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Comparing the greenness and sustainability of three routes to an HIV protease inhibitor intermediate†

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The greenness and sustainability of three different routes for the synthesis of (3*R*,3a*S*,6a*R*)-hexahydrofuro [2,3-*b*] furan-3-ol (bis-furan alcohol), an advanced intermediate for a group of HIV protease inhibitors, including the FDA approved darunavir, used in antiretroviral (ARV) therapy, were compared. The method involved a comparison of (i) waste generated using the *E*-factor and relative to industrial benchmarks using the innovative Green Aspiration Level (iGAL™) method, (ii) solvent usage on the basis of solvent intensity (SI) and properties according to the GSK solvent guide, and (iii) Green Motion™ scores according to the MANE methodology.

1. Introduction

Since the onset of the HIV-AIDS epidemic in 1981, 76.10 million people have been infected globally by the human immunodeficiency virus (HIV), with sub-Saharan Africa accounting for two-thirds of this total.[1] Antiretroviral (ARV) drugs, such as the HIV protease inhibitors, have the primary objective of keeping HIV patients alive and preventing viral transmission. According to the WHO, 36.70 million people worldwide were living with HIV in 2016 with approximately 21.70 million people receiving effective ARV therapy. However, 60% of HIV positive individuals in Southern and Eastern Africa have no access to ARVs, emphasizing the need for cost-effective, sustainable manufacture of ARVs. The structures of a group of 2nd generation HIV PIs, including the FDA approved darunavir, are shown in Fig. 1. These compounds, designed to overcome multi-drug resistance to 1st generation HIV PIs, all contain the (3*R*,3a*S*,6a*R*)-hexahydrofuro [2,3-*b*] furan-3-ol moiety, also known as the bis-THF alcohol.[2,3]

A cost analysis of various synthetic pathways to darunavir showed that the bis-THF alcohol moiety contributed to roughly half the cost of synthesizing the active ingredient.[4] This explains why numerous routes for its synthesis have been described.[2,3,4–13] In this study we have assessed the greenness and sustainability of the three most recent and innovative routes.[3,4,13]

Publication in 1992 of the amounts of waste generated per kg of product (The (E)nvironmental Factor), in various sectors of the chemical industry (Table 1),[14] served to focus attention on the high *E*-factors observed in pharmaceuticals manufacture. Furthermore, in 2012 it was estimated that branded and generic pharmaceutical industries produce ≥100 million kilograms of Active Pharmaceutical Ingredient (API) and more than 15 billion kilograms of co-produced waste per annum.[15] The envisaged costs of disposal of this enormous detritus burden provide a significant incentive for the pharmaceutical industry to reduce waste generation and increase resource efficiency to enable more affordable medication and minimise its environmental footprint.

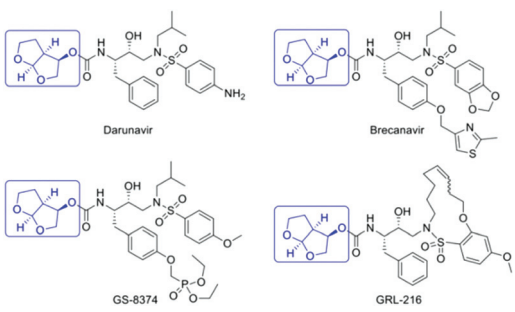

Fig. 1 Structures of HIV protease inhibitors containing the bis-THF alcohol moiety.

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Table 1 *E*-Factors in the chemical industry

Industry segment (examples)	Yearly production (tons)	*E*-Factor (kg waste per kg product)	No. synthetic steps
Pharmaceuticals (antibiotics, drugs, vaccines)	10–1000	25–>100	6+
Fine chemicals (coatings, electronic parts)	100–10 000	5–>50	3–4
Bulk chemicals (plastics, polymers)	10 000–1 000 000	<1–5	1–2
Petrochemical (solvents, detergents)	1 000 000–100 000 000	~0.1	Separations

The twelve principles of green chemistry, as defined and promulgated by Anastas and Warner in 1998,[16] provide a basis for assessing greenness:

1. Waste prevention instead of remediation
2. Atom efficiency
3. Less hazardous materials
4. Safer products by design
5. Innocuous solvents and auxiliaries
6. Energy efficient by design
7. Preferably renewable raw materials
8. Shorter synthesis (avoid derivatisation)
9. Catalytic rather than stoichiometric reagents
10. Design products for degradation
11. Analytical methodologies for pollution prevention
12. Inherently safer processes

Jiménez-González and Constable[17] classified the twelve principles into 5 metric categories to aid assessment of greenness. Thus, principles 1, 2, 5, 8 and 9 are concerned with mass efficiency, 3, 11 and 12 with health and safety, 6 with energy efficiency, 4 and 10 with waste generation and 7 with renewability of raw materials.

Our strategy entailed determining, for each synthetic pathway, (i) waste generation (*E*-factor),[14,18] (ii) greenness relative to industrial benchmarks following the innovative Green Aspiration Level (iGAL™) methodology,[19,20] (iii) solvent intensity and nature according to the GSK solvent guide,[21] and (iv) score according to the Green Motion™ methodology of MANE.[22]

Notwithstanding the importance of process greenness, in order to be sustainable a process must also be cost-effective and this is determined by, *inter alia*, the cost of raw materials and solvents and the number of unit operations. Hence, we have also assessed the effect of such parameters on the process economics.

It is also important to recognise that the bis-THF alcohol molecule contains three stereogenic centres and the desired product, the 3*R*,3a*S*,6a*R* isomer, is only one of the eight possible stereoisomers. The method used to obtain the required stereochemistry, *i.e.* the chirotechnology,[23] will directly influence the yield of product, the waste generated and, hence the greenness and economic viability of a synthetic route. The three routes which we have selected involve three different approaches to obtaining the required stereochemistry.

Green chemistry principles, metrics and assessment tools provide chemists and chemical engineers with guidelines and measures that aid in developing safer and less impactful products and processes. Full environmental assessments using Life Cycle Assessment (LCA) are only conducted at 'implementation and marketing' stages where there is greater availability of process data and lower risk of change in process design. Environmental assessments using green metrics and metric based tools are used during the conceptual design stage, where there are less process details, a high degree of process uncertainty and numerous potential synthetic procedures are compared.

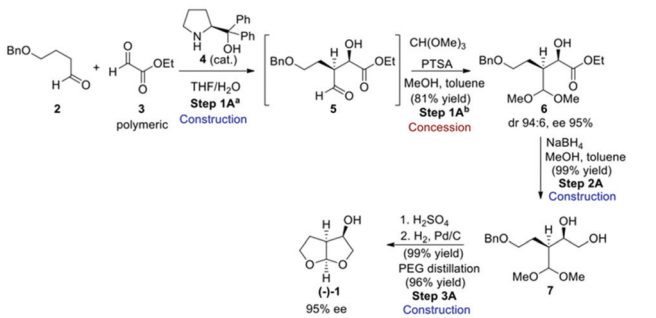
Examples of web-based tools and guides that are used in a conceptual design stage to assess process greenness are the iGAL™ and associated green scorecards, Green Motion™, and the GSK solvent sustainability guide.

2. Results and discussion

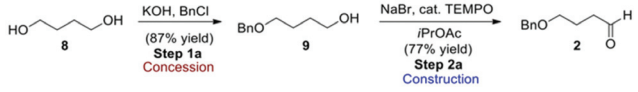
2.1 Selected routes to bis-THF alcohol

Three synthetic routes to the bis-THF alcohol (**1**) were assessed, each of which installed the key stereogenic centres using a different approach. Route A (Scheme 1)[13] made use of an enantio- and diastereoselective crossed aldol reaction between 4-butyloxy-1-butanal (**2**) and polymeric ethyl glyoxylate (**3**) in the presence of 3 mol% (*S*)-diphenylprolinol (**4**) to give aldol product **5**, which was protected as the acetal derivative **6** before isolation.

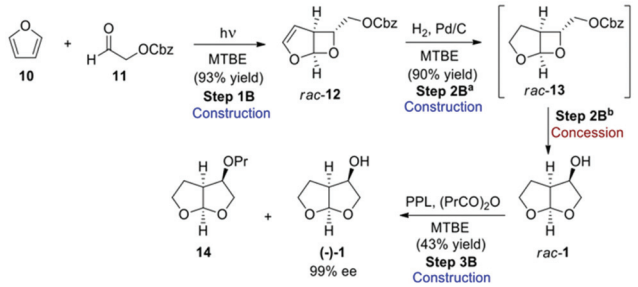
The required 2*R*,3*S*-stereochemistry was obtained, with product **6** being isolated in a diastereomeric ratio of 96 : 4 and with 95% ee. Quantitative ester reduction gave diol **7** which then underwent acetal exchange under acidic conditions and on benzyl deprotection to give the desired bis-THF product (−)-(**1**). Although the authors went on to improve the product ee through crystallisation to produce a carbonate-derived product salt, our assessment ended at the point of the bis-THF



Scheme 1 Route A for the preparation of bis-THF alcohol **1**.



Scheme 2 Preparation of ASM **2** for route A.



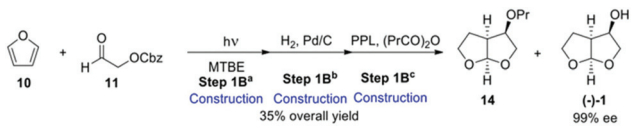
Scheme 3 Route B, which employs an enzymatic kinetic resolution.

synthesis with the dr and ee obtained from the original aldol reaction.

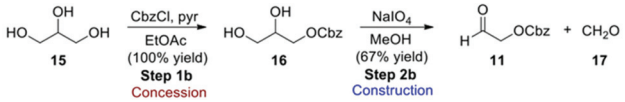
From an assessment perspective, the polymeric ethyl glyoxylate (**3**) qualifies as a commodity chemical and can be used as the starting point for the green metric determinations, however, 4-butyloxy-1-butanal (**2**) has to be considered as an advanced synthetic intermediate (ASM). Thus, a simple synthetic sequence to **2** (Scheme 2) based on a combination of established procedures[24–26] was devised for assessing the contribution of **2** to the overall metrics of route A. Benzyl protection of butane-1,4-diol (**8**) gives compound **9** which can be oxidised to the desired aldehyde derivative **2** using TEMPO.

In route B (Scheme 3),[3] the bis-THF was initially obtained in racemic form, and an enzymatic kinetic resolution using lipase was the key step in obtaining the desired enantiomer. Reaction of furan (**10**) with Cbz-protected aldehyde **11** under photocatalytic conditions gave rise to bicyclic *rac*-**12**, which was hydrogenated in the presence of palladium to give *rac*-**13**. This compound immediately undergoes rearrangement to give the desired bis-THF alcohol (**1**) in racemic form. The final resolution step was performed using porcine pancreatic lipase (PPL) in the presence of propionic anhydride in methyl *tert*-butyl ether (MTBE) to give propionate **14** and the desired bis-THF alcohol (–)-**1** in 99% ee. The authors describe both a step-by-step (Scheme 3), as well as a one-pot procedure (Scheme 4) for the preparation of **1**, and both methods were evaluated for "greenness".

The telescoping of the process was made possible by the judicious choice of MTBE as solvent for all of the reactions in the step-by-step procedure, and gave an overall final product yield of 35%.



Scheme 4 Route B as a one-pot process.



Scheme 5 Synthesis of ASM **11** for route B.

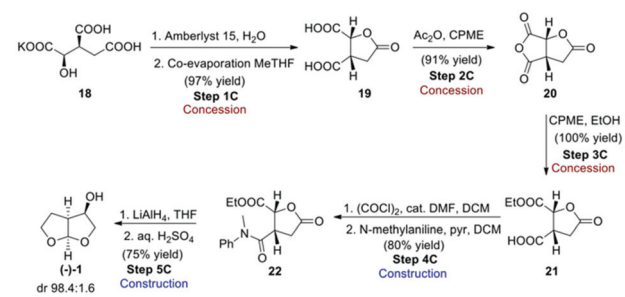
While furan is a cheap commodity chemical, aldehyde **11** must be considered an ASM, and therefore a synthetic route for its preparation was included in the evaluation (Scheme 5). Reaction of glycerol (**15**) with benzyl chloroformate gives Cbz-protected glycerol (**16**) which can undergo oxidative cleavage with sodium periodate to give the formaldehyde **17** and the desired Cbz-protected glycol aldehyde **11**.[3]

Route C, the final route evaluated (Scheme 6),[4] used the chiral pool approach for obtaining the desired stereochemistry by starting from enantiopure 2*R*,3*S*-potassium isocitrate (**18**). This starting material has the advantage of not being considered an ASM, as its cost of production should be as low as 50 USD per kg.[4] Potassium isocitrate (**18**) was neutralised with Amberlyst 15 ion-exchange resin in water, followed by water removal in the presence of methyl-tetrahydrofuran (Me-THF) as co-solvent. Subsequent heating of the resulting oil gave rise to lactone **19**. Treatment of the lactone with acetic anhydride in cyclopentyl methyl ether (CPME) gave cyclic anhydride **20** that was ring-opened with EtOH to give hemi-ester **21**. The free carboxylic acid group of **21** was amidated with *N*-methylaniline to give amide **22**. Conversion of **22** to the desired bis-THF alcohol (**1**) by reduction with $LiAlH_4$ formally involves a number of reactions, including reduction of the ester, lactone and amide functional groups to give an intermediate that then cyclises twice under acidic conditions to give the final acetal product (–)-(**1**).

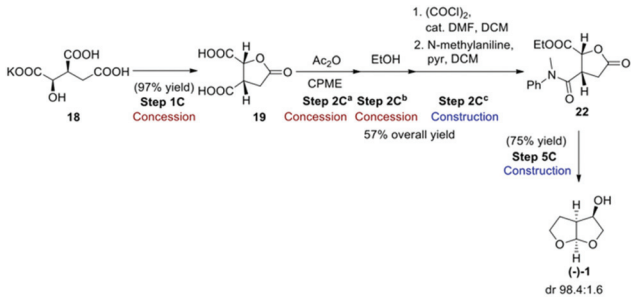
This reaction proceeds with excellent diastereoselectivity, giving the desired (–)-(**1**) in 98.4 : 1.6 dr. The authors also reported a one-pot procedure for the conversion of **19** to **22**, in 57% yield (Scheme 7). Both the original step-by-step procedure and the condensed synthesis were evaluated.

2.2 The *E*-factor

2.2.1 The *E*-factor methodology. The *E*-factor (kg waste per kg product) is the most well-known and widely used mass-



Scheme 6 Route C, starting from enantiopure **18**.



Scheme 7 Route C as a one-pot process from **19** to **22**.

based metric for quantifying the environmental impact of a chemical process.[14] A low *E*-factor correlates strongly with reduced manufacturing costs as a result of higher resource efficiency, reduced costs of waste disposal, better capacity utilisation, and reduced energy consumption.[19] Traditionally, it is based on the chemical process carried out at the manufacturing site, *i.e.* on a gate-to-gate basis. Hence, the *E*-factor is dependent on the starting point of the synthesis. However, the starting material should be readily available for a price of <$ 100 per kg. If not it is considered to be an advanced starting material (ASM) and the *E*-factor of its synthesis, known as the intrinsic *E*-factor, is included in the *E*-factor for the overall manufacturing process in order to provide a fair comparison between different routes.[19] Since *E*-factors are additive, the intrinsic *E*-factor may be simply added to the main synthesis *E*-factor to obtain an unbiased *E*-factor value for a complete synthetic pathway.

The original *E*-factor[14] considered all reagents used and solvent losses (assuming 90% solvent recovery if not known) in the process and work-up steps. Water was not included since it was thought that inclusion would lead to skewed *E*-factors. However, process water is generally contaminated with reactants, products and solvents and cannot be re-used without purification. Similarly, solvents are not always (efficiently) recycled. Hence, in the pharmaceutical industry there is an increasing tendency to include water and solvents in the *E*-factor. In order to go with the flow the use of simple (sE) and complete *E*-factors (cE) were introduced. The latter includes water and solvents and the former includes neither. The traditional *E*-factor, which can be calculated when all the data is available lies somewhere in between sE and cE. Waste generated by energy use, which could be expressed in kg CO_2 per kg product, was not included because multiple processes were conducted in the same multi-purpose equipment, generally without assigning energy use to specific products. If the data is available, waste generated from energy use could be included[27] but we note that for pharmaceuticals manufacture it is less important than for large volume bulk chemicals.

2.2.2 *E*-Factor route assessment. For each of the three routes, the sE, *E* and cE factors were calculated. Considering the early stage nature of the evaluated routes, we considered the *E*-factor to be the most applicable, but other values were also included for the sake of comparison. For routes A and B, the intrinsic *E*-factor calculated for the ASM synthesis was added to the *E*-factor value calculated for the main route. These calculations were for the preparation of sufficient ASM to give 1 kg of final product **1**. For routes B and C, both the one-pot and step-by-step procedures were evaluated. In cases where the products were reported as mixtures of diastereomers (product **6** in route A and final product **1** in route C) the yield of these steps was adjusted to record only the yield of the desired diastereomer. Catalysts (including biocatalysts) were excluded from the *E*-factor calculations.

Table 2 summarises the *E*-factor values obtained for each complete route, including ASM preparation where applicable. The *E*-factor values shown in parentheses are the contribution of the ASM synthesis to the total value.

It is clear that route A gave the lowest *E*-factor, irrespective of whether sE, *E* or cE calculations were used. One of the factors contributing to this is the route's high atom economy and good overall yield of product, calculated at 51% from butane-1,4-diol (**8**). Additionally, the high-yielding key crossed aldol reaction required only 3 mol% of chiral catalyst and gave good enantio- and diastereoselectivity. Advantages of this route include the fact that reactions were highly concentrated, and work-up procedures did not require large solvent volumes. In many instances, crude product was used without purification between steps, leading to a low total of 50 kg solvent and 41 kg of water being used per kg of bis-THF alcohol prepared, far less than for the other two routes.

The second best performing route in terms of *E*-factor was route B, with the one-pot procedure giving the best cE and *E* values. A major drawback of this method is the low overall yield of 23%, driven by the late-stage enzymatic kinetic resolution where more than half the material is lost in the final step. However, this step gave (−)-**1** in excellent enantioselectivity of 99%. The large amount of solvent used in the step-by-step procedure (727 kg kg^{-1} product), a result of column chromatography for product purification after each step, was significantly reduced in the optimised one-pot procedure to 307 kg by avoiding column chromatography until the final step. No water was used in route B, either during reaction or work-up. What is particularly striking for route B is the significant contribution of ASM synthesis to the total *E*-factor for the route. This emphasises the importance of choosing an appropriate and standardised starting point for *E*-factor calculations in order to make route comparisons meaningful.

Route C performed very poorly in terms of *E*-factor assessment, with large solvent and water volumes used in neutralis-

Table 2 A comparison of the *E*-factors for each of the assessed routes

	sE (kg kg^{-1})	*E* (kg kg^{-1})	cE (kg kg^{-1})
Route A	10 (3)	15 (6)	101 (58)
Route $B_{step\text{-}by\text{-}step}$	56 (44)	129 (65)	784 (262)
Route $B_{one\text{-}pot}$	58 (45)	90 (67)	371 (270)
Route $C_{step\text{-}by\text{-}step}$	73	128	1174
Route $C_{one\text{-}pot}$	218	288	1713

ations and extractions contributing to the high *E*-factor values. In addition, the one-pot route performed even worse than the step-by-step procedure, most likely because no route optimisation was done. Thus the step-by-step route used 548 kg of solvent and 553 kg of water per kg product produced and the one-pot route 697 kg solvent and 797 kg water per kg product. Overall reaction yield for the step-by-step procedure was good at 53%, but high solvent volumes and stoichiometric reagent use contributed to the route's poor performance in the *E*-factor metric.

A rough costing was completed for each route so that a comparison could be made between costing and *E*-factor. For reagents, the price was estimated based on the best price listed by reputable commercial suppliers and the cost was then divided by ten to make allowance for bulk discount. The cost of all process materials, including solvents and water was included, with no recycling being factored in. The estimated "total cost" for the preparation of 1 kg of bis-THF (**1**) by means of each route is shown in Table 3.

Clearly the one-pot preparation using route B was the most cost-effective at $717, followed by route A at almost double the cost. The most expensive of all the assessed routes at $5281 was the one-pot preparation using route C. In order to test the correlation between route cost and *E*-factor, each of the calculated cE-factors was plotted against the "total cost". Results of the plot are shown in Fig. 2 and it is clear that there is generally a clear linear relationship (R^2 = 0.96) between cost and cE-factor, with rising costs being associated with rising cE-factor. Route A is an outlier, with the estimated cost being much higher than expected in comparison to the cE-factor.

Table 3 Costing for the preparation of 1 kg bis-THF alcohol

	Cost (USD per kg)
Route A	1323
Route $B_{step\text{-}by\text{-}step}$	1650
Route $B_{one\text{-}pot}$	717
Route $C_{step\text{-}by\text{-}step}$	3197
Route $C_{one\text{-}pot}$	5281

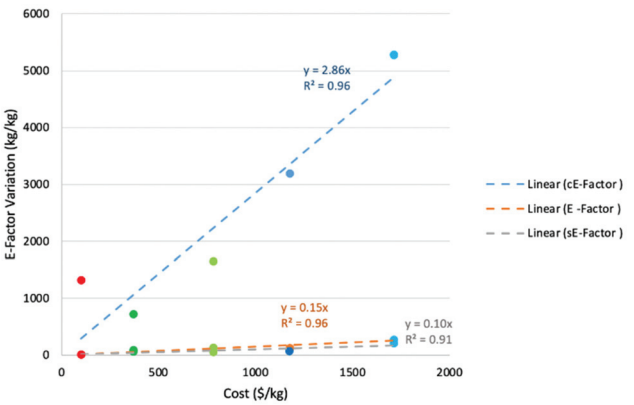


Fig. 2 Plots of *E*-factor variations against total cost.

A possible reason for this is that the individual cost for one of the required materials is particularly high, which drives the price much higher than expected based on cE-factor alone. Interestingly, a plot of original *E*-factor against total cost also proved to be linear (R^2 = 0.96) while the correlation of sE-factor against cost proved to be poorer but still mostly linear (R^2 = 0.91). These plots clearly illustrate the cost benefit associated with "greener" routes.

2.3 Innovative green aspiration level (iGAL™)

2.3.1. (iGAL™) and relative process greenness (RPG). From the viewpoint of increasing the greenness of manufacturing processes of, for example, pharmaceuticals, it is important to have a benchmark to aim for. This was the object of showing the estimated ranges of *E*-factors for various branches of the chemical industry in the original *E*-factor publication.[14] Similarly, the Green Aspiration Level (GAL™) was created[19] as a mass-based metric for comparing processes with respect to a benchmark based on the average waste generated per kg API in 46 commercial manufacturing processes from nine large pharmaceutical companies.[28] In order to compare processes on a level playing field the benchmark GAL was normalised by taking the process complexity (CP), based on Baran's % process ideality metric,[29] into account. The latter is the number of construction steps divided by the total number of synthetic steps. Construction steps are reactions that form skeletal C–C or C–heteroatom bonds and redox reactions that directly establish the correct functionality found in the final product, *e.g.* asymmetric reductions or oxidations. All other "nonstrategic" reaction types, including functional group interconversions and protecting group manipulations, are regarded as concession steps.

In 2018 a further refinement, the innovative Green Aspiration Level (iGAL™), was introduced.[20] iGAL is based on a statistical analysis of 64 drug manufacturing processes, involving 703 process steps across 12 companies. It is normalised by taking the salt free molecular weight (FMW) of the API rather than process complexity into account, based on the premise that process complexity is largely determined by molecular weight. The iGAL benchmark is the average cE divided by the average FMW of the 64 APIs assessed and was calculated to be 0.344. Hence, the goal for process innovation in drugs manufacture is to achieve a substantial reduction in waste compared to the iGAL of 0.344 × FMW of the API. The relative process greenness (RPG) for an individual process is the iGAL divided by the actual cE and is expressed as a percentage. As would be expected, the average cE decreases through the three development phases – early, late and commercial – of the drug manufacturing process. Table 4 presents the mean cE values collected for processes from three different development stages: early (23), late (21) and commercial (20).

Roschangar and coworkers used The Green Chemistry Innovation Scorecard, a web-based calculator,[30] to highlight the impact of innovation in waste reduction on drugs manufacture.[20] It compares Key Process Performance Indicators (KPPIs) – *E*-factor, CP, process ideality and RPG – of synthetic

Table 4 Average FMW, cE-Factor, and iGAL™ from 64 drug manufacturing processes[20]

Development phase	FMW (g mol^{-1})	iGAL™	cE-factor (kg kg^{-1})
Early	451	155	709
Late	464	160	352
Commercial	449	155	155

routes at three manufacturing stages: early development (before clinical testing), late development and commercial stage.

Future refinements of the iGAL™ and Green Scorecard are expected to incorporate the correlation between waste reduction and process economics in order to motivate a strong business case for using green chemistry to reduce the environmental footprint and render API manufacture more cost-effective.[31]

2.3.2 (iGAL™): performance of routes *vs.* early development phase benchmark. The iGAL metric compares the performance of synthetic routes to APIs with an average FMW of *ca.* 450. In contrast, we are assessing the greenness of a synthesis of a relatively low FMW (130) pharma intermediate, in considerably fewer steps than are required for the corresponding API, darunavir, which has an FMW of 548. Consequently, in order to enable application of the iGAL-RPG matrix (Table 5) to our synthesis routes, we used traditional *E*-factors rather than the high cE-factors in combination with an FMW of 130 for our calculations. As all the synthetic routes lead to the same target molecule (bis-THF alcohol), the FMW remains constant at 130 and the corresponding early development waste target (iGAL) is 45 (0.344 × 130) for all routes. Table 5 shows the RPG benchmark values, corresponding to industrial average values, for synthetic routes at the different development stages. Since the routes that we are assessing have only been conducted at laboratory scale, we used the industry benchmark for early development phase (pre-clinical trials), corresponding to an RPG benchmark of 35%.

The results of a comparison between Routes A to C and this benchmark value are shown in Table 6.

The highest RPG of 294% (*i.e.*, 45/15.25 × 100% = 294%), 8 times better than the industry benchmark (*i.e.*, 294%/35% = 8.33), was observed for Route $A_{step\text{-}by\text{-}step}$. According to the RPG matrix grid this places the route within the top 10% of green industrial performance and is rated 'excellent' in terms of mass-efficiency performance.

Route $B_{one\text{-}pot}$ was the next best performer in terms of this metric, with a 1.43 times less wasteful process than the industry average. Route $B_{step\text{-}by\text{-}step}$ and $C_{step\text{-}by\text{-}step}$ performed in line with the industry average benchmark while the unoptimised Route $C_{one\text{-}pot}$ performed worse than average. It should be noted, however, that the iGAL™ methodology does not determine which material category makes the greatest mass contribution to waste generated nor which contributes most to synthesis cost. Both of these are important considerations when determining and comparing green and sustainable drug manufacturing processes.

Although the iGAL™ metric was designed to assess complete API structures we believe that its use in assessing the synthesis of the bis-THF alcohol is justified as it is the most

Table 5 iGAL™ RPG matrix for green API manufacturing at various development stages[28]

			Minimum relative process greenness (RPG) rating		
Percentile	Code	Rating	Early development	Late development	Commercial
90%		Excellent	66%	146%	222%
70%		Good	48%	103%	168%
40%		Average	29%	59%	113%
		Below average			
RPG		**Industrial average**	**35%**	**73%**	**131%**

Table 6 Green KPPIs and RPGs of synthetic routes to bis-THF alcohol

	Synthetic Routes to bis-THF alcohol				
Indicator	$A_{step\text{-}by\text{-}step}$	$B_{one\text{-}pot}$	$B_{step\text{-}by\text{-}step}$	$C_{step\text{-}by\text{-}step}$	$C_{one\text{-}pot}$
E-Factor	15	90	127	128	288
Complexity	4	4	4	2	2
Total nr. steps	6	5	5	5	5
Process ideality (%)	67	80	80	40	40
RPG (%)	294	50	35	36	16
Performance *vs.* early Dev benchmark	8.33 times less wasteful	1.43 times less wasteful	1.01 time less wasteful	1.02 times less wasteful	2.14 times more wasteful
RPG *vs.* early Dev. (35%)	Top 10%	Top 30%	Top 60%	Bottom 60%	Bottom 40%
Performance percentile	Excellent	Good	Average	Average	<Average
Project status colour code					

complex and costly intermediate in the synthesis of ARVs such as darunavir (DRV).[4]

2.4 Solvent selection

2.4.1 Solvent selection guides. Solvents are used in both the reaction steps and downstream processing of API synthesis. They account for 80–90% of the total mass of non-aqueous material used, the majority of waste formed and 75–80% of the environmental life cycle impacts in drug manufacture.[32,33] Hence, the solvent intensity (SI), *i.e.* the total mass of solvents used per kg product, is an important green metric. Notwithstanding the considerable progress that has been made regarding the use of greener solvents in industrial organic synthesis there is still a certain reluctance to adopt greener alternatives, mainly owing to inconsistencies in purity and cost and difficulties in substantiating many greenness claims.[34]

Various drug companies have developed in-house solvent selection guides (SSGs) to stimulate replacement of environmentally undesirable solvents such as chlorinated hydrocarbons. Some of these are publicly available and are in reasonable agreement, with minor differences being attributable to varying company cultures. The first GSK SSG was published in 1999[35] and was later expanded to incorporate Life Cycle Assessment (LCA).[29,36] Pfizer was the first to use traffic light inspired colour coding – green, amber and red – to signify 'preferred', 'usable' and 'undesirable',[37] and Sanofi used a similar scoring system.[38]

The GSK guide was further refined and expanded from 47 to 110 and 154 solvents in 2011[39] and 2016,[40] respectively. Solvents are assigned a score of 1–10 in four sustainability categories – waste disposal, environmental impact, health and safety (EHS) – which in turn consist of multiple sub-categories. For example, waste consists of incineration, recycling, biotreatment and volatile organic chemical (VOC) emissions. A composite score that is the geometric mean of the four scores –<3.5 is red, 3.5–<7.5 is amber and >7.5 is green – is assigned to each solvent. The ACS Green Chemistry Institute's Pharmaceutical Round Table Consortium (ACS-GCPR) and the European CHEM21 collaborative research project adopted the concept of basing solvent evaluations on EHS statements. The latter consortium divides 51 solvents into four categories – recommended, problematic, hazardous and highly hazardous – and, in contrast with the GSK methodology, the lower the score the greener the solvent.[41]

We have followed the GSK methodology that is a freely available web-based tool. The equations for calculating the scores in the four categories and the composite score are shown in eqn (1)–(5).

$$\text{Waste} = \sqrt[4]{\text{incineration} \times \text{recycling} \times \text{Biotreatment} \times \text{VOC emission}} \quad (1)$$

$$\text{Environmental impact} = \sqrt{\text{air impact} \times \text{aqueous impact}} \quad (2)$$

$$\text{Health} = \sqrt{\text{exposure potential} \times \text{health hazard}} \quad (3)$$

$$\text{Safety} = \sqrt{\text{flammability and explosion potential} \times \text{reactivity and stability}} \quad (4)$$

$$\text{Composite} = \sqrt[4]{\text{waste} \times \text{environmental impact} \times \text{health} \times \text{safety}}. \quad (5)$$

In Fig. 3 a variety of common solvents are divided into structural classes, *e.g.* alcohols, esters, *etc.*, and ranked according to their sustainability in order to facilitate selection of greener and more sustainable solvents.

2.4.2 Solvent selection assessment. It is evident from Fig. 4 that excessive usage of organic solvents is an environmental issue with all of the routes to the bis-THF alcohol, particularly in the B routes where these solvents amount to 83 and 93% of the total mass of raw materials (see also Table 7). In the A and C routes both organic solvents and water contribute significantly to the total.

The solvent intensities (kgs solvent per kg product) for each synthetic pathway are shown in Table 7. Notably, $B_{\text{step-by-step}}$ and both C routes have enormous SIs and one-pot processes are generally less solvent and energy intensive than the corresponding step by step procedures, indicating the importance of process optimisation. Thus, use of route $B_{\text{one-pot}}$ results in a 57.70% reduction in SI compared with route $B_{\text{step-by-step}}$. In

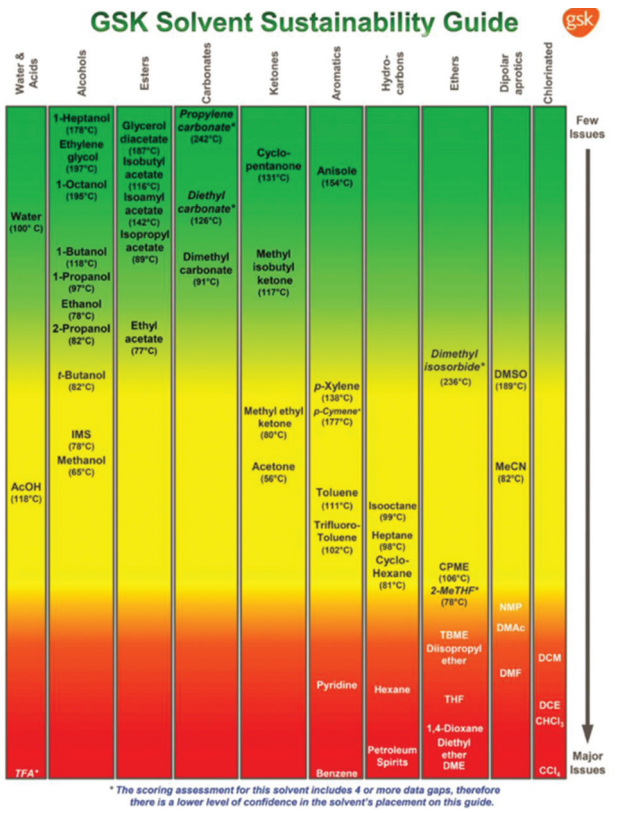


Fig. 3 GSK solvent sustainability guide.

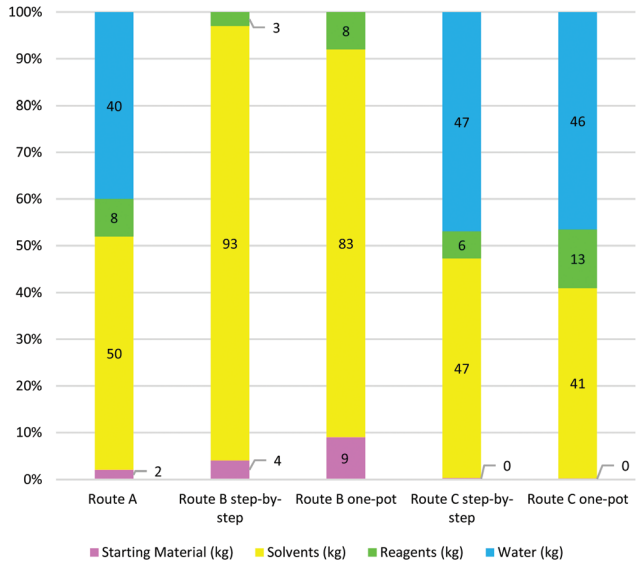


Fig. 4 Materials used in synthetic pathways to bis-THF alcohol.

contrast, route $C_{step\text{-}by\text{-}step}$ used less solvent than the one-pot alternative, which is attributed to the reaction conditions not being optimised in the latter process.

In addition to being major contributors to waste, solvents represent a significant cost item (see Table 7) and potential health hazard in industrial organic syntheses. We adopted the GSK solvent guide, which employs a traffic light inspired colour code, based on multiple sustainability factors, for assessing the relative greenness of solvents used in each synthetic pathways.

Table 8 illustrates the solvent masses and profiles per synthetic pathway, as classified according to the GSK solvent guide. The boiling point is shown owing to its significant role in determining the solvent's colour profile. The quantity of each solvent is illustrated underneath the boiling (or melting) point. The total number of solvents used for the entire synthetic route (including ASM synthesis where relevant) are provided in the last row of the table. Since water was assigned its own material category (in calculating *E*-factors) and has negligible environmental impact, it was eliminated from Table 8 and the solvent analysis.

Two important solvent properties are flammability and CMR (carcinogenicity, mutagenicity and reprotoxicity) status. Orange to red colour rankings and high penalty points are assigned to solvents with boiling points lower than 80 °C. For example, ethyl acetate (EtOAc) (b.p. 77 °C) scores lower than isopropyl acetate (iPrOAc) (b.p. 89 °C) but this difference is minimal compared with the enormous problems associated with diethyl ether (Et_2O, b.p. 35 °C).

Route $A_{step\text{-}by\text{-}step}$ has an SI of 50 and the main solvents used are iPrOAc and toluene (PhMe) with minor amounts of 2-propanol, methanol (MeOH), acetic acid, tetrahydrofuran (THF) and polyethylene glycol (PEG_{400}). Unfortunately, this route also uses 3 kg of "highly hazardous" Et_2O per kg product which essentially disqualifies it with regard to use on an industrial scale. Alternatives for Et_2O as an extraction solvent, with fewer environmental and health hazards, include Me-THF, ethyl *tert*-butyl ether (ETBE), CPME and iPrOAc.

The SI of route $B_{step\text{-}by\text{-}step}$ is 727 and the cost contribution of solvents is 81%. An advantage of the step-by-step route is that the same solvent, MTBE, is used in three successive steps

Table 7 Solvent intensity and cost contribution of synthetic routes

Synthesis route	cE-factor (kg kg^{-1})	SI (kg solvent per kg product)	Contribution of solvents to total material mass (%)	Contribution of solvents to total material cost (%)
A	101	50	50%	39
$B_{step\text{-}by\text{-}step}$	784	727	93%	81
$B_{one\text{-}pot}$	371	307	83%	30
$C_{step\text{-}by\text{-}step}$	1174	548	47%	41
$C_{one\text{-}pot}$	1713	697	41%	39

Table 8 Solvent masses and profiles per synthetic pathway

Route A	Route B step-by-step/one-pot	Route C step-by-step/one-pot
Isopropyl acetate (iPrOAc) (89 °C) 26 kg	Ethyl acetate (EtOAc) (77 °C) 115 kg/115 kg	Ethyl acetate (EtOAc) (77 °C) 24 kg/25 kg
Di-ethyl ether (Et_2O) (35 °C) 3 kg	Methanol (MeOH) (65 °C) 103 kg/103 kg	Toluene (PhMe) (111 °C) 255 kg/242 kg
2-Propanol (82 °C) 5.19 kg	Ethyl acetate (EtOAc) (77 °C) 62 kg/23 kg	Cyclopentyl methyl ether (CPME) (106 °C) 34 kg/70 kg
Polyethylene glycol (PEG_{400}) (mp 8 °C) 1.05 kg	Methyl *tert*-butyl ether (MTBE) (55 °C) 358 kg/33 kg	Methyl tetrahydrofuran (Me-THF) (78 °C) 32 kg/41 kg
Methanol (MeOH) (65 °C) 2.18 kg	Cyclohexane (c-hexane) (81 °C) 89 kg/33 kg	Tetrahydrofuran (THF) (65 °C) 28 kg/29 kg
Acetic acid (118 °C) 0.7 kg		Dichloromethane (DCM) (40 °C) 175 kg/289kg
Toluene (PhMe) (111 °C) 9.3 kg		
Tetrahydrofuran (THF) (65 °C) 2.25 kg		
8	**4**	**6**

which facilitates combining them into a one-pot process. However, large quantities of MTBE and relatively large amounts of mixtures of cyclohexane (c-hexane) and EtOAc were used, the latter in flash chromatographic purification of both intermediates and product. EtOAc (62 kg) was also used together with MeOH in the synthesis of the ASM. Much smaller amounts of MTBE were used in the one-pot procedure and flash chromatography was only used to purify the product.

In route C both the step-by-step and one-pot procedures use 6 different solvents. The SI of the step-by-step procedure is 548 with the main contributors being PhMe (255 kg) and dichloromethane (DCM; 175 kg) together with smaller amounts of EtOAc (24 kg), THF (28 kg), Me-THF (32 kg) and CPME (34 kg). DCM is a highly problematic (red colour) solvent with major environmental, health and safety (EHS) issues and constitutes a serious disadvantage with regard to greenness and sustainability. In the one-pot procedure even larger amounts of solvents are used (SI = 697) comprising mainly PhMe (242 kg) and DCM (289 kg). Dimethylformamide (DMF), a suspect reprotoxic agent, was used, albeit in catalytic quantities (2 drops). A merit of both route C procedures is that they use bio-based ethers (CPME and Me-THF) that have lower water solubility and less hazardous properties.

In short, solvents play an important role in determining the greenness and sustainability of organic syntheses based on their major contributions to *E*-factors, overall process costs and environmental hazards. Based on our analysis, despite its high SI, route $B_{one\text{-}pot}$ is the greenest process from the point of view of solvent use. It is also worth noting, in the context of replacement of undesirable solvents, that it is generally speaking easier to replace solvents used for extraction purposes than those used as a reaction medium.

2.5 Green Motion

2.5.1 Green Motion methodology. Green Motion™ is "an eco-conscious web-based tool[42] for optimum products" developed by the flavour and fragrance manufacturer, MANE, for assessing the greenness and sustainability of their products and processes.[22] In green motion the twelve principles of green chemistry are consolidated to seven fundamental concepts: raw material, solvent selection, hazard and toxicity of reagents, reaction efficiency, process efficiency, hazard and toxicity of final product and waste generation. Each process is assessed by assigning penalty points on the basis of the seven criteria which have been translated into a questionnaire requiring simple yes/no answers, pictograms, numerical values or a selection of multiple choice options. Deduction of the penalty points from 100 affords a total score. Hence, the higher the score the more sustainable and the lower the environmental impact of the process or product.

1: *Raw materials*: Raw materials of natural origin and processes involving only natural materials or catalysts are rewarded.

2: *Solvent selection*: Solvents are classified into 5 categories based on health, safety and environmental impacts. The severest penalties are assigned to the carcinogenic, mutagenic and reprotoxic (CMR) solvents, and no penalty points to solvent-free processes.

3 and 6: *Hazard and toxicity of solvents, reagents and products*: Penalty points are assigned by applying the INERIS classification[43] to the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) pictograms.

4: *Reaction efficiency*: Includes the number of synthesis steps, reaction yield, catalysis, reaction selectivity (using protection and deprotection steps) as well as atom and carbon economy.

5: *Process efficiency*: Focuses on the most energy consuming and conserving operations in a process. For example, steam heating is assigned fewer penalty points than gas heating over the same operating time. Processes operating at ambient conditions in under 12 hours are assigned zero penalty points.

7: *Waste reduction*: The traditional *E*-factor metric is preferred over the process mass intensity (PMI) metric as it is additive and fits the Green Motion scoring method of zero penalty points being assigned to zero waste generation and both are "gate-to-gate" assessments.

The Green Motion concepts, criteria and penalty points are illustrated in Table 9. In our assessment we have used only concepts 3, 4, 5, 6 and 7 from Green Motion. Price and health and safety rather than natural origin are the important requirements for drug manufacture. In assessing the relative greenness of solvents used in each route, for consistency we used the GSK methodology to assign penalty points. Furthermore, The Green Motion™ tool focuses on processes at pilot scale rather than bench scale at which the bis-THF alcohol experimental procedures were assessed. The necessary adjustments made to the Green Motion™ methodology are explained in the ESI (ESI section 1, Table 1†).

2.5.2 Green Motion assessment. Green Motion™ is designed for assessing greenness of processes in the flavour and fragrance industry and certain criteria need to be adapted for API synthesis. For example, pharmaceutical companies are more concerned with the cost of the raw material and its EHS status rather than its natural or synthetic origin. Furthermore, the hazardous nature and toxicity of the final product is not considered when assessing APIs. Nevertheless, most criteria considered in Green Motion are equally important in API manufacture. Green Motion™ assigns a score between 0 and 100 for each category assessed. The closer to 100 the rating the more sustainable the process and lower the environmental impact.

2.5.2.1 Reaction category. Reactions with short reaction times, high yields, using (bio)catalysts, and a minimum number of solvents, without requiring protection and deprotection steps score well in the 'reaction' category. Reaction times and yields are shown in Table 10.

Both C routes have relatively low reaction times, high overall reaction yields and make use of potassium isocitrate, a non-hazardous starting material that is not an ASM, affording high 'reaction' scores. The main drawback of Route C procedures is the use of excessive amounts of six solvents, including DCM, together with stoichiometric amounts of reagents, reducing reaction scores.

Table 9 Green Motion™ concepts, criteria and penalty points.[40]

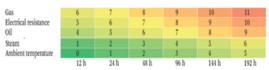
No.	*Concept*	Criteria	Unit [penalty points]
1	*Raw material*	Origin of material Natural process	Category: Synthetic [10], Hemi-synthesis [5], Natural [0] **Yes/No**
2	*Solvents*	Solvent class	**Category:** CMR [10], Petrochemical [5], Supercritical fluid [2], Renewable [2], Water [2], No solvent [0]
3	*Reagent/solvent hazard & toxicity*	GHS pictogram	**Pictogram:** 
4	*Reaction*	Yield No. synthesis steps No. solvents Carbon economy No. protection/deprotection steps Overall process time	**Percentage value** **Numerical value** **Numerical value** **Percentage value** **Numerical value** **Numerical value (hours)**
5	*Process*	Heating Cooling	**Category:** **Category:** 
		Reaction under pressure Distillation	**Yes/No** **Category:** Distillation under vacuum, distillation at atmospheric pressure, no distillation [0]
		Other process	**Category:** Hazardous processes (nitrification, chlorination *etc.*), energy-intensive process (liquid–liquid extraction, chromatography and so forth), None [0]
6	*Product hazard & toxicity*	GHS pictogram	**Pictogram:** 
7	*Waste*	*E*-Factor	**Numerical value (kg kg^{-1})**

Table 10 Overall reaction yield and reaction time per route

Synthesis route	Overall yield (%)	Reaction time (hours)
Route A	51	69
Route $B_{step\text{-}by\text{-}step}$	24	96
Route $B_{one\text{-}pot}$	23	174
Route $C_{step\text{-}by\text{-}step}$	53	51
Route $C_{one\text{-}pot}$	41	46

Both B routes have the disadvantage of low overall reaction yield, lengthy reaction time and addition of the Cbz protection group to the ASM, affording low 'reaction' scores. Conversely, the use of 100% atom efficient catalytic hydrogenation and three relatively benign solvents (EtOAc, MTBE and c-hexane) in the B routes contributes to the 'reaction' score. The higher 'reaction' score of the one-pot procedure is attributed to the large reduction in solvent quantity. Additionally, the efficient one-pot procedure and optimised reaction conditions contributed to route $B_{one\text{-}pot}$ having a better reaction score of 20.

In contrast, route $A_{step\text{-}by\text{-}step}$ uses eight different solvents, including highly hazardous Et_2O. Route A has a relatively good reaction score owing to its relatively high overall reaction yield of 51%.

2.5.2.2 Process category. For the process category various laboratory scale techniques had to be translated to process concepts from Green Motion as shown in ESI Table 1 in the ESI.† Both B routes operate at ambient temperatures and pressures thus receiving no penalty points for heating, cooling, or reaction steps under pressure. Despite receiving penalty points for using energy intensive flash column chromatography and rotary evaporation, both B routes returned the highest 'process' score of 55.

In contrast, route A makes use of cooling to 0 °C, reactions under pressure, liquid–liquid extraction and distillation under reduced pressure, affording an average 'process' score of 40. Similarly, both C routes involve heating and cooling (to −5 °C and −8 °C), reactions take place under pressure, rotary evaporation and atmospheric distillations are performed, and other energy intensive methods including crystallization and continuous extraction are used. Consequently, both C routes afforded the lowest 'process' scores of 30.

2.5.2.3 Waste category. For the 'waste' category we used the sE-Factor to measure waste generation as scores of zero were returned for all synthetic pathways when using *E*-factor or cE-Factor values. In contrast, use of the sE-factor returned a numerical score for all routes except for route $C_{step\text{-}by\text{-}step}$.

Route A generated the least waste and had the best 'waste' score of 80. Route $B_{step\text{-}by\text{-}step}$, route $B_{one\text{-}pot}$ and route

$C_{step\text{-}by\text{-}step}$ all returned 'waste' scores of 53 since they all had close sE-Factor values that fall within a certain Green Motion score range. For both B routes, the ASM accounted for more than 75% of the low 'waste' score, owing to its significant sE-factor contribution. If the ASM is disregarded favourable 'waste' scores of 85 are returned for both B routes owing to their use of photochemical reactions, which require a limited number and quantity of chemical reagents to perform successfully.

The lowest 'waste' score of 0 was returned for Route $C_{one\text{-}pot}$, attributed to the use of higher material quantities, *e.g.* an additional reagent (oxalyl chloride) as well as an increase in DMF catalyst and DCM and CPME solvent quantities, resulting in more than double the amount of waste compared with the route $C_{step\text{-}by\text{-}step}$ procedure. Additionally, the one-pot procedure did not replace the entire route $C_{step\text{-}by\text{-}step}$ synthetic pathway but rather a part thereof (Scheme 7) and reaction conditions were not optimised. Mainly owing to the high sE-Factor, route $C_{one\text{-}pot}$ was assigned the maximum penalty points affording a 'waste' score of 0.

2.5.2.4 Total score. A comparison of routes A, B and C was performed in accordance with the Green Motion™ concept – reaction, process and waste – and the total scores are shown in Table 11. The original output graphs from the Green Motion™ tool are illustrated in the ESI (ESI section 1.1, Fig. 1–5†). The 'hazards and toxicity of solvents and reagents' category is not included as it returned a score of zero for all synthetic pathways which we attribute to all routes being multi-step reactions, requiring a large variety of chemical materials each with their own respective GHS pictograms, accumulating the maximum number of penalty points, returning a score of zero.

Route A was overall the best performing route with the highest 'total' score of 19. This was mainly attributed to route A having the best 'waste' score, being a minimum of 27 points higher than the other routes.

Route $B_{one\ pot}$ and $B_{step\text{-}by\text{-}step}$ returned 'total' scores of 16 and 14 respectively. The major drawback of the B routes was their extremely low overall yield and high ASM sE-factor. Nonetheless, both B routes received good 'total' scores for their unique combination of green chemistry techniques including bio-catalysis, ambient reaction temperatures and pressures and renewable raw materials.

Finally, the lower 'total' scores of route $C_{step\ by\ step}$ and $C_{one\text{-}pot}$ of 11 and 4 respectively, are attributed to a variety of energy intensive process operations, stoichiometric amounts of reagents used and the large number and amounts of materials used, resulting in high waste generation.

Table 11 Green Motion™ concept ratings and overall score per synthesis route

Category	Route A	Route $B_{step\text{–}by\text{–}step}$	Route $B_{one\text{-}pot}$	Route $C_{step\text{–}by\text{–}step}$	Route $C_{one\text{-}pot}$
Reaction	27	15	20	32	35
Process	40	55	55	30	30
Waste	80	53	53	0	53
Total Green Motion score	**19**	**14**	**16**	**11**	**4**

2.6. The radial polygon

A radial polygon (in our case an octagon) provides a visual overview of multivariate performance indicators (Fig. 5).[44] Each vertex represents an ideal metric value and the centre of the octagon the least ideal value. The ideal green synthesis corresponds to a regular polygon. The less "green" the synthesis, the greater the distortion towards the centre[45] thus identifying weak points in a synthesis and providing guidance for optimisation.

Fig. 5 shows radial octagons for routes A, B and C. The route $B_{one\text{-}pot}$ procedure has the least distorted octagon, ranking highest in cost, AE, purity (% ee) and wastewater intensity (WWI) (total mass of process water per kg product). Route $B_{step\text{-}by\text{-}step}$ performed equally well to route $B_{one\text{-}pot}$ in terms of AE, purity (%ee) and WWI. The weakness of both routes is their low overall yields at 23% and 24%, respectively, a reflection of the fact that route B has a late stage kinetic resolution. The 'golden rule' of chirotechnology is that the resolution step be as early as possible in the synthesis.[23,46] A late resolution step has a negative effect on all waste materials including solvents, affording high *E*-Factors and SIs. Combination of an early resolution with a significant reduction in solvent would give B routes an ideal radial octagon.

Route A performed the best in *E*-factor, SI and Green Motion™ owing to the low material mass required. Further, both C routes afford the most distorted octagons but, on the other hand, they do start from an enantiomerically pure substrate, resulting in a favourable overall yield, with route $C_{step\text{-}by\text{-}step}$ having the best overall yield at 53%. The data used in plotting the octagons along with each synthetic pathway area coverage percentage are shown in the ESI (ESI section 2, Table 2†).

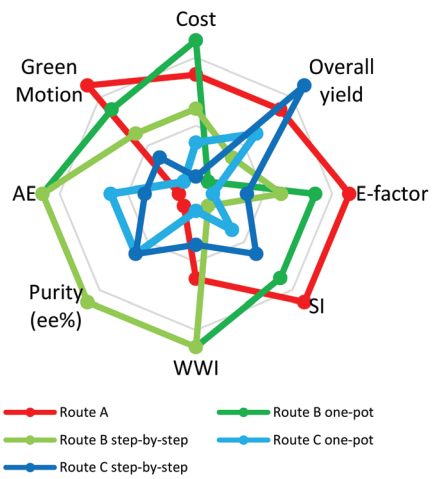


Fig. 5 Radial octagon of green performance indicators.

In summary, route $B_{one\text{-}pot}$ showed the greatest correlation with the ideal process, with 82.5% polygon area coverage, followed by route A (70%), route $B_{step\text{-}by\text{-}step}$ (67.50%), route $C_{step\text{-}by\text{-}step}$ (50%) and route $C_{one\text{-}pot}$ (40%). It is important to note that the percentages are merely representative of the ranking system used in generating the radial octagons.

2.7 Comparing the greenness and sustainability of routes to the THF-alcohol

As shown in Table 12, route B performed best in most of the green chemistry principles and was the greenest synthetic pathway to the bis-THF alcohol (ESI, section 3, Tables 3 and 4†).

Multiple factors contribute to process greenness and sustainability and defining the most eco-efficient process. Regarding resource efficiency and waste generation, it is important to include waste associated with synthesizing an ASM. Disregarding this would have meant that 40%, 51% and 74% of the waste associated with routes A, $B_{step\text{-}by\text{-}step}$ and $B_{one\text{-}pot}$ procedures, respectively, would have been neglected.

Route A had 'excellent' mass-efficiency with a low *E*-factor of 15 followed by route $B_{one\text{-}pot}$ with a 'good' mass-efficiency and moderate *E*-factor of 90 and route $C_{step\text{-}by\text{-}step}$ with an 'average' mass-efficiency and a high *E*-factor of 128.

Solvents were the greatest contributors to waste (see Table 7) and constitute the greatest environmental concern in all three routes. Solvent intensities ranged from 50 for route A to 697 for route $C_{one\text{-}pot}$. The total percentage of solvents in total material mass was 83% in route $B_{one\text{-}pot}$ and 93% in route $B_{step\text{-}by\text{-}step}$. However, it is not just a question of the amount of solvent but, perhaps more importantly, their EHS status. For example, 95% (>500 kgs per kg product) of the mass of solvents used in route C consists of hazardous and problematic solvents with significant health and safety issues. In contrast, 80% of the total solvent mass used in route $B_{one\text{-}pot}$ consists of EtOAc and MeOH, characterised as green solvents in the GSK guide. Solvents also constitute a significant contribution to total process costs and route $B_{one\text{-}pot}$ had the lowest solvent costs in manufacturing of 1 kg bis-THF alcohol. We conclude that solvent utilisation offers the greatest potential in reducing the environmental impact of bis-THF alcohol synthesis both qualitatively and quantitatively.

Table 12 Checklist of 12 principles of green chemistry for routes to THF-alcohol

The 12 Principles of Green Chemistry	Route A	Route B	Route C
1. Waste prevention	Yes	Yes	No
2. Atom economy	Yes	Yes	No
3. Less hazardous synthesis	No	Yes	No
4. Designing for safer products	N/A	N/A	N/A
5. Safer Solvents and Auxiliaries	No	Yes	No
6. Design for energy efficiency	No	Yes	No
7. Use of renewable feedstocks	No	Yes	Yes
8. Reduce derivatives	No	Yes	Yes
9. Catalysis	Yes	Yes	Yes
10. Design for degradation	N/A	N/A	N/A
11. Real-time analysis	N/A	N/A	N/A
12. Inherently safer chemistry	No	Yes	No

In the Green Motion™ study favourable scores were returned for reactions with short reaction times, high yields, using (bio)catalysts and low amounts of solvents under ambient conditions that generate less waste (low *E*-factors). Route $B_{one\text{-}pot}$, with a unique combination of green chemistry techniques including a one-pot procedure, bio-catalysis, ambient reaction temperatures and pressures, relatively green solvents and renewable raw materials originating from woody bio-mass, achieved a relatively high score of 16. In contrast, route $C_{one\text{-}pot}$ used a variety of energy intensive unit operations (atmospheric distillation, crystallization, continuous extraction, reactions under reduced pressure, heating and cooling) in combination with a variety of stoichiometric reagents, generating the most waste. This translated to the lowest total Green Motion score of 4 consistent with $C_{one\text{-}pot}$ being the least sustainable route.

Using a radial polygon visualisation tool to combine all the greenness variables assessed clearly showed that the route $B_{one\text{-}pot}$ procedure covered the highest radial polygon area, at 82.50%, confirming that it is the greenest route.

2.8 Summary and conclusions

In conclusion, the route $B_{one\text{-}pot}$ procedure was found to be the most efficient, scalable, inexpensive, environmentally friendly, and least health hazardous pathway for assembling the bis-THF alcohol. It adhered to several principles of green chemistry through the use of renewable, CO_2 neutral, wood based materials (xylochemistry), environmentally acceptable solvents (for waste minimisation and safety), photochemical reactions and bio-catalytic reactions under ambient operating conditions. It was overall the most sustainable route, scoring the best over multiple assessment criteria and demonstrating the triple win of green chemistry:

a. *Cost effectiveness* reflected in 77% and 43% cost reduction compared to routes $C_{step\text{-}by\text{-}step}$ and route A respectively,

b. *Environmental friendliness* with a reduced waste burden reflected in an acceptable *E*-factor of 90, below the API GCIPR benchmark of 130,

c. *Safety* as a result of 80% of the total solvents used having a green colour ranking and the use of less hazardous reagents and operating conditions.

Route $B_{one\text{-}pot}$ is the method of choice but there is room for improvement. It uses relatively large amounts of solvents which can probably be further reduced by avoiding flash chromatographic product purification. From a purely chirotechnology viewpoint it is the worst process as it involves a late resolution step whereas routes A and C involve a catalytic asymmetric synthesis and a chiral pool starting material, respectively. This is directly reflected in the overall lower yield (24%) of route B which is less than half that of routes A (51%) and C (53%).

One general conclusion is that methodologies that were developed in industry may need to be modified to enable meaningful comparisons between laboratory-scale recipes that often generate off-scale readings, particularly with regard to

amounts of solvents used. Finally, our analysis clearly shows the importance of using a number of different metrics to evaluate the relative greenness and sustainability of processes as some routes perform well when evaluated with one metric but poorly with other criteria.

2.9 Take home message

For those of us who are training the next generation of chemists: the best way to instil an awareness of green chemistry principles is to make sure they are applied in our research laboratories from day one. Such habits established at the beginning of a new chemist's career will be carried through to every future application. Students should be taught to always question the choice of reaction solvent rather than automatically use what has been previously reported in the literature. We should be deliberate about using green solvents for work-up – the more the precedent is set in the literature, the more others will follow. Moreover, we should strive to eliminate the use of "red" solvents from the research laboratory altogether. Catalytic reactions should be used, where feasible, to optimise atom economy and minimise waste formation.

With a view to industrial applications, *e.g.* in pharmaceuticals manufacture, raw materials should be not more than one step removed from bulk, commodity chemicals. Multi-step reactions should be performed as one-pot processes, thus avoiding the isolation of intermediates, and the solvent should be optimised for the overall process rather than for individual steps. The use of reaction steps involving high pressures or heating and, especially cooling, as well as work-up techniques, such as chromatography, requiring large amounts of solvents and lengthy throughput times, should be avoided. Solvents and catalysts should be recycled to minimise waste production and optimise cost effectiveness. Finally, a take home message for industrial chemists: less waste translates to lower costs of goods. In the prophetic words of the eminent 19th century organic chemist, A. W. von Hofmann (1818–1892):

"*In an ideal chemical factory there is, strictly speaking, no waste but only products. The better a real factory makes use of its waste, the closer it gets to its ideal, the bigger is the profit*".

Conflicts of interest

There are no conflicts to declare.

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