Supplementary Table S1. Assembled synthetic pathways for production of glucaric, adipic, muconic, acrylic and levulinic acids in *E. coli* and/or in *S. cerevisiae* from sugars. The table shows the compiled information about the combinations of enzymes that had been reported to be utilized in synthetic pathways aiming the production of the referred CAs. Note that endogenous enzymes of the host, as well as additional metabolic engineering strategies that could have been used to improve flux through the synthetic pathways (such as the co-expression of adjuvant enzymes) are not described in this table. Each enzymatic step is numbered so that it matches the graphical representations of the pathways in Figs. 2, 4, 5 and 6,. The combination of enzymes suggested by in silico metabolic retrobiosynthesis, albeit not validated in vivo, are highlighted in light grey. For those steps with no specific enzymes assigned, the E.C. number or the E.C. sub(sub)class are indicated. PCA – Protocatechuate;

Glucaric acid					
	Myo-inositol synthase (1)	**Myo-inositol oxygenase (2)**	**Glucoronic acid dehydrogenase (3)**	**Titer**	**Ref**
E. coli	*S. cerevisiae* Ino1	*Mus musculus* MIOX	*Pseudomonas syringae* Udh	1.13 g/L	[1]
	Scaffolded - *S. cerevisiae* Ino1	Scaffolded – *M. musculus* MIOX	Scaffolded - *P. syringae* Udh	2.5 g/L	[2]
S. cerevisiae	Endogenous Ino1	*M. musculus* MIOX	*P. syringae* Udh	1.6 g/L	[3]
	Endogenous Ino1	*Arabidopsis thaliana* MIOX	*P. syringae* Udh	0.94 g/L	[3]
	Endogenous Ino1	Stabilized *Arabidopsis thaliana* MIOX	*P. syringae* Udh	6 g/L	[4]
	Endogenous Ino1	*Talaromyces marneffei* MIOX	*P. syringae* Udh	1.76 g/L	[5]
P. pastoris	Endogenous Ino1	*M. musculus* MIOX	*P. putida* Udh	6.61 g/L	[6]

Muconic acid					
From dihydroshikimate					
	DHS hydratase (1)	**Protocatechuate decarboxylase (2)**	**Catechol 1,2-dioxygenase (3)**	**Titer**	**Ref**
E. coli	*K. pneumoniae* aroZ	*K. pneumoniae* aroY	*Acinetobacter calcoaceticus* CatA	38.6 g/L	[7]
	Bacillus thurigiensis AroZ	*K. pneumoniae* aroY	*P. putida* CatA	1.59 g/L	[8]
	C. glutamicum QsuB	*K. pneumoniae* aroY	*P. putida* CatA	1.58 g/L	[9]

		Bacillus thurigiensis AroZ	*K. pneumoniae* aroY	*Acinetobacter calcoaceticus* CatA		1.79 mg/L	[10]
		Fused *E. coli* AroD- *B. thurigiensis* AroZ	*K. pneumoniae* aroY	*Acinetobacter calcoaceticus* CatA		1.34 g/L	[8]
		K. pneumoniae aroZ	*K. pneumoniae* aroY	Engieered *Acinetobacetor sp.* CatA		1.53 g/L	[11]
S. cerevisiae		*Podospora anserina* aroZ	*K. pneumoniae* aroY	*Acinetobacter radioresistens* CatA		1.56 mg/L	[12]
		P. anserina aroZ	*K. pneumoniae* aroY	*Candida albicans* HQD2		~20 mg/L	[13]
		P. anserina aroZ	*Enterobacter cloacae* aroY	*C. albicans* HQD2		141 mg/L	[13]
		Neurospora crassa AroZ	*Commensalibacter intestini* AroY	*Cupriavidus necator* CatA		65 mg/L (from xylose)	[14]
		P. anserina aroZ	*Talaromyces atroroseus* GDC1	*A. radioresistens* CatA		1.24 g/L	[15]
P. putida		*Bacillus cereus* AsbF	*Enterobacter cloacae* aroY	Endogenous CatA		4.92 g/L	[16]
C. glutamicum		Endogenous qsuB	*K. pneumoniae* aroY	Endogenous CatA		4.5 g/L	[17]
From chorismate							
from 4-hydroxybenzoic acid	E. coli	**Chorismate pyruvate lyase (4)**	**4-HBA hydrolyase (5)**	**Protocatechuate decarboxylase (2)**	**Catechol 1,2-dioxygenase (3)**		
		Endogenous UbiC	PobA *P. Putida*	*K. pneumoniae* aroY	*P. putida* CatA	170 mg/L	[18]
		Endogenous UbiC	PobA *P. Aeruginosa*	*K. pneumoniae* aroY	*P. putida* CatA	819 mg/L	[9]
		Chorismate pyruvate lyase (4) Endogenous UbiC	**4-HBA decarboxylase (6)** *K. pneumoniae* kpdBCD	**Phenol hydrolase (7)** *Pseudomonas steutzeri* PhKLMOP	**Catechol 1,2-dioxygenase (3)** *P. putida* CatA	230 mg/L	[9]
from 2,3-dihydroxybenzoate	*E. coli*	**Isochorismate synthase (8)** Endogenous EntC and EntB	**2,3-dihydro-2,3-DHB dehydrogenase (9)** Endogenous EntA	**2,3-DHB decarboxylase (10)** *P. pneumonia* EntX	**Catechol 1,2-dioxygenase (3)** *P. putida* CatA	480 mg/L	[19]
from salicylate	*E. coli*	**Isochorismate Synthase (8)**	**Isochorismate pyruvate lyase (11)**	**Salicylate monoxygenase (12)**	**Catechol 1,2-dioxygenase (3)**		

		Endogenous EntC	*P. Fluorescens PchB*	*P. putida* nahG	*P. putida* CatA		1.5 g/L	[20]
		Fused *E. coli* AroC- E. coli *MenF*	*P. Aeruginosa* PchB	*P. putida* nahG	*P. putida* CatA		4.45 g/L	[8]
		Isochorismate synthase (8) Endogenous EntC	**Isochorismate pyruvate lyase (11)** *P. Aeruginosa* PchB	**Salicylate decarboxylase (13)** *T. Monoliforme* Sdc	**Phenol hydrolase (7)** *Pseudomonas steutzeri* PhKLMOP	**Catechol 1,2-dioxygenase (3)** *P. putida* CatA	484 mg/L	[9]
		From anthranilate						
	E. coli	**Anthranilate 1,2-dioxygenase (14)** *P. Aeruginosa* AntABC	**Catechol 1,2-dioxygenase (3)** *P. putida* CatA				389.96 mg/L	[19]
		From tyrosine						
	E. coli	**Tyrosine phenol lyase (15)** *Citrobacter brakii* tutA	**Phenol hydrolyase (7)** *Pseudomonas steutzeri* PhKLMOP	**Catechol 1,2-dioxygenase (3)** *P. putida* CatA			186 mg/L	[9]
Adipic acid								
		From 3-oxoadipyl-coA						
		3-Oxoadipyl-CoA thiolase (1)	**3- Hydroxyadipyl-CoA dehydrogenase (2)**	**2,3-Dehydroadipyl-CoA hydratase (3)**	**Adipyl-CoA dehydrogenase (4)**	**Adipyl-CoA thioesterase (5)**	**Titer**	**Ref**
Reverse adipate route	*E. coli*	Endogenous PaaJ	Endogenous PaaH	Endogenous PaaF	*C. acetobutylicum* Bcd	*M. musculus* Acot8	12 µg/L	[21]
		Endogenous PaaJ	Endogenous PaaH	Endogenous PaaF	*Acinetobacter bayly* DcaA	*A. Baylyi* TesB	6 mg/L	[22]
		Endogenous PaaJ	*C. acetobutylicum* Hbd	*C. acetobutylicum* Crt	*Euglena gracilis* Ter	*C. acetobutylicum* Ptb and Buk1 (phosphate transfer)	31 µg/L	[23]
		T. fusca Tfu_0875	*T. fusca* Tfu_2399	*T. fusca* Tfu_0067	*T. fusca* Tfu_1647	*T. fusca* Tfu_2577 and 2576	0.3 g/L	[24]
		T. fusca Tfu_0875	*T. fusca* Tfu_2399	*T. fusca* Tfu_0067	Engineered *T. fusca* Tfu_1647	*T. fusca* Tfu_2577 and 2576	0.23 g/L	[25]
		Endogenous PaaJ	Endogenous PaaH	Endogenous PaaF	*Treponema denticola* TdTer	*M. musculus* Acot8	170 mg/L	[26]
	S. cerevisiae	*T. fusca* Tfu_0875	*T. fusca* Tfu_2399	*T. fusca* Tfu_0067	*T. fusca* Tfu_1647	*T. fusca* Tfu_2577 and 2576	3.83 mg/L	[27]

	-	*3-Oxoadipyl-CoA Thiolase* 2.3.1.174 (validated)	**3-oxoadipyl-CoA transferase (6)** 2.8.3.6 (validated)	**3-oxoadipate dehydrogenase (7)** 1.1.1.172 (validated)	**3-Hydroxyadipate Dehydratase (8)** ?	**2-Enoate reductase (9)** ?	-	[28]
From PCA	*E. coli*	**PCA synthesis**. *P. putida* Fcs, Ech, Vdh, VanAb, PobA	**De-aromatization pathway** *P. putida* PcaGH, PcaB, PcaC,PcaD	**β-ketoadipic acid succinyl-CoA transferase** *P. putida* PcaIJ	**3-Oxo group reduction** *R. eutropha* PaaH1 and Ech and *T. denticola* TdTer	**CoA removal** *C. acetobutylicum* Ptb1 and Buk1	9.5 mg/L (from lignin)	[29]
Reverse β-oxidation followed by ω-reduction								
	E. coli	***3-ketoacyl-CoA thiolase (6)****Ralstonia eutropha* BktB	**Trans-enoyl-CoA Reductase (7)** *E. gracilis* Ter	**ω-Hydroxylase (8)** *P. putida* AlkBGT	**Alcohol Dehydrogenase (9)** *Acinetobacter spp* ChnD	**Aldehyde Dehydrogenase (10)** *Acinetobacter spp* ChnE	-	[30]
From 2-oxoadipic acid								
Through 2-Oxopimelic	*E. coli*	**2-oxoglutaric elongation (11)** AksA, AksD, AksE and AksF (*A. Vinelandii, & M. aeolicus Nankai and V. fluvialis*)		**2-Oxopimelic Decarboxylase (12)** *Lactococcus lactis* KdcA	**Adipic semialdehyde oxidation (13)** Unknown endogenous enzyme		0.3 g/L	[31]
Through 2-hydroxyadipic	-	**2-Hydroxyadipate dehydrogenase (14)** 1.1.1.-	**2-Hydroxyadipyl-CoA synthase (15)** 6.2.1.-	**2-Hydroxyadipyl-CoA (16)** 4.2.1.-	***Adipyl-CoA dehydrogenase (4)*** 1.3.1.44 (validated above)	***Adipyl-CoA thioesterase (5)*** 6.2.1.- (validated above)	-	[28]
From lysine	-	**Lysine transaminase (17)** 2.6.1.36 (validated)	**Allysine Oxidase (18)** 1.2.1.31 (validated)	**2-aminoadipic transaminase (29)** ?	**2-hexenedioic reductase (20)** E. coli NemA and S. pastorianus Oye1 (not validated)		-	[32]
From muconic acid								
	S. cerevisiae	**DHS Hydratase** *P. anserina* aroZ	**Protocatechuate Decarboxylase** *Enterobacter cloacae*	**Catechol 1,2-dioxygenase** *C. albicans* HQD2	**Enoate reductase** *Bacillus coagulans* MAR (MAR-BC)		2.6 mg/L	[33]

		aroY					
E. coli	***Isochorismate Synthase*** Endogenous EntC	***Isochorismate Pyruvate Lyase*** *P. Fluorescens PchB*	***Salicylate Monoxygenase*** *P. putida* nahG	***Catechol 1,2-dioxygenase*** *P. putida* CatA	***Enoate reductase*** *C. acetobutylicum ER*	12.4 mg/L	[34]
			From oxalyl-CoA				
-	**Methyltransferase** 2.1.1.197	**Condensation** 2.3.1.16/180	**Reductase, Dehydratase and Reductase** 1.1.1.100/36, 4.2.1.119 and 1.3.8/10/38/44	**Pymeloyl-ACP Methyl Esterase** 3.1.1.85		-	[35]
			From acetyl-CoA (Polyketide route)				
-	**Polyketide synthase** *Streptomyces spp.* PKS Bor (validated in vitro)						[36]
			Acrylic Acid				
			from glycerol				
E. coli	**Glycerol-3-P phosphatase** *S. cerevisiae* Gpp2	**Glycerol dehydratase** *K. pneumoniae* DhaB	**Aldehyde dehydrogenase** *C. necator* GabD4	**CoA transferase** *C. necator* YdiF	**CoA dehydratase** *A. flavithermus* Aflv_0566	0.12 g/L	[37]
			from 3-hydroxypropionate/4-hydroxybutyrate				
E. coli	**Malonyl-CoA reductase** *Metallosphaera sedula* Mcr	**Malonate semialdehyde Reductase** *M. sedula* Msr	**3-Hydroxypropionyl-CoA synthetase** *M. sedula* 3Hpcs	**3-Hydroypropionyl-CoA dehydratase** *M. sedula* 3Hpcd		13.28 mg/L	[38]
			from β-alanine				
E. coli	**Aspartate -1-Decarboxylase** *C. glutamicum* PanD	**β-alanine CoA transferase (Act)** *Clostridium propionicum* Act	**β-alanyl- CoA:ammonia lyase** *C. propionicum* Acl2	**Propionate CoA Transferase** *C. necator* YciA		237 mg/L	[39]
			Levulinic Acid				
			from 3-Oxoadipic acid				
	Succinyl-CoA transferase	**β-ketoadipyl-CoA thiolase (1)**	**3-Oxoadipyl-CoA transferase (2)**	**3-Oxoadipic acid decarboxylase (3)**			
E. coli	*Clostridium kluyveri* Cat1	Endogenous PaaJ	*P. putida* PcaIJ	Unknown endogenous		48 mg/L	[26]

					enzyme			
		C.kluyveri Cat1	Endogenous PaaJ	*P. putida* PcaIJ	*S. habrochaites* Mks1		71 mg/L	[26]
		C.kluyveri Cat1	Endogenous PaaJ	*P. putida* PcaIJ	*C. acetobutylicum* Adc		159 mg/L	[26]
		PCA synthesis (4) *P. putida* Fcs, Ech, Vdh, VanAb, PobA	**Dearomatization pathway (5)** *P. putida* PcaGH, PcaB, PcaC,PcaD	**3-Oxoadipic Acid decarboxylase (3)** *C. acetobutylicum* Adc			455 mg/L	[29]
	-	**3-DHS Dehydratase (6)** 4.2.1.118 (validated)	**PCA Decarboxylase, Catechol 1,2-Dioxygenase, Muconate cycloisomerase, muconolactone δ-isomerase and 3-oxoadipate enol-lactonase** 4.1.1.6, 1.3.11.1, 5.5.1.1., 5.3.3.4 and 3.1.1.24 (validated)			**3-Oxoadipic acid decarboxylase (3)** 4.1.1.112 (validated above)		[40]
		from pyruvic acid and acetaldehyde						
	-	**Aldolase (7)** 4.1.3.17 (validated)	**4-hydroxy-2-oxopentanoic acid oxidase (8)** ?	**2,4-Dioxovaleric dehydratase (8)** ?	**4-Oxo-2-Pentenoic reductase (8)** ?	**NADPH dehydrogenase (8)** 1.6.99.1 (validated)		[41]
		from D-ALA						
	-	**D-ALA transaminase (9)** 2.6.1.62/105		**Diaminovaleric ammonia lyase (10)** 4.3.1.15				[40]
	-	**Glutamate semialdehyde aminomutase (11)** 5.4.3.8 (requires engineering)		**Diaminovaleric ammonia lyase (10)** 4.3.1.15				[40]
		from lysine degradation						
		5-Amino valeric aminomutase (12) 5.4.3.3/5		**4-Aminovaleric transaminase (13)** 2.6.1.18				[40]
		Methacrylic Acid						
		from methacrylyl-CoA						
Through Isobutyryl-CoA	*E. coli*	**Isobutyryl-CoA synthase (1)** *P. chlorpraphis* AcsA	**Acyl-CoA oxidase (2)** *A. Thaliana* ACX4	**Hydroxybenzoyl-CoA thioesterase (3)** *Arthrobacter spp.* 4HBT			~ 250 μM	[42]
Through	-	**4-Hydroxyisobutyryl-CoA**	**3-Hydroxyisobutyryl-**	**Methacrylyl-CoA**				[43]

3-Hydroxyisobutyryl-CoA		**mutase (4)** 5.4.99.-	**CoA dehydratase (5)** 4.2.1.55/17	**transferase (3)** 6.2.1.13 (validated above)			
Through 2-Hydroxyisobutyryl-CoA	-	**Acetoacetyl-CoA thiolase (6)** 2.3.1.9 (validated)	**Acetoacetyl-CoA reductase (7)** 1.1.1.35 (validated)	**3-Hydroxyisobutyrate mutase (8)** 5.4.99.-	**2-Hydroxyisobutyryl-CoA dehydratase (9)** 4.2.1.54/167/157	**Methacrylyl-CoA transferase (3)** 6.2.1.13 (validated above)	[43]
from mesaconic acid							
	-	**Mesaconate Decarboxylase (10)** 4.1.1.6/77					
from 3-hydroxyisobutyric acid							
	-	**4-Hydroxyisobutyryl-CoA mutase (11)** 5.4.99.-		**3-Hydroxyisobutyryl-CoA hydrolase (12)** 3.1.2.4 (validated)		**3-Hydroxyisobutyrate dehydratase (13)** 1.1.1.291	[43]
	-	**Methylmalonyl-CoA reductase (14)** 1.2.1.-		**3-Hydroxyisobutyrate dehydrogenase (15)** 1.1.1.31 (validated)		**3-Hydroxyisobutyrate dehydratase (13)** 1.1.1.291	[43]
from 3-aminoIsobutyric acid							
	-	**Methylmalonyl-CoA Reductase (16)** 1.2.1.-		**3-Aminoisobutyrate Transaminase (17)** 2.6.1.22 (validated)		**3-Aminoisobutyrate ammonia lyase (18)** 4.3.1.1.	[43]

Supplementary Table S2: Described computational tools for assisted in silico pathway prospection. The table described the reaction rules used in the retrobiosynthesis search used by the tools, as well as the criteria used to rank the obtained candidate pathways. Information on the enzyme assignment performed is also indicated as well as the accompanying reference and the date of release of the tool.

Metabolic retrobiosynthesis tool	Reaction rules	Criteria used to rank pathways	Level of enzyme assignment	Comments	Ref	Year
UM-BBD	From literature on functional group transformations	Not performed by the tool	Identifies a specific enzyme	Applied to xenobiotic degradation; only allows KEGG compounds	[44]	2004
BNICE	From KEGG, BEM representation at the 3rd EC level	Not performed by the tool	Identifies a reaction rule to which the enzyme belongs to	-	[45]	2005
Biopath finder	Generated from all known classes of enzymes that operate on carbohyydrates	Pathway length	Identifies a reaction rule to which the enzyme belongs to	Only applied to central carbon metabolism	[46]	2010
PathPred	RDM patterns from KEGG RPAIR	Similarity of synthetic substrates with native ones	Identifies a KEGG Reaction	Applied to xenobiotic degradation, only allows KEGG compounds	[47]	2010
-	From KEGG	Binding site covalence, chemical similarity between synthetic and native substrates, thermodynamics, pathway length, and organism specificity	Identifies the full EC number	-	[48]	2010
Simpheny	From general E.C. information	Yield, pathway length, number of non-native steps, number of novel/synthetic steps and thermodynamics	Not described	Integration with GEMs	[49]	2011
GEM-Path	From general E.C. information. SMILES/SMARTS	Theoretical productivity	Identifies the full EC number	Integration with GEMs	[50]	2014
XTMS	Molecular signatures	Enzyme efficiency, toxicity, yield and thermodynamics	Based on the identification of similar reactions	Search tool is Retropath	[51]	2014

SimIndex and SimZyme	Chemical fingerprints and BNICE rules	Similarity between the synthetic and the native substrates	Identifies a full EC number	Algorithmic improvement by Byers -Waterman search	[52]	2015
M-Path	Reaction feature vectors based on KEGG RPAIR	Similarity between the synthetic and the native substrates	Based on the identification of similar KEGG reactions	Only allows KEGG compounds (in the demo server)	[53]	2015
ReactPred	From Metacyc SMILEs/SMARTS	Pathway length, thermodynamics, molecular size and substructure	Identifies a reaction rule	Reaction rules may be generated automatically from other libraries	[54]	2016
RetroPath 2.0	From Metacyc, SMILES/SMARTS	Can be done using an external tool (RP2paths)	Identifies a full EC number	-	[55]	2018
RING	From KEGG (small subset)	Pathway length	Identifies a reaction rule	Created small manual networks	[56]	2018
RePrime	From metRxn, based on molecular signatures and metabolite moieties	Implicit constrains in the MILP optimization problem	Identifies an enzyme ID	Integration w/ GEMs	[57]	2018
RetSynth	RetroRules	The min of number of genes added is the MILP objective	Identifies a full EC number	Integration w/ GEMs	[58]	2019
Transfor-MinER	From KEGG based on reaction center (RC) and the molecular environment (RCME)	Similarity between the synthetic and the native substrates	Based on similar KEGG reactions	-	[59]	2019
Retropath RL	From RetroRules database, accepts user reaction rules	It is not performed directly in the tool but using a separate procedure	Identifies a full EC number	-	[60]	2020

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