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A safe and alternate process for the reductions of methanesulfonates: Application in the synthesis of 1,2,3-triacetyl-5-deoxy-D-ribofuranoside

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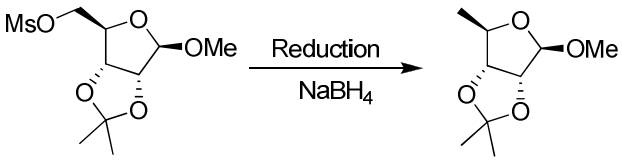
TOC Graphic



ABSTRACT:

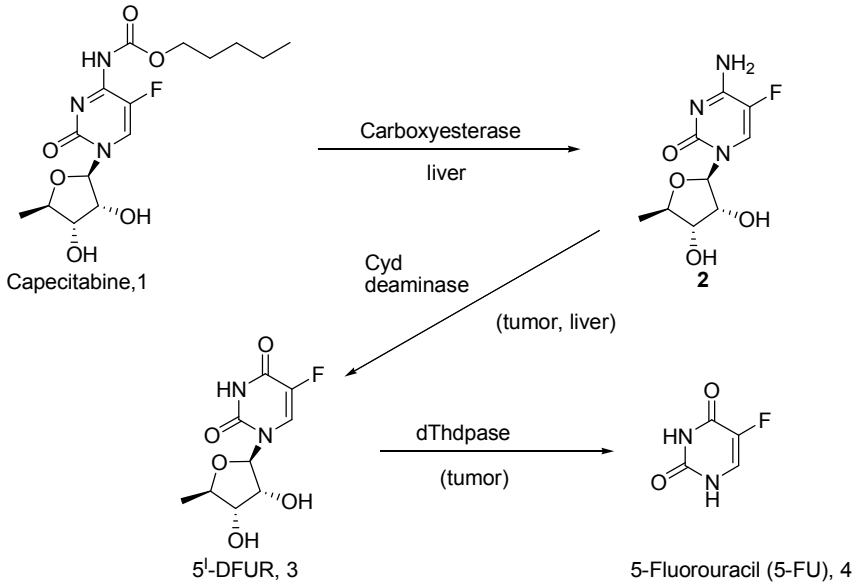
Diethylene glycol dimethyl ether, *diglyme* and 1,2-bis(2-methoxyethoxy)ethane, *triglyme* are found to be suitable and safe alternate solvents to DMSO for the reduction of methanesulfonate in sodium borohydride. Addition of anhydrous lithium chloride led to the complete reduction of methane sulfonate esters to the corresponding alkanes in presence of sodium borohydride in these solvents (*diglyme* and *triglyme*). This protocol is useful in the preparation of 1,2,3-triacetyl-5-deoxy-D-ribofuranoside, **7** a key intermediate of Capecitabine, **1** in the commercial scale.

Key words: Capecitabine; diethylene glycol dimethyl ether; reduction; methane sulfonates; sodium borohydride; lithium chloride

INTRODUCTION:

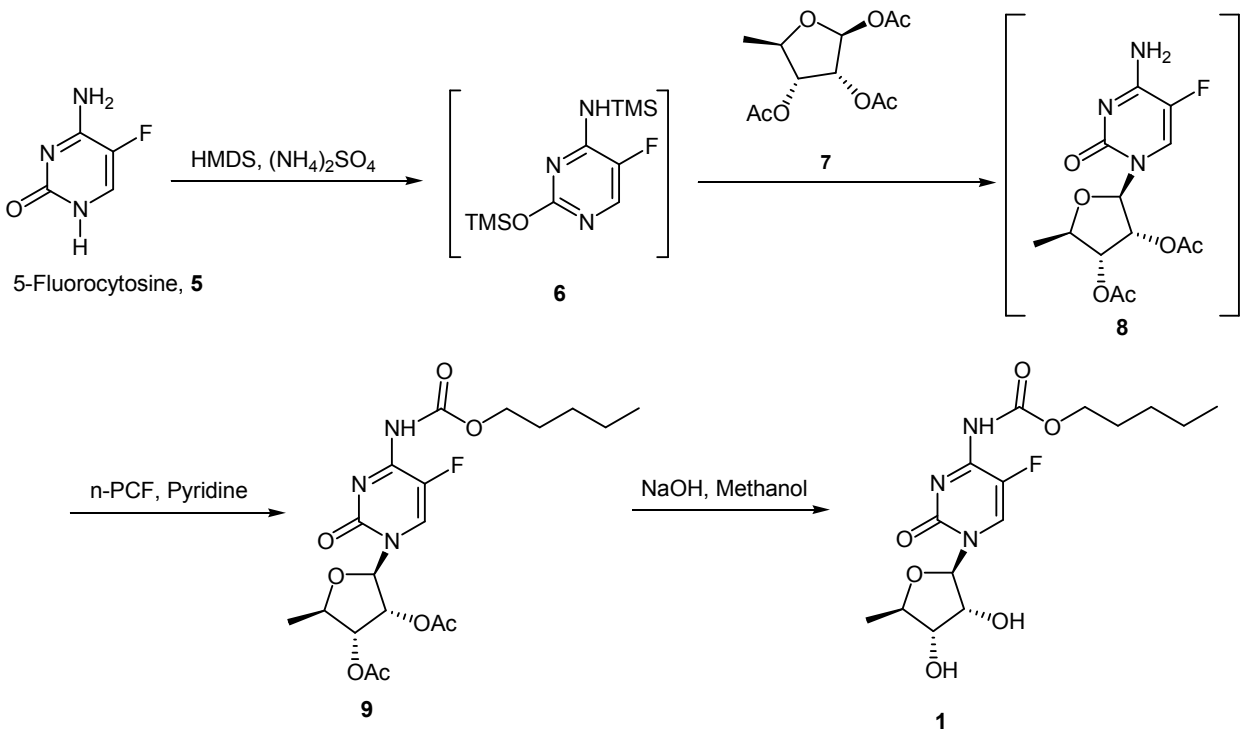
Capecitabine, **1** (Trade name; Xeloda), 5′-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine, is a fluoropyrimidine carbamate with antineoplastic activity.[1] It is an orally administered systemic prodrug of 5′-deoxy-5-fluorouridine, **3** (5′-DFUR) which is converted to 5-fluorouracil, **4** (5-FU) *invivo* (**Scheme-1)**.[2] It was approved for the use as a second-line therapy of metastatic breast, gastric, colorectal, bladder cancers and other malignancies.

Scheme-1: Metabolism of Capecitabine



The industrial preparation of capecitabine involves the use of 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranoside, **7** as a key starting material in the process chemistry (**Scheme-2)**.[1,3] This key unit is generally synthesized by peracetylation of 6-deoxy-D-ribofuranose, **14**. Essentially, 6-deoxy-D-ribofuranose, **14** is procured by the reduction of methyl-5-*O*-mesyl-2,3-*O*-isopropylidine-D-ribofuranose **12a**, or methyl-5-*O*-tosyl-2,3-*O*-isopropylidine-D-ribofuranose **12b** which in turn could be obtained from D-ribose, **10** in two steps. In this protocol, reduction of methane sulfonate or tosylate group to methyl is very significant step in the preparation of 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranoside, **7 (Scheme-3)**.[4] The transformation of methane sulfonate or tosylate to methyl group is usually carried out with sodium borohydride, a versatile reagent in organic synthesis which can be used in Lab or commercial scales for the reduction of a wide variety of functional groups like aldehydes,[5] esters[6] and tosylates & methanesulfonates.[7]

Scheme-2: Preparation of 5′-deoxy-5-fluoro-N- [(pentyloxy) carbonyl]-cytidine (Capecitabine)



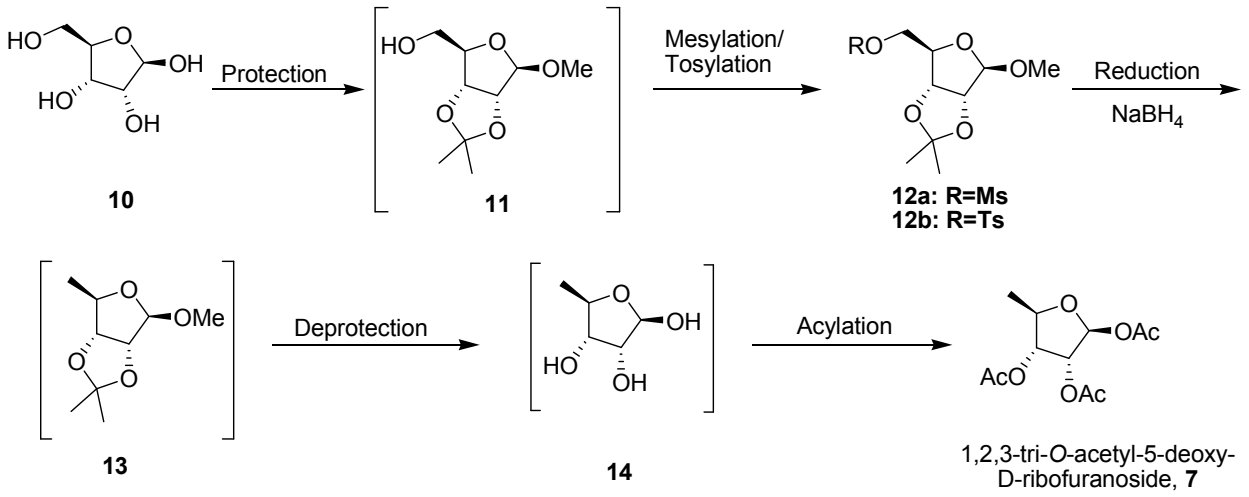
5-Fluorocytosine, **5**

6

RESULTS AND DISCUSSION:

DMSO or DMF is used as the most common solvent system to affect reductions of alkyl halides, esters, acyl chlorides and sulfonate esters such as methanesulfonates or tosylates, using sodium borohydride. However, reductions in these solvents generate large amounts of heat and hydrogen gases which need to be controlled. A violent exothermic reaction has been reported involving saturated solutions of sodium borohydride in DMF.[8a] Presence of moisture and elevated temperatures are also not suitable for the use of DMSO as solvent in scale.[8b] Hence, DMF and DMSO are not suitable solvents for the reduction of above substrates at higher temperatures in commercial scale due to this explosive nature. This necessitates the discovery of a safe and alternate solvent system to be used in a commercial scale. Herein, we report an alternate and safe solvent for the reduction of 2,3-*O*-isopropylidene-1-*O*-methyl-5-*O*-mesyl-D-ribofuranoside, **12a** with a combination of borohydride and lithium chloride in commercial scale.

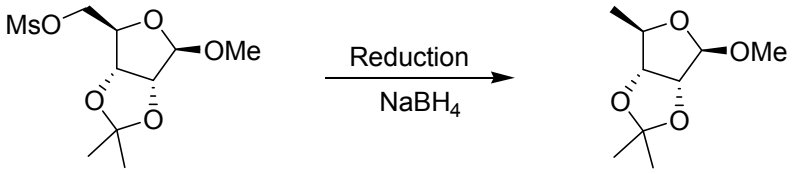
Scheme-3: Preparation of 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranoside



Reduction of sulfonates with sodium borohydride as a reducing agent in dipolar aprotic solvents[9] (HMPA, Me_2SO, sulfolane) and ethylene glycol oligomers (PEGs)[9c] under anhydrous conditions has been reported in the literature. The title compound, 1,2,3-triacetyl-5-deoxy-D-ribofuranoside, **7** was achieved by borohydride reduction of mesylate **12a** and tosylate **12b** in DMSO[4g] and the same reduction of **12b** was carried out in a mixture of THF and ether with LAH[2b]. Due to the explosive reactions involved with the use of DMSO, we have screened a number of protic, aprotic and mixed solvent systems for the reduction of methanesulfonate, **12a** to the corresponding methyl compound **13**. When compared with all aprotic solvents, our experiments revealed that, diglyme and triglyme are adequate solvents for this transformation. We checked the solubility of sodium borohydride and found almost insoluble in monoglyme and soluble in di & triglymes[10a] at ambient temperatures. In the prior art, diglyme was used as solvent with a borohydride for the reduction of alkyl halide and the reaction is slower than DMSO.[10b] To our knowledge, diglyme and borohydride was not used for the reduction of either sulfonates or tosylates in the preparation of 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranoside, **7**. Primary methanesulfonates are less reactive substrates; require higher temperature and catalyst for

reduction. Without catalyst methanesulfonates are not converted to corresponding alkyl group even though a large excess of borohydride is used.[11]

Scheme-4: Reduction of 2,3-*O*-isopropylidene-1-*O*-methyl-5-*O*-mesyl-D-ribofuranoside



12a **13**

Initially, the reduction of 2,3-*O*-isopropylidene-1-*O*-methyl-5-*O*-mesyl-D-ribofuranoside, **12a (Scheme-4)** was effected in methanol with 0.5 eq of sodium borohydride at ambient temperature. However, the reaction didn't proceed at all under these conditions (Table-1; entry no.1). It was also found that the reaction doesn't occur with more equivalents of the reagent (4.5 eq.) and even at higher temperatures (60-65°C) for prolonged time (entry no. 2). Conducting the reaction in a mixture of solvents like THF and methanol (entry no. 3) also did not give the fruitful results. Interestingly, the reaction proceeded (~50%) when a mixture of IPA and methanol was used (entry no. 4) as solvent system under reflux conditions. The reaction also did not proceed in other solvents like toluene and PEG-400 (entry nos. 5&6) even at higher temperatures. But, a complete conversion was observed using DMSO even in shorter time (entry no. 7) as reported in the literature.[2b,4a,4g]

Table-1: Reduction of Methanesulfonate without catalyst

S. No.	Solvent	Reagent (Eq.)	Temp. (°C)	Time (h)	Conversion by TLC	Remarks
1	MeOH	0.5	25-35	48	No conversion	No product formation observed
2	MeOH	4.5	60-65	72		

3	MeOH/THF	2.0	60-65	5		
4	MeOH/IPA	4.0	80-90	5	Conversion is observed	~50% product formation observed
5	Toluene	2.0	80-90	5	No conversion	RM remains as is
6	PEG-400	2.0	80-90	15	No conversion	RM turns into sticky mass.
7	DMSO	4.5	80-90	5	Complete conversion observed	Product formed

Later, the influence of the catalyst for the conversion of methanesulfonate to corresponding methyl group was investigated in different solvent systems with different catalysts, such as $MgCl_2$, $TiCl_4$, $AlCl_3$, and TOAB (Tetraoctyl ammonium bromide). The reaction was tried in toluene from ambient temperature to elevated temperature up to 110 ^oC but observed no conversion at all by TLC (Table-2; entry no. 1-4) even after prolonged period of time (entry 5). Though sodium borohydride is not soluble in toluene at ambient temperature, we thought reaction may proceed at higher temperatures in presence of these solvents. Also, the reaction did not proceed with sodium borohydride dissolved in a 2% aq. sodium hydroxide solution to the substrate in toluene or diphenyl ether in presence of tetraoctylammonium bromide (TOAB) catalyst (entry no. 5 &6). When the reaction was tried in polyethylene glycol-400 (PEG-400) in presence of lithium chloride catalyst at ambient temperature, conversion was observed by TLC, but reaction did not go to completion (entry no. 7). Similar result was obtained when the reaction was tried in IPA at 60-65^oC (entry no. 8) with LiCl as catalyst. Product decomposition was observed when the reaction was carried out in a mixture of IPA and methanol with a 0.5 eq. of LiCl as catalyst (entry no. 9).

Table-2: Reduction of Methanesulfonate with catalyst

S. No.	Solvent	Catalyst/Eq.	Temp. (°C)	Time (h)	Conversion by TLC	Remarks
1	Toluene	$MgCl_2$/0.5	108-110	10	No conversion	Product formation is not observed
2	Toluene	$TiCl_4$/0.5	108-110	10		
3	Toluene	$AlCl_3$/0.5	108-110	10		
4	Toluene	TOAB/0.2	80-90	5		
5	Toluene	TOAB/0.1	80-90	12	No conversion	$NaBH_4$ dissolved in 2% aq. NaOH solution
6	Diphenyl ether	TOAB/0.1	80-90	16	No conversion	
7	PEG-400	LiCl/0.5	25-35	15	Conversion observed	--
8	IPA		60-65	10		
9	IPA/MeOH		80-90	5	Less conversion observed	Product decomposition observed

Having seen the progress of the reaction with LiCl, we planned to carry out the reactions in presence of this catalyst by monitoring on a gas chromatograph (GC). These results are tabulated in table-3. When the reaction was carried out in DMSO at 80-90°C it took 6 h for completion to give 68% yield with 85% purity (entry no.1). When *N*-methylpyrrolidone (NMP) was used as a solvent 65% yield was observed with 76% purity (entry no. 2). Interestingly, the yield was improved substantially to 98% when the reaction was conducted in presence of 0.5 eq. of LiCl (entry no. 3). Similar yield is observed with better purity (87%) when a mixture of toluene and NMP were used as solvent again with catalytic amount of LiCl (entry no. 4). Due to the difficulty in the removal of NMP by distillation at lower temperatures, the reaction was carried out in mono, di and triglyme under similar reaction conditions. It was observed that the conversion is poor (43.6%) in monoglyme (entry no. 5) and good (74.0%) in triglyme (entry no.6). Since the boiling point is very high for triglyme hence, further experimentation is not

carried out. To our good fortune, when diglyme was used as a solvent along with LiCl, high purity product (92%) was observed with 90% yield, but the reaction is slow, took 16 h for completion (entry no.7). An experiment was carried out without LiCl to check its effect in the reaction and observed that reaction was not progressing to completion even for prolonged time (entry no.8). It is also interesting to note that addition of $NaBH_4$/ LiCl in four lots gave good conversion rather than single lot addition (entry no 9). It is understood that the sodium borohydride reacts with LiCl forming $LiBH_4$ in situ which enhances the reactivity. The formation of $LiBH_4$ is well documented in the literature.[10b] This enhanced reductive reactivity of the reagent system, $NaBH_4$/ LiCl is highly applicable in commercial scale as the use of $LiBH_4$ which is expensive and unstable can be avoided. An additional experiment was carried out by using lot wise addition of $LiBH_4$ in diglyme that proceeded smoothly (entry no.10), further confirmed the in situ formation of $LiBH_4$ in our regular reactions (entry no. 9). Single lot addition of $LiBH_4$ gave ~90% conversion observed by TLC. The process was optimized further and the required 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranoside, **7** was obtained in 81-87% yield and 97.66 to 97.90% purities. This technology was successfully transferred to the commercial scale and compound **7** was obtained in 87-89% yield with 97.24 to 97.50 purities (Table-4).

Further, the process was optimized for the synthesis of precursor, 2,3-*O*-isopropylidene-1-*O*-methyl-5-*O*-mesyl-D-ribofuranoside, **12a** (Scheme-3), intermediate, **9** and 5′-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine (Capecitabine, **1;** Scheme-2) in Lab and commercial scale. Capecitabine was successfully manufactured at 75.0 Kg scale in 79% yield and 99.8% purity.

Table-3: Reduction of methanesulfonate with $NaBH_4$ in presence of LiCl catalyst

S. No.	Input (g)	Solvent	Catalyst (eq.)	Time (h)	Yield (%)	Purity (%) (Product/SM)

1[a]	20.0	DMSO	-	6	68	85.45/0.5
2[a]	30.0	NMP	-	6	65	76.55/0.11
3[a]	20.0	NMP	LiCl/0.5	4	98	78.62/0.28
4[a]	20.0	Toluene +NMP	LiCl/0.5	4	98	87.62/0.57
5[a]	30.0	Monoglyme	-	24	75	43.64/44.51
6[a]	20.0	Triglyme	-	6	75	74.04/15.30
7[a]	**20.0**	**Diglyme**	**LiCl/0.5**	**16**	**90**	**92.33/1.40**
8[a]	20.0	Diglyme	-	20	60	65.0/21.50
9[b]	20.0	Diglyme	LiCl/2.45	16	90	97.38/1.15
10[c]	**5.0**	**Diglyme**	**--**	**12**	**86**	**--**

[a]2.0 eq $NaBH_4$ and 0.5 eq LiCl was used in each reaction and carried out 80-90°C; [b]2.45 eq of NaH_4 and 2.45 eq of LiCl used; [c]2.45eq of $LiBH_4$ used; NMP = *N*-Methylpyrrolidone

Table-4: Manufacturing details of 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranoside, 7 in the Plant

S. No.	Input (2,3-*O*-Isopropylidene -1-*O*-methyl-5-*O*-mesyl-D-ribofuranoside; Kg)	Output (Kg)	Yield		Purity by GC (% area)
			(w/w)	(%)	
1	98.0	80.0	0.82	89	97.50
2	98.0	77.9	0.80	87	97.24
3	98.0	79.0	0.81	87	97.40

Experimental procedures:

Preparation of 2,3-*O*-isopropylidene-1-*O*-methyl-5-*O*-mesyl-D-ribofuranoside, 12a

To a mixture of acetone (200 mL) and methanol (150 mL) was added D-Ribose (50 g; 0.33 mol), cooled the solution to 0-5°C and slowly added sulfuric acid (5.3 mL; 0.20 mol) and maintained for 1 h. The reaction mass was raised to ambient temperature and stir for 24-26 h. After completion of the reaction which was monitored by TLC, the reaction mass was adjusted to neutral pH with aq. 10% sodium carbonate solution and distilled out the solvent at below 50°C. The obtained residue was diluted with DCM (400 mL) and water (100 mL) and stirred for 15-20 min. The two phases were separated, washed the dichloromethane phase with water followed by sodium chloride solution. To the obtained DCM layer, triethylamine (83.1 mL; 0.61 mol) was added, cooled to 0-5°C and methane sulfonyl chloride solution (27.07 mL; 0.35 mol dissolved in 25 mL DCM) was added over a period of 30-45 min. The reaction mass was raised to ambient temperature and maintained for 1-2hrs. After completion of the reaction, which was monitored by TLC, the reaction mass pH was adjusted to neutral with 5% aq. sodium bicarbonate solution. The two phases were separated and the DCM layer washed with water followed by saturated sodium chloride solution. The DCM was distilled and the product was precipitated by adding water and stirred for 1h at 60-70°C followed by 2h at 5-10°C. The obtained material was filtered and dried to obtain 71.0 g colorless white solids of 2,3-*O*-isopropylidene-1-*O*-methyl-5-*O*-mesyl-D-ribofuranoside.^{1}H NMR spectral data were identical with those reported in the literature.[2b,4a,4g]

Preparation of 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranoside, 7: To a solution of 2,3-*O*-isopropylidene-1-*O*-methyl-5-*O*-mesyl-D-ribofuranoside 100g (0.35 mol) in diglyme (500 mL) was added sodium borohydride (32.5g; 0.86 mol, 2.45eq.) and lithium chloride (36.5g; 0.86 mol, 2.45eq.) in four lots. After addition of first lot, (sodium borohydride; 9.3g and lithium chloride; 10.5g) slowly the temperature was raised to 80-90°C and maintained for 4.0h. The reaction mass

was cooled to ambient temperature, added second lot reagents and slowly raised the temperature to 80-90°C and maintained for 4.0h. After addition of 4th lot (sodium borohydride; 4.6g and lithium chloride; 5.0g) reaction was maintained for 12.0h. After completion of the reaction which was monitored by GC, the reaction mass is cooled to room temperature, quenched with 1.0L 5% aq. acetic acid solution and stirred for 15 min. The product is extracted with dichloromethane up to TLC shows no product in the aqueous layer. The combined DCM layer was washed with water, concentrated to obtain a residue. To the residue was added 550 mL 0.1% aq. sulfuric acid and maintained for 5-6h at 80-90°C. After completion of the reaction which was monitored by TLC, adjusted the reaction mass pH to neutral with triethylamine and washed the reaction mass with 2X150 mL DCM to remove organic impurities. The left over aq. phase is concentrated to obtain a residue which was treated with TEA (75 mL; 0.54 mol) and DMAP (2.13 g; 0.017 mol) and acetic anhydride (132 mL; 1.4 mol) at -5 to +5°C for 4h. After completion of the reaction monitored by TLC the reaction mass was charged to cold water and adjusted the pH to neutral with sodium carbonate. The obtained precipitate was maintained for 2-3h, filtered and dried to obtain a colorless solid of 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranoside in 85-90% yield and > 95% purity, mp: 63-65^{o}C (lit 63-64 ^{o}C)[4a, 4g] and ^{1}H NMR spectral data[2b] were identical with those reported in the literature.

Preparation of 5'-Deoxy-5-fluoro-2′,3'-*O*-acetyl-N-pentyloxycarbonyl-cytidine, 9

A suspension of 5-fluorocytosine (52.0 g; 0.40 mol), hexamethyldisilazane (71.3 g; 0.44 mol), and ammonium sulphate (1.0 g; 0.008 mol) in toluene (100 mL) was heated at reflux temperature for 1.0-1.5h. Then the solvent was distilled at atmospheric pressure and cooled the reaction mass to ambient temperature. The obtained residue was dissolved in dichloromethane (400 mL), added

1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranoside (100.0 g, 0.38 mol), then cooled the reaction mass to 5-10°C and added stannic chloride (105g; 0.24 mol, in 50mL of dichloromethane) solution at 5-10°C and maintained for 30-45 min at the same temperature. After completion of the reaction which was monitored by TLC, solid sodium bicarbonate (200 g) was added and the obtained salts were removed by filtration. The organic layer was washed with aq. sodium bicarbonate, water followed by sodium chloride solution and distilled off DCM completely at atmospheric pressure. The obtained residue was dissolved in fresh dichloromethane added pyridine (36g, 0.46 mol), cooled to -5 to +5 ^{o}C, added n-pentyl chloroformate solution (60.7g; 0.80 mol, in 50 mL DCM) and maintained for 2-3 h. After completion of the reaction which was monitored by TLC, methanol (5 mL) was added and DCM distilled completely. To the residue was added toluene (400 mL) and the obtained salts were removed by filtration. The toluene layer washed with aq. sodium bicarbonate, water followed by sodium chloride solution and stripped off completely under reduced pressure and the product was isolated by adding diisopropyl ether (150 mL). The obtained precipitate was maintained for 2-3 h, filtered and dried to obtain 120g of off-white color solids of 5'-deoxy-5-fluoro-2',3'-*O*-acetyl-N4-pentyloxycarbonyl-cytidine.^{1}H NMR spectral data were identical with those reported in the literature.[2b,4g]

Preparation of 5′-Deoxy-5-fluoro-N-(pentyloxy carbonyl) cytidine (Capecitabine), 1

To a solution of acetyl protected capecitabine (120 g; 0.27 mol) in methanol (240 mL) at 0 to 5°C was added aq. sodium hydroxide solution (16 g; 0.40 mol, dissolved in 400mL water) and maintained the reaction for 15-30 min. After completion of the reaction which was monitored by TLC the reaction mass pH adjusted to neutral with aq. hydrochloric acid and the product was extracted with dichloromethane. The DCM layer was separated, washed with water followed by brine and dried over sodium sulphate. The DCM was distilled under reduced pressure and the

product was isolated from ethyl acetate and n-heptane. The obtained precipitate was maintained for 2-3 h, filtered and dried to obtain a white color solid of pure 5′-Deoxy-5-fluoro-N-(pentyloxy carbonyl) cytidine (capecitabine) in 78% yield. ^{1}H NMR spectral data were identical with those reported in the literature[2b,4g] and all other impurities complies as per USP monograph.

CONCLUSION:

In summary, we have successfully developed a facile and safe alternate method for the reduction of methanesulfonate with sodium borohydride/LiCl mixture in diglyme by avoiding DMSO. Compared to triglyme, the boiling point of diglyme is low and convenient to handle at scale during distillation. In addition to that the use of expensive $LiBH_4$ was avoided. We optimized this process in the Lab and demonstrated to produce 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranoside **7**, in the commercial plant. Also the process was optimized for other intermediates, 2,3-*O*-isopropylidene-1-*O*-methyl-5-*O*-mesyl-D-ribofuranoside and 5'-Deoxy-5-fluoro-2′,3'-*O*-acetyl-N4-pentyloxycarbonyl-cytidine along with capecitabine in the Lab. All this technology was transferred to commercial plant and produced ICH quality capecitabine in consistent yields.

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