purified by column chromatography to provide 12 g of compound **6** in 87% yield, containing unreacted compound **5** (lot 09GB005).

Therefore, the reaction was examined using different solvents and temperature. The results are shown in Table 10, in which all the examined reaction conditions were not better than the original condition. The original reaction condition was used in the scale-up, but monitored by HPLC analysis. The preparation of compound **6** was run in several scales, tabulated in Table 11.

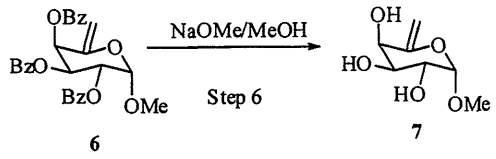
Table 10. Examination of Preparation of Compound 6

Experiment	Conditions	Comments
19MEM011	**5** (5 g), DBU (9.1 equiv), Toluene (13 vol), 100 °C, 72 h	• <1% (AUC) by HPLC of **5** remained after stirring over the weekend at 100 °C, but several major impurities were seen by HPLC that were not seen when run in THF. • Isolated 0.8 g, 20 % yield.
19MEM012	**5** (1.19 g), DBU (9.1 equiv), Toluene (13 vol), 100 °C	• After 1 h of heating HPLC shows **5** and **6** and several large impurities.
19MEM013	**5** (1.27 g), DBU (9.1 equiv), 2-MeTHF (13 vol), 80 °C, 24 h	• 4% (AUC) by HPLC of **5** remained after stirring overnight at 80 °C but several major impurities were seen by HPLC. The profile was similar to the profile in toluene. • Isolated 0.6 g, 60 % yield.

Table 11. Preparation of Compound 6

Lot Number	Input of Compound 5	Output of Compound 6	Yield (%)	Comments
09GB005	15.5 g	12.1 g	87	• 20 mol % of **5** remaining after 24 h reflux. • 79.8% (AUC) by HPLC, containing compound **5**.
19MEM015	79.3 g	25.7 g	40	• 72 h reflux, <5% of **5** remaining. • 88.6% potency by ^{1}H NMR of a colorless syrup that contains 1.8% compound **5** by HPLC (AUC) at 230 nm.
09GB012	26.55 g	16.7 g	79.5	• 40 h reflux, >4% of **5** remaining. • 95% (AUC) by HPLC at 230 nm.
19MEM018	50 g	31 g	78	• 24 h reflux, <5% of **5** remaining. • 83.6% potency by ^{1}H NMR of a colorless syrup that contains 2.7% compound **5** by HPLC (AUC) at 230 nm.
19MEM019	200 g	65 g	82	• 27 h reflux, <5% of **5** remaining. • Half of the crude was purified by column chromatography.

Step 6



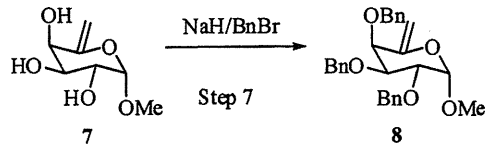
6 7

The reaction was conducted by following the provided procedure using NaOMe (0.1 equiv) in MeOH (25 vol). The reaction was stirred for 4 hours at room temperature, at which time TLC and HPLC analyses showed it was complete. The reaction mixture was concentrated and triturated with MTBE (20 vol) to afford compound **7** as a white solid.

Table 12. Preparation of Compound 7

Lot Number	Input of Compound 6	Output of Compound 7	Yield (%)
09GB014	16.5 g	5.4 g	91
19MEM020	120 g	40.7 g	94

Step 7



7 8

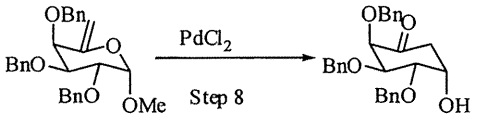
The reaction was carried out by following the provided procedure using NaH (6.2 equiv), BnBr (5.0 equiv) and nBu$_4$NI (catalytic amount) in DMF (40 vol) and THF (20 vol). The reaction was stirred at room temperature for 16 hours, at which time TLC analysis indicated that the reaction was complete. The reaction was worked up. Column chromatography afforded the compound **8** as a color less oil.

Table 13. Preparation of Compound 8

Lot Number	Input of Compound 7	Output of Compound 8	Yield (%)	Comments
09GB016	5.3 g	12.5 g	93	94.7% (AUC) by HPLC at 210 nm
19MEM022	40 g	87 g	85.6	Volumes were reduced to DMF (22.5 vol) and THF (11.25 vol)

Excess amount of benzyl bromide was used in the reaction and would not be removed efficiently during work up. Although the excess amount can be removed during column chromatography, the purification will be more efficient if the amount of benzyl bromide can be reduced.

Step 8



8 9

The reaction was performed by following the provided procedure using $PdCl_2$ (0.063 equiv), 1,4-dioxane (34 vol) and water (17 vol). The reaction mixture was stirred at 60 °C and monitored by TLC and HPLC analyses. After 4 hours, the reaction was complete and worked up. The crude product was purified by column chromatography to afford the compound **9** as a color less oil.

The reaction was also examined in a reduced reaction volume in 14 volumes of 1,4-dioxane and 7 volumes of water. The stereoisomer ratio in some of the later reactions was checked by ^1H NMR analysis. The results are shown in Table 14. From lot 09GB026 (21 vol of solvents) and 09GB027 (51 vol of solvents), the stereoisomer ratios were comparable and the reaction was scaled up to 76 g of compound **8**.

Table 14. Preparation of Compound 9

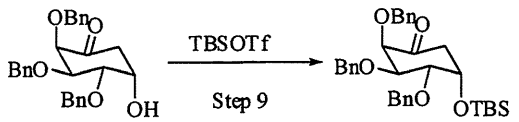
Lot Number	Input of Compound 8	Output of Compound 9	Yield (%)	Comments
09GB010	1.1 g	0.79 g	74.5	
09GB011	4 g	3.2 g	83	
09GB019	12 g	9.6 g	83	• 89% (AUC) by HPLC at 210 nm
09GB026	5 g	3.4 g	70	• 14 vol of 1,4 dioxane and 7 vol of water in the reaction. • Ratio of α and β isomers in the crude was 6.9:1. • 94% (AUC) by HPLC at 210 nm. • Isolated 0.9 g mixture of α and β isomers as 1.7:1 ratio, along with other impurity(s). • Isolated 0.18 g mixture of β isomer. • Overall ratio of α and β isomers after isolation was 8.4:1.
09GB027	5 g	3.2 g	66	• 34 vol of 1,4 dioxane and 17 vol of water in the reaction. • Ratio of α and β isomers in the crude was 6.7:1. • Isolated 0.9 g mixture of α and β isomers as 2.15:1 ratio, along with other impurity(s). • Overall ratio of α and β isomers after isolation was 9:1.

Table 14 Continued. Preparation of Compound 9

Lot Number	Input of Compound 8	Output of Compound 9	Yield (%)	Comments
19MEM024	76 g	47.2 g	64	• 14 vol of 1,4 dioxane and 7 vol of water in the reaction. • Ratio of α and β isomers in the crude was 6.4:1. • 47.2 g pure α isomers (2% β) were from two column purifications (22.2 g from the first column and 25 g from the second column). • Isolated mixture of α and β: 8.7 g (1:1), 11 g (7.5:1).

Regular column purification was tedious in this step. To bring large amounts of compound **9** by either regular column chromatography or ChembiFlash chromatography is not practical. The reaction using compound **9** containing relative more β-isomer could be examined to see if the isomer could be removed in the later stage. Another thought is to run the reaction using compound **6** since the ratio was much higher than the reaction using compound **8** as the starting material.

Step 9



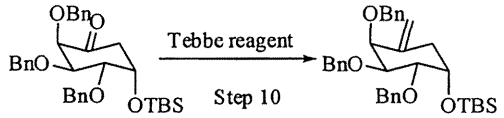
9 **10**

By following the provided procedure, the reaction was carried out using 2,6-Lutidine (5.0 equiv) and TBSOTf (1.2 equiv) in CH_2Cl_2 (22 vol) at −18 °C to −28 °C. After 2 hours, the reaction was deemed complete. The reaction was worked up by quenching with MeOH (0.3 vol) and stirred for 30 minutes. Reaction mixture was concentrated and the residue was azeotroped with toluene. The light yellow oil was dissolved in EtOAc and the solution was washed with water, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated to give crude product. There was about 50 wt% of 2,6-Lutidine triflate remaining. The crude product was purified by column chromatography to afford compound **10** as a colorless oil. During the column purification, 2,6-Lutidine was moved by the eluting solvent behind the product. Reducing amount of 2,6-Lutidine in the reaction will reduce the time and therefore help the column purification.

Table 15. Preparation of Compound 10

Lot Number	Input of Compound 9	Output of Compound 10	Yield (%)	Comments
09GB021	9.5 g	10.3 g	86	98% (AUC) by HPLC at 210 nm
19MEM025	53 g	58.5 g	88	

Step 10



10 **11**

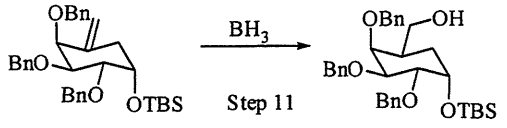
Methylenation of carbonyl of compound **10** was carried out by following the provided procedure in which 0.5 M Tebbe reagent (1.5 equiv, in toluene) was added into a solution of compound **10** in pyridine (7 vol) in THF (21 vol) while maintaining internal temperature at −40 °C to −45 °C. Once the addition was completed, the reaction mixture was stirred at room temperature. The reaction was complete in about 2 hours, at which time TLC analysis confirmed the completion. The reaction mixture was cooled to −40 °C and quenched with saturated $NaHCO_3$ and MTBE was charged before stirring at room temperature. Sticky solid coated on the flask. The slurry was filtered in a medium rate and the solid was washed with MTBE. The filtrate and washes were concentrated and the residue was azeotroped with toluene to remove some of the pyridine. The residue was charged with EtOAc and more solid was filtered and washed with EtOAc. Combined filtrate and washes were washed with water, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated to give the crude product. The crude product was purified by column chromatography to afford compound **11** as an oil.

Table 16. Preparation of Compound 11

Lot Number	Input of Compound 10	Output of Compound 11	Yield (%)	Comments
09GB015	3.75 g	2.81 g	75	• <5% compound **10** remaining.
09GB022	10.1 g	7.7 g	76	• About 15% compound **10** remaining. • 98% (AUC) by HPLC at 210 nm. • 9% compound **10** was recovered from the column.
19MEM026	53.5 g	47.7 g	90.6	• The reaction was complete after 1.5 hours. • Stick solid on the glasswall of the reactor during precipitation. • 5 wt% pyridine remained in the crude after work up; 71 wt% and 21 wt% before and azeotropying.

Commercial Tebbe reagent is expensive and only limited source is available. We have the amount to meet the current need for making 10 g of compound **A** and 50 g of **RCAI-56**. Wittig and alternative reagent such as Petasis's dimethyltitanocene (DMT) could be considered to examine in the future.

Step 11



11 12

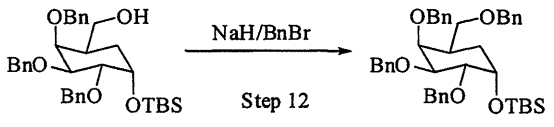
The reaction was carried out by following the provided procedure using 1.0 M BH_3•THF (5.0 equiv) in THF (22 vol). After the addition was completed, the reaction mixture was treated with aqueous 2.0 M NaOH solution and H_2O_2 (30% in water). After stirring for 1 hour, the batch was worked up and purified by column chromatography to afford compound **12** as a color less oil.

Table 17. Preparation of Compound 12

Lot Number	Input of Compound 11	Output of Compound 12	Yield (%)	Comments
09GB017	3.75 g	2.13 g	74	• 98% (AUC) by HPLC at 210 nm.
09GB023	7.6 g	6.1 g	77.7	• About 15% compound **10** remaining. • 91% (AUC) by HPLC at 210 nm.

The reaction currently only was run in less 10 g scale. Once more compound **11** is prepared, a relative larger scale reaction will be performed and at that time, stereochemistry and stereoisomers possibly generated in the reaction will be examined. From the isolated material, there was no isomer that was identified.

Step 12



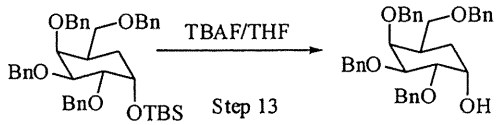
12 13

The reaction had been run in less than 10 g scale. By following the provided procedure using NaH (3.0 equiv), BnBr (2.0 equiv) and $n$$Bu_4NI$ (catalytic amount) in a mixture of DMF (15 vol) and THF (15 vol), the reactions progressed as expected. After the work up, the crude material was purified by column chromatography eluted to afford compound **13** as a colorless oil.

Table 18. Preparation of Compound 13

Lot Number	Input of Compound 12	Output of Compound 13	Yield (%)
09GB018	2.0 g	1.92 g	83
09GB024	6.0 g	6.5 g	93

Step 13



13 A

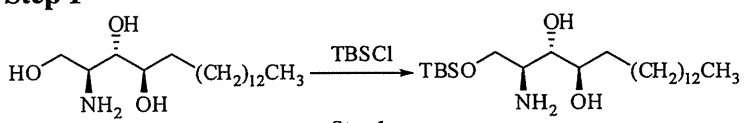
By following the provided procedure using TBAF (2.0 equiv), 1 M in THF (10 vol), the deprotection of TBS group have taken longer than the time described in the procedure, about 40 hours. After the reaction worked up, the crude product was purified by column chromatography to afford compound **A** as a colorless oil.

Table 19. Preparation of Compound A

Lot Number	Input of Compound 13	Output of Compound A	Yield (%)	Comments
09GB020	1.9 g	1.23 g	78	95% (AUC) by HPLC at 210 nm
09GB025	6.4 g	4.35 g	82	95% (AUC) by HPLC at 210 nm

3.2 Synthesis of Compound B

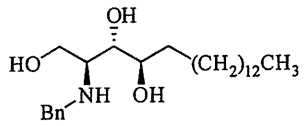
Step 1



14 15

The Step 1 for making compound **B** in the provided scheme was the preparation of compound **15'** (Figure 1) from compound **14**. The preparation of compound **15'** followed the literature procedure (*JOC*, **2004**, *69*, 7694–7699) using $NaBH_4$ instead of 2-picolineborane in the provided procedure. The reaction was attempted by using compound **14** (1.0 equiv) and benzaldehyde (1 equiv) in a mixed solvent of THF and dichloromethane in the presence of $MgSO_4$ (1.2 equiv). The reaction mixture was stirred at room temperature for 16 h, at which time ^1H NMR analysis indicated that the reaction was complete. The reaction mixture was filtered through Celite and the filter cake was washed with MeOH. The filtrate was concentrated and the residue was re-dissolved in MeOH and treated with $NaBH_4$. The mixture was stirred at room temperature overnight. However, most imine remained by ^1H NMR analysis.

Figure 1



15'

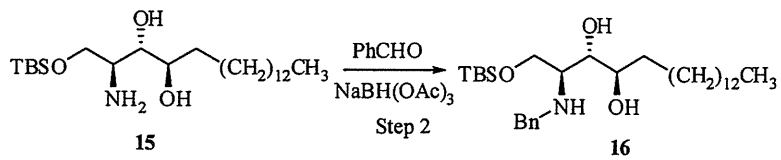
The imine formation was examined on 0.5 g scale in MeOH instead of THF and dichloromethane. Compound **14** was consumed after 4 hours. This condition was repeated on a bigger scale (20 g). Compound **14** (1.0 equiv) and benzaldehyde (1 equiv) were mixed with $MgSO_4$ (1.2 equiv) in MeOH (15 vol). The reaction mixture was stirred at room temperature for 16 hours, at which time the reaction was deemed complete (less than 1.0% of compound **14** remaining) by ^{1}HNMR analysis. The reaction mixture was filtered through Celite and the filter cake was washed with MeOH. Part of the filtrate was concentrated to give white solids. The solids were dissolved in THF (5 vol) and the solution was cooled to 0 °C. $LiAlH_4$ (4.5 equiv) was added at 0 °C and the reaction was stirred at room temperature for 16 hours. Impurities were observed by TLC and ^{1}HNMR analyses.

Therefore, preparation of compound **16** through alternative way, TBS protection followed by reductive amination, was examined. Compound **14** (5 g) and TBDMSCl (1.5 equiv) were mixed in pyridine (4.0 vol). The reaction mixture was stirred at room temperature for 16 hours, at which time TLC indicated that the reaction was deemed complete (less than 1.0% of compound **14** remaining). MeOH (4.0 vol) was added to the reaction mixture, and the solution was concentrated down to dryness. The residue was purified by column chromatography to afford the product **15** (6.3 g, 93% yield) as white waxy solids. A reaction using TBDMSCl (1.5 equiv) and imidazole (3.0 equiv) in THF (4.0 vol) was also examined, which provided product **15** (3.9 g, 57% yield) as white waxy solids. Due to the amount of pyridine used in scales, the reaction condition using imidazole has been applied on large scale.

Table 20. Preparation of Compound 15

Lot Number	Input of Compound 14	Output of Compound 15	Yield (%)
09DX011	20 g	17.1 g	63
09DX014	400 g	325 g	60

Step 2



15 16

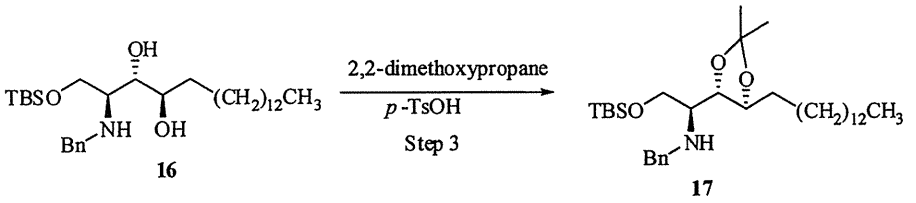
The preparation of compound **16** was carried out by using $NaBH(OAc)_3$ (2.5 equiv) and benzaldehyde (1.2 equiv) in THF (5.0 vol). The reaction mixture was stirred at room temperature and monitored by ^{1}HNMR and TLC analyses. After 16 hours, the reaction was deemed complete (less than 1.0% of compound **15** remaining). The reaction was worked up and purified by column chromatography to give compound **16** as an oil.

Table 21. Preparation of Compound 16

Lot Number	Input of Compound 15	Output of Compound 16	Yield (%)	Comments
09DX009	1 g	N/A	N/A	• The reaction was complete. • Combined 09DX010.
09DX010	2.9 g	2.7 g	58	
09DX013	17.1	17.1	83	
09DX015	10 g	N/A	N/A	• Used crude **15**. • Messy reaction.
09DX017	100 g	N/A	N/A	• Additional $NaBH(OAc)_3$ (1 equiv) and benzaldehyde (0.5 equiv), but no progress was observed. • Combined with 09DX018.
09DX018	215 g	208 g	55	

The reaction seemed sluggish during scale up and generated more impurities based on TLC analysis. Further investigation will be made in the future.

Step 3



The reaction was examined in different volumes of 2,2-dimethoxypropane and also the reaction described in the literature procedure (*JOC*, **2004**, *69*, 7694–7699) in which the reaction mixture containing *p*-TsOH•H_2O and compound **16** in benzene were run at reflux.

Table 22. Examination of Preparation of Compound 17

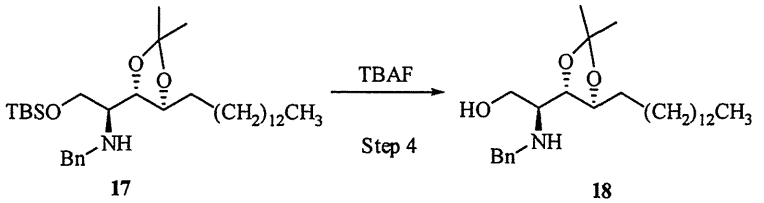
Experiment	Conditions	Comments
24LL015A	**16** (1.0 g, 1 equiv), *p*-TsOH•H_2O (1.03 equiv), DMP (25 vol)	• Relative cleaner by TLC analysis after 3 h rt. • After chromatographic purification, isolated 0.39 g, 36% yield.
24LL015B	**16** (1.0 g, 1 equiv), *p*-TsOH•H_2O (1.03 equiv), DMP (5 vol)	• Multiple spots by TLC analysis after 3 h rt. • After chromatographic purification, isolated 0.2 g, 18.5% yield. • All impurities do not have TBS group by ^{1}H NMR analysis.
24LL017A	**16** (1.0 g, 1 equiv), *p*-TsOH•H_2O (1.03 equiv), DMP (10 vol)	• Not as clean as lot 24LL015A.
24LL017B	**16** (1.0 g, 1 equiv), *p*-TsOH•H_2O (1.03 equiv), DMP (20 vol)	• Not as clean as lot 24LL015A.
24LL016B	**16** (1.0 g, 1 equiv), *p*-TsOH•H_2O (0.2 equiv), DMP (10 equiv), toluene (10 vol), rt to 80 °C	• Initially at rt for 3 hours, no product but starting material by TLC analysis. • Then the reaction was heated at 80 °C for 2 hours. An impurity spot showed along with starting material.
24LL018	**16** (12 g, 1 equiv), *p*-TsOH•H_2O (1.03 equiv), DMP (25 vol)	• 5 hours at rt • After chromatographic purification, isolated 9.24 g, 71% yield. • Product was confirmed by ^{1}H NMR analysis.

Among these reactions, the reaction condition in 25 vol of 2,2-dimethoxypropane (DMP) and *p*-TsOH•H_2O (1.03 equiv) was chosen. The reaction was carried out by using DMP (25 vol) and *p*-TsOH•H_2O (1.03 equiv). The reaction mixture was stirred at room temperature for 5 hours, at this point the reaction was deemed complete by TLC analysis. The reaction was worked up and the crude material was purified by chromatography to give a colorless oil.

Table 23. Preparation of Compound 17

Lot Number	Input of Compound 16	Output of Compound 17	Yield (%)
24LL018	12 g	9.24	71

Step 4

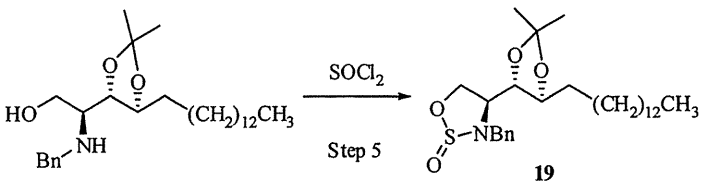


The deprotection of TBS group was carried out by following the provided procedure using a solution of TBAF in THF (1 M, 2.0 equiv) in THF (3 vol). The reaction mixture was stirred at room temperature for 1.5 hours, at which time there was almost no starting material by TLC analysis. The reaction was worked up and the crude material was purified by chromatography to provide compound **18** as a colorless oil.

Table 24. Preparation of Compound 18

Lot Number	Input of Compound 17	Output of Compound 18	Yield (%)
24LL021	9.2 g	7.03	96

Step 5



18 **19**

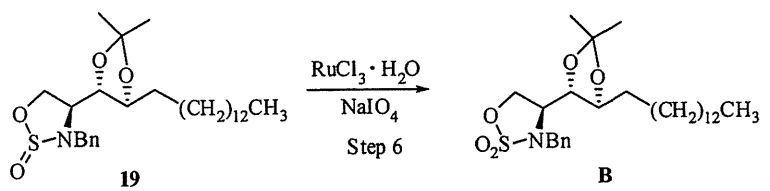
The reaction was run by following the provided procedure using triethylamine (3.0 equiv) and thionyl chloride (1.15 equiv) in dichloromethane (7 vol). The reaction was stirred at −35 °C to −45 °C for 30 minutes, at which time there was no starting material by TLC analysis. The reaction was worked up and concentrated for the next step.

Table 25. Preparation of Compound 19

Lot Number	Input of Compound 18	Output of Compound 19	Yield (%)
24LL022	0.36 g	0.38	98
24LL024	7.0 g	9.5 g	quantitative

This preparation of sulfamidite **19** was at −40 °C and by ^{1}H NMR analysis, it was a mixture of diasteromer which was used in the next step to produce a single isomer of sulfamidate **B**. The reaction will be examined at room temperature to compare if there is any difference of sulfamidates from sulfamidites formed at −40 °C and room temperature.

Step 6



19 **B**

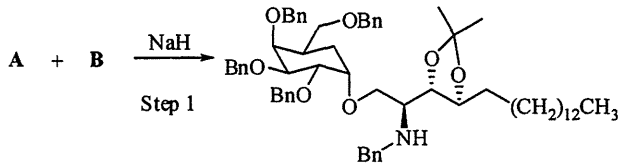
By following the provided procedure, except without using carbon tetrachloride and reducing the reaction volumes from 77 to the 21, the reaction was carried out by using sodium periodate (2 equiv) and ruthenium (III) chloride hydrate (0.05 equiv) in water (7 vol) and acetonitrile (14 vol) at 0–5 °C. After the addition was complete, the mixture was stirred at 0–5 °C for 15 minutes, at which time ^{1}H NMR analysis showed it was complete. The reaction was quenched with 20% sodium thiosulfate (5 vol) and then worked up. The crude material was purified by chromatography to provide a colorless oil.

Table 26. Preparation of Compound B

Lot Number	Input of Compound 19	Output of Compound B	Yield (%)
24LL023	0.38 g	0.32	82
24LL025	9.5	6.79	85

3.3 Synthesis of Compound RCAI-56

Step 1



25

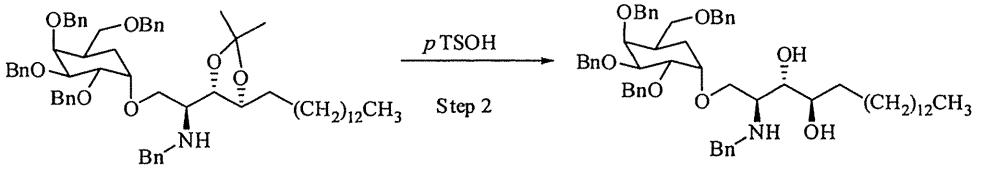
The reaction was carried out by following the provided procedure by initial charging NaH (3.2 equiv), compound **A** (1.0 equiv) and compound **B** (1.5 equiv) in a mixture of DMF (20 vol) and THF (20 vol) at 0 °C. As indicated in the provided procedure, the reaction was not complete after heating at 70 °C for 4 h, at which time compound **B** was consumed but compound **A** remained ≈30% by TLC analysis. Two consecutive additions of NaH (2.0 equiv) and a solution of compound **B** (1.5 equiv) in THF (20 vol) were added at 70 °C during the next 20 hours until there was less than 5.0% of compound **A** remaining. The reaction mixture was concentrated to a residue. The residue was dissolved in MTBE (130 vol), cooled to below 0 °C. 20% aqueous H_2SO_4 solution (120 vol) was added to hydrolyze the sulfamic acid for 30 minutes at 0 to 5 °C. Then the reaction mixture was neutralized with solid K_2CO_3 (pH ≈8 to 9) at 0 °C and MTBE (80 vol) was added. After the work up, the crude material was purified by chromatography to afford compound **25** as a colorless oil.

Table 27. Preparation of Compound 25

Lot Number	Input of Compound A	Output of Compound 25	Yield (%)
09GB028	0.5 g	0.6	70

An excess amount of **B** was used in the reaction because of the short half life of sulfamidate of **B** at 70 °C. Concerns to improve the usage of **B** will be examined in the future by adjusting the temperature and/or addition rate.

Step 2



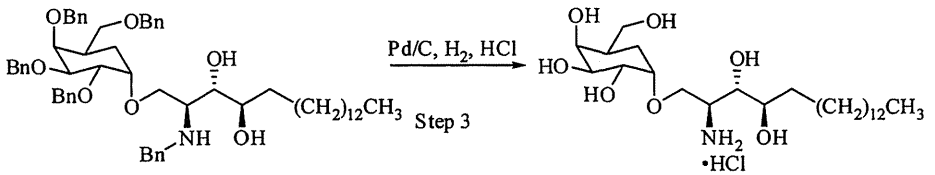
25 26

By following the provided procedure, the reaction was carried out using *p*-TsOH•H_2O (1.20 equiv) in MeOH (42 vol) and dichloromethane (21 vol). The reaction mixture was heated to 60 °C for 16 hours, at which time the reaction was complete by TLC analysis. The reaction was worked up and the crude material was purified by column chromatography.

Table 28. Preparation of Compound 26

Lot Number	Input of Compound 25	Output of Compound 26	Yield (%)
09GB030	0.5 g	0.37	77

Step 3



26 27

By following the provided procedure, the reaction was carried out by using 10% Pd/C in cyclohexene (3.5 mL) and MeOH (61 vol) in the presence of aqueous 1 M HCl (1 equiv). The reaction was heated to 65 °C overnight. By TLC analysis, the reaction was not complete and 6 M HCl (2 equiv) was added. After overnight, the reaction was still not complete. The reaction was concentrated and 10% Pd/C, cyclohexene (10 vol) and MeOH (61 vol) were charged in. The reaction is currently heating at 65 °C.

Due to the sluggishness of the reaction under the hydrogen transfer condition, pressurized hydrogenation and different catalysts are currently being examined in the future.

4.0 Experimental

Reagents and solvents were used as received from commercial suppliers. Reaction progress was monitored by high-performance liquid chromatography (HPLC) using an Agilent 1100 series instrument. Thin-layer chromatography (TLC) was performed using Analtech silica-gel plates and visualized by UV light (254 nm). Proton nuclear magnetic resonance spectra were obtained using a Bruker AV300 at 300 MHz for proton and 75 MHz for carbon.

4.1 Preparation of Compound A

Step 1 and Step 2. Preparation of Compound 3 (Ref: 19MEM021)

To a slurry of compound **1** (800 g, 4.120 mol, Chem-Impex lot # 001855-13071) in dichloromethane (8 L) was added DABCO (924 g, 8.240 mol, Oakwood lot # D04H) and TrCl (2297 g, 8.240 mol, Chem-Impex lot # 001353-20120477). The reaction was stirred at room temperature overnight. TLC analysis showed there was no starting material remaining. The reaction mixture was directly taken to the preparation of compound **3**. The reaction mixture was cooled with an ice bath and triethylamine (2084 g, 20.60 mol) and benzoyl chloride (2317 g, 16.48 mol) were added dropwise respectively while maintaining internal temperature below 30 °C. Once the addition was completed the reaction was stirred at room temperature overnight. Reaction was monitored by TLC analysis. After the reaction was complete, the mixture was cooled in an ice bath and quenched with water (5.6 L) along with addition of dichloromethane (5.6 L). The layers were separated. The aqueous layer was extracted with dichloromethane (4 L). The combined organic layer was washed with saturated $NaHCO_3$ (5.6 L). The layers were separated. The aqueous layer was extracted with dichloromethane (2.4 L). The combined organic layers was washed with half brine (5.6 L) and brine (5.6 L), dried over $MgSO_4$, and concentrated to give crude product compound **3** as a light brown oil (4.83 kg, quantitative). ^1H NMR analysis is consistent with the structure. Crude product was used in the next step without purification.

Step 3. Preparation of Compound 4 (Ref: 19MEM023)

p-TsOH•H_2O (470 g, 2.473 mol, Aldrich lot # MKBK9590V) was added to a solution of crude compound 3 (4830 g, crude, AMRI lot # 19MEM021) in a mixture of MeOH (41 L) and dichloromethane (5.4 L). The reaction mixture was stirred at room temperature overnight, at which time TLC indicated consumption of starting material. The reaction mixture was concentrated to a residue which was purified by silica gel chromatography eluted with 5–20% ethyl acetate in heptane to give compound **4** as a light brown oil. ^1H NMR analysis is consistent with the structure (see Attachment 1).

Step 4. Preparation of Compound 5 (Ref: 19MEM016 and 14KL0130A)

Imidazole (277 g, 4.070 mol, Chem-Impex lot # 04722JJ) and triphenylphosphime (517 g, 1.969 mol, Chem-Impex lot # 20100225) were added to a solution of compound **4** (665 g, 1.313 mol, AMRI lot # 14KL0090A) in toluene (12 L). The reaction mixture was heated to 50 °C and stirred at the same temperature until solids were dissolved. I_2 (500 g, 1.969 mol, GFS lot # C358686) was then added portionwise over 10 min and the temperature was increased to 70 °C and stirred for 2 h. The reaction was monitored by TLC and HPLC analyses. After 2 hours, the reaction was deemed complete (less than 1.0% of compound 4 remaining). The reaction mixture was cooled to room temperature and quenched with saturated $Na_2S_2O_3$ solution (7.8 L). The layers were separated. The aqueous layer was extracted with EtOAc (20 L). The organic layer was washed with water (2 × 7.8 L), followed by saturated $Na_2S_2O_3$ solution, brine (7.8 L), dried over $MgSO_4$, filtered, and concentrated to give the crude product. The crude product was purified by column chromatography eluted

with 5–25% EtOAc in heptane to afford the compound **5** (518 g, 64% yield) as a white solid (see Attachment 2).

Step 5. Preparation of Compound 6 (Ref: 19MEM019)

DBU (441 mL, 2.956 mol, Oakwood lot # G01D) was added to a solution of compound **5** (200 g, 0.324 mol, AMRI lot # 14KL0130A) in THF (2.6 L). The reaction mixture was heated at 68 °C and monitored by TLC and HPLC analyses. After 27 hours, HPLC analysis showed about 5.5% starting material remaining. The reaction was cooled to room temperature, quenched with water (1 L), and extracted with EtOAc (2 × 1.4 L). The organic layer was washed with saturated $Na_2S_2O_3$ solution (1 L), followed by saturated $NaHCO_3$ solution (1 L), brine (1 L), dried over $MgSO_4$, and concentrated to give the crude product (170.6 g). Half of the crude product was purified by column chromatography eluted with 0–15% EtOAc in heptane to afford compound **6** [65 g, 82% yield, AMRI lot # 19MEM019G, 83.6% potency by ^1H NMR analysis, 5.7% compound **5** by HPLC (AUC) at 230 nm] as a colorless thick syrup (see Attachment 3).

Step 6. Preparation of Compound 7 (Ref: 19MEM020)

NaOMe (1.33 g, 24.57 mmol, Aldrich lot # MKBJS212V) was added to a solution of compound **6** (120 g, 245.7 mmol) in MeOH (3000 mL). The reaction mixture was stirred at room temperature and monitored by TLC and HPLC analyses. After stirring overnight, the reaction was deemed complete (less than 1.0% of compound 6 remaining). The reaction was worked up. The reaction mixture was concentrated to give the crude product, which was triturated with MTBE (2400 mL) to afford compound **7** (40.7 g, 94% yield) as a white solid (see Attachment 4).

Step 7. Preparation of Compound 8 (Ref: 19MEM022)

NaH (32.8 g, 819.7 mmol) and nBu_4NI (catalytic) were added to a solution of compound **7** (40.0 g, 227.1 mmol, AMRI lot # 19MEM020B) in a mixture of DMF (300 mL) and THF (150 mL) at 0 °C. BnBr (159 mL, 1339.6 mmol) was charged while maintaining the temperature at 0–5°C. The reaction mixture was stirred at room temperature for 16 h and monitored by TLC and HPLC analyses. After 16 hours, the reaction was deemed complete (less than 1.0% of compound 7 remaining). The reaction was worked up by pouring into ice cold water (400 mL). The mixture was extracted with EtOAc (2 × 400 mL). The organic layer was washed with water (200 mL), followed by brine (200 mL), dried over $MgSO_4$, filtered, and concentrated to give the crude product. The crude product was purified by column chromatography eluted with 0–10% EtOAc in heptane to afford compound **8** (87 g, 85.6% yield) as a colorless oil (see Attachment 5).

Step 8. Preparation of Compound 9 (Ref: 09GB019)

$PdCl_2$ (0.3 g, 1.7 mmol) was added to a degassed solution of compound **8** (12 g, 26.9 mmol) in a mixture of 1,4-dioxane (420 mL) and water (210 mL) at room temperature. The reaction mixture was stirred at 70 °C and monitored by TLC and HPLC analyses. After 6 hours, the

reaction was deemed complete (less than 1.0% of compound 8 remaining). The reaction mixture was cooled to room temperature and EtOAc (240 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (2 × 60 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (60 mL), brine (60 mL), and dried over $MgSO_4$, filtered and concentrated to give crude product which was purified by column chromatography eluted with 0–30% ethyl acetate in heptane to afford compound **9** (9.6 g, 83% yield) as a colorless oil (see Attachment 6).

Step 9. Preparation of Compound 10 (Ref: 09GB021)

2,6-Lutidine (12.75 mL, 109.8 mmol) and TBSOTf (6.05 mL, 26.40 mmol) were added to a solution of compound **9** (9.5 g, 22.0 mmol) in dichloromethane (209 mL) while maintaining the internal temperature at −18 °C to −28 °C. Once the addition was completed, the reaction mixture was stirred at −18 °C to −28 °C and monitored by TLC and HPLC analyses. After 2 hours, the reaction was deemed complete (less than 1.0% of compound 9 remaining). The reaction was worked up by quenching with MeOH (3 mL). The batch was brought to room temperature and stirred for 30 min. Reaction mixture was concentrated and the residue was azeotroped with toluene (2 × 50 mL). The light yellow oil was dissolved in EtOAc (200 mL). The solution was washed with water (50 mL) followed by saturated NaHCO3 (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to give crude product. The crude product was purified by column chromatography eluted with 0–20% ethyl acetate in heptane to afford compound **10** (10.3 g, 86% yield) as a colorless oil (see Attachment 7).

Step 10. Preparation of Compound 11 (Ref: 09GB022)

To the Tebbe reagent (0.5 M in toluene, 27.7 mmol) was added to a solution of compound **10** (10.1 g, 18.5 mmol) and pyridine (70.7 mL) in THF (212 mL) while maintaining the internal temperature at −40 °C to −45 °C. Once the addition was completed, the reaction mixture was stirred at room temperature and monitored by TLC analysis. After 4 hours, the reaction was deemed complete (less than 15.0% of compound 10 remaining). The reaction mixture was cooled to −40 °C to −45 °C and quenched with saturated $NaHCO_3$ (100 mL) and stirred for 30 minutes. The batch was warmed to room temperature and MTBE (200 mL) was added. The mixture was stirred for 20 minutes. The precipitated solid were filtered and washed with MTBE (100 mL). The combined organic filtrate and wash were concentrated and the residue was azeotroped with toluene (2 × 100 mL). The yellow semi solids were re-dissolved in EtOAc (200 mL), filtered, and washed with EtOAc (50 mL). Combined filtrate and washes were washed with water (50 mL) followed by saturated $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated to give the crude product. The crude product was purified by column chromatography eluted with 0–20% ethyl acetate in heptane to afford compound **11** (7.7 g, 76% yield) as a colorless oil (see Attachment 8).

Step 11. Preparation of Compound 12 (Ref: 09GB023)

BH_3•THF (1.0 M in THF, 69.8 mL, 69.8 mmol) was added to a solution of compound **11** (7.6 g, 14.0 mmol) in THF (22 vol) while maintain internal temperature 0 to −5 °C. Once the addition was completed, the reaction mixture was stirred at room temperature and monitored

by TLC analysis. After 2 hours, the reaction was deemed complete (less than 1.0% of compound 10 remaining). The reaction mixture was cooled to 0 to −5 °C and quenched with aqueous NaOH solution (2.0 M, 176 mL) followed by aqueous 30% H_2O_2 (33 mL) while maintain internal temperature 0 to 10 °C. After stirring for 1 hour, the batch was warmed to room temperature and MTBE (70 mL) was added. The layer was separated and the aqueous layer was extracted with MTBE (70 mL). Combined organic layers were washed with water (40 mL) followed by saturated $NaHCO_3$ (40 mL) and brine (40 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography eluted with 0–25% EtOAc in heptane to afford compound **12** (6.1 g, 77.7% yield) as a colorless oil (see Attachment 9).

Step 12. Preparation of Compound 13 (Ref: 09GB024)

NaH (1.28 g, 32.0 mmol), BnBr (2.32 mL, 21.3 mmol) and nBu_4NI (1.28 g) were added to a solution of compound **12** (6.0 g, 10.7 mmol) in a mixture of DMF (90 mL) and THF (90 mL) at 0 °C. The reaction mixture was stirred at room temperature and monitored by TLC analysis. After 16 hours, the reaction was deemed complete (less than 1.0% of compound 12 remaining). The reaction mixture was poured into ice cold water (60 mL) and extracted with EtOAc (2 × 60 mL). The organic layer was washed with water (30 mL), followed by brine (30 mL), dried over $MgSO_4$, and concentrated to give the crude product which was purified by column chromatography eluted with 0–10% EtOAc in heptane to afford compound **13** (6.5 g, 93% yield) as a colorless oil (see Attachment 10).

Step 13. Preparation of Compound A (Ref: 09GB025)

A solution of TBAF (1.0 M in THF, 19.6 mmol) was added to a solution of compound **13** (6.4.g, 9.8 mmol) in THF (64 mL) at room temperature. The reaction mixture was stirred at room temperature and monitored by ^1H NMR and HPLC analyses. After 40 hours, the reaction was deemed complete (less than 5.0% of compound 13 remaining). The reaction was worked up by quenching with water (64 mL) and extracting with EtOAc (2 × 96 mL). The organic layer was washed with water (32 mL), followed by brine (32 mL), dried over $MgSO_4$, and concentrated to give the crude product which was purified by column chromatography eluted with 0–25% EtOAc in heptane to afford compound **A** (4.35 g, 82% yield) as a colorless oil (see Attachment 11).

4.2 Preparation of Compound B

Step 1. Preparation of Compound 15 (Ref: 09DX014 and 14KL0187)

Compound **14** (400 g, 1.26 mol, Indofine lot # XX) and imidazole (257 g, 3.78 mol) were mixed in THF (1.6 L). TBDMSCl (284.8 g, 1.89 mol) was added. The reaction mixture was stirred at room temperature. The reaction was monitored by TLC analysis. After 16 hours, the reaction was deemed complete (less than 1.0% of compound 14 remaining). EtOAc (4 L) was added to the reaction mixture, and the solution was washed with water (3 × 2 L). The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was loaded onto a silica column and eluted with 25% heptanes in EtOAc, EtOAc, and 5% MeOH

in EtOAc. The fractions of interest were concentrated to afford compound **15** (325 g, 60% yield) as white solids (see Attachment 12).

Step 2. Preparation of Compound 16 (Ref: 09DX017, 09DX018, and 14KL0210)

Compound **15** (215 g, 0.5 mol) and $NaBH(OAc)_3$ (264 g, 1.2 mol) were mixed in THF (1075 mL). Benzaldehyde (63.4 g, 0.6 mol) was added at room temperature. The reaction mixture was stirred at room temperature and monitored by 1H NMR and TLC analyses. After 16 hours, the reaction was deemed complete (less than 1.0% of compound 15 remaining). EtOAc (1.35 L) and saturated $NaHCO_3$ (1.35 L) were added. The layers were separated and the organic layer was washed with saturated $NaHCO_3$ (1.35 L). Combined aqueous layers were extracted with EtOAc (700 mL). Combined organic layers were washed with brine (350 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was combined with the crude from a 100 g run and purified by column chromatography eluted with 20% EtOAc in heptane to give compound **16** (208 g, 55% yield) as an oil (see Attachment 13).

Step 3. Preparation of Compound 17 (Ref: 24LL018)

To a solution of compound **16** (12 g, 22.99 mmol) in 2,2-dimethoxypropane (300 mL) was added *p*-TsOH•H2O (4.50 g, 23.68 mmol). The reaction mixture was stirred at room temperature for 5 hours. TLC analysis on the sample quenched with saturated $NaHCO_3$ showed there was not starting material. Ethyl acetate (150 mL) and saturated $NaHCO_3$ (60 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (30 mL). Combined organic layers were washed with brine (60 mL) and concentrated. The crude material was purified chromatographically eluted with 4–10% ethyl acetate in heptane to provide compound **17** (9.24 g, 71.5% yield) as a colorless oil (see Attachment 14).

Step 4. Preparation of Compound 18 (Ref: 24LL021)

To a solution of compound **17** (9.2 g, 16.37 mmol) in THF (30 mL) was added a solution of TBAF in THF (1 M, 32.7 mL). The reaction mixture was stirred at room temperature for 1.5 hours, at which time there was almost no starting material by TLC analysis. The reaction was quenched with water (30 mL) and ethyl acetate (30 mL) was added. The layers were separated and aqueous layer was extracted with ethyl acetate (30 mL). Combined organic layers was washed with brine (30 mL) and concentrated. The crude material was purified chromatographically eluted with 25–50% ethyl acetate in heptane to give compound **18** (7.03 g, 96% yield) as a colorless oil (see Attachment 15).

Step 5. Preparation of Compound 19 (Ref: 24LL024)

To a solution of compound **18** (7 g, 15.64 mmol) in dichloromethane (50 mL) was added triethylamine (6.54 mL, 46.91 mmol). The mixture was cooled to <–70 °C. Thionyl chloride (1.31 mL, 17.98 mmol) was added. After addition, the mixture was warmed to –40 °C and stirred at –35 °C to –45 °C for 1 hour, at which time there was no starting material by

TLC analysis. The reaction was quenched with water (21 mL) and the layers were separated. Organic layer was washed with water (21 mL) and brine (21 mL), dried over MgSO4, and concentrated to give crude product **19** (9.5 g, quantitative). The material was taken to the next step without purification (see Attachment 16).

Step 6. Preparation of Compound B (Ref: 24LL025)

To a solution of compound **19** (9.5 g, crude, lot # 24LL024) in CH_3CN (112 mL) was added a solution of sodium periodate (6.7 g, 31.28 mmol) and ruthenium (III) chloride hydrate (0.16 g, 0.782 mmol) in water (56 mL) at 0–5 °C. After the addition was complete, the mixture was stirred at 0–5 °C for 15 minutes, at which time ^1H NMR analysis showed it was complete. The reaction was quenched with 20% sodium thiosulfate (40 mL). The mixture was concentrated to an aqueous residue. *tert*-Butyl methyl ether (MTBE, 50 mL) was added and the layers were separated. The aqueous layer was extracted with another MTBE (50 mL). The combined organic layers were washed with brine (21 mL), dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography eluted with 5–10% ethyl acetate in heptane to provided compound **B** (6.79 g, 85% yield) as a colorless solid (see Attachment 17).

4.3 Preparation of Compound **RCAI-56**

Step 1. Preparation of Compound 25 (Ref: 09GB028)

NaH (0.117 g, 2.8 mmol) was added to a solution of compound **A** (0.5 g, 0.9 mmol) in a mixture of DMF (10 mL) and THF (5 mL) at 0 °C. After stirring at 0 °C for 1 hour, a solution of compound **B** (0.68 g, 1.3 mmol) in THF (5 mL) was added at 0 °C. The reaction mixture was slowly heated to 70 °C and stirred at that temperature for 4 hours. The reaction was monitored by TLC analysis. After 4 hours, the reaction was not completed (compound **B** was consumed but compound **A** remained ≈30% by TLC analysis). Additional NaH (0.035 g, 0.88 mmol) and a solution of compound **B** (0.23 g, 0.43 mmol) in THF (5 mL) were added at 70 °C and stirred for overnight. After overnight, the reaction was not completed (compound **B** was consumed but compound **A** remained ≈15% by TLC analysis). Additional NaH (0.035 g, 0.88 mmol) and a solution of compound **B** (0.23 g, 0.43 mmol) in THF (5 mL) were added at 70 °C and stirred for 4 hours. After 4 hours, the reaction was deemed complete (less than 5.0% of compound **A** remaining). The reaction mixture was concentrated to a residue. The residue was dissolved in MTBE (65 mL) and cooled to below 0 °C. 20% aqueous H_2SO_4 solution (60 mL) was added dropwise at 0 to 5 °C. After stirring at 0 °C for 30 minutes, the reaction mixture was neutralized with solid K_2CO_3 (pH ≈8 to 9) at 0 °C. After stirring at 0 °C for 40 minutes, MTBE (40 mL) and water (20 mL) were added to this mixture. The mixture was filtered through a pad of Celite and the pad was washed with MTBE (2 × 10 mL). Combined organic layers was washed with water (2 × 10 mL) followed by saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), dried over solid K_2CO_3, filtered, and concentrated to give the crude. The crude material was purified by chromatography eluted with 0–25% ethyl acetate in heptane to afford compound **25** (0.6 g, 70% yield) as a colorless oil (see Attachment 18).

Step 2. Preparation of Compound 26 (Ref: 09GB030)

To a solution of compound **25** (0.5 g, 0.5 mmol) in MeOH (21 mL) and dichloromethane (10.5 mL) was added *p*-TsOH•H_2O (0.12 g, 1.20 equiv). The reaction mixture was stirred at 60 °C for 16 hours, at which time the reaction was complete by TLC analysis. The reaction mixture was cooled to room temperature and concentrated to a residue which was then dissolved in EtOAc (15 mL) and saturated $NaHCO_3$ (5 mL) was added. The layers were separated. The aqueous layer was extracted with EtOAc (5 mL). Combined organic layers were washed with saturated $NaHCO_3$ solution (2.5 mL) and brine (2.5 mL), dried over $MgSO_4$, filtered and concentrated to give crude material which was purified by column chromatography with 10–80% EtOAc in heptane to give compound **26** (0.37 g, 77% yield) as oil (see Attachment 19).

Step 3. Preparation of Compound 27 (Ref: 09GB031)

To a solution of compound **26** (0.35 g, 0.4 mmol) in MeOH (21.35 mL) and cyclohexene (3.5 mL) at room temperature was added 1 M HCl (0.38 mL, 0.38 mmol) and 10% Pd/C (62 mg). The reaction mixture was stirred at 65 °C for 16 hours, at which time the reaction was checked by TLC analysis which showed not complete. 6 M HCl (0.13 mL, 0.8 mmol) and Pd/C (62 mg) were and stirred for another 16 hours, at which time TLC analysis still showed starting material. The reaction mixture was filtered and concentrated. The residue was dissolved in MeOH (21.35 mL) and to the solution was charged with cyclohexene (3.5 mL), and 10% Pd/C (62 mg). The reaction mixture was currently heated at 65 °C.

5.0 Analytical (Temporary)

HPLC Method 1

Column: Water XBridge C18, 3.5 µm, 4.6 × 75 mm, P/N 186003034
Column Temperature: Ambient temperature
Flow Rate: 1.0 mL/min
Detection: 230 and 210 nm
Analysis Time: 36 min
Mobile Phase A: 0.05% TFA in water
Mobile Phase B: 0.05% TFA in acetonitrile

Table 29

Time (min)	% A	% B
0.0	95	5
15.0	1	99
30.0	1	99
31.0	95	5
36.0	95	5