = 6.6 Hz, 1 H), 3.33 (s, 3 H), 3.03 (s, 1 H), 1.87 (dd, *J* = 4.2, 14.4 Hz, 1 H), 1.53 (d, *J* = 14.4 Hz, 1 H), 1.21 (d, *J* = 6.6 Hz, 3 H), 1.13 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 99.18, 76.51, 62.17, 55.14, 50.29, 36.77, 27.84, 17.10.

Anal. Calcd for $C_8H_{17}NO_3$: C, 54.84; H, 9.78; N, 7.99. Found: C, 54.68; H, 9.53; N, 7.90.

(3a*S*,4*S*,6*R*,7a*S*)-6-Methoxy-1-(4-methoxybenzyl)-4,7a-dimethylhexahydropyrano[4,3-*d*]oxazol-2-one (19)

Acetyl chloride (385 mg, 0.35 mL, 4.9 mmol) was added to MeOH (7 mL). After stirring for 15 min, the solution was added to **15a2** (151 mg, 0.35 mmol). The solution was stirred for 5 d and most of the solvent was removed in vacuo. Then, sat. aq $NaHCO_3$ was added and the mixture was extracted with EtOAc. The organic layers were washed with brine and dried (Na_2SO_4). After removal of the solvent, the crude product was purified by flash chromatography (silica gel,

PE–EtOAc 2:1) to afford the desired product **19** as a single diastereomer (colorless oil); yield: 113 mg (100%).

$[\alpha]_D^{25}$ +27.60 (*c* 0.98, $CHCl_3$).

IR (film): 1743, 1514, 1407, 1247, 1124, 1054 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.5 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 4.46 (d, *J* = 15.4 Hz, 1 H), 4.21 (d, *J* = 15.4 Hz, 1 H), 4.18 (t, *J* = 5.7 Hz, 1 H), 3.90–3.94 (m, 2 H), 3.80 (s, 3 H), 3.22 (s, 3 H), 1.89 (dd, *J* = 5.4, 14.9 Hz, 1 H), 1.48 (dd, *J* = 6.1, 15.1 Hz, 1 H), 1.32 (d, *J* = 6.6 Hz, 3 H), 1.31 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.16, 157.76, 129.96, 129.50, 113.96, 96.96, 80.36, 62.86, 57.90, 55.25, 54.95, 43.67, 34.86, 25.90, 15.62.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{23}NO_5$: 321.1576; found: 321.1574.

(3a*S*,4*S*,6*R*,7a*S*)-6-Methoxy-4,7a-dimethylhexahydropyrano[4,3-*d*]oxazol-2-one (20)

To the solution of **19** (16 mg, 0.050 mmol) in MeCN–H_2O (1:1, 2 mL) was added CAN (71 mg, 0.13 mmol) at r.t. The solution was stirred for 22 h and quenched with sat. aq $NaHCO_3$. After extraction with EtOAc, the organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed and the crude product was purified by flash chromatography (silica gel, PE–EtOAc 1:1 → 1:2) to afford **20**; yield: 5 mg (50%).

$[\alpha]_D^{24}$ –11.25 (*c* 0.45, MeOH).

IR (film): 3298, 1749, 1056 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.79 (t, *J* = 6.0 Hz, 1 H), 4.04 (d, *J* = 1.7 Hz, 1 H), 3.97 (dq, *J* = 1.6, 6.6 Hz, 1 H), 3.38 (s, 3 H), 2.06 (dd, *J* = 5.6, 15.0 Hz, 1 H), 1.67 (dd, *J* = 6.6, 15.0 Hz, 1 H), 1.43 (s, 3 H), 1.32 (d, *J* = 6.6 Hz, 3 H).

^1H NMR (500 MHz, D_2O): δ = 5.88 (br s, 1 H), 4.85 (dd, *J* = 5.7, 8.4 Hz, 1 H), 4.35 (d, *J* = 1.5 Hz, 1 H), 4.13 (dq, *J* = 1.5, 6.4 Hz, 1 H), 3.40 (s, 3 H), 2.20 (dd, *J* = 5.8, 15.3 Hz, 1 H), 1.70 (dd, *J* = 8.4, 15.3 Hz, 1 H), 1.39 (s, 3 H), 1.25 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.60, 97.19, 82.64, 63.44, 55.02, 54.71, 36.39, 28.28, 15.66.

(2*S*,3*S*,4*S*,6*R*)-4-Amino-6-methoxy-2,4-dimethyltetrahydropyran-3-ol (21)

The solution of **20** (5 mg, 0.025 mmol) in 15% aq KOH (0.5 mL) was refluxed for 2 h. After diluting with brine, the aqueous solution was extracted with EtOAc thoroughly. The combined organic layers were washed with brine and dried (Na_2SO_4). After removal of the solvent, the residue was purified by flash chromatography (silica gel, EtOAc–MeOH–Et_3N 100:5:10) to afford known compound **21** as a colorless oil; yield: 3.5 mg (80%).

$[\alpha]_D^{24}$ –105.12 (*c* 0.1, MeOH) {lit. $[\alpha]_D$ –132 (*c* 1.4, MeOH)[13g] or $[\alpha]_D$ –118 (*c* 0.09, MeOH)[9b]}.

IR (film): 3357, 1726, 1287, 1126, 1051 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.75 (d, *J* = 4.3 Hz, 1 H), 4.01 (q, *J* = 6.4 Hz, 1 H), 3.32 (s, 3 H), 3.09 (s, 1 H), 1.83 (dd, *J* = 4.3, 13.9 Hz, 1 H), 1.59 (d, *J* = 13.8 Hz, 1 H), 1.37 (s, 3 H), 1.29 (d, *J* = 6.5 Hz, 3 H) [Lit.[13g] ^1H NMR (300 MHz, $CDCl_3$): δ = 4.74 (d, *J* = 4.4 Hz, 1 H), 4.01 (q, *J* = 6.6 Hz, 1 H), 3.32 (s, 3 H), 3.02 (br, 1 H), 1.78 (dd, *J* = 4.4, 13.6 Hz, 1 H), 1.54 (d, *J* = 13.6 Hz, 1 H), 1.32 (s, 3 H), 1.29 (d, *J* = 6.6 Hz, 3 H)].

Acknowledgment

We thank the National Institutes of Health, General Medical Sciences (GM-13598), and the National Science Foundation for their generous support of our programs. Mass spectra were obtained from the Mass Spectrometry Facility, University of San Francisco, supported by the NIH Division of Research Resources.

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