Supporting Information

Method	GC	**Method No.**		**Purpose**	Monitor the in-process reaction, methanol and dihydropyran content, potency

Conditions 60°C, 10 C/min to 250 C; hold at 250 C for 5 minutes

Detector Type	FID	**Column Type**	HP-5
Head Pressure	8 p.s.i	**Column Dimensions**	30m x 0.32 mmID
Injection volume	2 μL	**Column I.D.**	1 μm film thickness
Split Ratio	50/1	**Injector Temp.**	250°C
Split Flow	50	**Detector Temp.**	280°C
Total Flow	83		

Relative Retention Time

	Material		RT (min)	Comments
	Methanol		1.1	Dilute in DMF
	Acetonitrile		1.3	Dilute in DMF
	THF		1.8	Dilute in DMF
	Methylene Chloride		1.3	Dilute in DMF
	Dihydropyran		2.1	Dilute in Acetonitrile
	Morpholine		3.1	Dilute in Acetonitrile
	4		18.3	Dilute in Acetonitrile
	3		12.1	Dilute in Acetonitrile
	2 methyl lactate		2.5	Dilute in Acetonitrile

Sample Preparation

	Process Stream	Compound of Interest	Procedure
1	Reaction	**4,3**	10 (μL) of reaction mixture diluted into 1.0 mL acetonitrile
2	Residual Solvent Concentration	Methanol THF	10 (μL) of reaction mixture diluted into 1.0 mL

Method	GC	**Method No.**		**Purpose**	Chiral resolution of methyl lactate
Conditions 60°C, 50 C/min to 150 C; hold at 150 C for 5 minutes					
Detector Type	FID			**Column Type**	Restek Rt-βDEXse
Head Pressure	8 p.s.i			**Column Dimensions**	30m x 0.32 mmID
Injection volume	1 μL			**Column I.D.**	0.25 μm film thickness
Split Ratio	20/1			**Injector Temp.**	200°C
Split Flow	50			**Detector Temp.**	200°C
Total Flow	60				

Relative Retention Time

	Material		RT (min)	Comments
6	(R)-methyl lactate		6.16	
6	(S)-methyl lactate **2**		7.70	

Sample Preparation

	Process Stream	Compound of Interest	Procedure
1	Pre-synthesis	**2**	Dilute in 50% ethyl alcohol/50% hexane

Method	**HPLC**	**Method No.**		**Purpose**	Optical Purity of **3**	
Conditions						
Instrument		Agilent		**Column Type**	Chiralcel OD	
Detector Type		UV		**Size & Packing**	4.6x 250mm	10.0 μm
Monitoring Wavelength		210 nm		**Temperature**	RT	
Recording time		35 min		**Flow Rate**	1.0 mL/min	
Equilibration Time		5 min		**Sampler Flush Solvent**	Mobile Phase	
Mobile Phase		50% Isopropyl alcohol/50% Hexane				

Retention Times

	Material	**RRT**	**RT (min)**	**Comments**
	3 (R)		26.3	
	(S)		30.2	

Sample Preparation

	Process Stream	**Compound of Interest**	**Inj. Vol**	**Procedure**
1	Reaction mixture	**3**	5.0 μL	Dilute to within the linear range (~2 mg/mL)

Method	**HPLC**	**Method No.**		**Purpose**	Optical Purity of **4** and **3**

Conditions			
Instrument	Agilent	**Column Type**	Chiralcel AS-H, Diacel Inc.
Detector Type	UV	**Size & Packing**	4.6x 250mm 5.0 μm
Monitoring Wavelength	210 nm	**Temperature**	RT
Recording time	20 min	**Flow Rate**	1.0 mL/min
Equilibration Time	5 min	**Sampler Flush Solvent**	Mobile Phase
Mobile Phase	20% Isopropyl alcohol/80% Hexane		

Retention Times

	Material	**RRT**	**RT (min)**	**Comments**
	3 (R)		13.0	
	3 (S)		10.7	
	4 (R)		6.8	
	4 (S)		9.8	
	17 (R)		7.7	
	17 (S)		6.4	

Sample Preparation

	Process Stream	**Compound of Interest**	**Inj. Vol**	**Procedure**
1	Reaction mixture	**3** and **4**	5.0 μL	Dissolve in 50% isopropyl alcohol/50% hexane

Method	GC	**Method No.**		**Purpose**	Monitor the in-process reaction for converting **4** to **7**.
Conditions 60°C, 10 C/min to 250 C; hold at 250 C for 5 minutes					
Detector Type	FID			**Column Type**	5% diphenyl/95% dimethyl polysiloxane (Restek Rtx-5 capillary)
Head Pressure	8 p.s.i			**Column Dimensions**	30m x 0.32 mmID
Injection volume	2 μL			**Column I.D.**	1 μm film thickness
Split Ratio	50/1			**Injector Temp.**	250°C
Split Flow	50			**Detector Temp.**	280°C
Total Flow	83				

Relative Retention Time

	Material		RT (min)	Comments
	Difluorobenzene		1.9	Dilute in CH2Cl2
	1-Bromo-2,4-difluorobenzene		4.8	Dilute in CH2Cl2
	7		16.2	Dilute in CH2Cl2
	4		18.2	Dilute in CH2Cl2
	Methylene chloride		1.2	
	Ethyl Acetate		1.6	
	n-Heptane		2.1	
	Tetrahydrofuran		1.7	
	N,N-dimethylformamide		2.9-3.0	

Sample Preparation

	Process Stream	Compound of Interest	
1	Reaction streams	**4** **7** Difluorobenzene 1-Bromo-2,4-difluorobenzene	One ml of reaction mixture is quenched into 5 ml of water with 0.5% acetic acid. The quenched mixture is then extracted with 5 ml of methylene chloride. Two ml of the organic layer is then passed through a 0.2 um syringe filter containing ca.150 mg of 4 A molecular sieves and bottled for analysis.
2	Final Concentration	**4,7**	Sample is dissolved in DMF, 1:50

Method	**HPLC**	**Method No.**		**Purpose**	Optical Purity of **7**	
Conditions						
Instrument		Agilent		**Column Type**	Chiralcel AD-R, Diacel Inc.	
Detector Type		UV		**Size & Packing**	4.6x 250mm	5.0 µm
Monitoring Wavelength		245 nm		**Temperature**	RT	
Recording time		30 min		**Flow Rate**	1.0 mL/min	
Equilibration Time		5 min		**Sampler Flush Solvent**	Mobile Phase	
Mobile Phase		40% Acetonitrile/60% Water				

Retention Times

	Material		**RT (min)**	**Comments**
	7 (R)		22.4	
	7 (S)		18.9	

Sample Preparation

	Process Stream	**Compound of Interest**	**Inj. Vol**	**Procedure**
1	Reaction mixture	**7**	5.0 μL	Remove solvent, dilute in mobile phase

Method	**HPLC**	**Method No.**		**Purpose**	Reaction monitoring of **7** to **8** to **9** to **10**

Conditions				
Instrument	Agilent	**Column Type**	Xterra C18, Waters Assoc.	
Detector Type	UV	**Size & Packing**	4.6 x 150mm	3.5 μm
Monitoring Wavelength	210 nm	**Temperature**	RT	
Recording time	20 min	**Flow Rate**	1.0 mL/min	
Equilibration Time	5 min	**Sampler Flush Solvent**	90% Acetonitrile 10% Water	
Mobile Phase	A: Acetonitrile B: Water	**Gradient**	Time 0: 90%B Time 50: 10%B Time 55: 90%B	

Retention Times

	Material	**RRT**	**RT (min)**	**Comments**
	7		25.6	
	8		28.5	
	9		21.3	
	10		11.2	

Sample Preparation

	Process Stream	**Compound of Interest**	**Inj. Vol**	**Procedure**
1	Reaction mixture	**7,8,9,10**	5.0 μL	Dissolve in 50% acetonitrile/50% water

Method	**HPLC**	**Method No.**		**Purpose**	Optical Purity of **12**
Conditions					
Instrument		Agilent		**Column Type**	Chiralcel AD, Diacel Inc.
Detector Type		UV		**Size & Packing**	4.6x 250mm 5.0 µm
Monitoring Wavelength		210 nm		**Temperature**	RT
Recording time		20 min		**Flow Rate**	1.0 mL/min
Equilibration Time		5 min		**Sampler Flush Solvent**	Mobile Phase
Mobile Phase		35% Ethyl Alcohol/65% Heptane			

Retention Times

	Material	**RT (min)**	**Comments**
	12 undesired (R,S)	14.1	Non-fully characterized HPLC marker available
	12 desired	16.4	

Sample Preparation

	Process Stream	**Compound of Interest**	**Inj. Vol**	**Procedure**
1	Reaction mixture	**12**	5.0 μL	Remove solvent, dilute in mobile phase

Method	**HPLC**	**Method No.**		**Purpose**	Reaction monitoring of **10**,**16** and **12**

Conditions				
Instrument	Agilent	**Column Type**	AS=303 ProPack C18, YMC Assoc.	
Detector Type	UV	**Size & Packing**	4.6 x 150mm	5.0 μm
Monitoring Wavelength	260 nm	**Temperature**	RT	
Recording time	10 min	**Flow Rate**	1.0 mL/min	
Equilibration Time	5 min	**Sampler Flush Solvent**	40% Acetonitrile 60% Water	
Mobile Phase	40% Acetonitrile/60% Water			

Retention Times

	Material	**RT (min)**	**Comments**
	10	4.5	
	10 (S,R)	3.7	
	16	7.6	
	16 (S,R)	5.7	
	12	7.9	
	12 (S,S)	5.4	

Sample Preparation

	Process Stream	**Compound of Interest**	**Inj. Vol**	**Procedure**
1	Reaction mixture	**10**, **16**, **12**	5.0 μL	Dissolve in 40% acetonitrile/60% water

Method	**HPLC**	**Method No.**		**Purpose**	Optical Purity of **10**	
Conditions						
Instrument		Agilent		**Column Type**	Chiralcel AD, Diacel Inc.	
Detector Type		UV		**Size & Packing**	4.6x 150mm	5.0 µm
Monitoring Wavelength		210 nm		**Temperature**	RT	
Recording time		20 min		**Flow Rate**	1.0 mL/min	
Equilibration Time		5 min		**Sampler Flush Solvent**	Mobile Phase	
Mobile Phase		90% Hexane/10% Ethyl Alcohol				

Retention Times

	Material	**RT (min)**	**Comments**
	10 desired	18.19	
	10 undesired	21.87	

Sample Preparation

	Process Stream	**Compound of Interest**	**Inj. Vol**	**Procedure**
1	Reaction mixture	**10**	5.0 μL	Remove solvent, dilute in mobile phase

Method	**HPLC**	**Method No.**		**Purpose**	Reaction monitoring of **12** and **13**

Conditions				
Instrument	Agilent	**Column Type**	ODS-AQ C18, YMC Assoc.	
Detector Type	UV	**Size & Packing**	4.6 x 250mm	5.0 μm
Monitoring Wavelength	260 nm	**Temperature**	RT	
Recording time	15 min	**Flow Rate**	1.0 mL/min	
Equilibration Time	5 min	**Sampler Flush Solvent**	40% Acetonitrile 60% Water	
Mobile Phase	40% Acetonitrile/60% Water/0.02% Acetic acid			

Retention Times

	Material	**RT (min)**	**Comments**
	13	8.1	
	12	9.5	

Sample Preparation

	Process Stream	**Compound of Interest**	**Inj. Vol**	**Procedure**
1	Reaction mixture	**12,13**	10.0 μL	Dilute in mobile phase

Method	**HPLC**	**Method No.**		**Purpose**	Optical purity of **13**
Conditions					
Instrument		Agilent		**Column Type**	Chiralcel OD, Diacel
Detector Type		UV		**Size & Packing**	4.6 x 250mm 5.0 μm
Monitoring Wavelength		215 nm		**Temperature**	RT
Recording time		30 min		**Flow Rate**	1.0 mL/min
Equilibration Time		5 min		**Sampler Flush Solvent**	80% Hexane 20% Ethyl Alcohol
Mobile Phase		80% Hexane/20% Ethyl Alcohol			

Retention Times			
	Material	**RT (min)**	**Comments**
	13 desired	16.2	
	13 undesired	20.1	

Sample Preparation				
	Process Stream	**Compound of Interest**	**Inj. Vol**	**Procedure**
1	Reaction mixture	**13**	5.0 μL	Dilute in mobile phase

Method	**HPLC**	**Method No.**		**Purpose**	Reaction monitoring of **13** and **14**	
Conditions						
Instrument		Perkin Elmer		**Column Type**	ODS-A C18, YMC Assoc.	
Detector Type		UV		**Size & Packing**	4.6 x 150mm	10.0 μm
Monitoring Wavelength		205 nm		**Temperature**	RT	
Recording time		15 min		**Flow Rate**	1.0 mL/min	
Equilibration Time		5 min		**Sampler Flush Solvent**	Mobile Phase	
Mobile Phase		56% Methanol/44% Water-Acetic acid (2000:7)				

Retention Times			
	Material	**RT (min)**	**Comments**
	14 (diastereoisomer and ethyl acetate)	3.1	
	13	3.8	
	14	7.7	

Sample Preparation				
	Process Stream	**Compound of Interest**	**Inj. Vol**	**Procedure**
1	Reaction mixture	**13,14**	20.0 μL	5 μL of reaction mixture is added to a mixture of 1 mL MTBE and 200 μL of 10% K_2CO_3. Then dilute 200 μL of organic layer to 700 μL with 70% methanol/30% water.

Method	**HPLC**	**Method No.**		**Purpose**	Reaction monitoring of **1** and **14**

Conditions				
Instrument	Perkin Elmer	**Column Type**	ODS-AQ C18, YMC Assoc.	
Detector Type	UV	**Size & Packing**	4.6 x 150mm	5.0 μm
Monitoring Wavelength	265 nm	**Temperature**	RT	
Recording time	15 min	**Flow Rate**	1.0 mL/min	
Equilibration Time	5 min	**Sampler Flush Solvent**	Mobile Phase	
Mobile Phase	55% Acetonitrile/45% 20mM Ammonium Acetate, pH 4.5			

Retention Times

	Material	**RT (min)**	**Comments**
	1	10.4	
	14	3.1	
	1 diastereomer	6.3	
	1 acylated by bromoacetophenone impurity	8.4	

Sample Preparation

	Process Stream	**Compound of Interest**	**Inj. Vol**	**Procedure**
1	Reaction mixture	**1**, **14**	20.0 μL	Samples diluted in acetonitrile.

Method	**HPLC**	**Method No.**		**Purpose**	Optical Purity of **1**	
Conditions						
Instrument		Agilent		**Column Type**	Chiralcel AD-R, Diacel Inc.	
Detector Type		UV		**Size & Packing**	4.6x 150mm	5.0 µm
Monitoring Wavelength		245 nm		**Temperature**	RT	
Recording time		30 min		**Flow Rate**	1.0 mL/min	
Equilibration Time		5 min		**Sampler Flush Solvent**	Mobile Phase	
Mobile Phase		40% Acetonitrile/60% Water				

Retention Times			
	Material	**RT (min)**	**Comments**
	1	18.9	
	1 enantiomer	22.4	

Sample Preparation				
	Process Stream	**Compound of Interest**	**Inj. Vol**	**Procedure**
1	Reaction mixture	**1**	1.0 μL	Remove solvent, dilute in mobile phase