Total synthesis of triazole-linked *C*-glycosyl flavonoids in alternative solvents and environmental assessment in terms of reaction, workup and purification

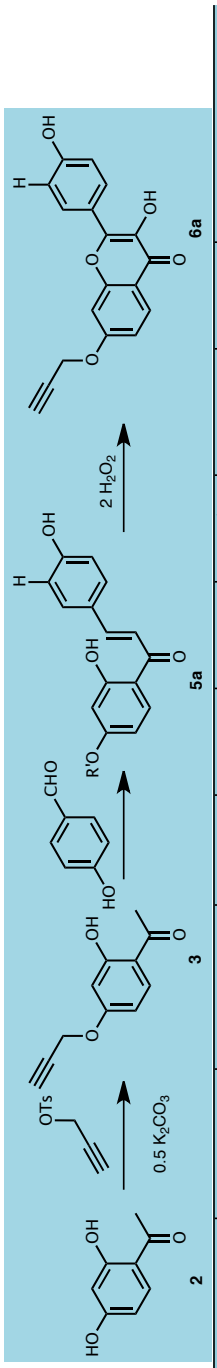
Freddy Pessel, Isabelle Billault and Marie-Christine Scherrmann*

Université Paris Sud, ICMMO, UMR CNRS 8182, Bâtiment 420, 91405 Orsay, France; E-mail: marie-christine.scherrmann@u-psud.fr.

Supporting information

Contents

Synthesis of **6a**, step 1 (preparation of **3**), inputs



Step 1										
Compounds	coef. stoech.	MW (g/mol)	Volume (mL)	Density	Mass (g)	mol	stoechi. Ratio ϕ [a]	biΣυiMi [a]	S [a]	bi(TS) [b]
Main substrate (**2**): 2',4'-dihydroxyacetophenone	1	152,15			10,551	0,06934604				
Product: 2'-hydroxy-4'-propargyloxyacetophenone (**3**)	1	190,198			10,816	0,05686705				
reagents										
Propargyle *p*-toluenesulfonate	1	210,25	12	1,215	14,58	0,06934602	0,99999966	-7,10833E-05		-5,87101E-08
K2CO3	0,5	138,21			5,751	0,04161059	1,20008561	13,82691641		0,011420116
solvents & auxiliaries (reaction)										
PEG(OMe)2 250			35	1,03	36,05				36,05	
Workup										
H2O			80	1	80					
HCl 37%			7	1,18	8,26					
									88,26	
purification										
EtOH 96% recrist.			38	0,79	30,02					
EtOH 96% rinsing			30	0,79	23,7					
										53,72

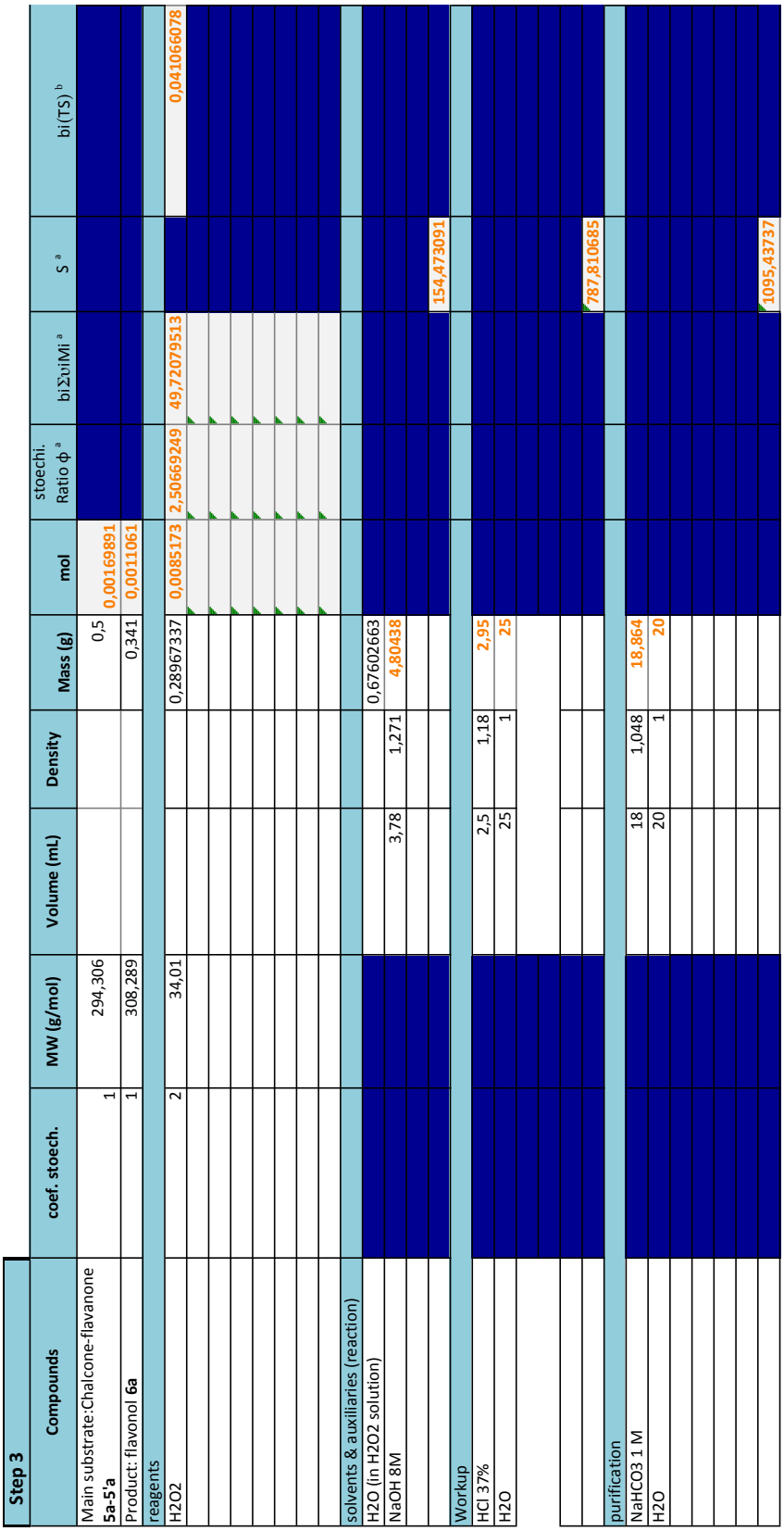
[a] See: J. Augé, *Green Chem.*, 2008, **10**, 225-231; J. Augé and M.-C. Scherrmann *New J. Chem.*, 2012, **36**, 1091–1098.
[b] for the total synthesis of **1a**

Synthesis of **6a**, step 2 (preparation of **5a, 5'a),** inputs

Step 2							stoechi.			
Compounds	**coef. stoech.**	**MW (g/mol)**	**Volume (mL)**	**Density**	**Mass (g)**	**mol**	**Ratio ϕ [a]**	**biΣυiMi [a]**	**S [a]**	**bi(TS) [b]**
Main substrate: 2'-hydroxy-4'-propargyloxyacetophenone **3**	1	190,198			0,9977	0,00524559				
Product : chalcone-flavanone **5a-5'a**	1	294,306			1,3	0,00441717				
reagents										
4-hydroxybenzaldehyde	1	122,12			0,6406	0,00524566	1,00001407	-21,9743766		-0,018149377
solvents & auxiliaries (reaction)										
Acetic acid	60,05		1,5	1,048	1,572					
Pyrrolidine	71,12		2,15	0,866	1,8619					
									37,2266838	
Workup										
AcOEt			40	0,925	37					
NaCl 12%			12	1,0857	13,0284					
NaCl sat			15	1,197	17,955					
MgSO4					3					
									769,526365	
purification										
EtOH 96% recrist.			5,5	0,79	4,345					
H2O			3	1	3					
EtOH 96% rinsing			10	0,79	7,9					
									165,270041	

[a] See: J. Augé, *Green Chem.*, 2008, **10**, 225-231; J. Augé and M.-C. Scherrmann *New J. Chem.*, 2012, **36**, 1091–1098.
[b] for the total synthesis of **1a**

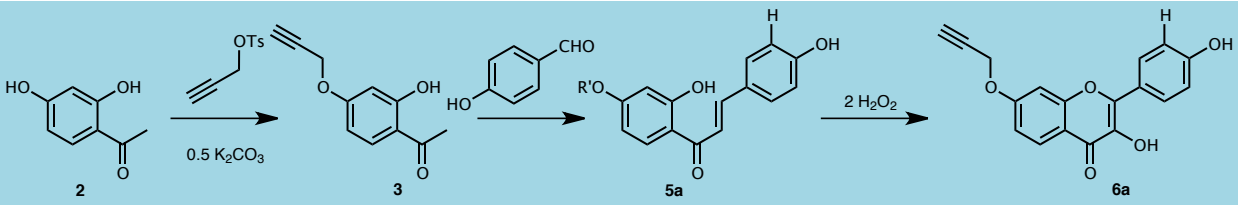
Synthesis of **6a**, step 3 (preparation of **6a**), inputs



Step 3										
Compounds	coef. stoech.	MW (g/mol)	Volume (mL)	Density	Mass (g)	mol	stoechi. Ratio ϕ [a]	biΣυiMi [a]	S [a]	bi(TS) [b]
Main substrate:Chalcone-flavanone **5a-5'a**	1	294,306			0,5	0,00169891				
Product: flavonol **6a**	1	308,289			0,341	0,0011061				
reagents										
H2O2	2	34,01			0,28967337	0,0085173	2,50669249	49,72079513		0,041066078
solvents & auxiliaries (reaction)										
H2O (in H2O2 solution)					0,67602663					
NaOH 8M			3,78	1,271	4,80438					
									154,473091	
Workup										
HCl 37%			2,5	1,18	2,95					
H2O			25	1	25					
									787,810685	
purification										
NaHCO3 1 M			18	1,048	18,864					
H2O			20	1	20					
									1095,43737	

[a] See: J. Augé, *Green Chem.*, 2008, **10**, 225-231; J. Augé and M.-C. Scherrmann *New J. Chem.*, 2012, **36**, 1091–1098.
[b] for the total synthesis of **1a**

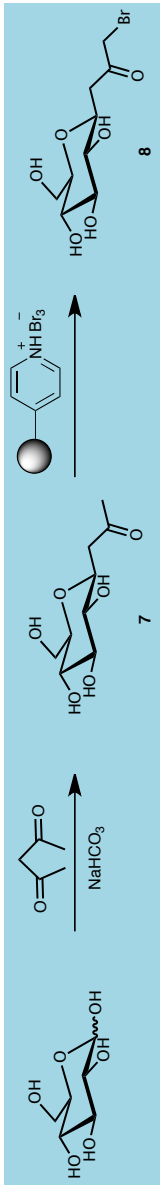
Metrics of steps 1,2,3 and cumulative metrics for the synthesis of **6a**



metrics branch	Step 1	Step 2	Step 3
mass of main substrate	10,551	0,9977	0,5
Msubstrate	152,15	190,198	294,306
mol of main substrate	0,06934604	0,005245586	0,001698912
mass of product	10,816	1,3	0,341
Mproduct	190,198	294,306	308,289
mol of product	0,056867054	0,004417171	0,001106105
mass of reagents	20,331	0,6406	0,289673373
mass of solvents and auxiliaries (reaction)	36,05	3,4339	5,480406627
mass of auxiliaries (workup)	88,26	70,9834	27,95
mass of auxiliaries (purification)	53,72	15,245	38,864
Σ(biΣυiMi)	13,82684532	-21,9743766	49,72079513
Sr	36,05	37,22668377	154,4730911
Sw	88,26	769,526365	787,8106846
Sp	53,72	165,2700411	1095,437368
s(ΣυiMi)	178,03	972,0230899	2037,721144
ΣυiMi =	431,505	312,318	362,326
AE =	0,440778207	0,942328012	0,850860827
yield =	0,820047608	0,842073906	0,651066668
RME	0,350236384	0,793505463	0,431824108
GME	0,051772995	0,01423868	0,004665859
MIr	6,188239645	3,901692308	18,38733138
MIw	8,160133136	54,60261538	81,96480938
MIp	4,966715976	11,72692308	113,9706745
MI	19,31508876	70,23123077	214,3228152
E	18,31508876	69,23123077	213,3228152
Cumulative metrics (step 1-> n)	**Step 1**	**step 1 + step 2**	**step 1 + step 2 + step 3**
nthprod	0,056867054	0,047886263	0,031177149
mth P	10,816	14,09321439	9,611572216
PMI (step 1-> n)	19,31508876	84,28735696	336,4450395
PMIR (step 1-> n)	6,188239645	7,883466688	28,48039104
PMIW (step 1-> n)	8,160133136	60,86520372	171,2099761
PMIP (step 1-> n)	4,966715976	15,53868656	136,7546724
Yield (step 1-> n)	0,820047608	0,690540693	0,449588028
ΣυiMi (step 1-> n)	431,505	553,625	621,645
GAE (step 1-> n)	0,440778207	0,531598103	0,495924523
Σ(bi) [a]	0,032043303	-0,014716697	0,066876214
sr [a]	1,204752317	1,90865945	5,283160994
sw [a]	2,949554494	22,3430151	38,17327217
sp [a]	1,795264757	5,704098356	30,4910581
(1+Σ(bi)+s) [a]	6,981614871	30,94105621	75,01436748
PMI =(1+Σ(bi)+s)/(εAE) [a]	19,31508876	84,28735696	336,4450395
GRME [a]	0,350236384	0,372573169	0,208985565

[a] See: J. Augé, *Green Chem.*, 2008, **10**, 225-231; J. Augé and M.-C. Scherrmann *New J. Chem.*, 2012, **36**, 1091–1098.

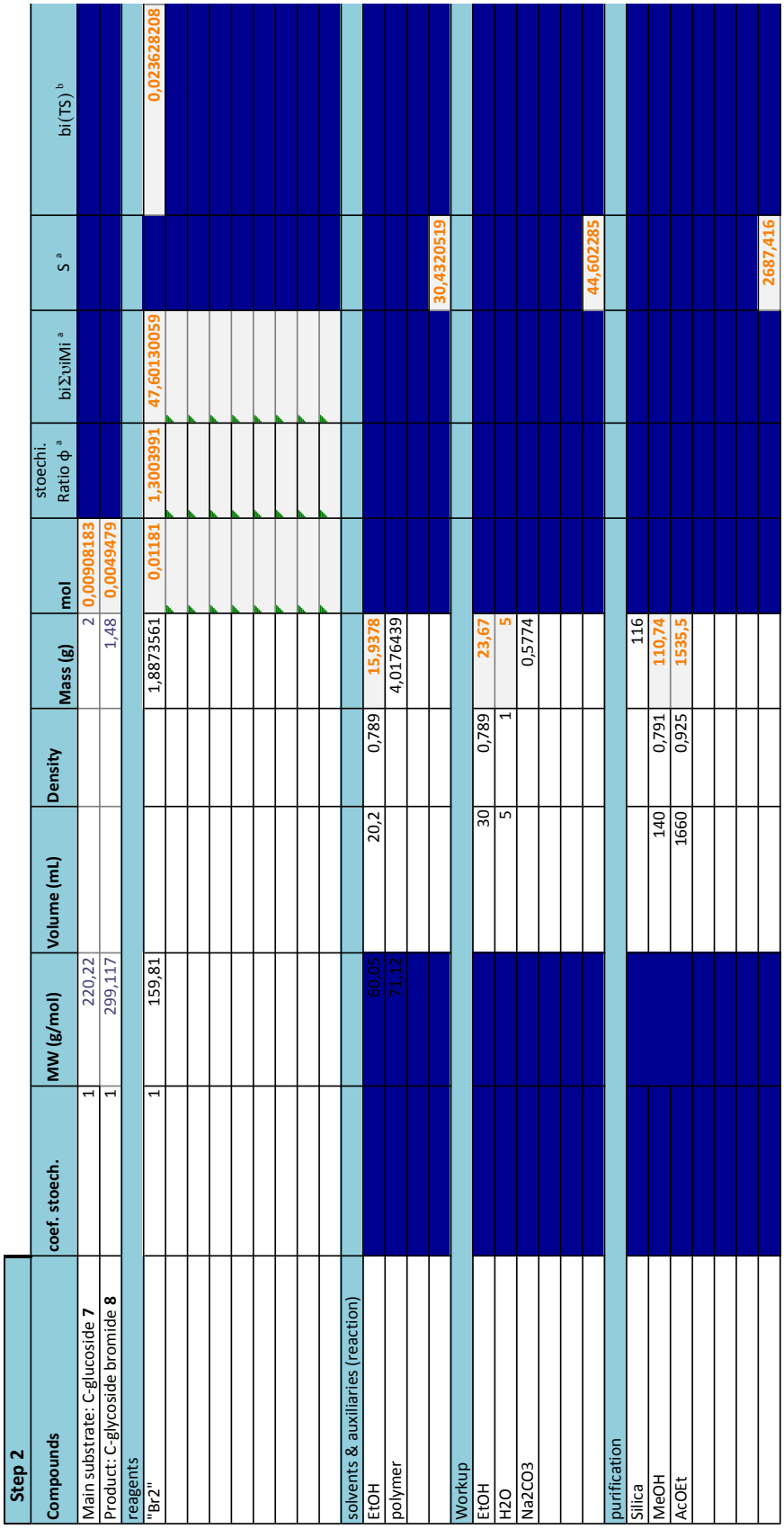
Synthesis of **8**, step 1 (preparation of **7**), inputs



Step 1										
Compounds	coef. stoech.	MW (g/mol)	Volume (mL)	Density	Mass (g)	mol	stoechi. Ratio ϕ [a]	biΣυiMi [a]	S [a]	bi(TS) [b]
Main substrate: D-glucose	1	180,156			2,5	0,01387686				
Product: C-glucoside **7**	1	220,22			3,05	0,01384979				
reagents										
2,4-pentanedione	1	100,12	1,8	0,975	1,755	0,01752897	1,2631793	26,349512		0,012197577
NaHCO3	1	84,01			1,75	0,02083085	1,5011213	42,0992		0,025233026
solvents & auxiliaries (reaction)									10	
H2O			10	1	10					
Workup										
AcOEt			20	0,925	18,5					
Dowex					15,3					
H2O			25	1	25					
purification									58,8	
									0	

[a] See: J. Augé, *Green Chem.*, 2008, **10**, 225-231; J. Augé and M.-C. Scherrmann *New J. Chem.*, 2012, **36**, 1091–1098.
[b] for the total synthesis of **1a**

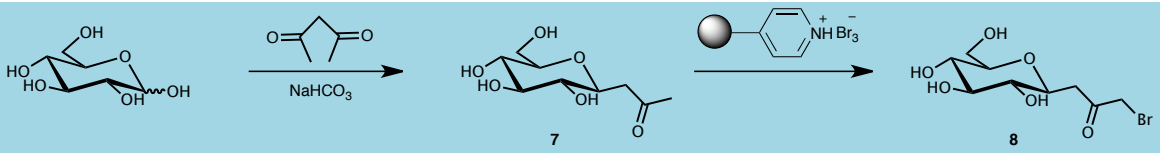
Synthesis of **8**, step 2, inputs



Step 2										
Compounds	coef. stoech.	MW (g/mol)	Volume (mL)	Density	Mass (g)	mol	stoechi. Ratio ϕ [a]	biΣνiMi [a]	S [a]	bi(TS) [b]
Main substrate: C-glucoside **7**	1	220,22			2	0,00908183				
Product: C-glycoside bromide **8**	1	299,117			1,48	0,0049479				
reagents										
"Br2"	1	159,81			1,8873561	0,01181	1,3003991	47,60130059		0,023628208
solvents & auxiliaries (reaction)									30,4320519	
EtOH	60,05		20,2	0,789	15,9378					
polymer	71,12				4,0176439					
Workup									44,602285	
EtOH			30	0,789	23,67					
H2O			5	1	5					
Na2CO3					0,5774					
purification									2687,416	
Silica					116					
MeOH			140	0,791	110,74					
AcOEt			1660	0,925	1535,5					

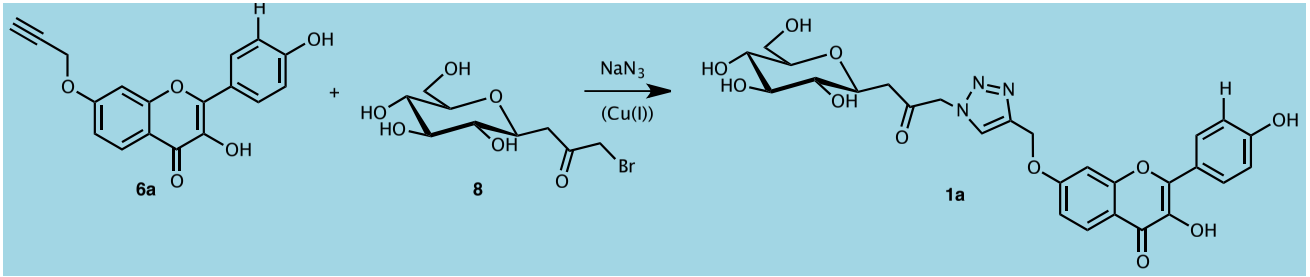
[a] See: J. Augé, *Green Chem.*, 2008, **10**, 225-231; J. Augé and M.-C. Scherrmann *New J. Chem.*, 2012, **36**, 1091–1098.
[b] for the total synthesis of **1a**

Metrics of steps 1 and 2and cumulative metrics for the synthesis of **8**



metrics branch	Step 1	Step 2
mass of main substrate	2,5	2
Msubstrate	180,156	220,22
mol of main substrate	0,013876862	0,009081827
mass of product	3,05	1,48
Mproduct	220,22	299,117
mol of product	0,013849787	0,004947897
mass of reagents	3,505	1,8873561
mass of solvents and auxiliaries (reaction)	10	19,9554439
mass of auxiliaries workup	58,8	29,2474
mass of auxiliaries purification	0	1762,24
Σ(biΣυiMi) [a]	68,448712	47,60130059
Sr	10	30,43205195
Sw	58,8	44,602285
Sp	0	2687,416
s(ΣυiMi)=Sr+Sw+Sp	68,8	2762,450337
ΣυiMi =	364,286	380,03
AE =	0,604525016	0,787087861
yield =	0,99804886	0,544812899
RME=m(product)/(mass substrate + mass reagents)	0,507910075	0,380721488
GME	0,040772676	0,000815279
MIr	5,247540984	16,11
MIw	19,27868852	19,76175676
MIp	0	1190,702703
MI	24,52622951	1226,574459
E	23,52622951	1225,574459
Cumulative metrics (step 1-> n)		
nthprod	0,013849787	0,007545542
mth P	3,05	2,257
PMI (step 1-> n)	24,52622951	1258,366661
PMIR (step 1-> n)	5,247540984	21,84992025
PMIW (step 1-> n)	19,27868852	45,81403855
PMIP (step 1-> n)	0	1190,702703
Yield (step 1-> n)	0,99804886	0,543749893
ΣυiMi (step 1-> n)	364,286	524,096
GAE (step 1-> n)	0,604525016	0,570729408
Σ(bi) [a]	0,187898278	0,221428923
sr [a]	1,978181978	5,559345426
sw [a]	11,63171003	14,21765635
sp [a]	0	369,5155978
(1+Σ(bi)+s) [a]	14,79779029	390,5140285
PMI =(1+Σ(bi)+s)/(εAE) [a]	24,52622951	1258,366661
GRME [a]	0,507910075	0,254074592

[a] See: J. Augé, *Green Chem.*, 2008, **10**, 225-231; J. Augé and M.-C. Scherrmann *New J. Chem.*, 2012, **36**, 1091–1098.



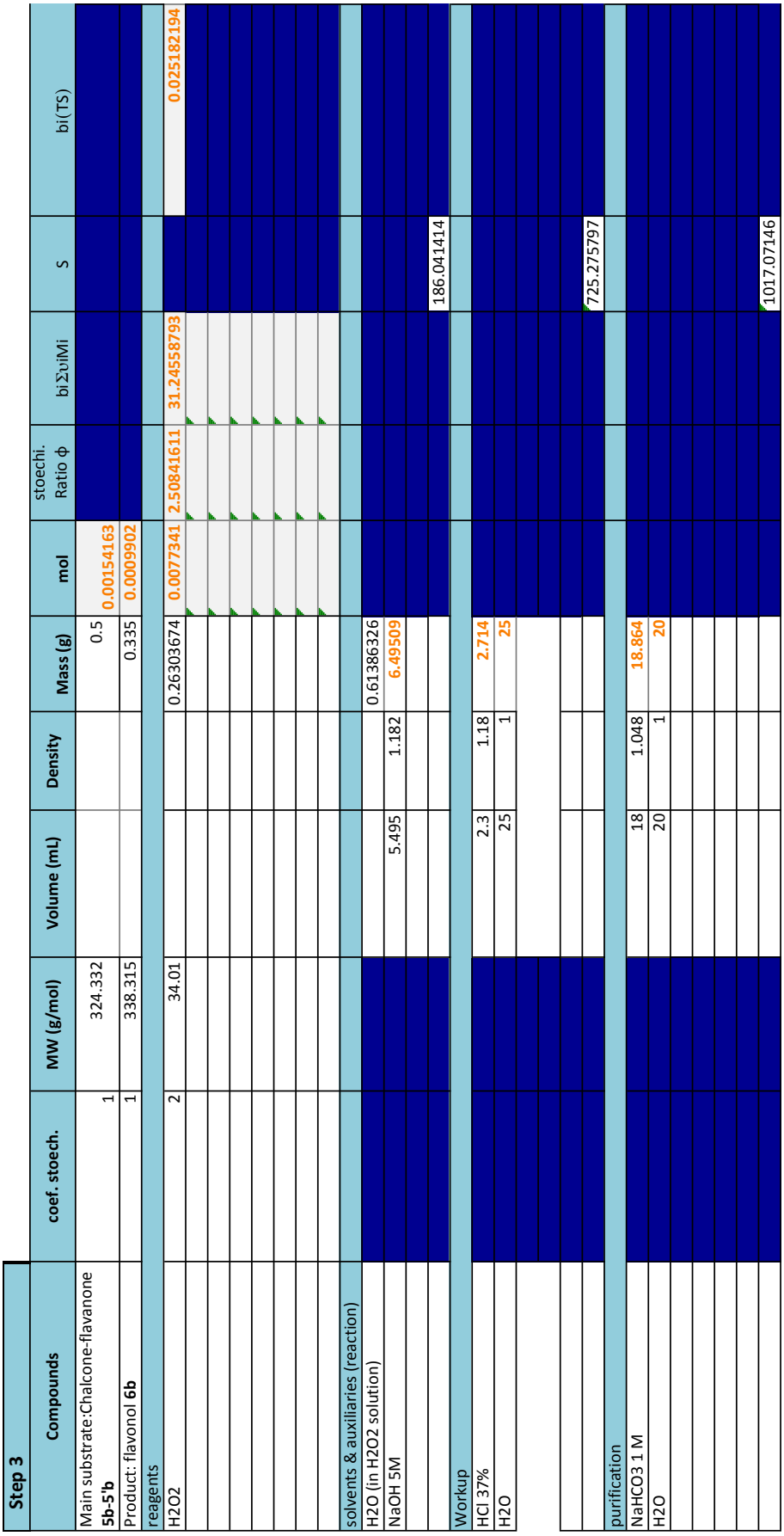
Step 1

Compounds	coef. stoech.	MW (g/mol)	Volume (mL)	Density	Mass (g)	mol	stoechi. Ratio ϕ	biΣυiMi	S
Main substrate: flavonol **6a**	1	308.289			0.05	0.00016219			
Product: glycosyl flavonol **1a**	1	569.523			0.084	0.00014749			
reagents									
C glycoside bromide **8**	1	299.117			0.0533	0.00017819	1.09868738		
NaN3	1	65.01			0.0121	0.00018613	1.14760711	-31.46806346	
solvents & auxiliaries (reaction)									
PEG 2000					0.327				
H2O (for CuSO4 and NaAsc. solutions)			0.046	1	0.046				
CuSO4 5H2O (0,352 M)					0.00202141				
NaAsc. (0,704 M)					0.0032078				0.37822921
Workup									
H2O			15	1	15				
HCl 1 M					0.029				
H2O rinsing					2				
									17.029
purification									
									0

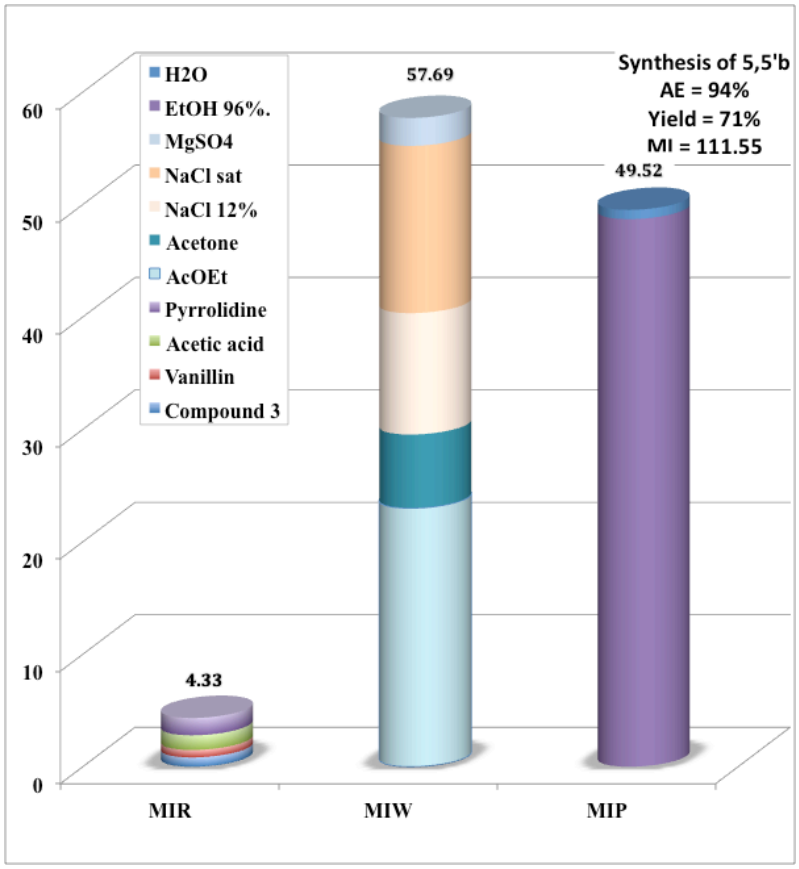
Synthesis of **6b**, step 2 (preparation of **5b, 5'b),** inputs

Step 2									
Compounds	**coef. stoech.**	**MW (g/mol)**	**Volume (mL)**	**Density**	**Mass (g)**	**mol**	stoechi. Ratio ϕ	biΣυiMi	S	bi(TS)
Main substrate: 2'-hydroxy-4'-propargyloxyacetophenone **3**	1	190.198			0.9977	0.00524559				
Product : chalcone-flavanone **5b-5'b**	1	324.332			1.207	0.0037215				
reagents										
vanilin	1	152.15			0.7981	0.00524548	0.99998003	-27.38224783		-0.022068558
solvents & auxiliaries (reaction)										
Acetic acid	60.05		1.5	1.048	1.572					
Pyrrolidine	71.12		2.15	0.866	1.8619					
									37.2266838	
Workup										
AcOEt			30	0.925	27.75					
NaCl 12%			12	1.0857	13.0284					
NaCl sat			15	1.197	17.955					
MgSO4					3					
aceton			10	0.791	7.91					
									754.999513	
purification										
EtOH 96% recrist.			64.4	0.79	50.876					
H2O			1	1	1					
EtOH 96% rinsing			10	0.79	7.9					
									648.02768	

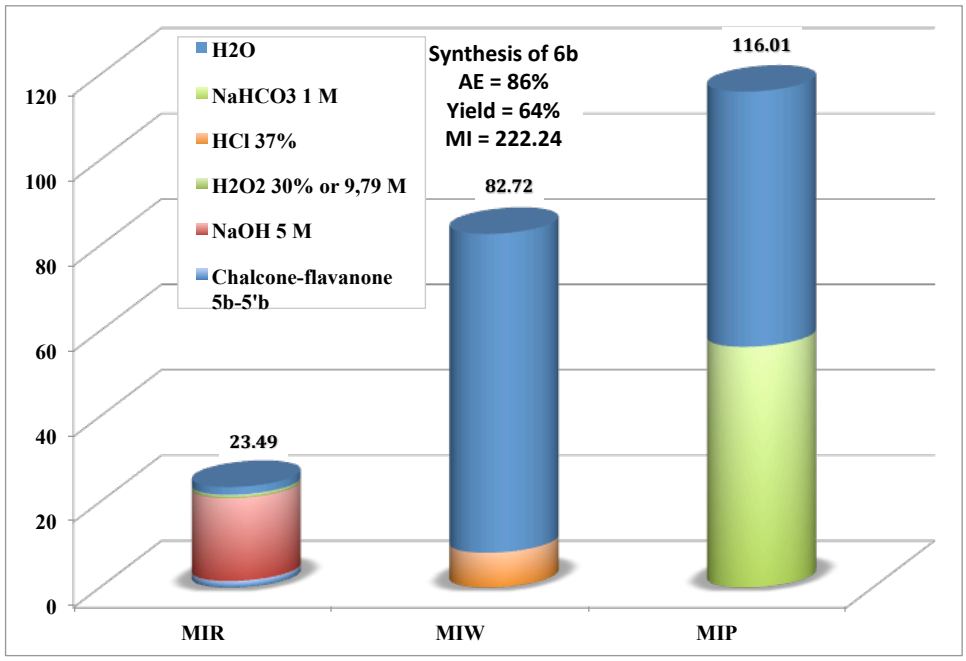
Synthesis of **6b**, step 3, inputs



Step 3										
Compounds	coef. stoech.	MW (g/mol)	Volume (mL)	Density	Mass (g)	mol	stoechi. Ratio ϕ	biΣυiMi	S	bi(TS)
Main substrate:Chalcone-flavanone **5b-5'b**	1	324.332			0.5	0.00154163				
Product: flavonol **6b**	1	338.315			0.335	0.0009902				
reagents										
H2O2	2	34.01			0.26303674	0.0077341	2.50841611	31.24558793		0.025182194
solvents & auxiliaries (reaction)										
H2O (in H2O2 solution)					0.61386326					
NaOH 5M			5.495	1.182	6.49509					
									186.041414	
Workup										
HCl 37%			2.3	1.18	2.714					
H2O			25	1	25					
									725.275797	
purification										
NaHCO3 1 M			18	1.048	18.864					
H2O			20	1	20					
									1017.07146	



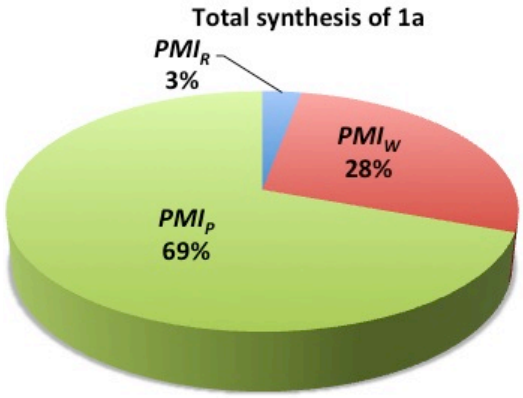
Amount and nature of reactants and auxiliaries for the synthesis of **5,5'b** ($g/g_{product}$) for the reaction (MI_R), the workup (MI_W) and the purification (MI_P).



Amount and nature of reactants and auxiliaries for the synthesis of **6b** ($g/g_{product}$) for the reaction (MI_R), the workup (MI_W) and the purification (MI_P).

Metrics of the final step and cumulative metrics for the synthesis of **1a**

metrics branch	Final step
mass of main substrate: 6a	0.05
Msubstrate 6a	308.289
mol of main substrate 6a	0.000162185
mass of substrate 8	0.0533
Msubstrate 8	299.117
mol of substrate 8	0.000178191
mass of product 1a	0.084
$\phi_{8,6a}$= mol8/mol6a	1.098687383
Mproduct	569.523
mol of product	0.000147492
mass of reagents	0.0654
mass of solvents and auxiliaries (reaction)	0.378229206
mass of auxiliaries workup Sw	17.029
mass of auxiliaries purification Sp	0
Σbi*ΣυiMI	-31.46806346
Sr*ΣυiM	0.378229206
Sw*ΣυiM	17.029
Sp*ΣυiM	0
s*ΣυiMi	17.40722921
ΣυiMi =	672.416
AE =	0.846980143
yield =	0.909402289
RME	0.727902946
GME	0.004793801
MIr	5.876538171
MIw	202.7261905
MIp	0
MI	208.6027286
E	207.6027286



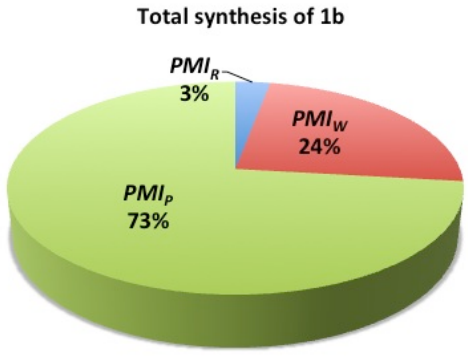
Cumulative metrics (step 1-> n)	branch (6a)	branch (8)	Total synthesis 1a
PMI (step 1-> n)	336.4450395	1258.366661	1206.101479
PMIR (step 1-> n)	28.48039104	21.84992025	35.46368461
PMIW (step 1-> n)	171.2099761	45.81403855	333.7069888
PMIP (step 1-> n)	136.7546724	1190.702703	836.9308056
Yield (step 1-> n) from Glc		0.543749893	0.450071062
Yield (step 1-> n) from 2	0.449588028		0.408856382
σ2 = Yield from 2/Yield from Glc			0.908426282
a2=(σ2-1)*Mglc/ΣυiMi			-0.013625886
ΣυiMi (step 1-> n)	621.645	524.096	1210.751
Sr	227.7497749	183.5463961	484.0037176
Sw	1645.59705	469.407706	5388.514021
Sp	1314.427409	12199.86367	13514.29108
S	3187.774234	12852.81777	19386.80881
sr			5.76464005
sw			64.17893625
sp			160.9595562
s			230.9031325
GAE (step 1-> n)	0.495924523	0.570729408	0.470388214
Σ(bi)			0.069405037
1+Σ(bi)+s+a_2			231.9589116
MI =(1+Σ(bi)+s+a2)/(εAE)			1206.101479
GRME=(εAE)/(1+Σ(bi)+a2)			0.182160467
E			1205.101479
GME = 1/MI			0.000829118
GME %			0.082911763

Synthesis of **1b**, inputs

Step 1									
Compounds	coef. stoech.	MW (g/mol)	Volume (mL)	Density	Mass (g)	mol	stoechi. Ratio ϕ	biΣυiMi	S
Main substrate: flavonol **6b**	1	338.315			0.0503	0.00014868			
Product: glycosyl flavonol **1b**	1	599.549			0.08	0.00013343			
reagents									
C glycoside bromide **8**	1	299.117			0.0664	0.00022199	1.49307028		
NaN3	1	65.01			0.015	0.00023073	1.55190225	-27.30921555	
solvents & auxiliaries (reaction)									
PEG 2000					0.297				
H2O (for CuSO4 and NaAsc. solutions)			0.046	1	0.042				
CuSO4 5H2O (0,352 M)					0.00184563				
NaAsc. (0,704 M)					0.00292886				0.34377449
Workup									
H2O			15	1	15				
HCl 1 M					0.029				
H2O rinsing					2				
									17.029
purification									
									0

Metrics of the final step and cumulative metrics for the synthesis of **1b**

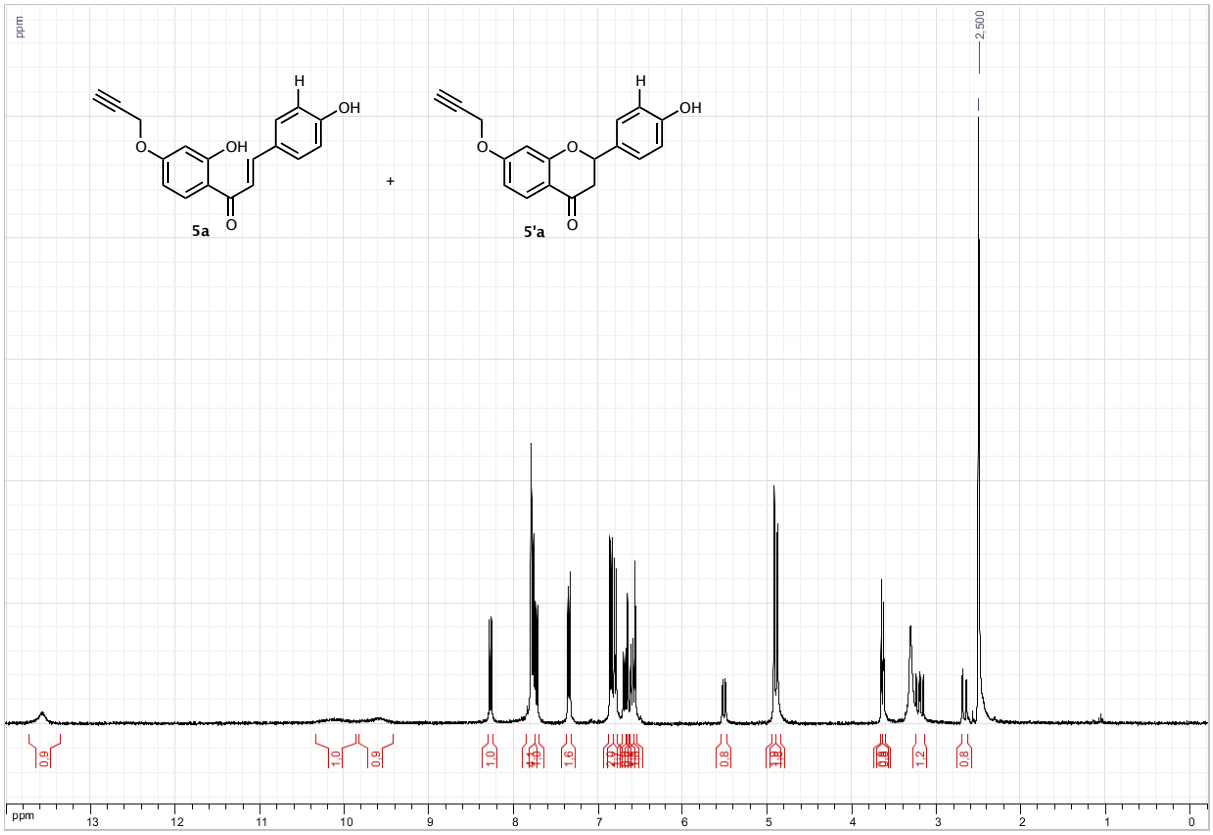
metrics branch	Final step
mass of main substrate: 6b	0,0503
Msubstrate 6b	338,315
mol of main substrate 6b	0,000148678
mass of substrate 8	0,0664
Msubstrate 8	299,117
mol of substrate 8	0,000221987
mass of product 1b	0,08
$\phi_{8,6b}$= mol8/mol6b	1,493070283
Mproduct	599,549
mol of product	0,000133434
mass of reagents	0,0814
mass of solvents and auxiliaries (reaction)	0,34377449
mass of auxiliaries workup Sw	17,029
mass of auxiliaries purification Sp	0
Σbi*ΣυiMI	-27,30921555
Sr*ΣυiM	0,34377449
Sw*ΣυiM	17,029
Sp*ΣυiM	0
s*ΣυiMi	17,37277449
ΣυiMi =	702,442
AE =	0,853521002
yield =	0,897467174
RME	0,607441154
GME	0,00457026
MIr	5,943431125
MIw	212,8625
MIp	0
MI	218,8059311
E	217,8059311



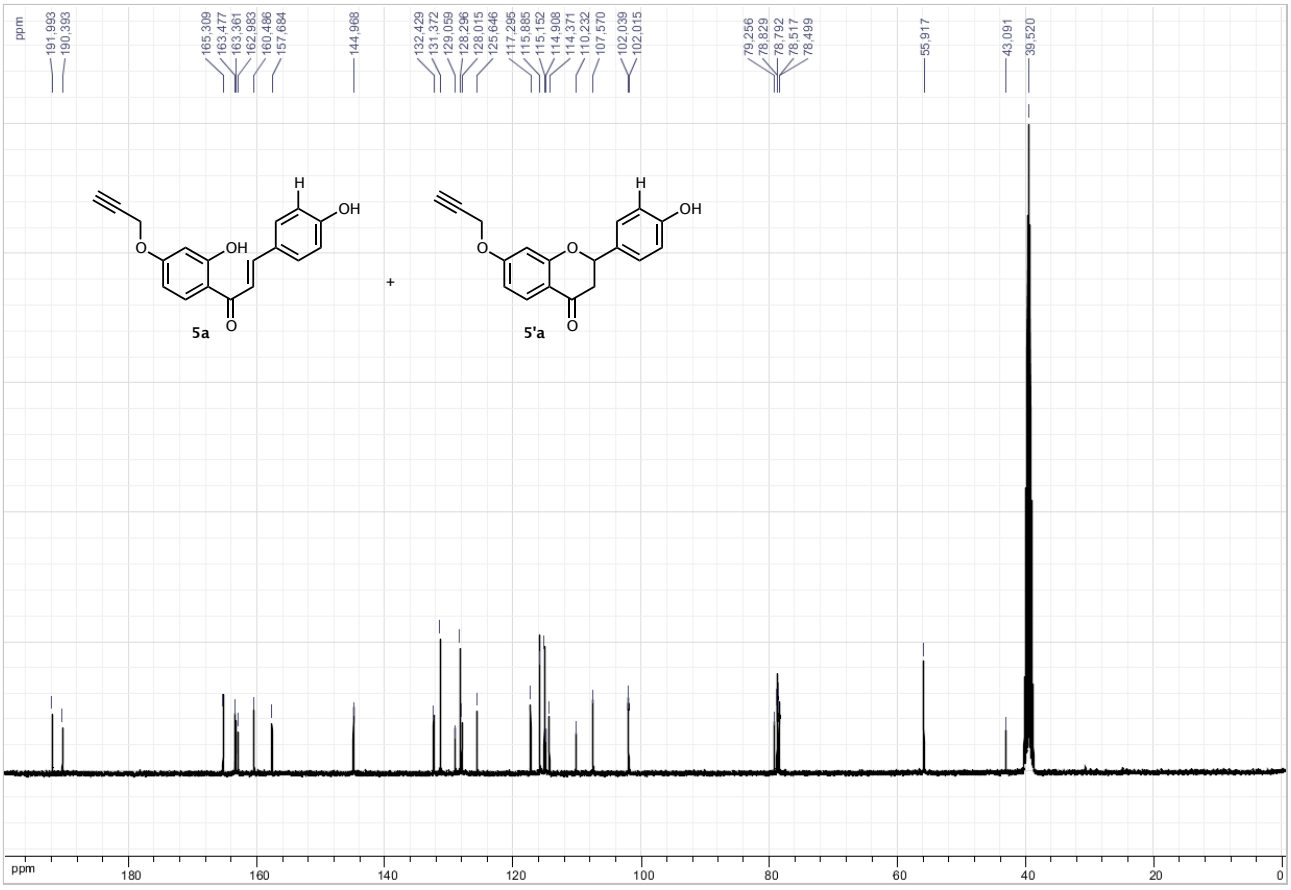
Cumulative metrics (step 1-> n)	branch (6b)	branch (8)	Total synthesis 1b
PMI (step 1-> n)	409,8447364	1258,366661	1519,481388
PMIR (step 1-> n)	34,87367292	21,84992025	44,54693678
PMIW (step 1-> n)	178,9144924	45,81403855	363,3806391
PMIP (step 1-> n)	196,0565712	1190,702703	1111,553812
Yield (step 1-> n) from Glc		0,543749893	0,326841734
Yield (step 1-> n) from 2	0,373685167		0,335370171
σ2 = Yield from 2/Yield from Glc			1,026093475
a2=(σ2-1)*Mglc/ΣυiMi			0,003788659
ΣυiMi (step 1-> n)	651,675	524,096	1240,781
Sr	259,3180975	207,3209055	526,5566073
Sw	1568,53531	530,2094334	5066,786042
Sp	1718,819144	13780,09504	15498,91418
S	3546,672551	14517,62538	21092,25683
sr			6,119673694
sw			58,88650304
sp			180,1293462
s			245,135523
GAE (step 1-> n)	0,519146814	0,570729408	0,483202918
Σ(bi)			0,095450946
1+Σ(bi)+s+a_2			246,2347626
PMI =(1+Σ(bi)+s+a2)/(εAE)			1519,481388
GRME=(εAE)/(1+Σ(bi)+a2)			0,147421767
E			1518,481388
GME = 1/MI			0,000658119
GME %			0,065811928

2’,4-dihydroxy-4’-propargyloxychalcone (5a) and 4’-hydroxy-7-propargyloxyflavanone (5’a).

^{1}H-NMR (360 MHz; DMSO)

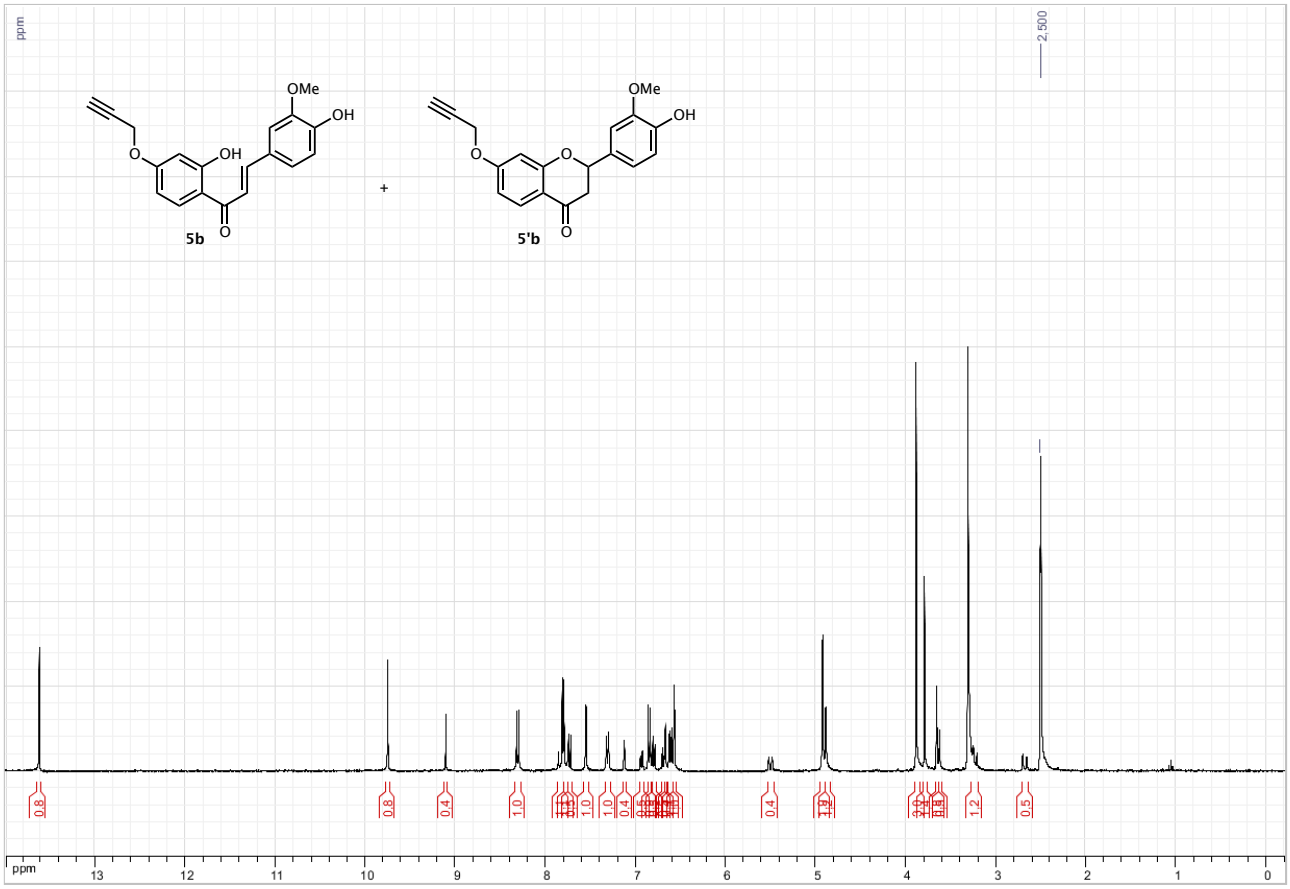


^{13}C-NMR (90.6 MHz; DMSO)

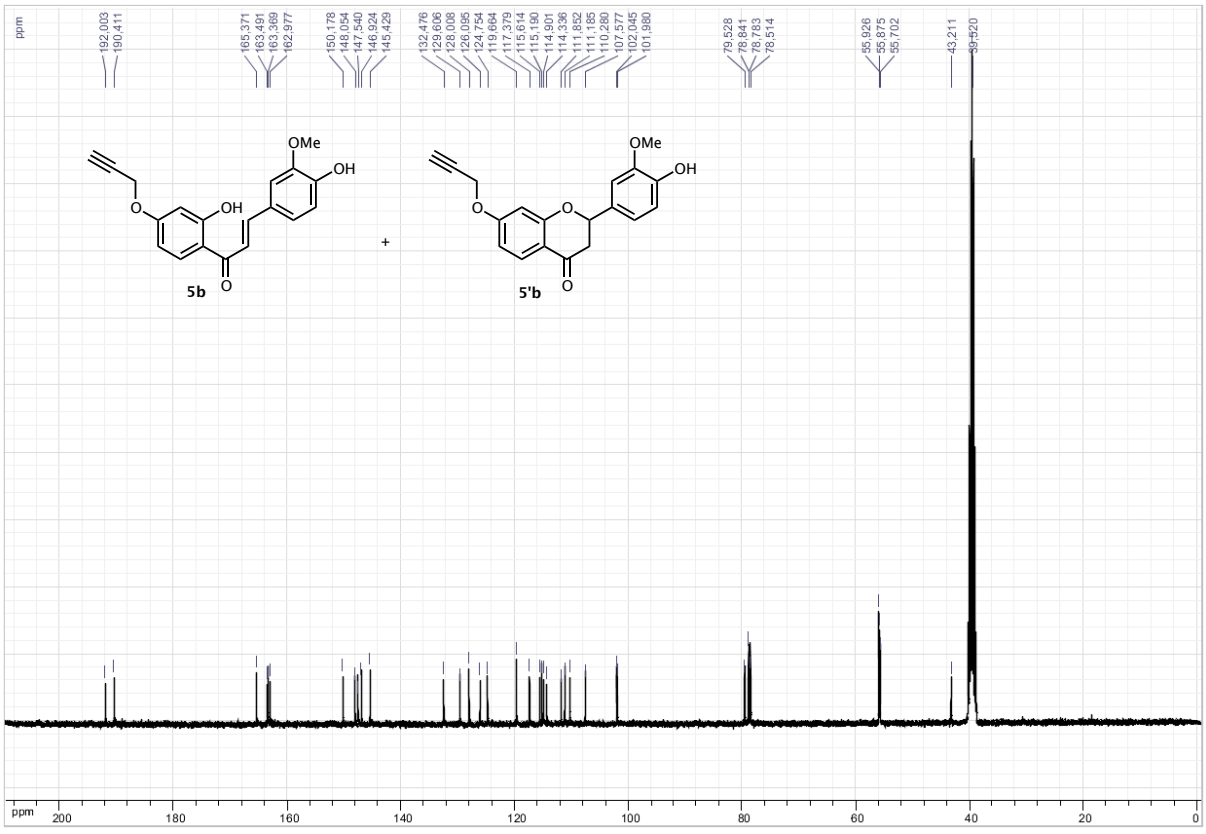


4-hydroxy-3-methoxy-4'-propargyloxychalcone (5b) and 4'-hydroxy-3'-methoxy-7-propargyloxyflavanone (5'b).

^{1}H-NMR (360 MHz; DMSO)

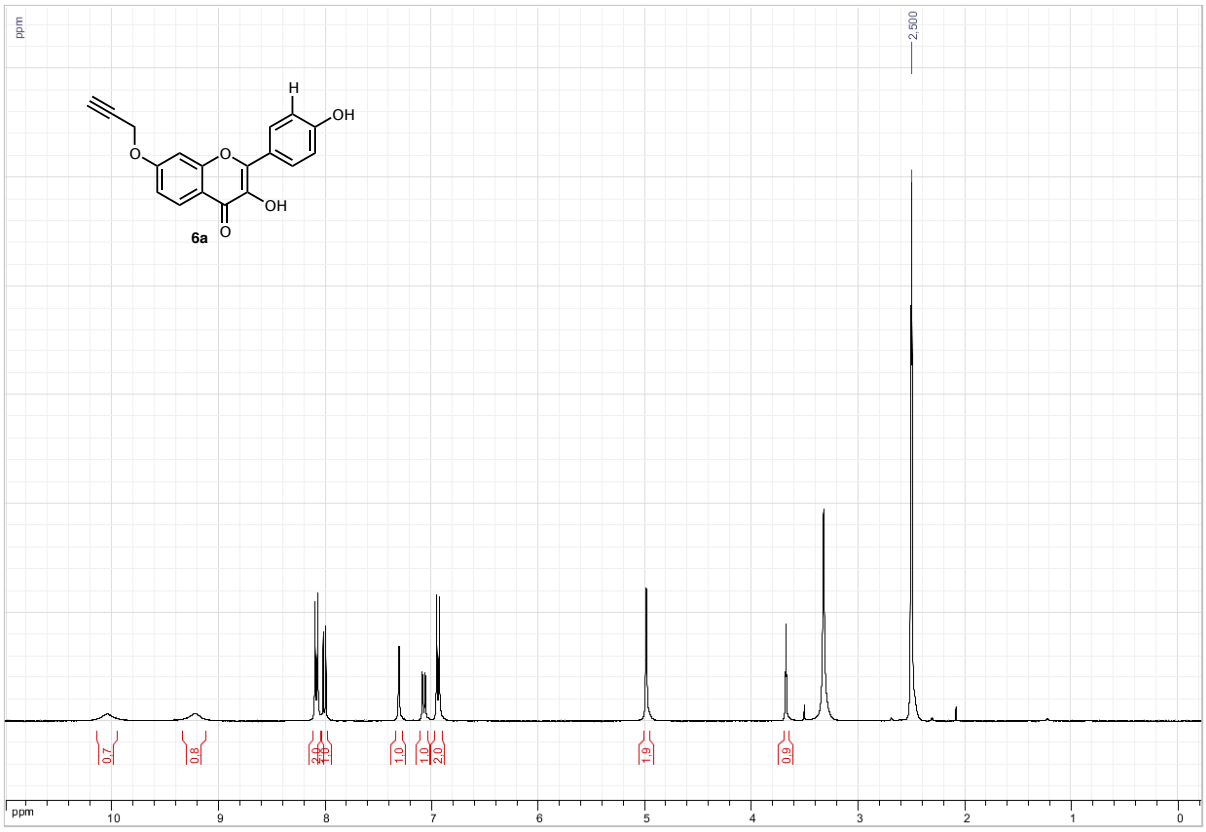


^{13}C-NMR (90.6 MHz; DMSO)

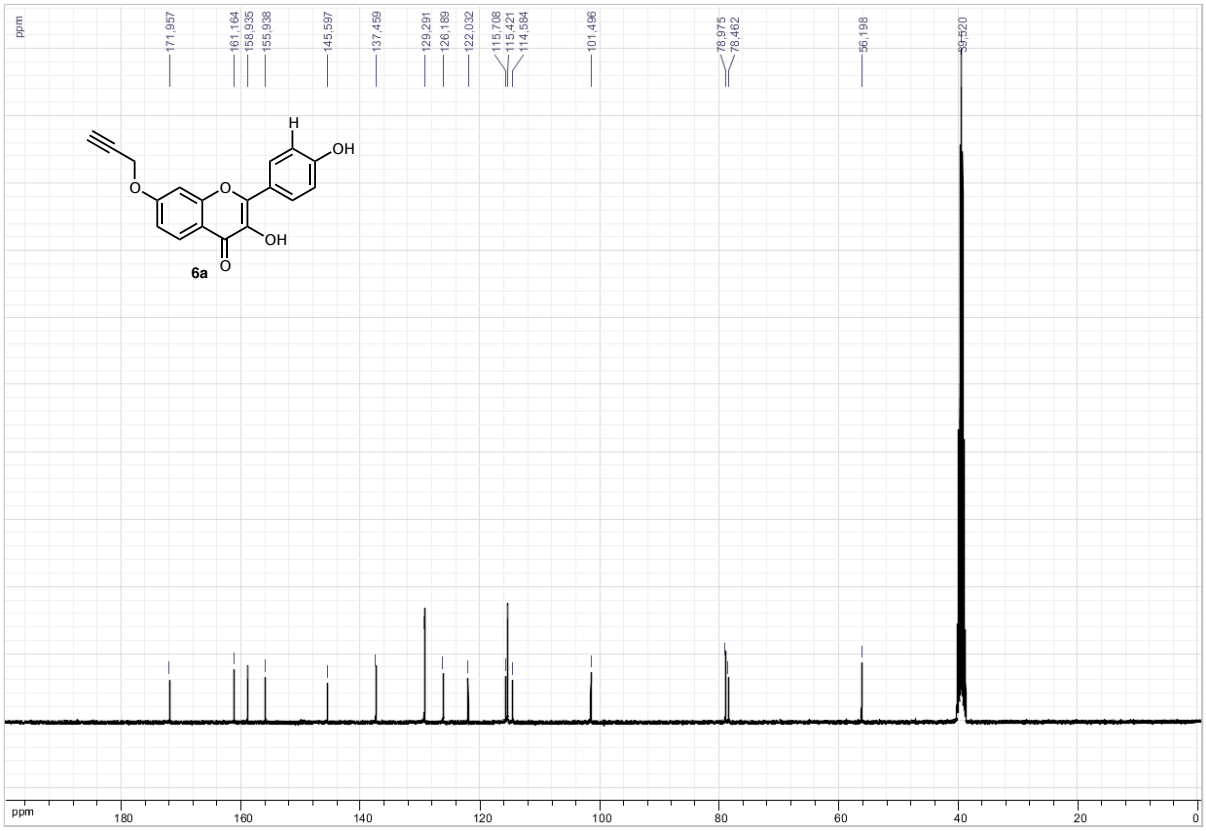


4’-hydroxy-7-propargyloxyflavonol 6a.

^{1}H-NMR (360 MHz; DMSO)

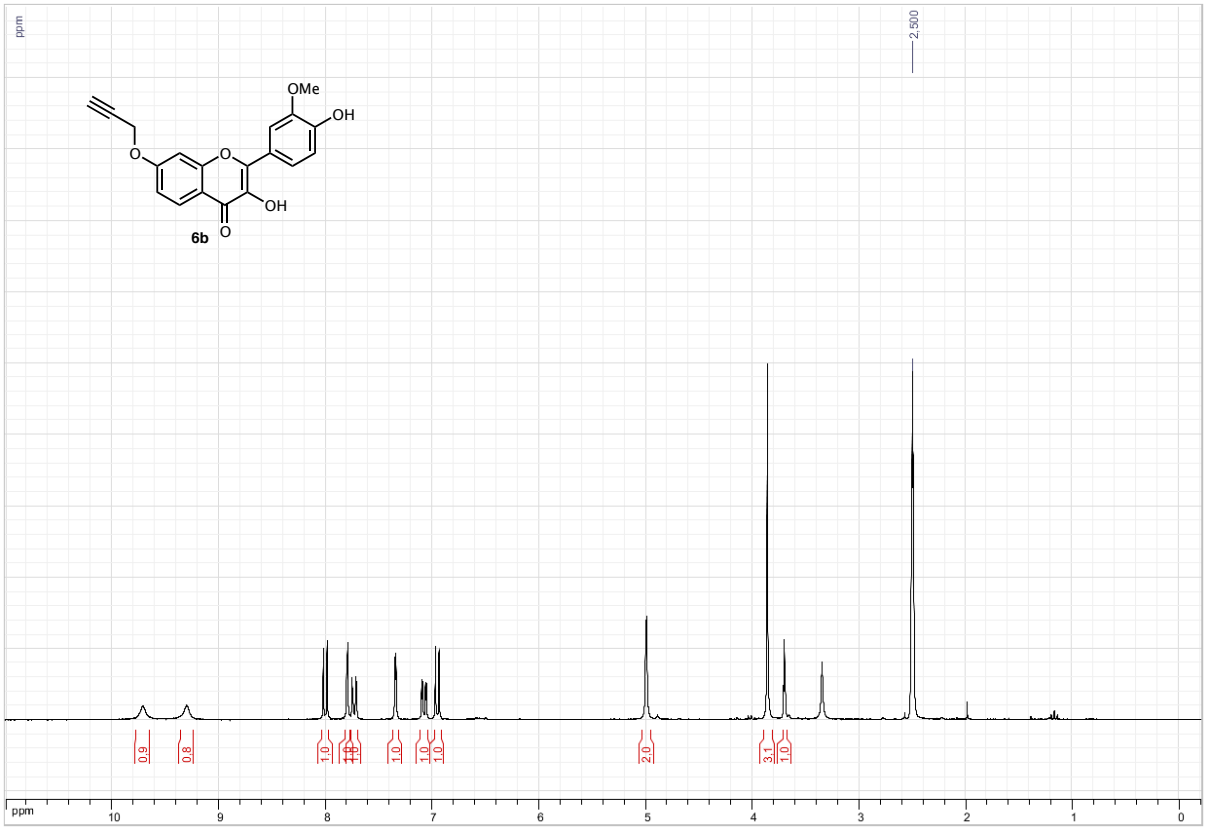


^{13}C-NMR (90.6 MHz; DMSO)

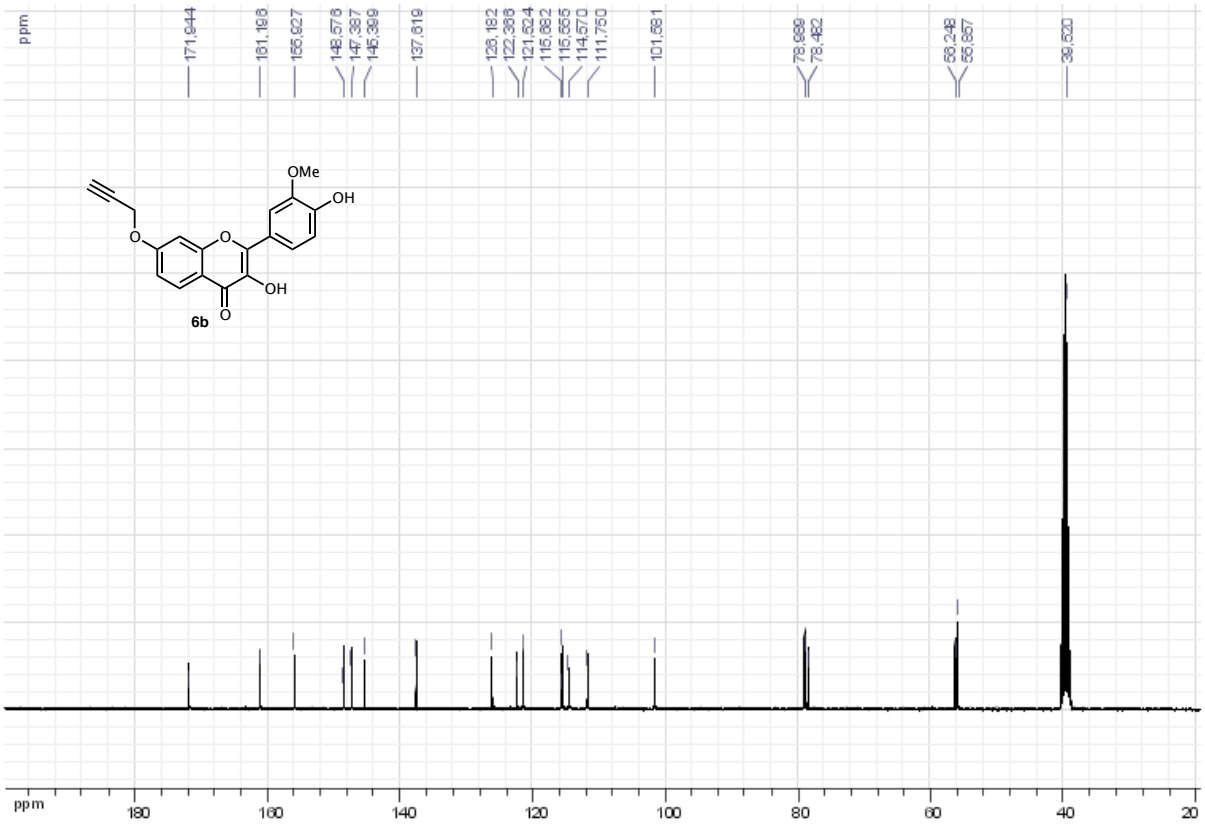


4’-hydroxy-3’-methoxy-7-propargyloxyflavonol 6b.

^{1}H-NMR (360 MHz; DMSO)

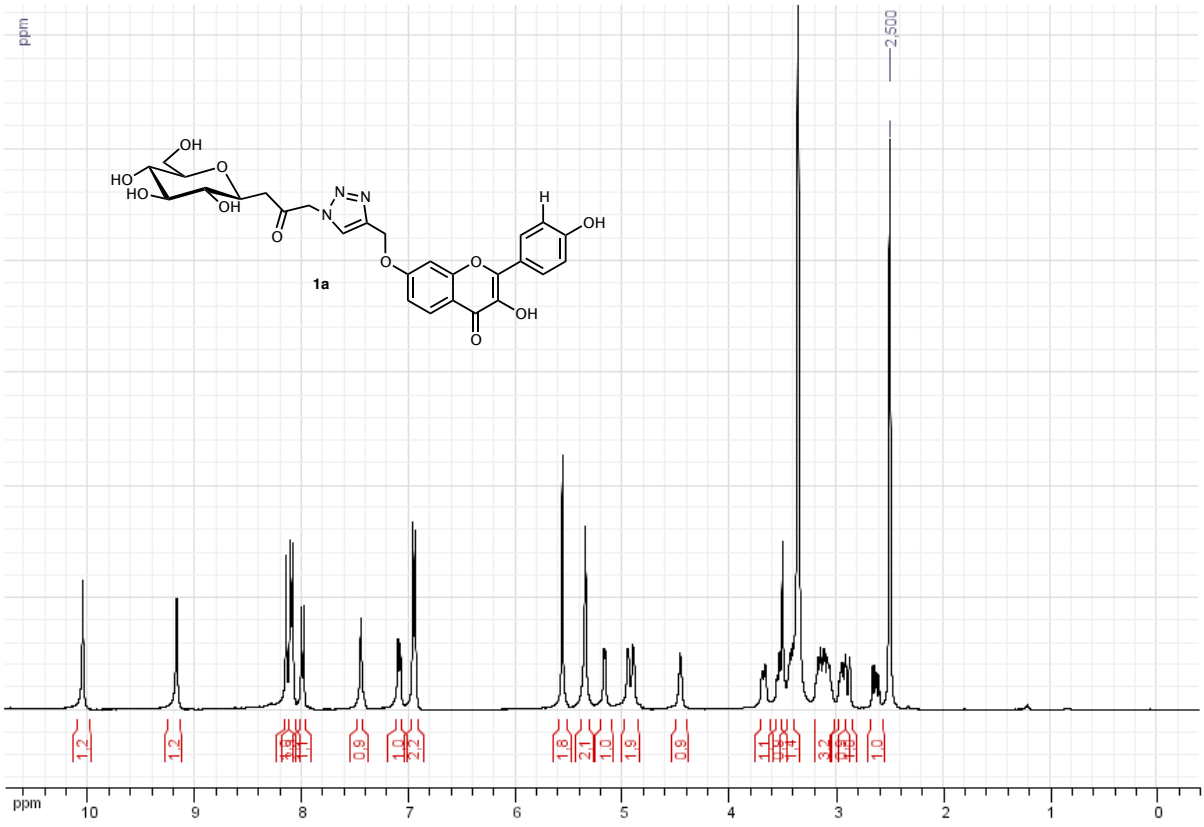


^{13}C-NMR (90.6 MHz; DMSO)

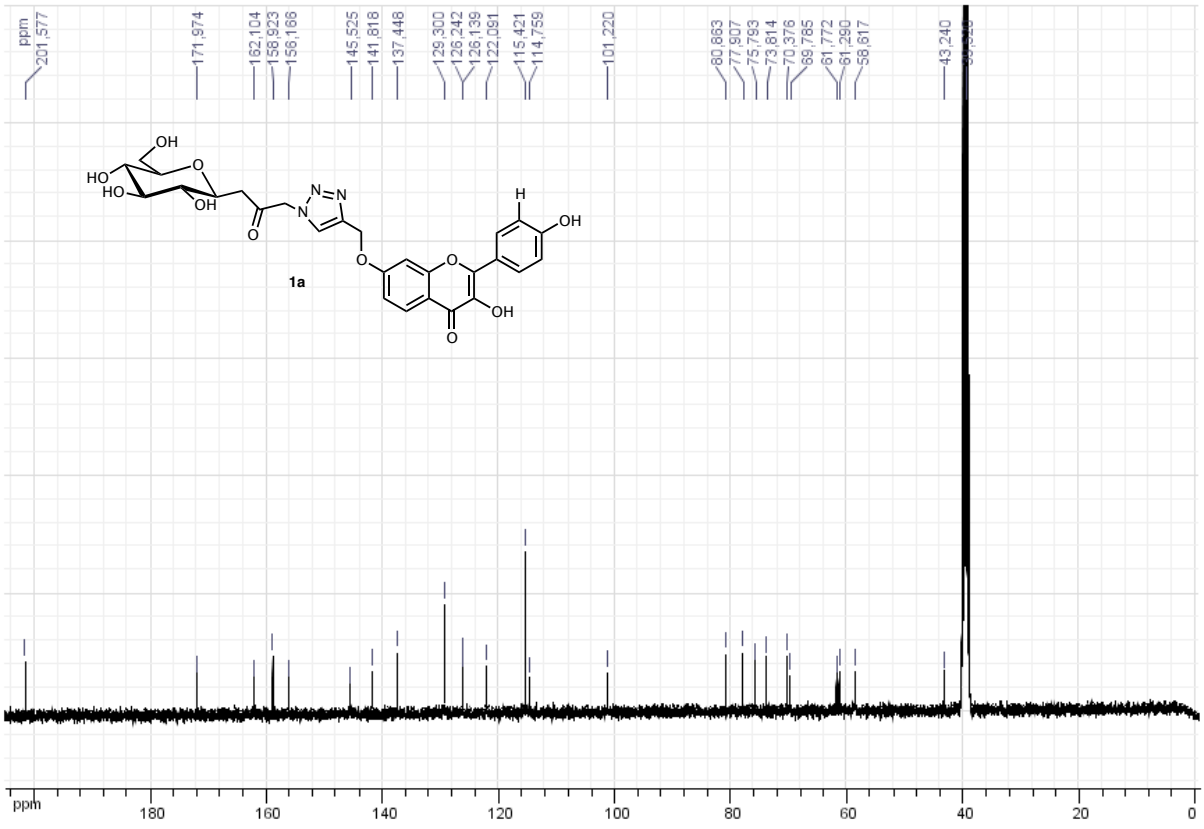


Triazole-linked flavonoide-sugar 1a.

^{1}H-NMR (400 MHz; DMSO)

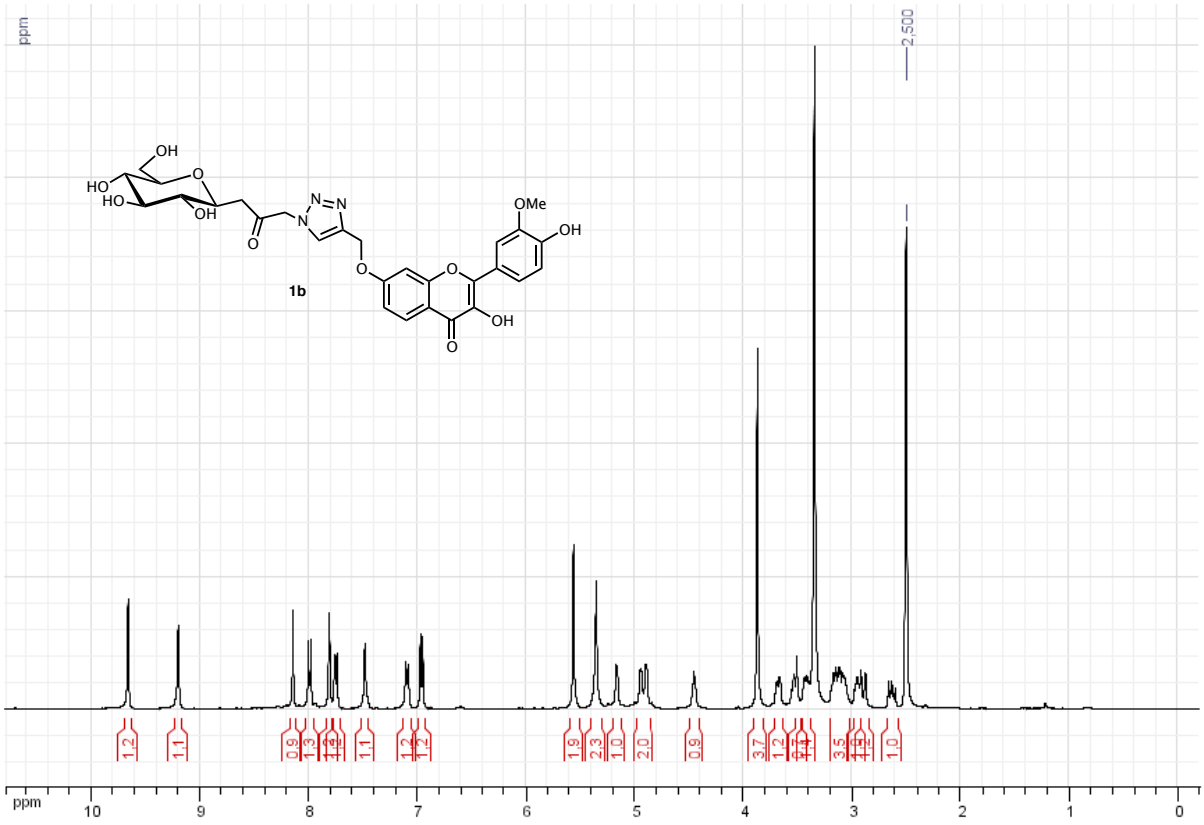


^{13}C-NMR (100.6 MHz; DMSO)



Triazole-linked flavonoide-sugar 1b.

^{1}H-NMR (400 MHz; DMSO)



^{13}C-NMR (100.6 MHz; DMSO)