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APPENDIX 2

Overcoming Barriers to Green Chemistry in the Pharmaceutical Industry - The Green Aspiration Level™ Concept

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F. Roschangar,[a] R. A. Sheldon[b] and C. H. Senanayake[a]

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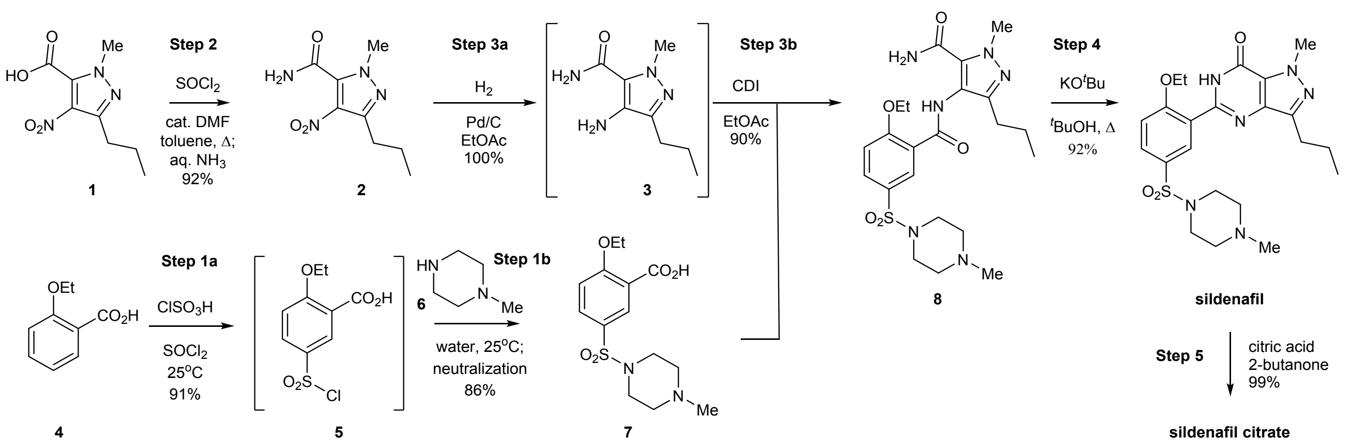
Appendix 2 – Detailed Analysis of commercial Viagra™ process

Here we provide details of our analysis of the commercial Viagra™ process. To start our analysis, we evaluate the process deploying the sEF and cEF metrics in combination with our starting point concept. The overall commercial process scheme for Pfizer's Viagra™ is shown in Scheme 1.

The table includes required step information such as molar equivalence, input and output weights, and the Sigma-Aldrich material catalog pricing[1] for their respective largest available quantity in order to verify raw material status under our starting point model. Materials that do not meet the $100/mol price target to qualify as raw materials are highlighted in red color in the 'Price per Mol' column, and indicate that their respective



Scheme 1. Pfizer's Commercial Synthesis of sildenafil citrate (Viagra™).

The synthesis starting points are pyrazole **1** and benzoic acid **2**. As a first step, we establish the material table for the process steps based on Pfizer's publications, and determine the amounts of all materials required to make 1 kg of sidenafil citrate (Table 1).

synthesis should be considered for E factor analysis. With this information in hand, we can readily determine the amounts of raw materials, reagents, solvents, water, and products for each step and the overall process, and thus derive the sEF and cEF. For comparative purposes we include the traditional E factor which assumes 90% solvent recycling if no data are available[2] and entirely discounts process water (Table 2).

Scheme 2. Sub-Process for 1-Methyl-4-nitro-3-propyl-1H-pyrazole-5-carboxylic Acid (1).

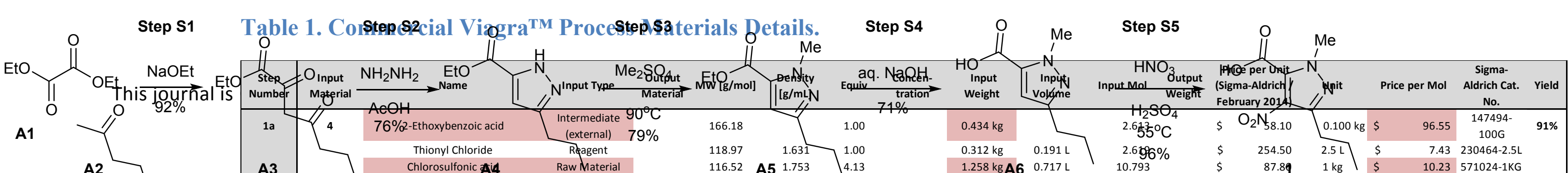


Table 1. Commercial Viagra™ Process Materials Details.

Step Number	Input Material	Name	Input Type	Output Material	MW [g/mol]	Density [g/mL]	Equiv	Concen-tration	Input Weight	Input Volume	Input Mol	Output Weight	Price per Unit (Sigma-Aldrich / February 2014)	Unit	Price per Mol	Sigma-Aldrich Cat. No.	Yield
1a	4	2-Ethoxybenzoic acid	Intermediate (external)		166.18		1.00		0.434 kg		2.613		$ 58.10	0.100 kg	$ 96.55	147494-100G	91%
		Thionyl Chloride	Reagent		118.97	1.631	1.00		0.312 kg	0.191 L	2.619		$ 254.50	2.5 L	$ 7.43	230464-2.5L	
		Chlorosulfonic acid	Raw Material		116.52	1.753	4.13		1.258 kg	0.717 L	10.793		$ 87.8[illegible]	1 kg	$ 10.23	571024-1KG	

Table 2. sEF, cEF, and E factor Analysis of the Commercial Viagra™ Process.

Step Number	Raw Materials	Reagents	Solvents (excl. Water)	Water	Product	Step sE-Factor	sE-Factor Contribution to Process	Step cE-Factor	cE-Factor Contribution to Process	E-Factor Contribution to Process
1a+b	2.2 kg	0.3 kg	0.0 kg	12.2 kg	0.7 kg	2.8 kg/kg	1.9 kg/kg	21.1 kg/kg	14.1 kg/kg	1.9 kg/kg
2	1.1 kg	0.4 kg	1.8 kg	1.7 kg	0.4 kg	2.8 kg/kg	1.1 kg/kg	11.9 kg/kg	4.6 kg/kg	1.3 kg/kg
3a+b	1.1 kg	0.3 kg	10.7 kg	0.0 kg	0.8 kg	0.7 kg/kg	0.6 kg/kg	13.9 kg/kg	11.3 kg/kg	1.7 kg/kg
4	0.8 kg	0.2 kg	3.1 kg	8.1 kg	0.7 kg	0.5 kg/kg	0.3 kg/kg	16.1 kg/kg	11.6 kg/kg	0.7 kg/kg
5	1.0 kg	0.0 kg	8.7 kg	0.0 kg	1.0 kg	0.0 kg/kg	0.0 kg/kg	8.7 kg/kg	8.7 kg/kg	0.9 kg/kg
TOTAL	3.6 kg	1.3 kg	24.3 kg	22.1 kg	1.0 kg		3.9 kg/kg		50.3 kg/kg	6.4 kg/kg

The total process product amount equals the amount of Step 5 product, and the total raw materials are the sum of the raw materials used in Steps 1-5 minus the amount of Step 1-4 products since they have a net mass effect of zero kg on the overall process as they are used as raw materials for the subsequent step. Our result for Sheldon's traditional E factor is 6.4 kg/kg and corresponds well with Pfizer's reported 6 kg/kg

Table 3. Material Table for the 1-Methyl-4-nitro-3-propyl-1H-pyrazole-5-carboxylic Acid (1) Sub-Process.

Step Number	Input Materials	Name	Input Type	Output	MW [g/mol]	Density [g/mL]	Equiv	Concen-tration	Input Weight	Input Volume	Input Mol	Output Weight	Price per Unit (Sigma-Aldrich / February 2014)	Unit	Price per Mol	Sigma-Aldrich Cat. No.	Yield
S1																	
	A1	Diethyl oxalate	Raw Material		146.14	1.076	1.000		1.894 kg	1.761 L	12.963		$ 113.50	3 kg	$ 5.53	135364	70%
	A2	2-Pentanone	Raw Material		86.13	0.809	1.000		1.117 kg	1.380 L	12.963		$ 441.00	20 kg	$ 1.90	W284203-20KG	
		Sodium	Reagent		22.99		0.500		0.149 kg		6.482		$ 178.50	0.450 kg	$ 9.12	282065-450G	
		Ethanol, denatured	Solvent		46.07	0.789	31.715		18.940 kg	24.006 L	411.123		$ 2,730.00	200 L	$ 0.80	187380-200L	
		Ethyl 2,4-dioxoheptanoate	Intermediate (external)	A3	186.21							1.690 kg					
S2																	
	A3	Ethyl 2,4-dioxoheptanoate	Intermediate (external)		186.21		1.000		1.690 kg		9.074		n/a				96%
		Hydrazine hydrate	Raw Material		50.05	1.029	1.098		0.499 kg	0.485 L	9.966		$ 123.50	1 kg	$ 6.18	225819-1KG	
		Acetic acid	Solvent		60.05	1.049	6.496		3.540 kg	3.374 L	58.943		$ 334.00	18 L	$ 1.06	A6283-18L	
		Ethyl 3-n-propylpyrazole-5-carboxylate	Intermediate (external)	A4	182.22							1.587 kg					
S3	A4	Ethyl 3-n-propylpyrazole-5-carboxylate	Intermediate (external)		182.22		1.000		1.587 kg		8.711		n/a				79%
		Dimethyl sulfate	Raw Material		126.13	1.333	1.008		1.107 kg	0.831 L	8.777		$ 853.00	18 L	$ 4.48	D186309-18L-KL	
		Dichloromethane	Solvent		84.93	1.325	15.719		11.630 kg	8.777 L	136.933		$ 618.00	18 L	$ 2.20	270997-18L-P1	
		Sodium carbonate monohydrate	Reagent (Workup)		124.00		1.008		1.088 kg		8.777		$ 181.00	2.5 kg	$ 8.98	230952-2.5KG	
		Water	Water (Workup)		18.02	1.000	55.914		8.777 kg	8.777 L	487.079		$ -				
		1-Methyl-3-n-propylpyrazole-5-carboxylic acid ethyl ester	Intermediate (external)	A5	196.25							1.351 kg					
S4	A5	1-Methyl-3-n-propylpyrazole-5-carboxylic acid ethyl ester	Intermediate (external)		196.25		1.000		1.351 kg		6.882		n/a				71%
		Sodium hydroxide	Reagent		40.00		3.000		0.826 kg		20.645		$ 339.50	12 kg	$ 1.13	221465-12KG	
		Water	Water		18.02	1.000	55.494		6.882 kg	6.882 L	381.899		$ -				
		Concentrated hydrochloric acid	Reagent (Workup)		36.46	1.200	3.044	37%	2.065 kg	1.720 L	20.951		$ 327.50	15 L	$ 1.79	320331-6X2.5L	
		1-Methyl-3-propylpyrazole-5-carboxylic acid	Intermediate (external)	A6	168.20							0.822 kg					
S5	A6	1-Methyl-3-propylpyrazole-5-carboxylic acid	Intermediate (external)		168.20		1.000		0.822 kg		4.886		n/a				96%
		Sulfuric acid, 95-98%	Reagent		98.08	1.840	12.626		6.051 kg	3.288 L	61.691		$ 418.50	15 L	$ 1.49	320501-6X2.5L	
		Nitric acid, fuming, 90%	Raw Material		63.01	1.480	1.367		0.421 kg	0.284 L	6.680		$ 594.00	0.5 L	$ 50.58	309079-500ML	
		Sulfuric acid, 95-98%	Reagent		98.08	1.840	2.680		1.284 kg	0.698 L	13.095		$ 418.50	15 L	$ 1.49	320501-6X2.5L	
		Water	Water (Workup)		18.02	1.000	199.661		17.580 kg	17.580 L	975.561		$ -				
		1-Methyl-4-nitro-3-propyl-1H-pyrazole-5-carboxylic acid	Intermediate (external)	1	213.19							1.000 kg					

Table 4. sEF, cEF, and E factor Analysis for the 1-Methyl-4-nitro-3-propyl-1H-pyrazole-5-carboxylic Acid (1) Sub-Process.

Step Number	Raw Materials	Reagents	Solvents (excl. Water)	Water	Product	Step sE-Factor	sE-Factor Contribution to Sub-Process	Step cE-Factor	cE-Factor Contribution to Sub-Process	E-Factor Contribution to Sub-Process
S1	3.0 kg	0.1 kg	18.9 kg	0.0 kg	1.7 kg	0.9 kg/kg	1.5 kg/kg	12.1 kg/kg	20.4 kg/kg	3.4 kg/kg
S2	2.2 kg	0.0 kg	3.5 kg	0.0 kg	1.6 kg	0.4 kg/kg	0.6 kg/kg	2.6 kg/kg	4.1 kg/kg	1.0 kg/kg
S3	2.7 kg	1.1 kg	11.6 kg	8.8 kg	1.4 kg	1.8 kg/kg	2.4 kg/kg	16.9 kg/kg	22.8 kg/kg	3.6 kg/kg
S4	1.4 kg	1.6 kg	0.0 kg	8.2 kg	0.8 kg	2.6 kg/kg	2.1 kg/kg	12.5 kg/kg	10.3 kg/kg	2.1 kg/kg
S5	1.2 kg	7.3 kg	0.0 kg	17.6 kg	1.0 kg	7.6 kg/kg	7.6 kg/kg	25.2 kg/kg	25.2 kg/kg	7.6 kg/kg
TOTAL	5.0 kg	10.2 kg	34.1 kg	34.5 kg	1.0 kg		14.2 kg/kg		82.8 kg/kg	17.6 kg/kg

of actual waste. The process sEF, which excludes solvents and process water, is calculated as 3.9 kg/kg, and the all-inclusive cEF is 50.3 kg/kg.

Table 5. Conversion of Intrinsic E factors to E factor Process Contributions for Compound 1.

sEF	INTRINSIC cEF Contribution to Compound 1 Sub-Process	E-Factor
14.2 kg/kg	82.8 kg/kg	17.6 kg/kg
	x Quantity needed to make 1 kg of sildenafil citrate	
x	0.424	
	=	
sEF	**cEF Contribution to Sildenafil Citrate Process**	**E-Factor**
6.0 kg/kg	**35.1 kg/kg**	**7.5 kg/kg**

Next we assess the synthesis starting point matter. While raw materials chlorosulfonic acid ($10.23/mol), 1-methylpiperazine (**6**; $24.64/mol), ammonium hydroxide solution ($2.27/mol), citric acid ($9.72/mol), and 2-ethoxybenzoic acid (**4**, $96.55/mol) meet our 'raw material standard', one primary synthesis starting point 1-methyl-4-nitro-3-propyl-1H-pyrazole-5-carboxylic acid (**1**, not available from Sigma-Aldrich's website) does not meet the requirement. Some may disagree with the proposed raw material rules, but these help emphasize, in a very simple way, that this raw material is significantly more complex than the other process raw materials and its intrinsic E factor ought to be included in order to arrive at a fair overall process waste figure. So we begin the process of determining the intrinsic E factor of the critical raw material.

Pyrazole starting point **1** is derived in five steps from readily available raw materials diethyl oxalate (**A1**; $5.53/mol) and 2-pentanone (**A2**; $1.90/mol) (Scheme 2)[3] In analogy to the sildenafil citrate process discussed above, we first derive the material table for the process to produce 1 kg of compound **1** (Table 3), and then perform the E factor analysis (Table 4).

As a result, the *intrinsic* sEF, E factor, and cEF for 1-methyl-4-nitro-3-propyl-1H-pyrazole-5-carboxylic acid (**1**) are determined as 14.2, 17.6, and 82.8 kg/kg, respectively, which when multiplied with the quantity of **1** needed to produce 1 kg of sildenafil citrate (0.424 kg), provide the sEF, E factor, and

Table 6. sEF, cEF, and E factor Analysis of the commercial Viagra™ Process starting from Commodity Raw Materials.

Step Number	Input Material	Raw Materials	Reagents	Solvents (excl. Water)	Water	Product	Step sE-Factor	sE-Factor Contribution to Process	Step cE-Factor	cE-Factor Contribution to Process	E-Factor Contribution to Process
TOTAL		2.1 kg	1.1 kg	0.0 kg	3.0 kg	0.4 kg		2.8 kg/kg		5.8 kg/kg	2.8 kg/kg
1a+b		2.2 kg	0.3 kg	0.0 kg	12.2 kg	0.7 kg	2.8 kg/kg	1.9 kg/kg	21.1 kg/kg	14.1 kg/kg	1.9 kg/kg
2	1							6.0 kg/kg		35.1 kg/kg	7.5 kg/kg
		1.1 kg	0.4 kg	1.8 kg	1.7 kg	0.4 kg	2.8 kg/kg	1.1 kg/kg	11.9 kg/kg	4.6 kg/kg	1.3 kg/kg
3a+b		1.1 kg	0.3 kg	10.7 kg	0.0 kg	0.8 kg	0.7 kg/kg	0.6 kg/kg	13.9 kg/kg	11.3 kg/kg	1.7 kg/kg
4		0.8 kg	0.2 kg	3.1 kg	8.1 kg	0.7 kg	0.5 kg/kg	0.3 kg/kg	16.1 kg/kg	11.6 kg/kg	0.7 kg/kg
5		1.0 kg	0.0 kg	8.7 kg	0.0 kg	1.0 kg	0.0 kg/kg	0.0 kg/kg	8.7 kg/kg	8.7 kg/kg	0.9 kg/kg
TOTAL		5.3 kg	5.6 kg	38.8 kg	36.7 kg	1.0 kg		9.9 kg/kg		85.5 kg/kg	13.8 kg/kg

cEF *contributions* of **1** to the sildenafil citrate process of 6.0, 7.5, and 35.1 kg/kg, respectively (Table 5).

By not considering the intrinsic E factor, the sildenafil citrate analysis inherently assumed an E factor contribution of 0.424 kg/kg for compound **1** in the commercial process, which equals the compound's mass needed to produce 1 kg of sildenafil citrate., Thus, we effectively discounted between 5.6 kg (= 6.0 – 0.4) in terms of sEF, 7.1 kg for E factor, and 34.7 kg for cEF of intrinsic waste associate with the production of 1 kg compound **1**. If this material, as we assume, is not a commodity and is specifically made for the Viagra™ process, the intrinsic waste must therefore be considered in an objective process greenness analysis.

When including the intrinsic E factor of the non-commodity-type raw material **1**, the overall sildenafil citrate process analysis changes as shown in Table 6. We observe significant increases of the E factors, with the sEF jumping from 3.9 kg/kg using Pfizer's synthesis starting point to 9.9 kg/kg using our proposed commodity-type starting principles, the E factor going from 6.4 to 13.8 kg/kg, and the cEF changing from 50.3 to 85.5 kg/kg.

Therefore, depending on the type of E factor utilized, the exclusion of the two non-commodity-type raw materials in the analysis of the commercial Viagra™ process does not account for 40-60% of the process waste. This example shows how widely E factors can vary depending on the selected synthesis starting points, and thereby stresses the importance of implementing an industry-wide standardized starting point concept. Otherwise individual researchers will continue to select different starting points and render green process analysis and benchmarking less meaningful.

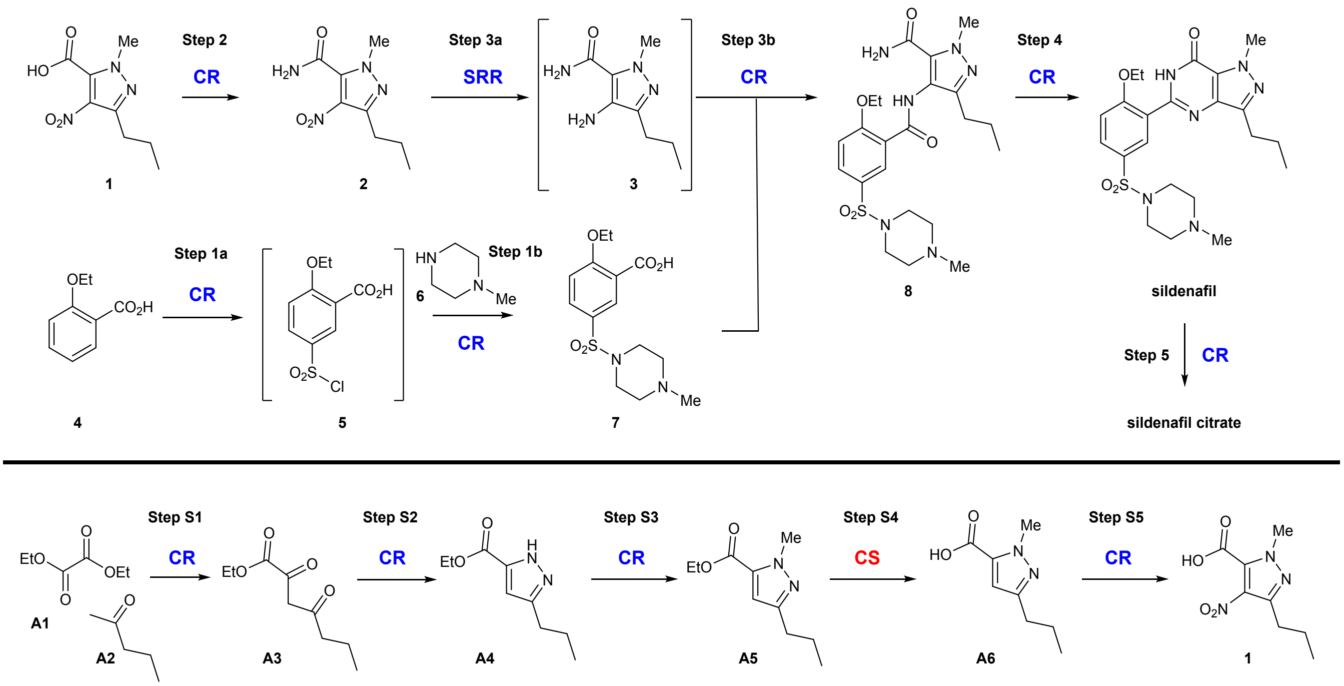
Before we can evaluate the process against the industrial Green Aspiration Level (GAL) for the commercial Viagra™ process, we need to determine its process complexity. By applying process ideality Equation 3 (see paper) and process complexity Equation 4 (see paper) to the entire Viagra™ process, including steps S1 through S5 according to our starting point definition, as shown in **Error! Reference source not found.**, we obtain a process complexity of 11 along with an ideality metric of 92% (Table 7).

Table 7. Ideality Analyses for Viagra™ Process and Sub-process.

Target	Transforma-tions	Strategic Redox Reactions	Construction Reactions	Concession Steps	%Ideality	Complexity
Viagra	12	1	10	1	92%	11
1	5	0	4	1	80%	4

We also apply ideality analysis to the sub-processes for intermediate **1**. The functional intergroup conversion from the ethyl ester to the corresponding carboxylic acid in step S4 for intermediate **1** leads to reduced %ideality and reflects the only concession step in the entire Viagra™ process.

Given a process Complexity of 11, we can determine Viagra's process GALs (Table 8). We also determine the GALs for the sub-process leading to external intermediate **1.**



Scheme 3. 'Complete' Commercial Viagra™ Process (CR = Construction Reaction, SRR = Strategic Redox Reaction, CS = Concession Step).

Table 8. Green Aspiration Level (GAL) for the Commercial Viagra™ Process.

Commercial Process	Complexity	sEF-based Analysis		cEF-based Analysis	
		tGAL [kg/kg]	GAL [kg/kg]	tGAL [kg/kg]	GAL [kg/kg]
Viagra™	11	3	33	19	209
1	4		12		76

With the GALs available, we are ready to determine Relative Process Greenness (RPG, Table 9). Since we did not analyze Viagra's™ earlier development process for the purposes of this discussion, we also did also not determine the Relative Process Improvement (RPI).

Table 9. RPG Analysis for Commercial Viagra™ Process.

Commercial Process	sEF-based Analysis			cEF-based Analysis		
	Actual [kg/kg]	GAL [kg/kg]	Relative Process Greenness (RPG)	Actual [kg/kg]	GAL [kg/kg]	Relative Process Greenness (RPG)
Viagra™	10	33	330%	86	209	243%
1	14	12	86%	83	76	92%

We derive that the 'complete' commercial Viagra™ process is 'very green', i.e. it exceeds its aspiration level, which represents the current industry average as reported by the ACS GCI Pharmaceutical Roundtable, 2.8 fold in terms of sEF and 2.5-fold in terms of cEF, and is therefore significantly more mass-efficient. The RPG in terms of solvents and process water could be improved for intermediate **1** [RPG(sEF)<< 100]. However, we note that while we drew the synthesis information of the intermediates from the literature, it is highly likely that their processes were subsequently improved by third party manufacturers under trade secret agreements.

1 The pricing is based on Sigma-Aldrich's online catalog information as of March 2014.

2 See paper, reference 37.

3 See paper, reference 77.