## **Supporting Information**

Me	thod	GC	Method N	No.			Purpose		Monitor the in-process redihydropyran content, po	
Cor	nditions	s 60°C, 10 C/min	to 250 C; h	old at 250 C f	or 5 n	ninute	es			
Det	tector T	ype	FID						ın Type	HP-5
	ad Pres		8 p.s.i						nn Dimensions	30m x 0.32 mmID
	ection v		2 μL						nn I.D.	1 μm film thickness
_	it Ratio	)	50/1						or Temp.	250°C
_	it Flow		50				Det	ect	tor Temp.	280°C
	tal Flow		83							
Rel		etention Time							1	
	Materi	**				RT (n	nin)		Comments	
	Metha	nol				1.1			Dilute in DMF	
	Acetoi	nitrile			1	1.3			Dilute in DMF	
	THF				1	1.8			Dilute in DMF	
	Methy	lene Chloride			1	1.3			Dilute in DMF	
	Dihyd	ropyran			2	2.1			Dilute in Acetonitrile	
	Morph	oline			3	3.1			Dilute in Acetonitrile	
	4				1	18.3			Dilute in Acetonitrile	
	3				1	12.1			Dilute in Acetonitrile	
	2 me	thyl lactate			2	2.5			Dilute in Acetonitrile	
Sar	nple Pr	eparation								
		s Stream		Compound o	f Inter	rest	Procedu			
1	Reacti	on	4,3				10 (μL)	of	reaction mixture diluted	into 1.0 mL acetonitrile
2	Residu	Residual Solvent Concentration Me TH				10 (μL) of reaction mixture diluted into 1.0 mL			into 1.0 mL	

Me	thod	GC	Method N	0.		_	Purp	pose	Chiral resolution	of methyl	lactate
Cor	nditions	60°C, 50 C/1	nin to 150 C; h	old at 150 C fo	or 5	minut	es				
Det	tector T	ype	FID				(	Colur	nn Type	R	estek Rt-βDEXse
Hea	ad Pres	sure	8 p.s.i				(	Colur	nn Dimensions	3	0m x 0.32 mmID
Inj	ection v	olume	1 μL				(	Colur	nn I.D.	0	.25 μm film thickness
Spl	it Ratio	1	20/1				]	Inject	or Temp.	2	00°C
Spl	olit Flow otal Flow		50	-				Detec	tor Temp.	2	00°C
Tot	otal Flow		60								
Rel	Relative Retention Time		ie				-			-	
	Materi	al				RT (r	min)		Comments		
6	(R)-me	ethyl lactate				6.16					
6	(S)-me	thyl lactate	2			7.70					
Sar	Sample Preparation					<u> </u>					
	Process Stream		Compound of Interest Prod		t Procedure						
1	Process Stream Pre-synthesis			2		Dilute in 50% ethyl alcohol/50% hexane				ne	

Me	thod	HPLC	Method	l No.		Purpo	ose	Optical Purity of	3	
Coı	ndition	S		-		_	_			
Inst	trumer	nt	Agilent			Colu	mn	Туре	Chiralcel OD	
Det	tector T	Гуре	UV			S	ize d	& Packing	4.6x	10.0
									250mm	μm
Mo	nitorin	g Wavelength	210 nr	n		Tem	pera	ature	RT	
Rec	cording	g time			Flow	Ra	te	1.0 mL/min		
Equ	uilibrat	tion Time			Sam	pler	Flush Solvent	Mobile Phase		
Mo	Equilibration Time 5 min  Mobile Phase 50% Isopropyl alcohol									
			Hexane							
Ret	tention	Times								
	Mate	rial			RRT	RT (m	in)	Comments		
	<b>3</b> (R)					26.3				
	(S)					30.2				
San	nple Pi	reparation		-	-					
	Proce	ess Stream	Compound of	Interest	Inj. Vol	Pr	ocedure			
1	Reaction mixture 3					5.0 μL	Di	lute to within the li	inear range (~2 mg/	mL)

Metl	hod	HPLC	Method	l No.		P	urpose	e	Optical Purity of 4	and 3	
Cone	ditions			-							
Instr	rument	t	Agilent				Colum	ın 🛚	Гуре	Chiralcel AS-H,	Diacel
										Inc.	
Dete	ector T	ype	UV				Size &	e P	acking	4.6x	5.0
										250mm	μm
		g Wavelength	210 nn	n			Гетре			RT	
	ording		20 min				Flow F			1.0 mL/min	
Equi	ilibrati	on Time	5 min			5	Sample	er l	Flush Solvent	Mobile Phase	
Mob				propyl alcohol/8	0%						
	Hexane detention Times										
Rete	ention [	Гimes									<u>-</u>
	Materi	ial			RRT	RT	[ (min	)	Comments		
	<b>3</b> (R)					13.	.0				
	<b>3</b> (S)					10.	.7				
	<b>4</b> (R)					6.8	3				
	<b>4</b> (S)					9.8					
	<b>17</b> (R)					7.7	7				
	<b>17</b> (S)					6.4	1				
Sam	ple Pre	eparation									
	Process Stream Compound			Compound of	Interest	Inj.	Vol	Pro	ocedure		
1					5.0	$\mu$ L	Dis	ssolve in 50% isopi	ropyl alcohol/50%		
	Reaction mixture 3 and 4						1	hex	ane		

Method	I GC	Method				Purp	ose	Monitor the in-proce	ess reaction for
Wicthoo		No.				ı uı p		converting 4 to 7.	
Conditi	ons 60°C, 10 C/min to	250 C; hol	d at 250 C fo	r 5	minu	tes		Ţ.	
Detecto	ог Туре	FID					Colui	mn Type	5% diphenyl/95% dimethyl polysiloxane (Restek Rtx-5 capillary)
Head P		8 p.s.i						mn Dimensions	30m x 0.32 mmID
	on volume	2 μL						mn I.D.	1 μm film thickness
Split Ra		50/1						tor Temp.	250°C
Split Fl Total F		50 83					Detec	ctor Temp.	280°C
_	e Retention Time	03							
Kelauv	Material				RT (	min)		Comments	
	Difluorobenzene	ifluorobenzene				111111)		Dilute in CH2Cl2	
	1-Bromo-2,4-difluorobenzene				4.8			Dilute in CH2Cl2	
	7		16.2				Dilute in CH2Cl2		
	7 4				18.2			Dilute in CH2Cl2	
	Methylene chloride								
	Ethyl Acetate				1.6				
	n-Heptane			2.1					
	Tetrahydrofuran				1.7				
	N,N-dimethylforman	nide			2.9-3	3.0			
Sample	Preparation				<u></u>			<u> </u>	
	Process Stream		Compound o Interest	of					
1	Reaction streams  4 7 Difluoro 1-Bromo difluorob			ļ-		water with then extrac ml of the or um syringe		th 0.5% acetic acid. In octed with 5 ml of me organic layer is then the filter containing car sieves and bottled for	or analysis.
2	Final Concentration		4,7		_	Sam	ple is	dissolved in DMF,	1:50

Me	thod	HPLC	Method	No.			P	urpose	Optical Purity of	7	
Coı	nditions	5	_	<del>-</del>			_		_		
Inst	trumen	t	Agilent					Colum	n Type	Chiralcel AD-R,	
										Diacel Inc.	
Det	tector T	ype	UV					Size	e & Packing	4.6x	5.0
										250mm	μm
Mo	Monitoring Wavelength 245 nm Recording time 30 min						,	Tempe	rature	RT	
Rec	Recording time 30 min							Flow Rate		1.0 mL/min	
Equ	Equilibration Time 5 min							Sample	er Flush Solvent	Mobile Phase	
Mo	bile Ph	ase	40% Ac	etonitril	e/60% Wa	ater					
Ret	tention	Times									
	Mater	ial				RT	(min)	) Co	mments		
	7 (R)					22.4	4				
	7 (S)				18.9	)					
San	ample Preparation				-			=			
	Process Stream Compound				ound of In	iterest	Inj.	Vol	Procedure		
1	Reaction mixture 7						5.0	μL I	Remove solvent, dili	ute in mobile phase	

Me	thod	HPLC	l No.		Purpo	ose	Reaction monitor	ing of <b>7</b> to <b>8</b> to <b>9</b> to	10	
Coı	nditions	3								
Inst	trumen	t	Agilent			Colu	mn	Туре	Xterra C18, Water Assoc.	ers
Det	ector T	уре	UV			Size	& F	Packing	4.6 x 150mm	3.5 µm
Mo	nitorin	g Wavelength	n		Tem	pera	iture	RT		
	cording		20 min			Flow	Ra	te	1.0 mL/min	
Equ	uilibrat	ion Time			Sam	pler	Flush Solvent	90% Acetonitrile 10% Water		
Mo	bile Ph	ase	onitrile		Grad	lient	t	Time 0: 90%B		
			er					Time 50: 10%B		
									Time 55: 90%B	
Ret	ention	Times				_				
	Mater	ial			RRT	RT (m	in)	Comments		
	7					25.6				
	8					28.5				
	9					21.3				
	10					11.2				
San	mple Preparation				_	_				
	Proces	ss Stream	Compound of	Interest	Inj. Vol	Pr	ocedure			
1	Reacti	on mixture	7,8,9,10		5.0 μL		ssolve in 50% acet	onitrile/50% water		

Me	ethod	HPLC	Method	d No.		Pur	pose	Optical Purity of 1	2	
Co	ndition	S		<del>-</del>		_		-		
Ins	trumer	nt	Agilent			Co	lumi	1 Туре	Chiralcel AD, Dia	acel
									Inc.	
Det	tector T	Гуре	UV				Size	& Packing	4.6x	5.0
									250mm	μm
Mo	Monitoring Wavelength 210 nm					Te	mpe	rature	RT	
Rec	Recording time 20 min					Fle	ow R	ate	1.0 mL/min	
Equ	Equilibration Time 5 min					Sa	mple	r Flush Solvent	Mobile Phase	
Mo	bile Ph	ase	35% Et	hyl Alcohol/65%	Heptane					
Ret	tention	Times								
	Mater	rial			RT (mi	n)	Comments			
	<b>12</b> un	desired (R,S)			14.1		No	n-fully characterized	HPLC marker avail	lable
	12 desired				16.4					
Sar	Sample Preparation									
	Process Stream Compound o				of Interest   I		ol F	rocedure		
1					5.0 μ		μL Remove solvent, dilute in mobile phase			

Me	thod	HPLC	l No.		Purpo	se	Reaction monitor	ing of <b>10,16</b> and <b>12</b>	,	
Cor	ndition	S								
Inst	trumer	nt	Agilent			Colu	mn	Туре	AS=303 ProPact YMC Assoc.	k C18,
Det	ector T	Гуре	UV			Size	& I	Packing	4.6 x 150mm	5.0 μm
Mo	nitorin	g Wavelength	260 nn	n		Tem	pera	ature	RT	
Rec	ording	time	10 min			Flow	Ra	te	1.0 mL/min	
Equ	juilibration Time 5 min 5 min 40% A actoritiila/60%				Samj	pler	Flush Solvent	40% Acetonitrile 60% Water	•	
Mo	<b>Iobile Phase</b> 40% Acetonitrile/60%			% Water						
Ret	etention Times				<u>.</u>					
	Mater	rial			RT (mi	n)		Comments		
	10				4.5					
	<b>10</b> (S,	R)			3.7					
	16				7.6					
	<b>16</b> (S,	R)			5.7					
	12				7.9					
	<b>12</b> (S,S)			5.4						
San	ample Preparation									
	Process Stream Compound o			of Interest	Inj. Vol	Pr	ocedure			
1					5.0 μL	Di	issolve in 40% acet	tonitrile/60% water		

Me	thod	HPLC	Method	No.			Pur	pose	Optical Purity of	10	
Coı	ndition	s		-			_				
Ins	trumen	ıt	Agilent				Co	lumn	Туре	Chiralcel AD, D	iacel
										Inc.	
Det	tector T	Гуре	UV					Size	& Packing	4.6x	5.0
										150mm	μm
Mo	nitorin	g Wavelength	210 nn	ı			Te	mper	ature	RT	
Rec	cording	time	20 min				Flo	w Ra	ite	1.0 mL/min	
Equ	uilibrat	ion Time	5 min				Sai	mpler	Flush Solvent	Mobile Phase	
Mo	Mobile Phase 90% Hexane/10% Eth			Ethyl .	Alcohol						
Ret	tention	Times									
	Mater	rial				RT (mi	n)	Con	nments		
	<b>10</b> de	sired				18.19					
	<b>10</b> un	desired				21.87					
		·							·	·	
San	nple Pr	eparation									
	Proce	ss Stream		Compou	nd of I	nterest	Inj. V	ol P	rocedure		
1	Reaction mixture 10					5.0 μL	R	emove solvent, dilu	te in mobile phase		

Me	thod	HPLC	Method	l No.		Purpo	ose	Reaction monitor	ring of <b>12</b> and <b>13</b>	
Cor	nditions	S								
Ins	trumen	t	Agilent			Colu	mn '	Туре	ODS-AQ C18, Y Assoc.	/MC
Det	ector T	ype	UV			Size	& P	Packing	4.6 x 250mm	5.0
										μm
Mo	nitorin	g Wavelength	260 nr	n		Tem	pera	ture	RT	
Rec	cording time 15 min					Flow	Rat	te	1.0 mL/min	
Equ	quilibration Time 5 min					Sam	pler	Flush Solvent	40% Acetonitrile 60% Water	e
Mo	bile Phase 40% Acetonitrile/60%									
			Water/0	0.02% Acetic acid	1					
Ret	ention	Times				_			-	
	Mater	ial			RT (mi	n)		Comments		
	13				8.1					
	12				9.5					
San	nple Preparation									
				Compound of	Interest	Inj. Vol	Pr	ocedure		
1	Reaction mixture 12,13			12,13		10.0 μL	Di	lute in mobile pha	ise	
						•				

Me	thod	HPLC	Method	l No.		Purpo	ose	Optical purity of 1	3	
Cor	nditions	S		-		-	-			
Ins	trumen	t	Agilent			Colu	mn '	Туре	Chiralcel OD, D	Diacel
		-	****						4.6.270	<b>1.7.</b> 0
Det	tector T	ype	UV			Size	& P	Packing	4.6 x 250mm	5.0
Ma	!4 ~!	a Wanalan ath	215			Т		.4	RT	μm
		g Wavelength	215 nm	1		Tem				
Rec	cording time 30 min					Flow	Rat	te	1.0 mL/min	
Equ	quilibration Time 5 min					Sam	pler	Flush Solvent	80% Hexane 20% Ethyl Alcol	hol
Mo	bile Ph	ase	80% He	exane/20% Ethyl	Alcohol					
Ret	tention	Times								
	Mater	ial			RT (mi	n)		Comments		
	13 de	sired			16.2					
	<b>13</b> un	desired			20.1					
Sar	mple Preparation							-		
	Process Stream Compound			Compound of	Interest	Inj. Vol	Pro	ocedure		
1	Reaction mixture 13				5.0 μL	Dil	lute in mobile phas	e		
	1									

Me	thod	HPLC	Method	l No.		Purpo	se	Reaction monitor	ing of <b>13</b> and <b>14</b>	
Conditions										
Instrument			Perkin Elmer			Colu	Column Type		ODS-A C18, YMC	
									Assoc.	
Detector Type			UV				Size & Packing		4.6 x 150mm	10.0
										μm
Mo	Monitoring Wavelength			205 nm				ature	RT	
Rec	Recording time			15 min			Flow Rate		1.0 mL/min	
Equ	uilibrat	tion Time	5 min			Sam	Sampler Flush Solvent		Mobile Phase	
Mobile Phase			56% Methanol/44% Water-Acetic			:				
				acid (2000:7)						
Ret	Retention Times									
Material					RT (mi	n) Comments				
	14 (diastereoisomer and			etate)						
	13			3.8						
	14			7.7						
San	nple Pr	reparation								
	Process Stream		Compound of	Interest	Inj. Vol	Pr	Procedure			
1	Reaction mixture		13,14		$20.0 \mu L$	5 إ	μL of reaction mixture is added to a mixture			
									200 μL of 10% K <sub>2</sub> C	
								f organic layer to 70	)0 μL	
					with 70% methanol/30% water.					

Me	thod	HPLC	Method No.		Purpo	ose	Reaction monitoring of 1 and 14				
Conditions											
Instrument			Perkin Elmer			Colu	mn	Туре	ODS-AQ C18, YMC		
									Assoc.		
<b>Detector Type</b>			UV			Size	& I	Packing	4.6 x 150mm	5.0	
									μm		
Monitoring Wavelength			265 nm			_	_	ature	RT		
Recording time			15 min			Flow	Ra	te	1.0 mL/min		
Equilibration Time			5 min			Sam	Sampler Flush Solvent		Mobile Phase		
Mo	Mobile Phase			55% Acetonitrile/45% 20mM							
			Ammonium Acetate, pH 4.5								
Retention Times											
	Mater	ial		RT (min)				Comments			
	1				10.4						
	14				3.1	3.1					
	1 diast	ereomer		6.3							
1 acylated by bromoacetophenone impur				ne impurity	8.4	8.4					
Sample Preparation											
	Proces	ss Stream		Compound of	of Interest	Inj. Vol	Pr	ocedure			
1	Reaction mixture 1, 14				20.0 μL	Sa	nples diluted in acetonitrile.				
						,		•			

Method HPLC		Method	Method No.		Pu	rpose	Optical Purity of <b>1</b>					
Conditions												
Instrument			Agilent			C	olumi	1 Туре	Chiralcel AD-R,			
										Diacel Inc.	Diacel Inc.	
<b>Detector Type</b>			UV				Size & Packing		4.6x	5.0		
								150mm μ			μm	
<b>Monitoring Wavelength</b>			245 nm				T	empe	emperature RT			
Rec	Recording time			30 min			F	Flow Rate		1.0 mL/min		
Equ	<b>Equilibration Time</b>			5 min			Sa	ample	r Flush Solvent	Mobile Phase		
Mo	Mobile Phase			40% Acetonitrile/60% Water								
Ret	Retention Times											
	Mater	rial				RT (min)		Comments				
	1											
1 enantiomer				22.4								
Sample Preparation												
	Process Stream			Comp	ompound of Interest   In			. Vol Procedure				
1 Reaction mixture				1 1			$1.0 \mu$	ıL R	Remove solvent, dilute in mobile phase			