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Computational Synthesis Planning Using Big Data

Computational Syntese planlægning ved hjælp af big data

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Abstract

Resumé

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2 Introduction MANGLER

kkk [2]

3 Overview

This section briefly describes what each of the following sections contain, thus making it easier for the reader to find points of interest.

- Section 4 contains definitions that is used in this thesis. What is a compound, a reaction, a synthesis plan and how is a hypergraph defined?
- Section 5 tells the reader about the design decisions that was made in the process of creating a hypergraph using the $C++$ programming language.
- Section 6 describes the principles behind Yen's algorithm and the conversion of the algorithm so that it may be used with hypergraphs. It also describes how the algorithm have been modified to handle larger instances of hypergraphs.
- Section 7 describes the two different shortest path algorithms implemented: An algorithm using a dynamic approach using recursion[6] and a Dijkstra inspired approach called STB-Dijkstra[5]. I furthermore contains the results of the testing made to ensure the correctness of the algorithms.
- Section 8 contains a description of the Beilstein database and how it is possible to extract data through the browser interface Reaxys. It also contains an evaluation of the data quality and suggests solutions to handle eventual problems with the data.

- Section 9 shows the results of running the algorithms on Beilstein data and contains a discussion of the results and a description on how the data was produced.
- Section 10 discusses possible alterations to the written algorithms to handle errors, and some ideas to interesting manipulation of the data from Beilstein.

4 Preliminaries

This section contains definitions that will be used throughout this paper. For the hypergraph specific part, it is assumed that the reader have a basic understanding of graph theory.

4.1 Compounds

A compound is a chemical substance composed of atoms held together by chemical bonds. A compound can be converted to a different chemical composition by interaction with a second chemical compound via a chemical reaction. In this process, bonds between atoms are broken in both of the interacting compounds, and then bonds are reformed so that new associations are made between atoms. Schematically, this reaction could be described as AB + CD -> AD + CB, where A, B, C, and D are each unique atoms; and AB, AD, CD, and CB are each unique compounds. To express the composition of a compound, chemical formula is used. A chemical formula is a way of expressing information about the proportions of atoms that a particular chemical compound is made of, using the standard abbreviations for the chemical elements, and subscripts to indicate the number of atoms involved. An example of this could be water that consists of two hydrogen atoms and a single oxygen atom which is written as H_2O.

4.2 Reactions

A chemical reaction is a transformation from one set of compounds, denoted educts, to another set of compounds, denoted products. Reactions can have different properties such as relocating bonds and/or moving functional groups. Each reaction has their own yield and usually the more complex a reaction is, the lower the yield becomes. This is due to the fact that reactions often are balanced and nothing is removed. An example is the following reaction:

$$CH_4 + 2O_2 \rightarrow CO_2 + 2H_2O \tag{1}$$

The yield of the reaction is dependent of what we would determine as the goal of the reaction. In the above example would it depend on if we want to create carbon dioxide or water. A reaction could of course have multiple yields stating how much the yield is for each of the products. Throughout this thesis there will be two different graphical versions of a reaction as show below.

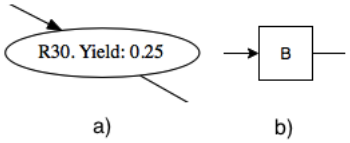


Fig. 1: **a)** Reaction when part of output files from program. Consisting of "R"+ID and the yield of the reaction. **b)** Reaction when drawn as minor example for thesis. Always have capital letters as identifiers.

4.3 Synthesis Plans

A synthesis plan is a series of reactions that produces a target compound. The synthesis plans will usually have a reverse tree like structure where the root is the target compound and the leaves are starting compounds. All complete hypergraphs in this paper marks the target compound as red, and the starting compounds as green.

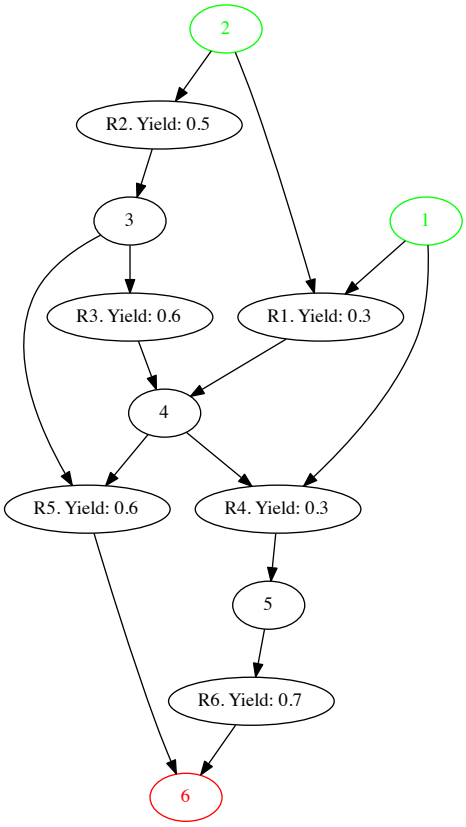


Fig. 2: Example of a complete hypergraph

When a synthesis plan is created the nodes are not colored. It is however easy to see that the compounds with in-degree = 0 is the starting compounds, and the only compound with out-degree = 0 is the target compounds.

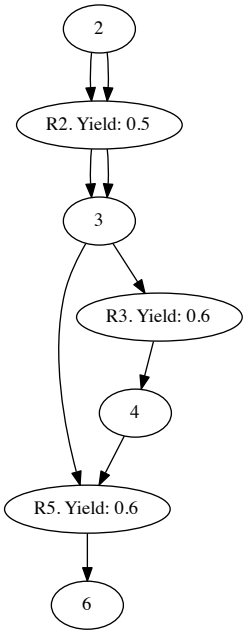


Fig. 3: Example of a synthesis plan given the hypergraph in fig. 2

4.4 Hypergraphs and Hyperpaths

Hypergraphs
A directed hypergraph h is a set V of vertices and a set E of hyperedges, where each hyperedge $e = (T(e), H(e))$ is an ordered pair of non-empty multi-sets of vertices. The set $T(e)$ is denoted as the tail of the hyperedge and $H(e)$ is the head. If $|H(e)| = 1$ then the hyperedge is denoted as a B-hyperedge. If all edges in the hypergraph is B-hyperedges, then the graph is denoted a B-hypergraph. This paper will only consider hypergraphs that are B-hypergraphs. A hypergraph $H' = (V', E')$ is a subhypergraph of $H = (V, E)$ if $V' \subseteq V$ and $E' \subseteq E$.[3]

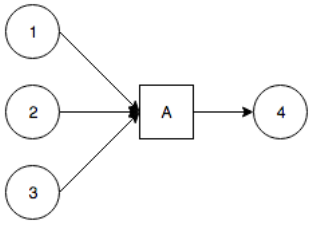


Fig. 4: Example of hyperedge A. $T(A) = \{1, 2, 3\}$, $H(A) = \{4\}$

Hyperpaths

A path P_{st} from s to t in a B-hypergraph is a sequence $P_{st} = \langle e_1, e_2, e_3, ..., e_q \rangle$ of B-hyperedges such that $s \in T(e_1)$ and $t = H(e_q)$ and $H(e_i) \in T(e_{i+1})$ for $i = 1..q-1$. Its length $|P_{st}|$ is the number q of hyperedges. If $t \in T(e_1)$, then P_{st} is a cycle. A hypergraph is acyclic if it does not contain any cycles. [3]
A hyperpath $\pi_{st} = (V_\pi, E_\pi$ from a source vertex s to a target vertex t in a B-hypergraph H is a subhypergraph of H with the following properties: If $t = s$, the $V_\pi = \{s\}$ and $E_\pi = \emptyset$. Otherwise, E_π can be ordered in a sequence $\langle e_1, e_2, ..., e_q \rangle$ such that

1. $T(e_i)\{s\} \cup \{H(e_1), h(e_2, ..., h(e_i - 1)\}$ for all i
2. $t = H(e_q)$
3. Every $v \in V_\pi \setminus \{t\}$ has at least one outgoing hyperarc in E_π, and t has zero.
4. Every $v \in V_\pi \setminus \{s\}$ has at least one ingoing hyperarc in E_π, and s has zero. [3]

5 Designing a hypergraph in C++

A hypergraph consists of nodes and hyperedges. These where implemented as two structs that have their own seperate attributes.

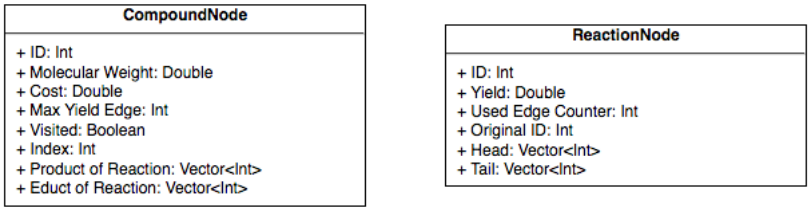


Fig. 5: The structure of CompoundNodes (nodes) and ReactionNodes (hyperedges)

There are some non-trivial attributes in the CompoundNode struct.The difference between Molecular weight and the cost is that the cost is the accumulated weight of the given starting materials that is used to reach this compound, and the molecular weight is the actual weight the compound it self. This of course means that if a compound is a starting compound, then the cost and the molecular weight is the same.
The Max Yield Edge attribute is an identifier to the hyperedge that is used to reach this compound. The first time a compound is reached the attribute is changed to hold the ID of the reaction from where the algorithm came. If the compound is reached and the cost of the compound is changed, then the attribute would change, so that it always points to the edge used to calculate the current cost of the compound.
Visited and Index are attributes used when the hypergraph is pruned (Section 7.2.2) and to keep track of a CompoundNodes position in the priority queue

used when running STB-Dijkstra (Section 7.2).
The two vectors, Product of Reaction and Educt of Reaction, are lists containing information on which reactions the compound is a product of and which reactions it is a educt to. This is used to make traversal of the hypergraph easy.

The ReactionNode also contains some non-trivial attributes. The Used Edge Counter is used by the STB-Dijkstra algorithm (Section 7.2) to make sure that all educts to a reaction have had their min cost evaluated before the reaction can be used. The Original ID attribute is used when we need to change a hyperedge into a B-Hyperedge. If there is more than one product of a reaction we need to split the reaction into multiple new reactions, so that the hyperedge becomes legal. It is for result purpose needed to have a pointer to the original ID of the reaction.

The hypergraph is designed to consist of four dynamic lists, vectors, to facilitate quick lookup time and fast attribute reseting. The two vectors compoundList and reactionList are list of size V and E respectively, containing pointers to the compounds and reactions of the given hypergraph. These two vectors are used to reset the attributes of the compounds and reactions after each iteration of the algorithms. The compoundLookupList and reactionLookupList vectors are used to have have a constant lookup time at the cost of space. Both are vectors of pointers to compounds and reactions, just as compoundList and reactionList, but are of size N and M instead, where N is the highest compoundID and M is the highest reactionID. This means that if a reaction with ID 235406 is added to the hypergraph, a pointer to the reaction is pushed to to the back of reactionList and added to reactionLookupList[235406]. This makes it possible to edit a single compound or reaction in $\mathcal{O}(1)$ time, using the lookupLists, and to edit all compounds or reactions in $\mathcal{O}(V)$ and $\mathcal{O}(E)$ respectively.
If the structure was only used on homemade hypegraphs where we would label the compounds from $0, 1, ...N$ and the reactions $0, 1, ..., M$, we would only need the two lookupLists, since we would have two vectors of size $V = N$ and $E = M$ and still have the constant lookup time. However, when working on real data we could have a hypergraph with the reactionIDs 6, 12820 and 50003829 as the only reactionsNodes in the hypergraph. This would result in a vector of size 50003829 but we only have three entries in the vector. So when we need to reset the attributes in the use of the shortest path algorithms we would have to run through the whole vector. This is where the two second lists are useful. Even though we have a reactionLookupList of size 50003829 the reactionList in this hypergraph would only be of size 3. Notice that since we are working with pointers to, and not copies of, compoundNodes or reactionsNodes there is no problem in only changing the attributes by accessing it through one of the lists.

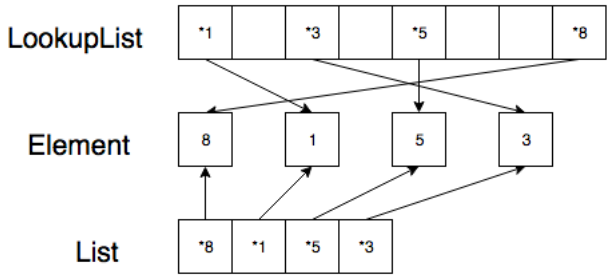


Fig. 6: Illustration of the difference between List and LookupList.

6 Finding The K-Best Synthetic Plans

This section describes how to find the K-Best paths of a hypergraph modifying an algorithm made by Jin Y. Yen. The section starts out by describing the work flow of the algorithm, and then proceeds to deal with the alterations that are needed to run the algorithm on a hypergraph.

6.1 Yen's Algorithm

Yen's algorithm is an algorithm that computes the K-shortest paths for a graph with non-negative edges. It was publish in 1971 and uses any shortest path algorithm to find the best path and then proceeds to find the $K-1$ deviation of the best path. [4]
It starts out by finding the best path using a shortest path algorithm. Once the best path have been found it uses the path to find all the potential second best paths by fixing and removing edges in the graph.
By using the same first vertex as the original path but removing the first edge, it forces the shortest path algorithm to take another route through the graph and thereby creating a potential second best path. This is added to the list of potential paths and the algorithm can continue to derive other paths from the best path. By fixing the first edge in the previous best plan, Yen's algorithm forces the shortest path algorithm to take the first edge which it now shares with the best path. However, now the algorithm have removed the second edge from the original path and once again forces the shortest path algorithm to find alternative routes. This process is then repeated until we reach the next to last vertex in the best path.
By sorting the list of potential paths, it has the second best path at the start of the list and it can add it to the final list of best path. The algorithm then repeats on the second best path to find the third best path. This is done until all K-best path have been found or there are no more paths to find.

6.2 Yen's Algorithm On Hypergraphs

We use the principles from Yen's algorithm to make our own algorithm that will work on hypergraphs. To handle the problem of generating all derived paths from our best path in our hypergraph, we use a method called Backwards-Branching. [3] [5] [6]

Algorithm 1: Backwards Branching for B-Hypergraph

```
1  function Back−Branch(H,π)
2      B=∅
3      for i = 1 to q do
4          Let H^i be a new hypergraph
5          H^i.V = H.V
6          // Remove hyperarc from H
7          H^i.E = H.E \{π.p(v_i)}
8          // Fix Back tree
9          for j = i+1 to q do
10             H^i.BS(vj) = \{π.p(v_j)\}
11         B = B ∪ \{H^i\}
12     return B
```

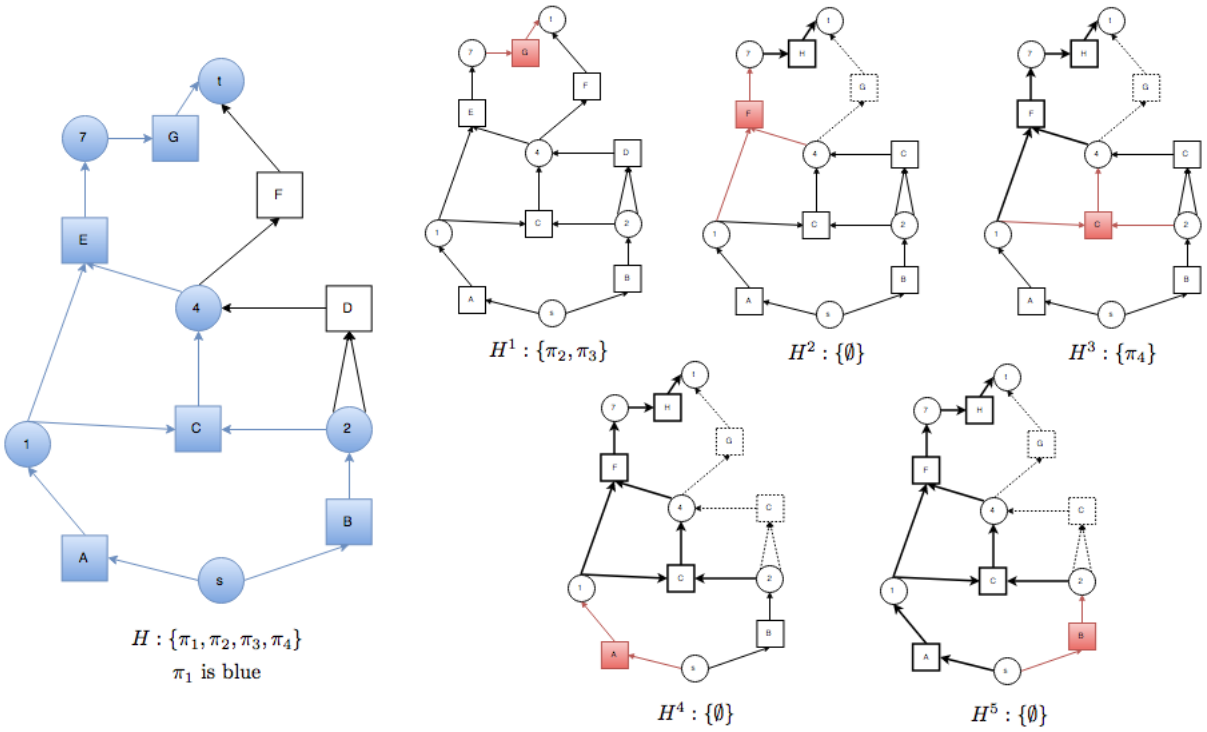


Fig. 7: An example of branching for hypergraphs. H is the original hypergraph. The vertices and hyperedges marked with blue are part of the best path. The rest of the figure illustrates the backwards branching. Each of the smaller figures shows a hypergraph H^i and how it is created from H. Dotted hyperedges and red heyperedges are not part of the hypergraph, but have been deleted due to branching. Hyperedges in bold are fixed hyperedges. When hyperedges are fixed it leads to other hyperedges being deleted (dotted). The caption beneath each hypergraph represents the possible paths that are available in the given hypergraph.

However, this algorithm have a problem when working on a larger hypergraph. It demands that each time we make alterations on the hypergraph we have to make a copy, H^i, of the graph, H, with the exception of the hyperedges that is removed when fixing the back tree and removing $\pi.p(v_i)$.
This could easily work for smaller graphs, but if we use this on a hypergraph that would contain all of the data from beilstein, we would have to copy a graph of multiple GigaBytes.
To handle this problem I came up with the idea of creating an overlay for the graph instead of copying it. The overlay would work as an transparent on top of the original graph, stating which edges still is accessible. This is done by creating a *vector<bool>* which has a length of R, where R is the number of reactions. Normally a reaction would contain at least 28 bytes of data:

- 3x ints of 4 bytes each
- 1x double of 8 bytes
- 1x *vector<int>* head of length one of at least 4 bytes
- 1x *vector<int>* tail of length N (number of educts) of at least 4 bytes

This can be reduced dramaticly by using the *vector<bool>*, since c++ only uses 1 bit per boolean in the vector instead of the regular 1 byte per boolean.[7] This means if working on a hypergraph with 40 million reactions, we would be able to create an overlay using 5 MB of space per alternated graph, instead of copying a hypergraph were the reactions alone uses at least 1,12 GB per copy.
As the figure below shows, we never change or remove anything on the hypergraph. We simply create the following overlay:

Reaction	A	B	C	D
Usable	true	true	true	false
Bit Representation	1	1	1	0

And then when trying to use an edge, we ask: "Does overlay at reaction A exist?". If yes, you can use it. If no, the edge have been "removed", and therefore cannot be used.

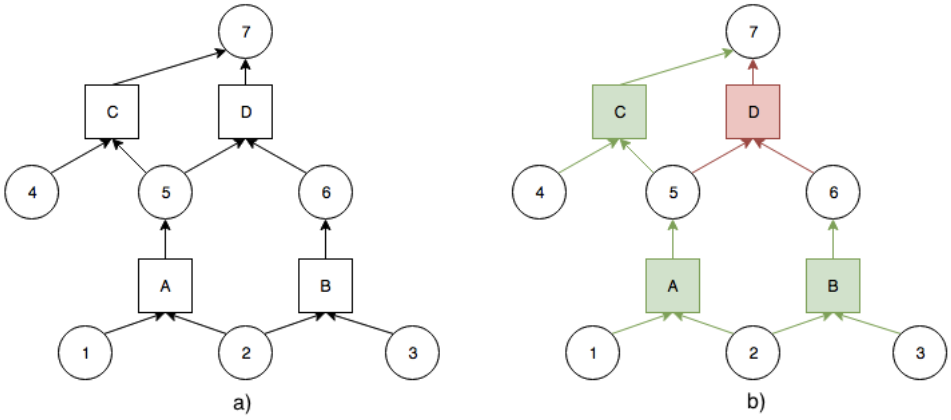


Fig. 8: a) The original hypergraph. b) The original hypergraph, but using the overlay. If the reaction is green it is still usable. If red then it have been "removed" from the hypergraph.

This of course means that the algorithm for back-branch have to be changed accordingly. Instead of the hypergraph as input we now give it an overlay. This overlay is changed so it fits with the new layout of the graph. Instead of deleting hyperedges in the copy, we now simply changes the boolean at the index of the hyperedge.id. True if we should "add" the hyperedge and false when we want to "remove" a hyperedge.

Algorithm 2: Backwards Branching for B-Hypergraph using overlay

```
1  function BackwardsBranching(π, Overlay)
2      List B = ∅
3      // q = Path length
4      for i = 1 to q do
5          //remove i'th hyperedge from Path in overlay
6          Set Overlay[π[i]] to false
7          //fix the backtree
8          for j = i downto 1  do
9              vertex C <− π[j].head
10             for each hyperedge into C
11                 Set Overlay[reaction.id] to false
12             Set Overlay[π[j]] to true
13         endfor
14         B = B ∪ {Overlay}
15     endfor
16     return B
17 endfunction
```

Now that we have the branching in place are we able to construct an algorithm that are similar to Yen's algorithm, but can run on hypergraphs. As input it takes a start node (s), a goal node (t), and an integer K, where K is the number of best paths we want to find. The algorithm, however, only takes a single node as its starting node, which is a problem when working with hypergraphs. The

reason for this is that the size of the tail of a hyperedge usually is larger than 1 and this by default gives us more than one starting node. This is fixed by making s a dummy node that have an hyperedge $e = (H|1|, T|1|)$ to each of the starting nodes, transforming the multiple sources to a single source.
The algorithm creates a heap, L, and a list, A, which will contain the K-best paths once the algorithm is finished. It then finds the best path using a shortest path algorithm and inserts it into the heap. Inside the loop it extracts the best path found from the heap and performs a backward branching, and finds all possible paths in the branches. If there is a path from s to t, then this path is added to the heap. The algorithm either terminates if the heaps is empty (No more paths available) or once it have found the K-best paths.

Algorithm 3: K-Shortest Paths Algorithm in B-Hypergraph

```
1  function YenHyp(s, t, K)
2      L = new heap with elements (overlay, π)
3      A = List of shortest paths
4      //(Graph is default overlay (all true))
5      π = shortestPath(Graph, s,t)
6      Insert (Graph, π) into L
7      for k = 1 to K do
8          if L = ∅
9              Break
10         endif
11         (Overlay′, π′) = L.pop
12         add π′ to A
13         for all Overlay^i in BackwardBranching((Overlay′,π′)) do
14             π^i = shortestPath(Overlay^i, s, t)
15             if π^i is complete
16                 Insert( H^i, π^i) into L
17             endif
18         endfor
19     endfor
20     return A
21 endfunction
```

YenHyp makes K iterations. In each iteration the length of a hyperpath determines the number of calls to the shortest path algorithm. The worst case for the length of the hyperpath is $\mathcal{O}(|V|)$. Hence the running time of YenHyp becomes:

$$\mathcal{O}(K \cdot |V| \cdot SP) \tag{2}$$

Where SP is the running time for the shortest path algorithm used.

6.3 Cost Function

Before we are able to find the K-best paths of our hypergraph, we should be able to compare them with each other. To do this we use a additive weight function defined in the following way on a given hyperpath π_{st} from s to t:

$$W(u) = \begin{cases} w(p(u)) + F(p(u)), & \text{if } u \in V \setminus \{s,\ starting\ nodes\}. \\ C, & \text{Starting Nodes.} \\ 0, & \text{Otherwise} \end{cases} \quad (3)$$

$W(u)$ define the cost of node u and C is in this particular case, the molecular weight of a compound. The predecessor function p is used to find the hyperedge $e = p(u)$ which have u as head. The function F is a non-decreasing function of the sum of the weights of the nodes in the tail to e. Each of the nodes are multiplied by the retroyield of the edge, $1/yield$.

$$F(p(u)) = \sum (W(Tail(p(u)) \cdot (1/yield_{p(u)}) \quad (4)$$

We are now able to distinguish between the paths found and extract the K-best plans. [6]

7 Shortest Path

This section describes two different approaches to the shortest path problem in a hypergraph. A dynamic approach proposed by Carsten Grønbjerg Lützen and Daniel Fentz Johansen [6] and a Dijkstra inspired approach proposed by Lars Relund Nielsen, Kim Allan Andersen and Daniele Pretolani [5].

7.1 Dynamic Approach

The dynamic approach to find shortest path in a hypergraph is an algorithm proposed by Carsten Grønbjerg Lützen and Daniel Fentz Johansen in their Master thesis *A Computational and Mathematical Approach to Synthesis Planning.*[6]. It uses recursion to calculate the cost of compounds.

7.1.1 Approach

The dynamic approach starts at the target compound and moves away from it step by step in a recursive manner. Once it hits a starting compound it backtracks through the recursions, using the now gained cost to calculate the cost of those along its path. The approach can be defined as following:

$$Cost(V) = \min_{e \in productOfReaction} 1/yield_e \cdot \sum_{u \in Tail(e)} Cost(u) \quad (5)$$

The cost of a node V is the minimum over all the possible ways to synthesize it. The cost of a potential approach to synthesize node V is the sum of cost of the educts involved times the retroyield of the reaction required for transforming the educts to the product V .[6]

Algorithm 4: Dynamic programming for finding the best path

```
1 function Min(V)
2     if(V) is starting material
3         return Cost of V
4     endif
5     mincost <− inf
```

```
6     for all e ∈ BS(V) do
7         cost <− cost of e
8         for all u ∈ Tail(e) do
9             cost <− cost + Min(u)
10        endfor
11        if mincost ≤ cost
12            mincost <− cost
13            V.minedge <− e
14        endif
15    endfor
16    return mincost
17 endfunction
```

The worst hypergraph that we could run the algorithm on a hypergraph where each hyperedge $e = (|T| = 1, |H| = 1)$. When connected these would form a linked list which would lead to the running time of $\mathcal{O}(V + E)$.

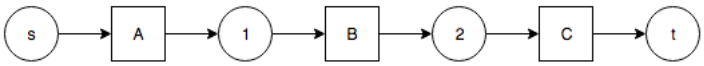


Fig. 9: Example of worstcase scenario of a hypergraph

7.1.2 Problems

A problem with the dynamic approach is that it does not work on hypergraphs with cycles due to its recursive nature. When a cycle it hit, it will start an endless loop to figure out the cost of a node.

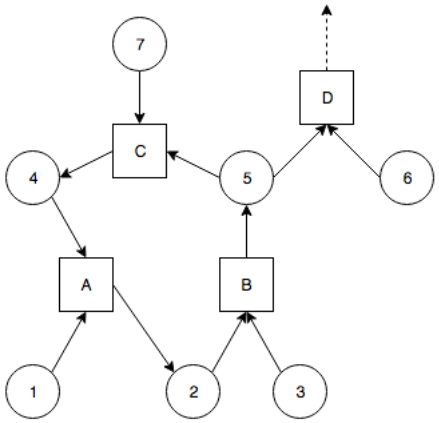


Fig. 10: Example of graph with cycle.

As seen in the example in fig. 10, the algorithm enters the cycle in reaction D. When trying to calculate the weight of 5, it needs the weight of 2 and 3. 3 is a starting node, so the weight is the weight of the compound itself. 2 however needs the weight of 1 and 4. Again 1 is a starting node, so no calculations are

needed. 4 however needs the weight from 7 and 5. Now we hit 5 again, and the loop starts. This could of course be handled by removing an edge from the hypergraph, and thereby breaking the cycle. This however would effect the results, because how do we know that the edge we remove would not have contributed to a better result in the end. This is where Nielsen et. el STB-Dijkstra algorithm comes into play.

7.2 The STB-Dijkstra Algorithm

Nielsen algorithm, or SBT-Dijkstra, is an algorithm that uses the same principles as shortest path algorithm conceived by Edsger W. Dijkstra in 1956. The original Dijkstra is asymptotically the fastest known single-source shortest-path algorithm for arbitrary directed graphs with unbounded non-negative weights. [8] Nielsen et. al. have modified it to be used on hypergraphs.

7.2.1 Approach

The algorithm requires that the cost of all nodes in the hypergraph is ∞ and that the hyperedge property $kj = 0$. It then adds the dummy node s to its priority queue. As long as the priority queue is not empty it will extract the minimum, and for each hyperedge going out of u increase the kj counter in the given hyperedge. Once the counter is equal to the size of the tail of the hyperedge, the algorithm can proceed to calculate the weight of the node v, which is the head of the hyperedge. Should the existing weight of v be larger than the newly calculated weight, the algorithm updates the weight to the newly found weight and adds v to the priority queue, given that the node have not been added from another edge. If the cost changes, the min-edge attribute is also set to be the edge from which the new cost have been calculated.

Algorithm 5: STB-Dijkstra for finding the best path

```
1  Initialization: Set W(u) = ∞ ∀ u ∈ V, k_j = 0 ∀ e_j ∈ E,Q = {s} and W(s) = 0
2  function SBT−Dijkstra
3      while (Q = ∅) do
4          select and remove u ∈ Q such that W(u) = min{W(x)|x ∈ Q}
5          for (e_j ∈ FS(u)) do
6              k_j < −kj + 1
7              if (k_j = |T(e_j)|)
8                  v <− h(e_j)
9                  if (W(v) > w(e_j) + F(e_j))
10                     if (v ∉ Q
11                         Q <− Q ∪ \{v\}
12                     endif
13                     W(v) <− w(e_j)+ F(e_j)
14                     p(v) <− e_j
15                 endif
16             endif
17         endfor
18     endwhile
19 endfunction
```

When node u is removed from the candidate set Q (the priority queue), $W(u)$ is the minimum weight of all hyperpath from s to u. The condition in line 7 ensures that each hyperedge e_j is processed only once after the minimum cost for its tail nodes have been determined. The implementation of the priority queue, Q, dictates the running time of the algorithm. I have followed Nielsen et. al. example and chosen a heap structure. Since I have decided to implement the simple binary heap the running time of the algorithm becomes: $\mathcal{O}(E\ log_2(V) + size(h))$. The size of the hypergraph, h, is the sum of the cardinalities of its hyperedges:

$$size(h) = \sum_{e \in E} |e|. \tag{6}$$

Where the cardinality of a hyperedge e is the number of nodes it contains, i.e. $|e| = |T(e)| + 1$.[5]

7.2.2 Optimizing For Large Hypergraphs

Since the STB-Dijkstra algorithm expands to the whole graph it might check nodes that is not a part of the hyperpath we are looking for. If we look at the hypergraph in fig. 11, is it easy to see that given the starting nodes 1,2,3,4 and the goal 10, that there is no need to use the hyperedges R2, R4, and R8, since they never would lead to our goal.

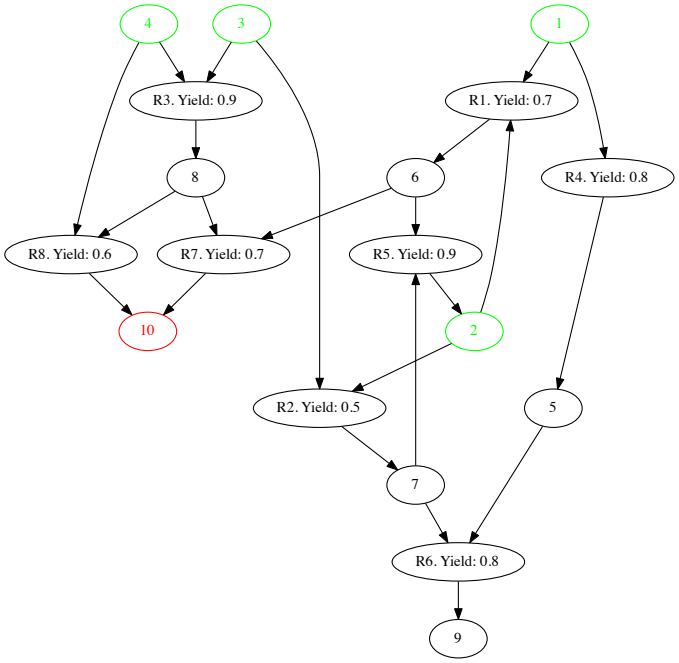


Fig. 11

I therefore decided to combine the dynamic approach with STB-Dijkstra algorithm. The dynamic approach starts at the goal node, and travel through the hypergraph until it reaches s, thereby only using nodes on the way from goal to start. The algorithm however had the problem of not being able to work on hypergraphs that contained a cycle, and we could not just delete an edge when we hit a cycle since it could lead to wrong results.
We can however use the dynamic algorithm to mark the edges it hits on the way from goal to start. This would make it able to detect when it hits a cycle, since the node would already have been marked, and simply just skip the node and proceed to the next in its potential path. Once the algorithm is finished, we can transform the markings to an overlay that limits the hypergraph so it only "consist" of the reactions hit by the dynamic algorithm. Using this overlay reduces the search space of the STB-Dijkstra from the whole hypergraph to only concern the hyperedges that will lead to a path from s to t.

Algorithm 6: Reduce STB-Dijkstra search space

```
1  graphOverlay is a list of size = #hyperedges where all entries are false.
2  function reduceGraph(graphOverlay, v, s)
3      if (v.id = s.id)
4          return graphOverlay;
5      endif
6      if (v.visited = false)
7          for(reaction : v.ingoingEdge )
8              for (tailCompound : reaction->tail)
9                  v.visited <- true;
10                 graphOverlay = reduceGraph(graphOverlay, tailCompound, s);
11             endfor
12             graphOverlay[reaction.id] <- true;
13         endfor
14     endif
15     return graphOverlay;
```

Since the running time for the dynamic approach was $\mathcal{O}(V + E)$, the combined running time becomes:

$$\mathcal{O}((V + E) + (E\ log_2(V) + size(h))) \tag{7}$$

The $(V + E)$ is however removed since the $E\ log_2(V) + size(h)$ dominates. This results in a running time of:

$$\mathcal{O}(E\ log_2(V) + size(h)) \tag{8}$$

The reason that the terms V and E does not change since in worst case are we not able to prune any of the hypergraph away using the dynamic approach.

7.3 Testing

In the development phase of my implementation of the algorithms have I used some small instances of hypergraphs that would be easy to check if they were correct by running the algorithms by hand and check the results. The hypergraphs have previously been used in [6] (A.1) and [3] (A.2). In this phase I also

created small tests to check how the algorithms would handle cycles (A.4) and deadends (A.3). However, to be able to test my implementations on a larger automated scale, I had my colleague Rojin Kianian use the program SynthWorker to create some random generated hypergraph. SynthWorker is the product of Carsten Grønbjerg Lützens and Daniel Fentz Johansens master thesis [6]. It have been tested thoroughly and can therefore be used to test the correctness of my implementations. The smaller graphs, A.4,A.3, A.2, A.1, were all hardcoded in seperate testprograms, but when we started working with the automated test, we had to agree on a input format. We decided to go with a dot inspired format, which I already had used to visualize the hypergraphs and the output plans. The format contains of declarations and edges. It starts of by declaring all reactions and compounds. A compound is declared as following:

ID, Identifier, notS/S, "Weight", Weight, "Cost", Cost;

An example could be the following compound: ID: 4, Weight = 5, Cost = 6,25, which is not a starting compound. This would be written in the input file as:

4 N notS Weight 5 Cost 6.25 ;

The notS/S argument is to determine whether a compound is a starting compound (S) or a just a compound (notS). As for a reaction the format should be:

ID, Identifier, "Yield", Yield in decimal;

So the reaction with ID = 6 and a yield of 80 % would be:

6 R Yield 0.8 ;

As the reader might have guessed the "identifier" is either N or R, which tells us whether it is a compound = N or a reaction = R. The format then states that once all compounds and reactions have been declared, they should be followed by a line which separates the declarations and the edges. This line should always state "REACTIONS" to indicate that the following lines are edges. The connections between compounds and reactions are written in the regular dot notation: s->t. This creates an edge going from s to t. If s is an ID of a reaction, then it states that t is a part of s' tail. If t is an ID of a reaction, then s is a part of t's head. The example shows how reaction ID=3 is connected to its educts and products. The educts are compound ID=1 and compound ID=2 and the product is compound ID=0.

0->3 ;
3->1 ;
3->2 ;

The test program written takes a hypergraph in the described format, the number of compounds and reactions, number of plans we wish (K) and a score table from SynthWorker. It then creates the hypergraph, tries to find K best plans of the graph and the compares the results with those from the score table. To handle the minor issue of rounding errors a σ can be assigned in the code. As of this moment $\sigma = 0,00007$. This constant have been chosen by running the tests with different values and noticing at what value the results became noticeable

different.

Test	Compounds	Reactions	Hypergraph	Plans existing	Plans found	Algorithm	#Errors
1	7	13	B.1	22	22	Dynamic	0
1	7	13	B.1	22	22	STB-Dijkstra	0
2	11	20	B.2	20	20	Dynamic	0
2	11	20	B.2	20	20	STB-Dijkstra	0
3	8	14	B.3	22	22	Dynamic	0
3	8	14	B.3	22	22	STB-Dijkstra	0
4	40	128	B.4	476	476	Dynamic	17
4	40	128	B.4	476	473	STB-Dijkstra	85
5	13	46	B.5	2121	2121	Dynamic	5
5	13	46	B.5	2121	2121	STB-Dijkstra	5
6	206	1045	B.6	50 (limited)	50	Dynamic	0
6	206	1045	B.6	50 (limited)	50	STB-Dijkstra	0
7	35687	170002	B.7	50 (limited)	50	Dynamic	0
7	35687	170002	B.7	50 (limited)	50	STB-Dijkstra	0

As the table above shows, there is errors in the fourth and fifth test. However at a closer inspection the errors with the dynamic approach in test four and five and the errors with STB-Dijkstra in test five, are of minor concern since the problem is that the result is off by 0,0001. The 85 error in test four using STB-Dijkstra, is a misleading problem. The design of the test expects that the algorithms finds the same paths as SynthWorker. The problem is not that the STB-Dijkstra have found 85 wrong paths, but that it have only found 473 of the 476 path available. This means that each time a path is not found the path comparisons shifts by one, leading to faulty comparisons.

Why the STB-Dijkstra algorithm fails to find the three missing paths is a problem that have not been solved. It is suspected to have something to do with the priority queue implemented and the ordering of the nodes within. There are a lot of error prints from the decrease-key function, stating that the key given is not smaller than the one already existing. These errors have only been seen when running on the tests from Rojin, and I suspect that it is because there are many paths with the same cost, and that this leads to some problems in the if statements that checks whether a newly calculated cost is lower than the existing, thus leading to a potential false instead of true.

8 Beilstein Data

The Beilstein database is the largest database in the field of organic chemistry. Since 2009, the content has been maintained and distributed by Elsevier Information Systems in Frankfurt under the name "Reaxys". The content covers more than 200 years of chemistry and has been abstracted from several thousands of journal titles, books and patents. Today the data is drawn from selected journals (400 titles) and chemistry patents, and the extraction process for each reaction or substance data included needs to meet three conditions:

1. It has a chemical structure

2. It is supported by an experimental fact (property, preparation, reaction)

3. It has a credible citation

Journals covered include *Advanced Synthesis and Catalysis, Angewandte Chemie, Journal of American Chemical Society, Journal of Organometallic Chemistry, Synlett* and *Tetrahedron.* [9][10]

8.1 Data Access

As mentioned above the content of the database is maintained and distributed by Elsevier Information Systems under the name "Reaxys". Reaxys[1] is accessible through any browser and is easy to navigate. It is possible to find a compound or a reaction and locate all the documents in which they have been a part of. An example would be the compound Strychnidin-10-one which is referenced in 1442 documents. This is also possible the other way around. Through Reaxys is it possible to search for a specific paper using keywords, authors, publication year, Journal title, etc. Once the paper have been found it is possible to see reactions and compound that are connected to this particular article. All data connected to a article, reaction or compound can be exported and downloaded through the Reaxys interface in different formats. In this thesis I have used the XML format to extract data from the database. It is important to notice that to use Reaxys properly, a login is required. I have here used the "sign in by your institution" function, making it possible to use the WAYF (Danish Universities and Higher Education) as a login.

8.2 Data Assessment

During my work with the data from the Beilstein database have I found several issues when it comes to using it to find shortest paths. First problem is that there are multiple instances of the same compound, each with a different Reaxys IDs. As seen in fig.12 have I found four different IDs for the compound Dysidiolide. These were found when I tried to reproduce the different synthesis plans of Dysidiolide from [1] using the referenced articles where each synthesis plan origins. E. J. Corey's version of Dysidiolide have the ID 8171938, Boukouvalas have two different with ID 7601810 and 7910427 and Danishefsky have the ID 7910428.
Since we have four different IDs for Dysidiolide we can't state a single goal compound to our program that would result in giving us these three synthesis plans. To handle this problem the program can take several goal compounds as an input, and by creating a dummy node t are we able to give the illusion of a single target.

[1] https://new.reaxys.com/

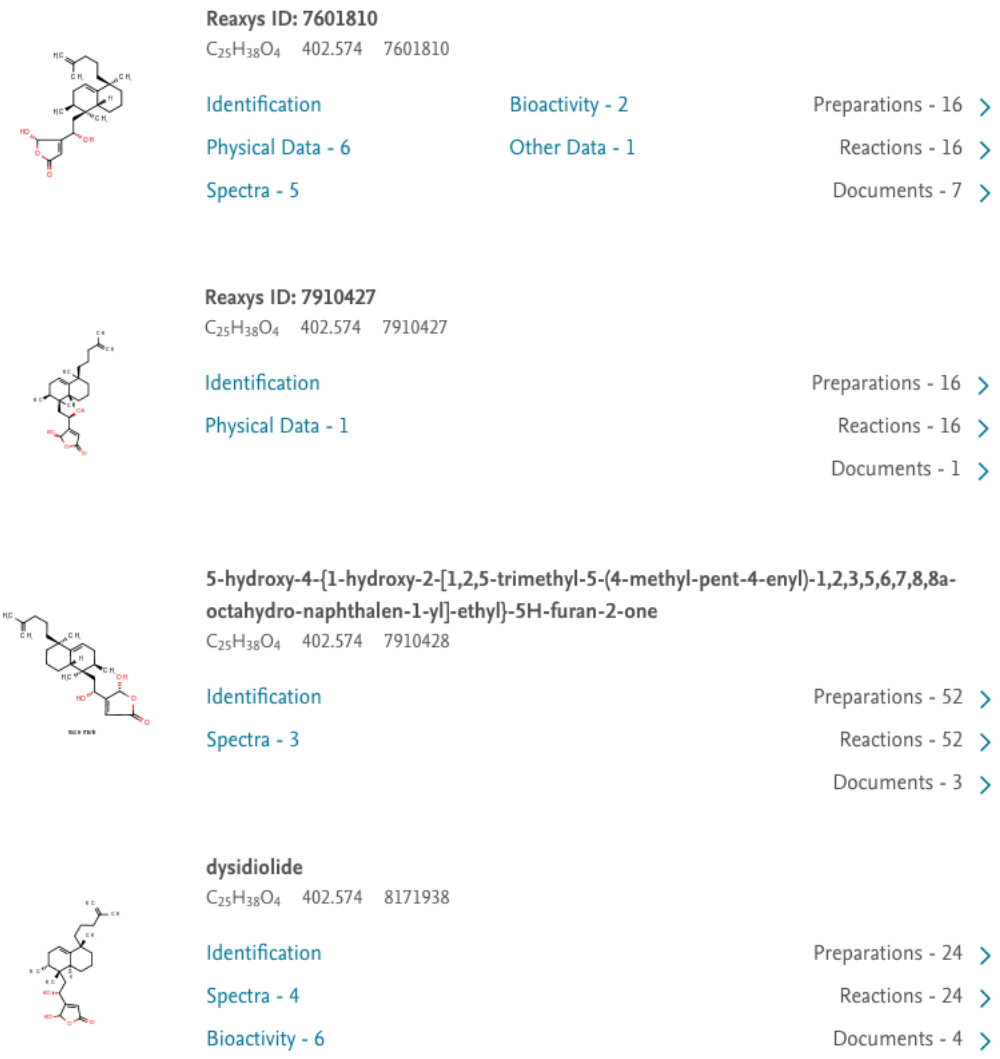


Fig. 12: Four different instances of Dysidiolide in Reaxys.

So what is causing this multiple ID issue? If we study fig. 12 can we see that the molecular weight and molecular formular are exactly the same, however if we look at the close up of the molecular structure in fig. 13 the compounds are not structured in the same way, even though the compounds are the same. The main differences is:

1. Which way some of the substructures are facing. Example: The lower $C_4O_3H_4$ is rotated differently in each instance or that we write H_2C instead of CH_2.
2. How the bond between two chemical elements are notated. Example: The bond to the OH in the bottom of the structure is either a "single" (d), "single down" (a) (c) or "single up or down" (b).

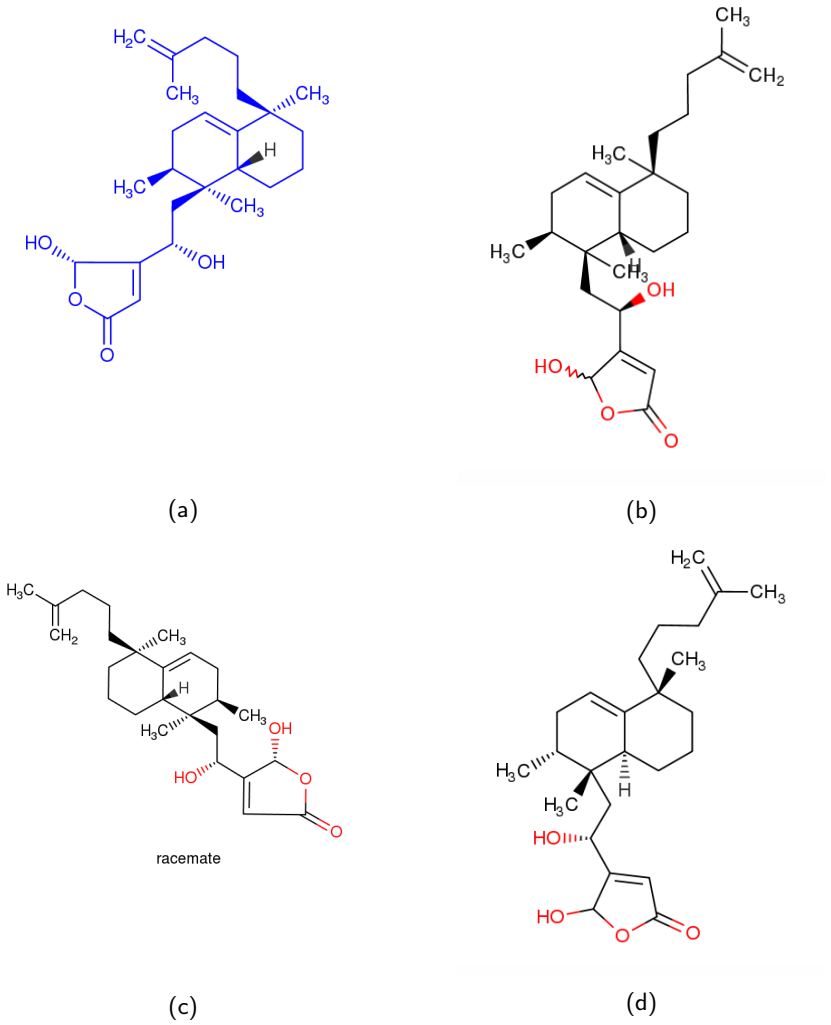


Fig. 13: Different versions of Dysidiolide: (a) ID 7601810 , (b) ID 7910427, (c) ID 7910428, (d) ID 8171938

Second issue is the problem of a reaction not having an educt or a product(fig: 14). This leaves the reaction incomplete and makes it useless in the graph construction. If there is no educt the hyperedge created will have an indegree of 0, and thereby making it unreachable. If there is no product the hyperedge will have an outdegree of 0, making it a deadend.

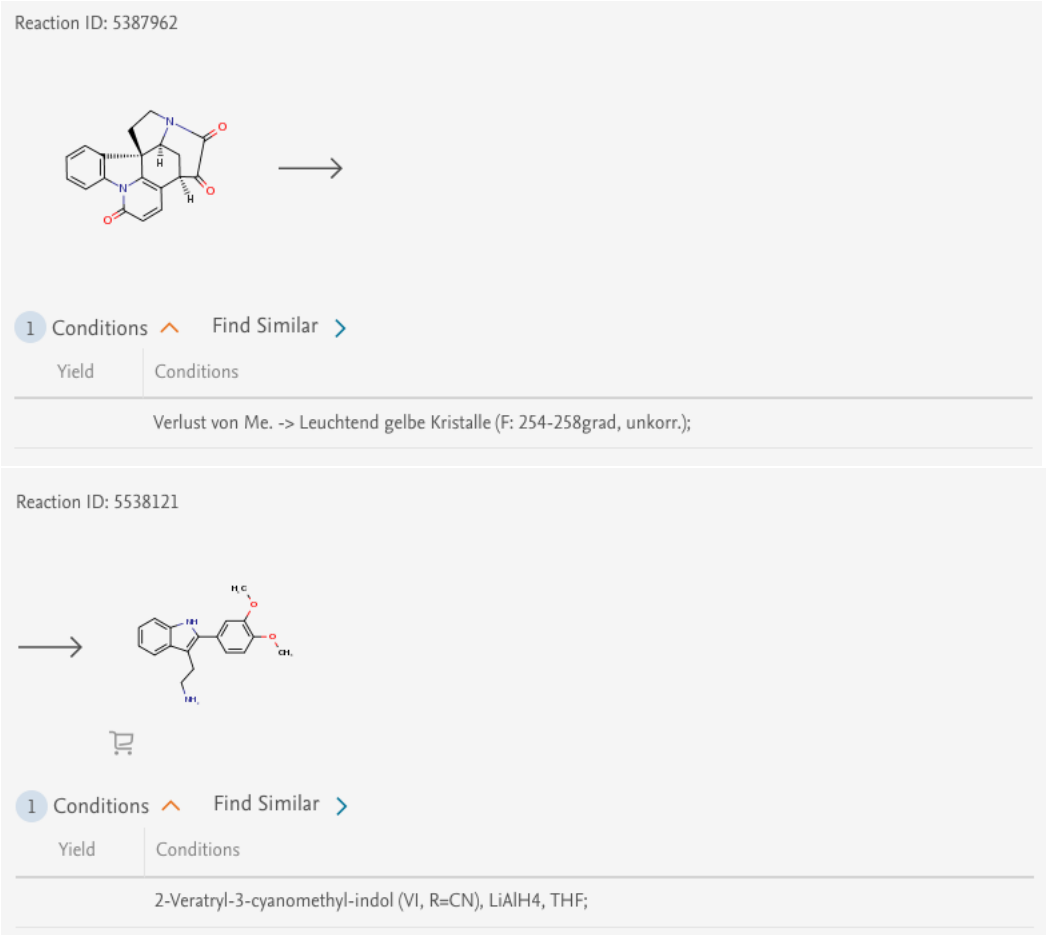


Fig. 14: Example of reactions that either is missing educts or products.

Third issue is that some reactions contains educts where a compound isn't linked to a compound in the database. This results that the name of the compound is written instead of the usual structure diagram (fig 15). This issue does not give problems when it comes to the construction of the hypergraph. The compound is simply just not added to the hypergraph. This however results in a slightly misleading result if the user does not look up the reaction in Reaxys where the name of the educt is stated. Example: If $A + B \rightarrow C$ but B is not given an compound ID the reaction would look like $A \rightarrow C$ in the hypergraph.

Fig. 15: Example of an reaction with a missing educt.

Forth issue is multireactions. (fig 16) A mulitreaction is a reaction with its own ID, but it consists of an educt and a product were there are multiple reaction steps, s, between the two compounds. This means that instead of s different reactions with their own ID and yield we get a single reaction without a yield. The yield for each reaction in the multistep reaction is often stored as a part of the reaction text, but not easy extractable. The multistep reaction should however only consist of individual reactions that already are in the database.
The solution to this problem have been to not include all reactions labelled as "Multi-step reaction" to the extraction from the database. Since the steps should be saved as individual reactions this would not cause any harm to possibility of finding the exact same path, but only using all s steps instead of one.

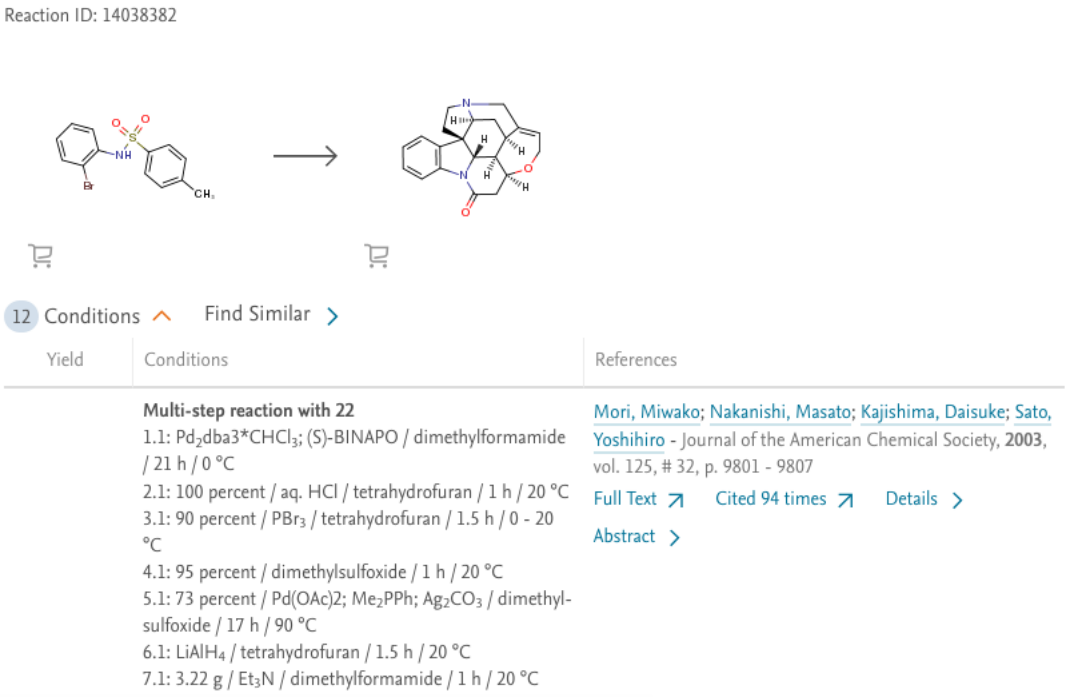


Fig. 16: Example of a multistep reaction.

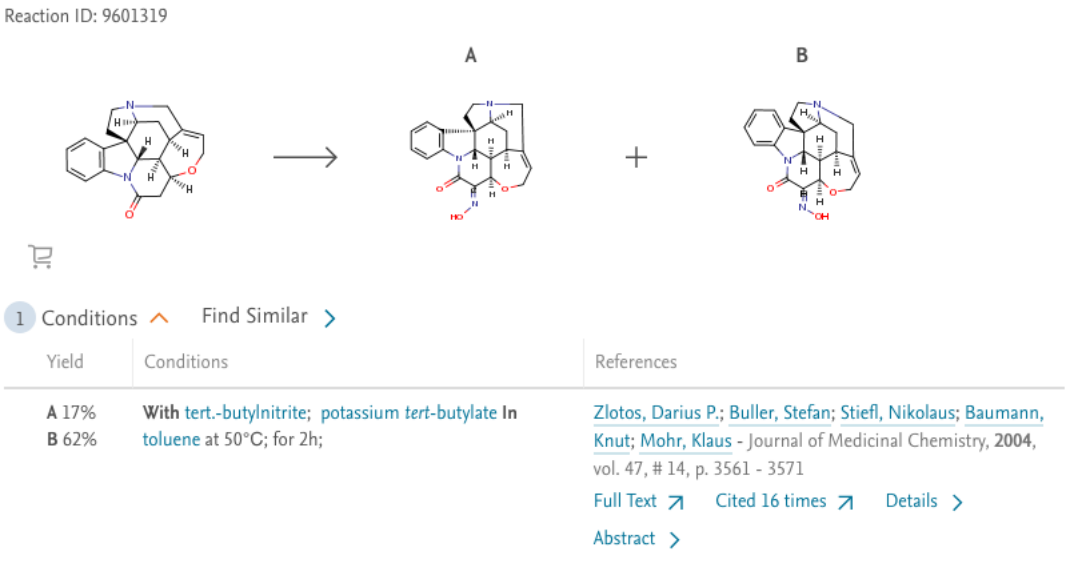


Fig. 17: Example of a reaction with multiple products

Fifth issue is reactions which have more than one product (fig. 17). If this becomes a part of our hypergraph it is no longer a B-hypergraph. This is a problem since both shortest paths algorithms only works on B-hypergraphs. This

problem is however solved after the graph have been created by the method $convertToBHypergraph()$ in Hypergraph.hpp. The method iterates through the reaction list and if it encounters a non B-hyperedge, the hyperedge is added to a list of non B-hyperedges. For each of the non fixed B-hyperedges, e, it creates $|H(e)|$ new hyperedges, e_i, where $T(e_i) = T(e)$ and $H(e_i) = H(e)[i], \forall\ i \in \mathbb{N}, 1 \leq i \leq |H(e)|$ (fig. 18). Each of the new reactions contains an original-ID variable that points to the original hyperedge. This is only used to print the correct ID when the edge is used in a synthesis plan.

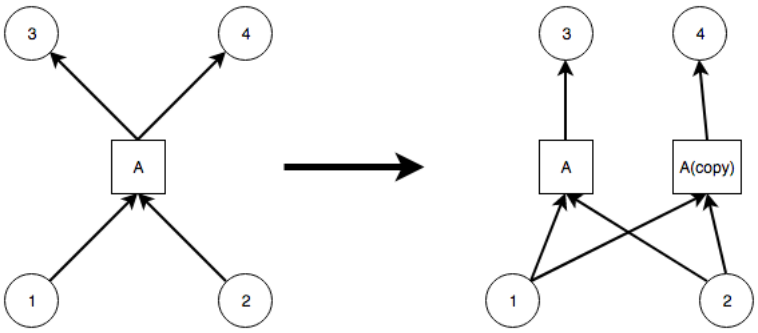


Fig. 18: Convertion to B-Hyperedge

9 Results MANGLER

9.1 Pre-work

HOFFMAN - XML Files etc.

9.2 Strychnine

Plan	Reactions	Starting weight
1	C.1	2471,93
2	C.2	3941,73
3	C.3	4577,65
4	C.4	5871,33
5	C.5	6076,83
6	C.6	8186,61
7	C.7	8558,73
8	C.8	13054,3
9	C.9	13647,7
10	C.10	19444,8
11	C.11	20125,4
12	C.12	20328,7
13	C.13	21040,2
14	C.14	21587,3
15	C.15	44400,5
16	C.16	277503

9.3 Colchicine

Plan	Reactions	Starting weight
1	C.17	1719,6
2	C.18	3373,05
3	C.19	50401,9
4	C.20	119547
5	C.21	136227

9.4 Dysidiolide

Plan	Reactions	Starting weight
1	C.22	6801,04
2	C.23	8647,76
3	C.24	10080,6
4	C.25	12385,7
5	C.26	12729
6	C.27	15597,5
7	C.28	21165,7
8	C.29	22294,4
9	C.30	23259
10	C.31	27928,3

9.5 Asteriscanolide

Plan	Reactions	Starting weight
1	C.32	649,346
2	C.33	5175,63
3	C.34	13549,2

9.6 Lepadiformine

Plan	Reactions	Starting weight
1	C.35	841,29
2	C.36	1061,41
3	C.37	1129,16
4	C.38	5138,44
5	C.39	7629,88
6	C.40	8116,89

9.7 Discussion

kkkk [1]

10 Future work

This section describes possible correction of errors that was discovered close to deadline or missing features of the program. It also contains ideas for further work on the data from Beilstein.

10.1 Expanding

The idea of expanding is to have either a compound or an existing synthesis plan and to expand on these. If we have a single target compound, it would be possible to expand step-wise from that compound. By doing this we are able to find all compounds from which it is possible to create the target by using only B reactions. Once the expansion have been made the K-shortest algorithm could run using all compounds of the hypergraph that have a in-degree = 0 as staring compounds.

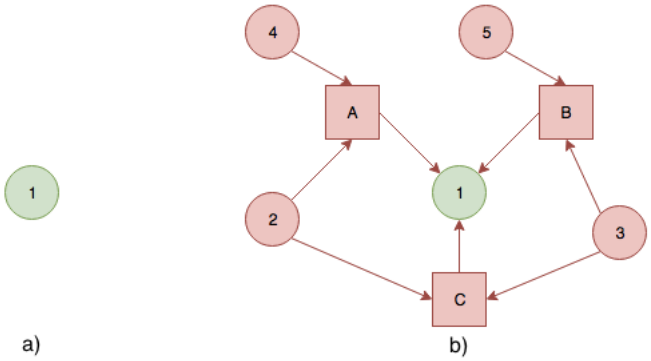


Fig. 19: **a)** The target compound. **b)** After a single expansion from target compound

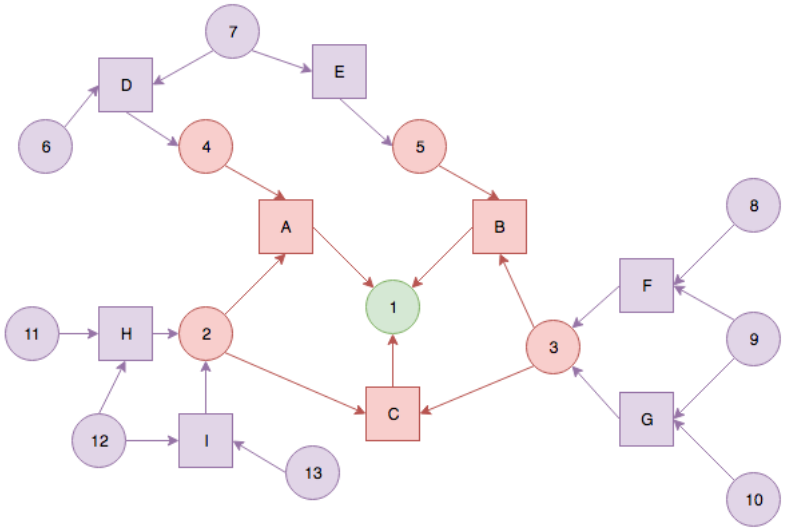


Fig. 20: The hypergraph after a two expansions from target compound

If we instead would have a existing synthesis plan, or perhaps a set of synthesis plans, from a published article. We could expand on each of the compounds in the plan. Even though we use already known reactions the reactions that are added might reveal connections that have not been used before to create that specific target compound. If we look at fig. 21 we can see that the expansion of the known synthesis plan have revealed a new path from compound 3 to the target compound 1 through the reactions G and F. It also reveals another way of creating compound 3 with the use of reaction H. If reaction H have a better yield than reaction C, it might result in a better plan. The author of the synthesis plan could simply have forgotten about reaction H or he did not know that a new reaction had been discovered, and therefore only thought that C was an option.

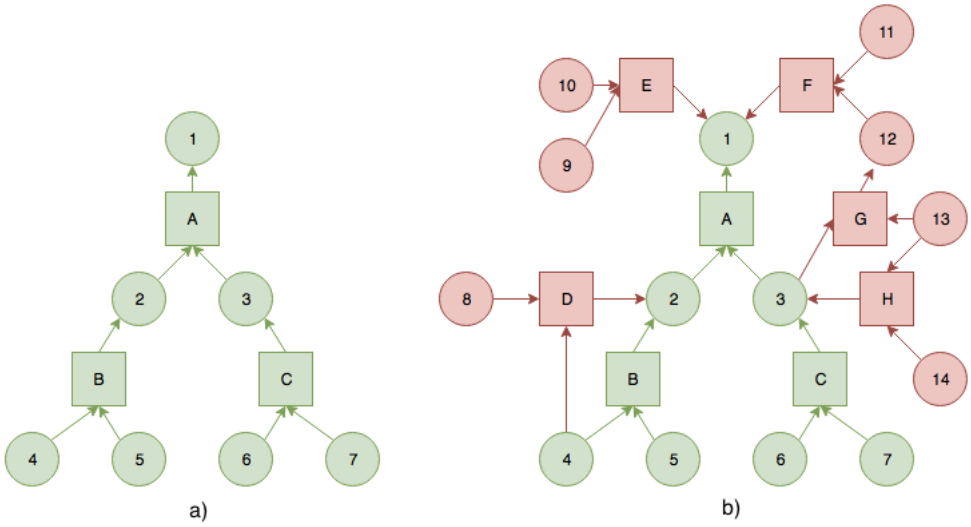


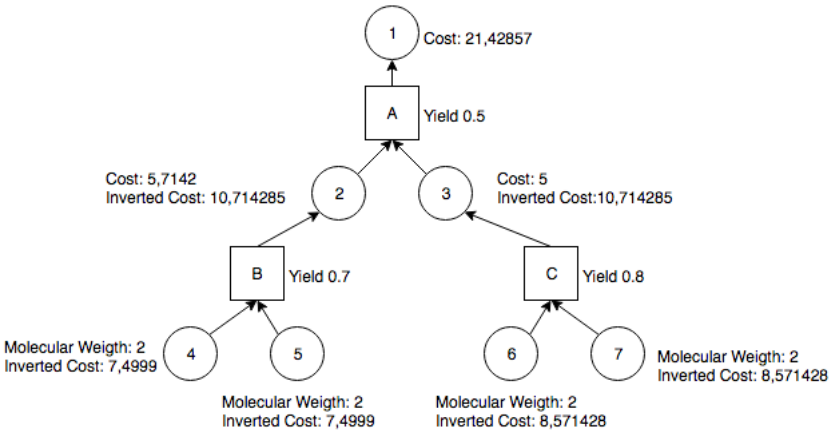
Fig. 21: **a)** A hypergraph made from an existing synthesis plan. **b)** A single step expansion of the given synthesis plan.

10.2 Error handling

That the program throws a segmentation fault when the dynamic approach is used on a hypergraph with cycles, is of course not preferable. It should however use the visited attribute of the CompoundNodes for cycle detection. If an already visited node is visited again it should abort the algorithm, print an error messsage so that the user may know why the algorithm fails. The problem with STB-Dijkstra in test 4 7.3 should be investigate so that the problem can be fixed. As mentioned before it only seems to happen in the tests made by SynthWorker and in a hypergraph with many equally good paths, but should non the less be fixed.

10.3 Specific start weight

At the time of deadline, the results of the shortest path algorithms is the accumulated weight of the starting materials. This is a good way of determining if a path is better than another. It would however be a good thing to know how much of each of the individual staring materials should be used to create the target compound, for pratical purposes. To calculate the individual weight of the staring materials, we would need to implement a Depth-First-Search inspired algorithm that starts in the goal compound and traverses the synthesis plan towards the starting materials. For each reaction, e, it comes through on its path, the cost of $H(e)$ is divided with the retroyield $(1/yield_e)$ and passed on to the nodes in $T(e)$ as the "inverted cost". When the algorithm hits a starting compound it divides the cost of the goal compound with the inverted cost of the staring material found by the DFS and multiplies it with the molecular weight of the starting compound.



If we use the example above we can see that the result of the shortest path algorithms were 21,42857. By calculating the inverse cost from the target and down to the staring compounds 4, 5, 6, 7 leads to the following starting weights of the compounds:

$$\{4, 5\} = (21, 42857/7, 4999) \cdot 2 \approx 5, 71436 \tag{9}$$

$$\{6, 7\} = (21, 42857/8, 571428) \cdot 2 = 5 \tag{10}$$

By dividing these results with the molecular weight of the compounds, we would get how many times of each starting compound we would need to create a single target compound.

11 Conclusion MANGLER

Books

[1] R. W. Hoffmann, *Elements of Synthesis Planning*. Springer Berlin Heidelberg, 2009.

Articles

[2] S. Szymkuc, E. P. Gajewska, T. Klucznik, K. Molga, P. Dittwald, M. Startek, M. Bajczyk, and B. A. Grzybowski, "Computer-assisted synthetic planning: The end of the beginning", *Angewandte Chemie International Edition*, no. 55, pp. 5904–5937, 2016.

[3] R. Fagerberg, C. Flamm, R. Kianian, D. Merkle, and P. F. Stadler, "Finding the K best synthesis plans", 2017, Unpublished Article.

[4] J. Y. Yen, "Finding the K shortest loopless paths in a network", *Management Science*, vol. 17, no. 11, pp. 712–716, Jul. 1971.

[5] L. R. Nielsen, K. A. Andersen, and D. Pretolani, "Finding the K shortest hyperpaths: Algorithms and applications", 2002.

Other

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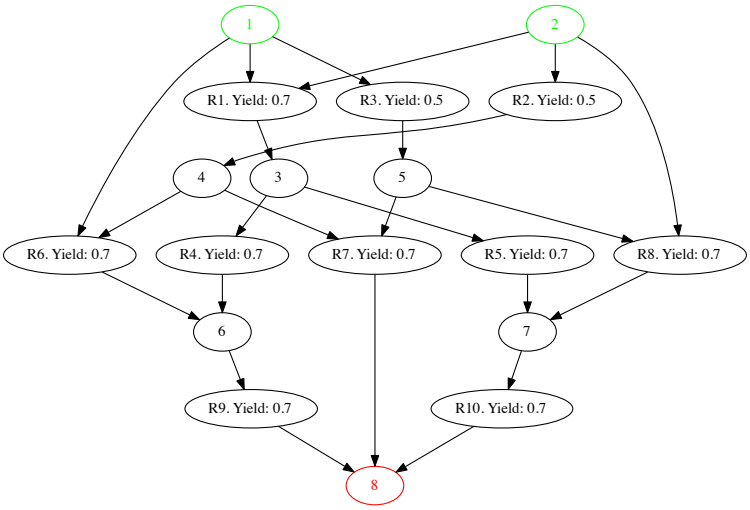
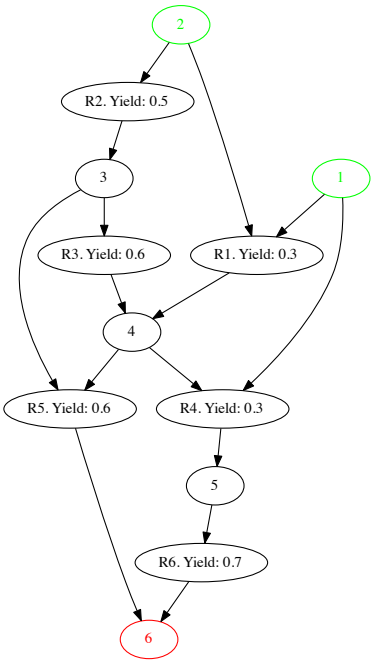
[10] Oct. 2017. [Online]. Available: `https://en.wikipedia.org/wiki/Beilstein_database`.

A Test Graphs

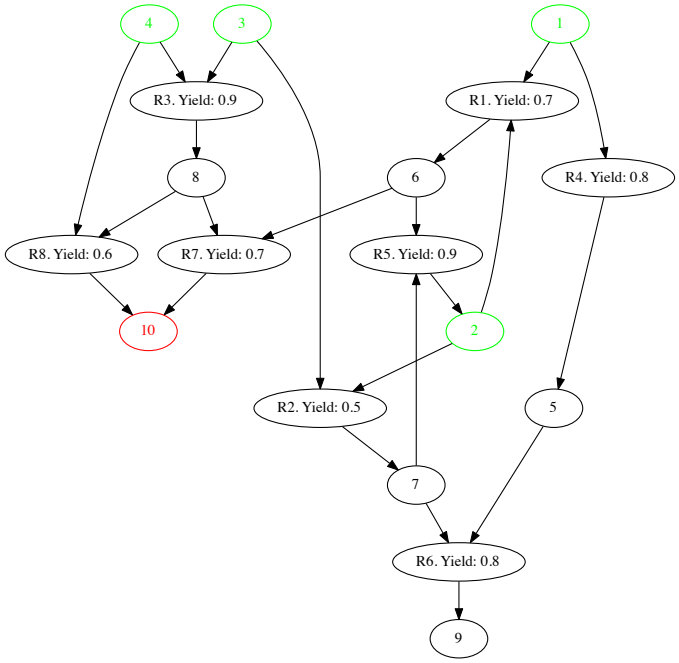
A.1 Thesis Graph



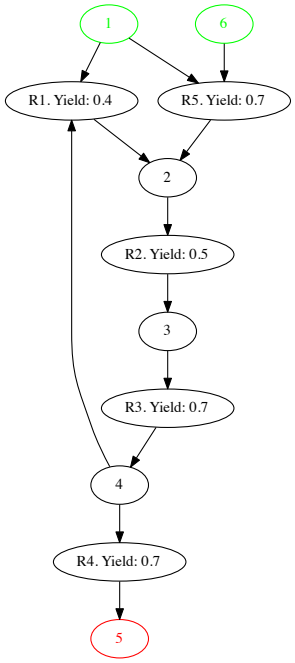
A.2 Paper Graph



A.3 Deadend Graph

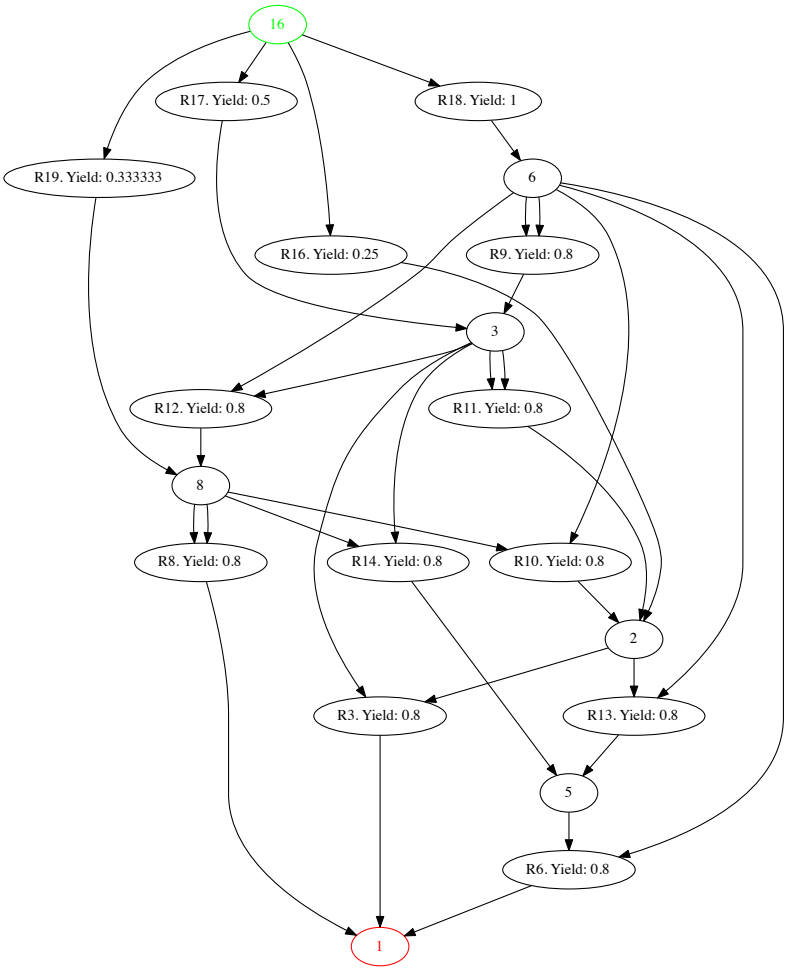


A.4 Cycle Graph



B Rojin Tests MANGLER

B.1 Rojin Test 1



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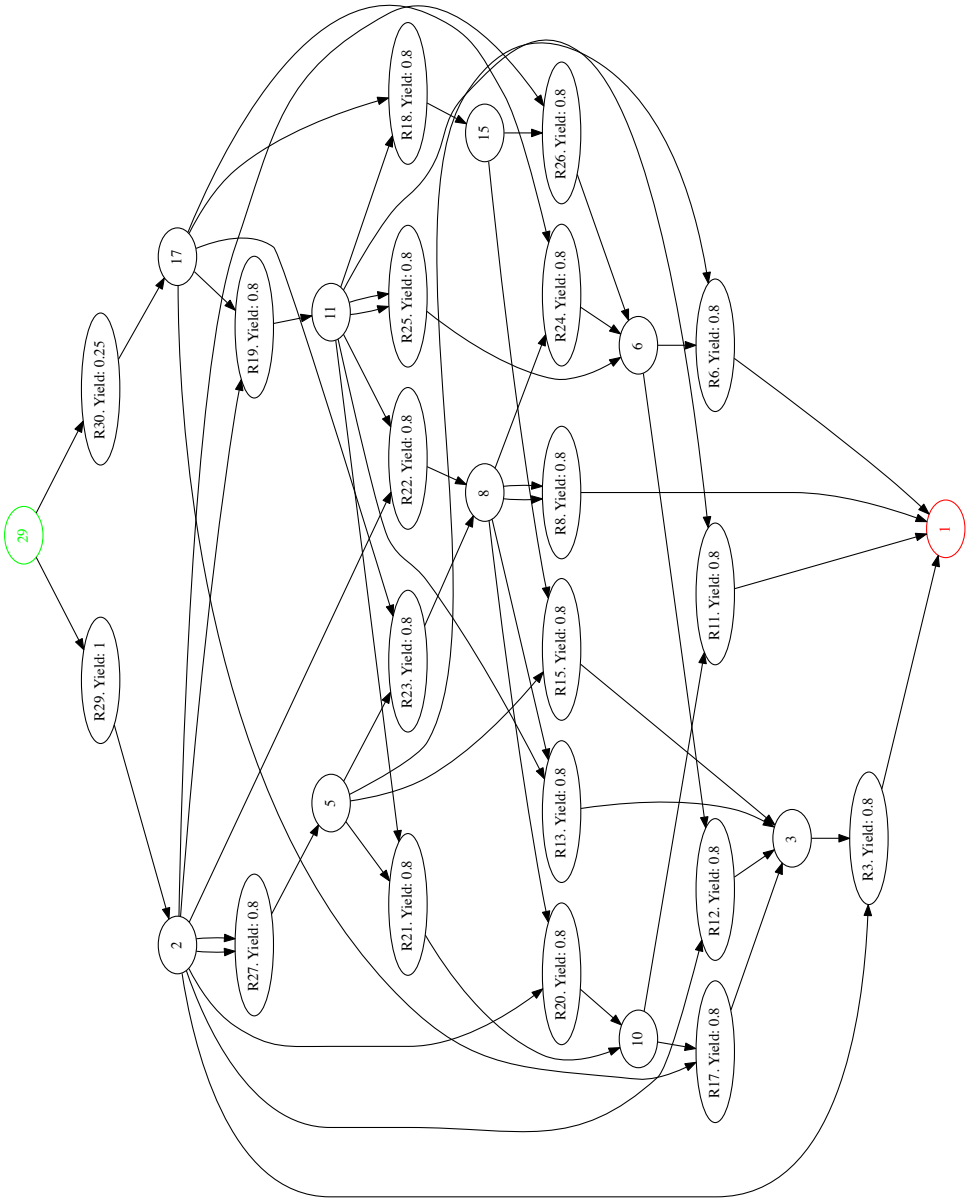
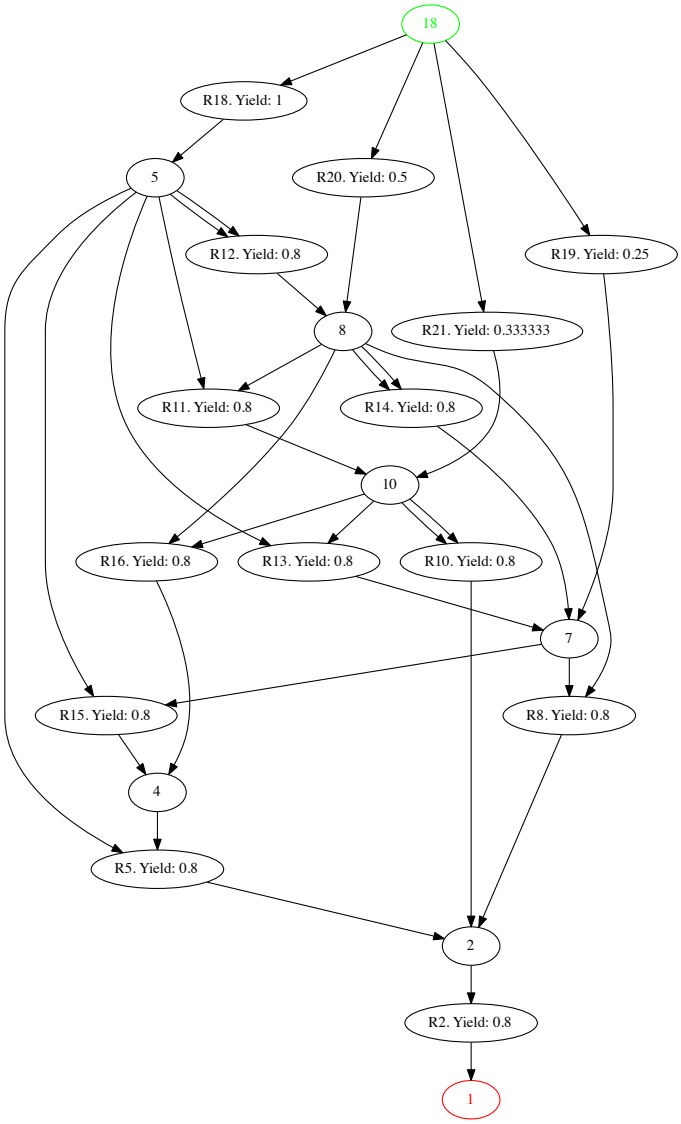


B.3 Rojin Test 3



B.4 Rojin Test 4

Hypergraph to big to be on page. Press here to see pdf.

B.5 Rojin Test 5

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B.6 Rojin Test 6

Hypergraph to big to be on page. Press here to see pdf.

B.7 Rojin Test 7 MANGLER GRAF

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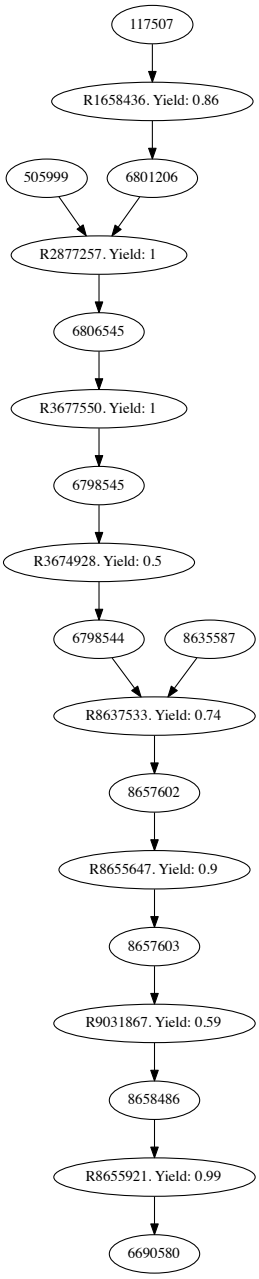
C Synthesis Plans

C.1 Strychnine plan 1



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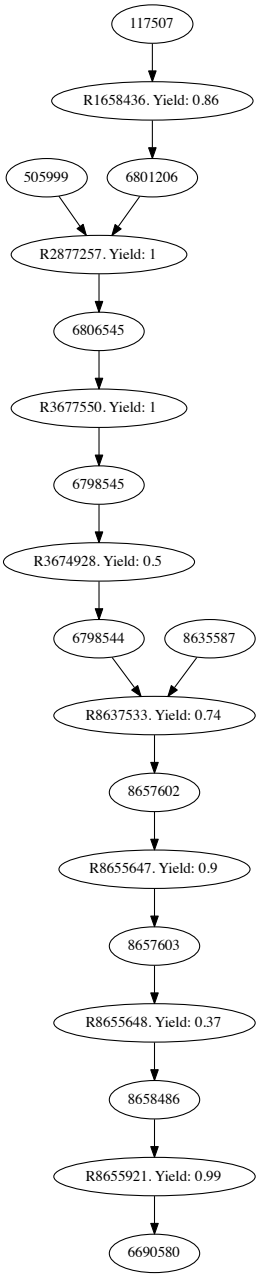

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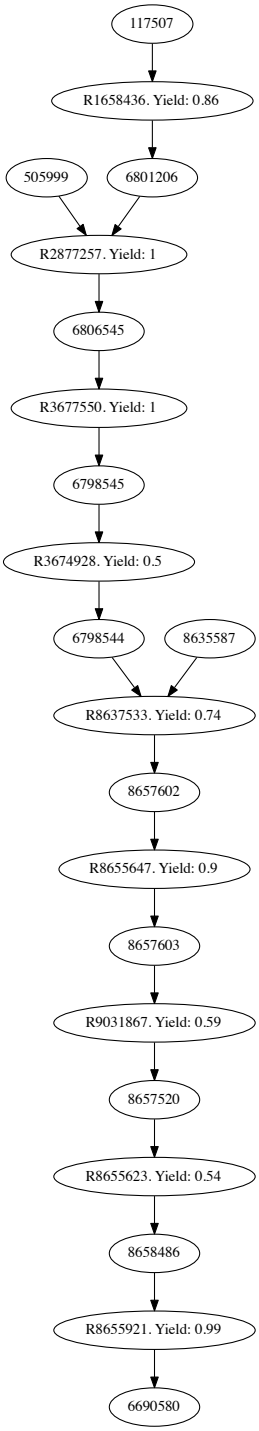
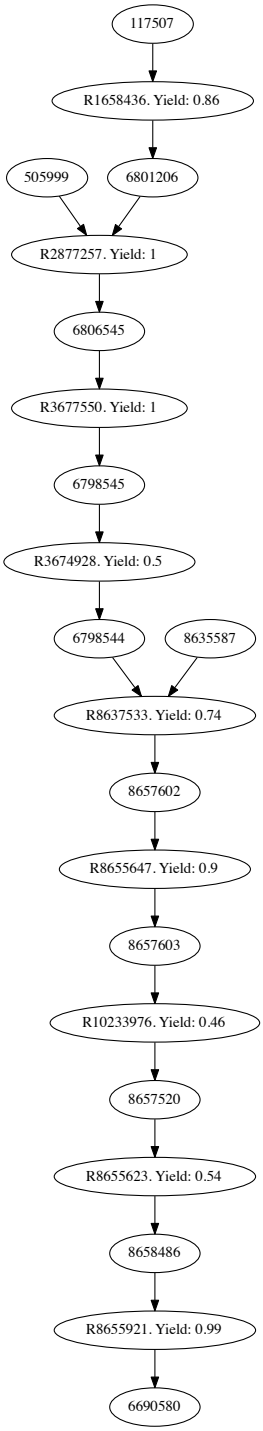


C.4 Strychnine plan 4



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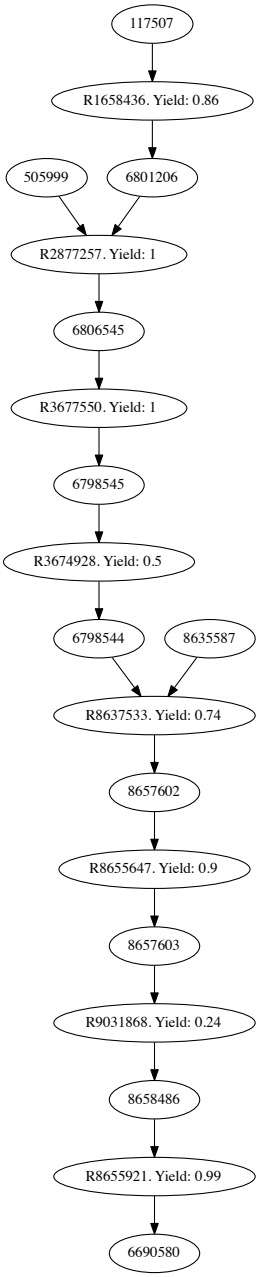
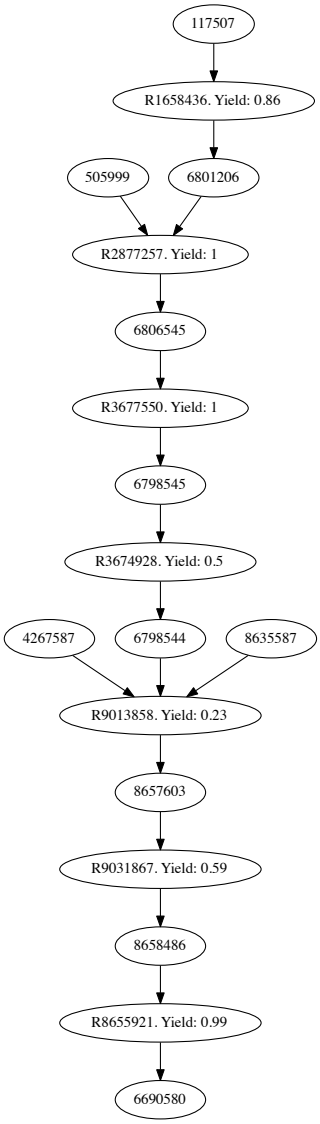
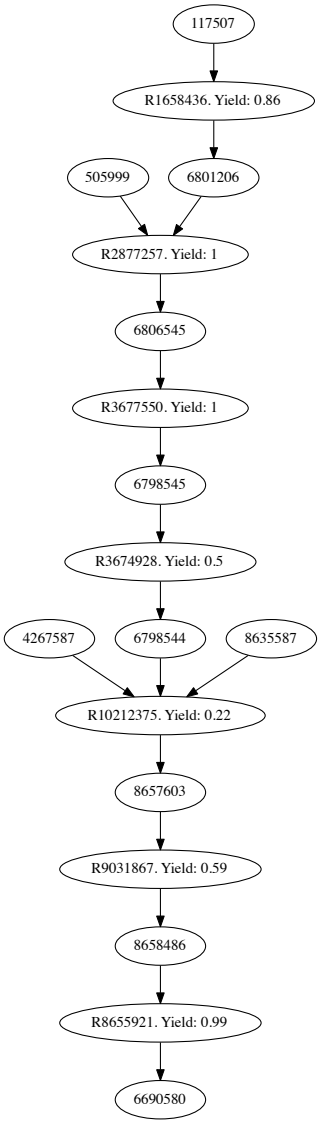


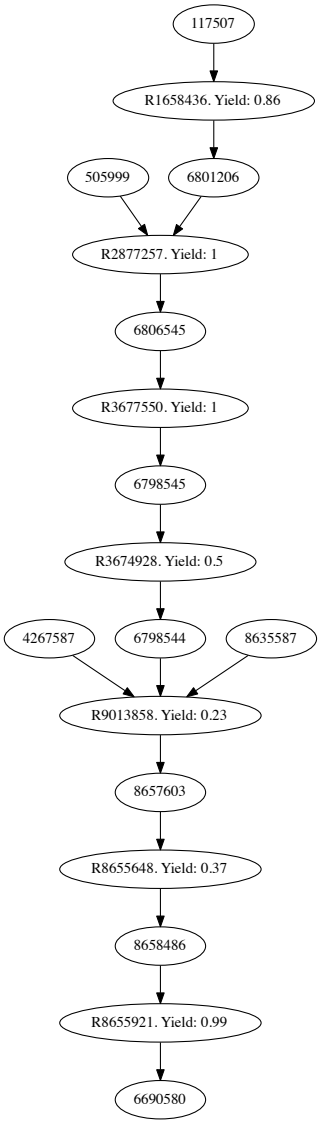
C.6 Strychnine plan 6



C.7 Strychnine plan 7



C.8 Strychnine plan 8



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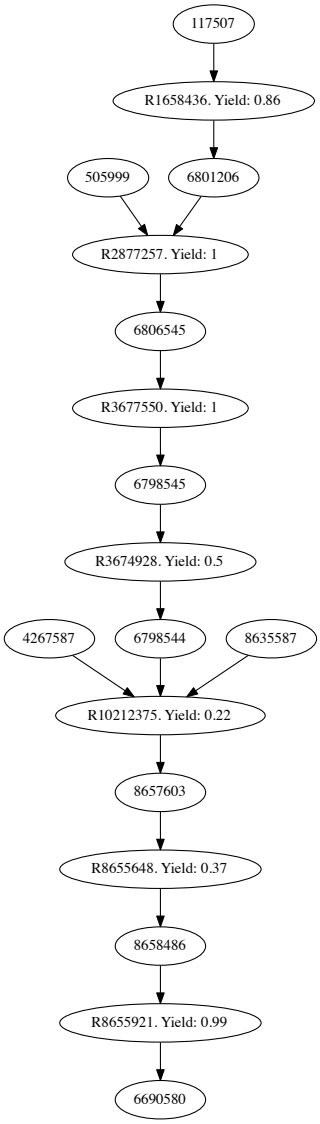

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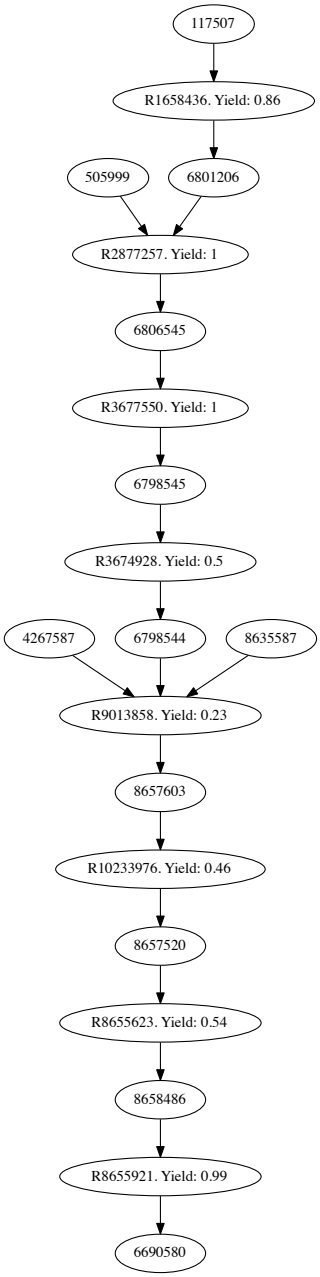

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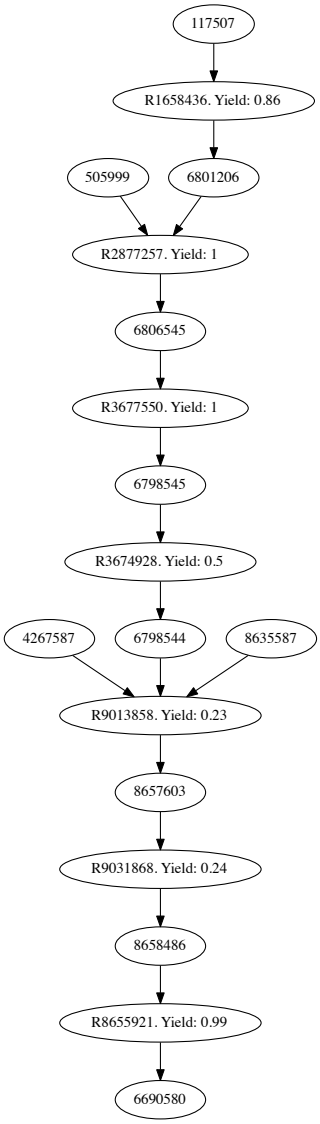

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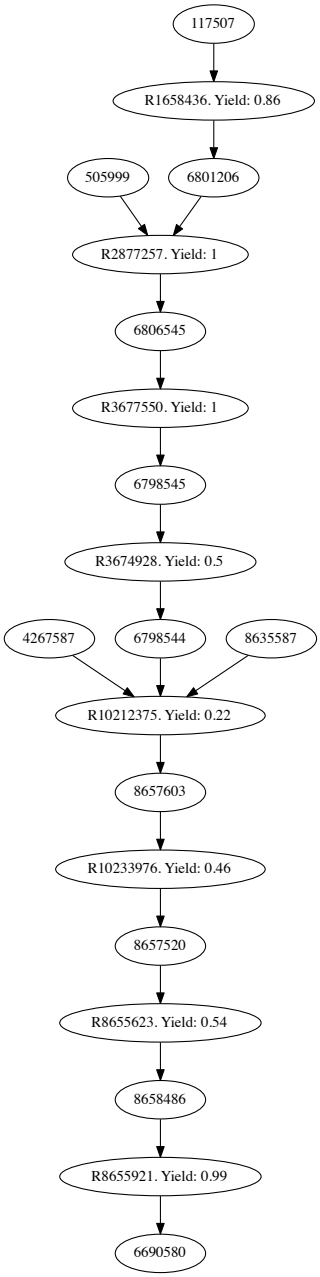

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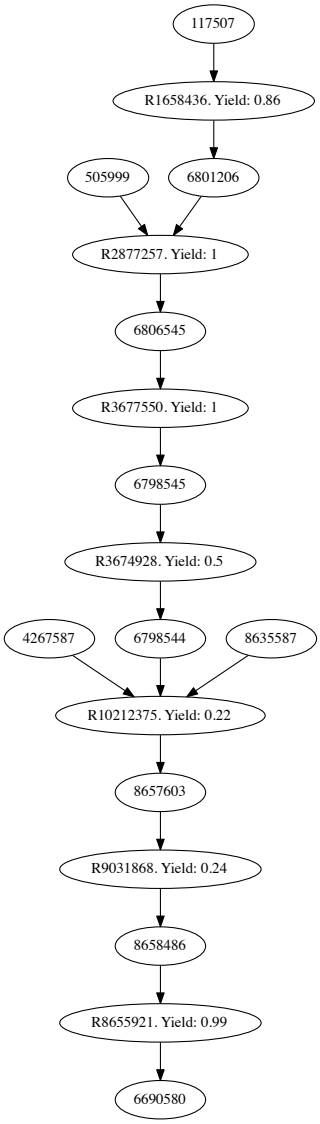

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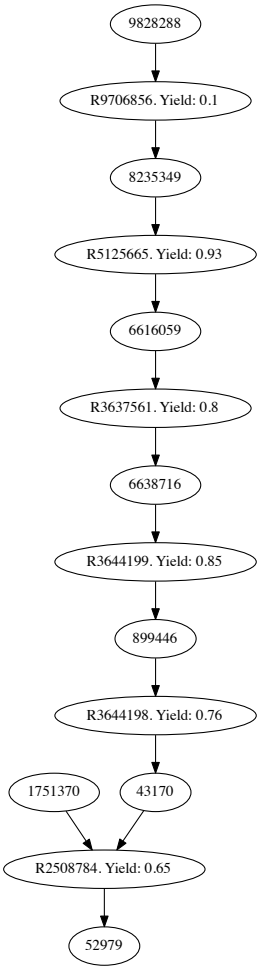

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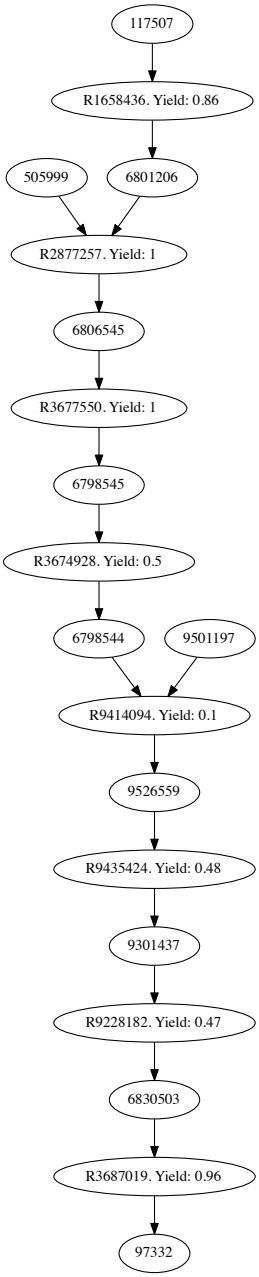

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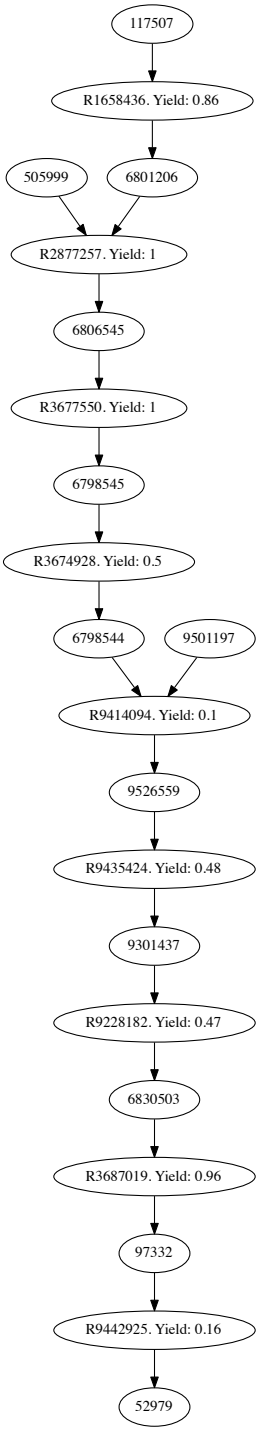

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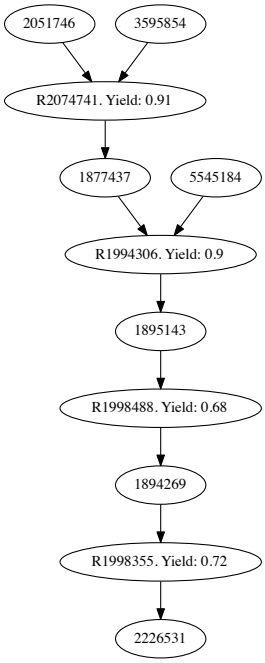

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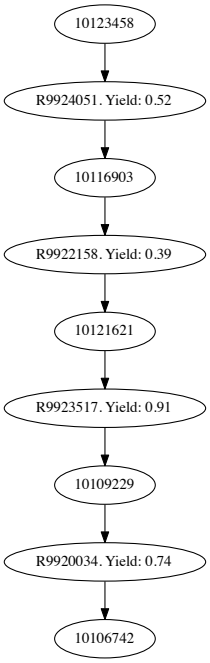

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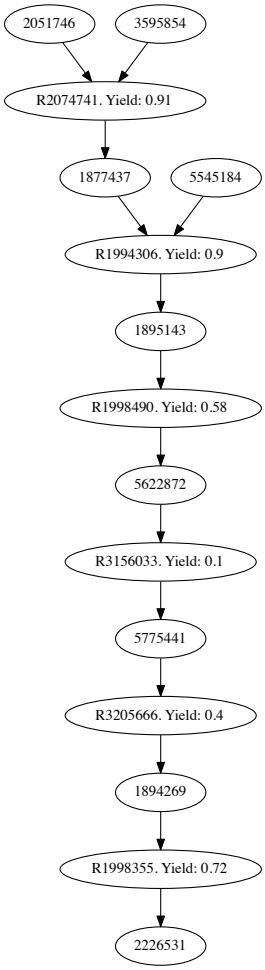

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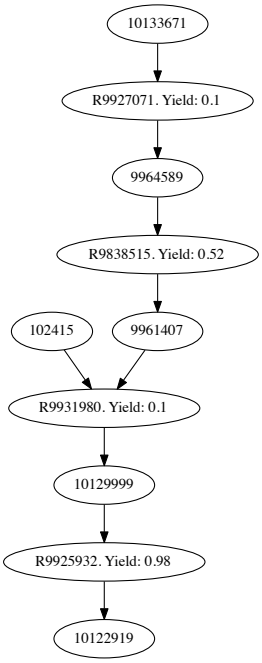

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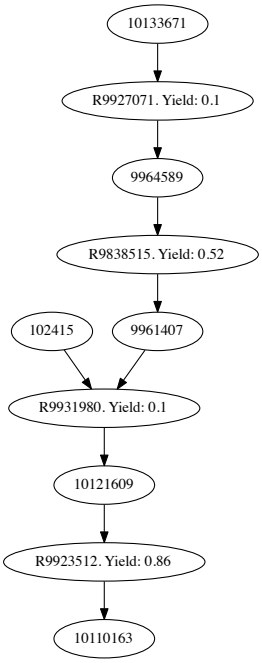

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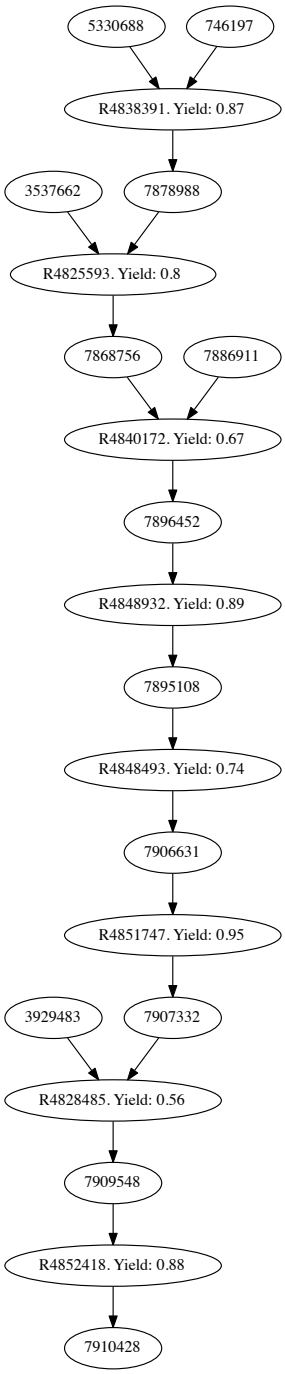

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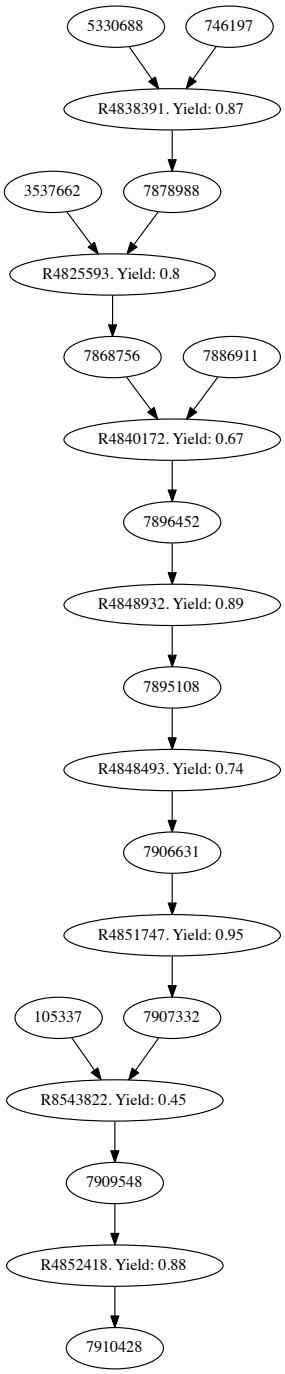

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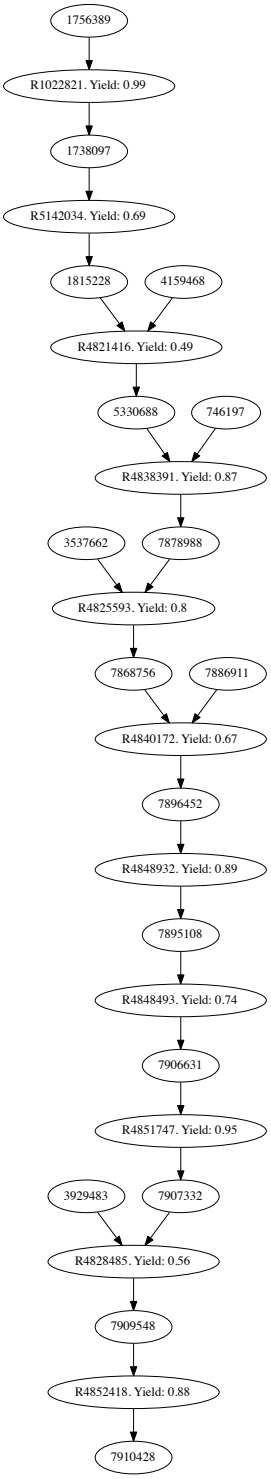

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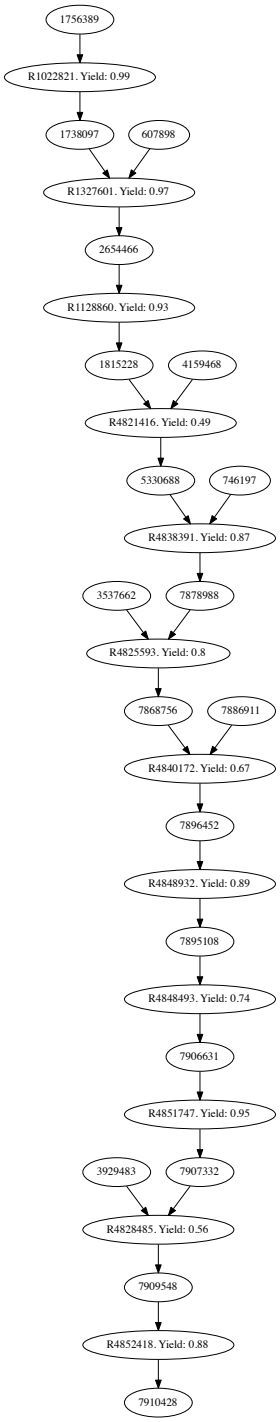

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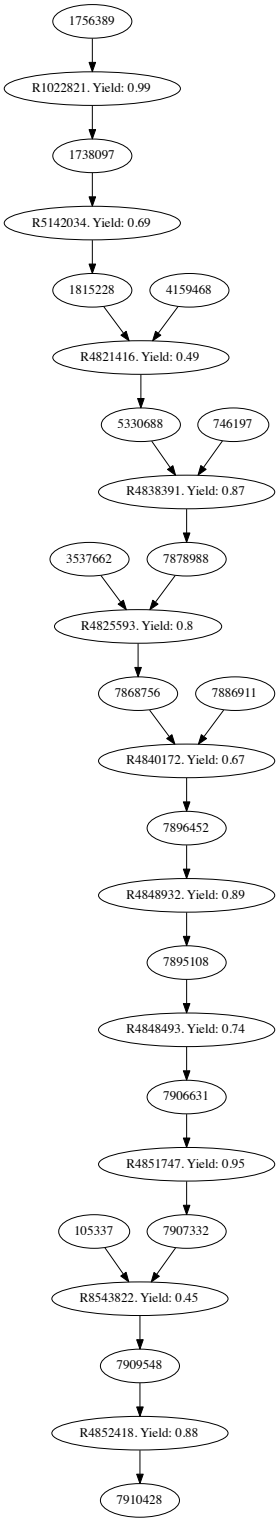

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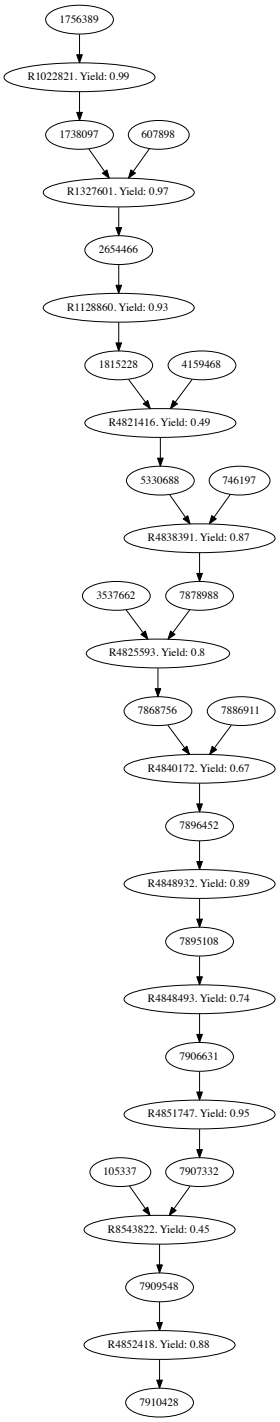

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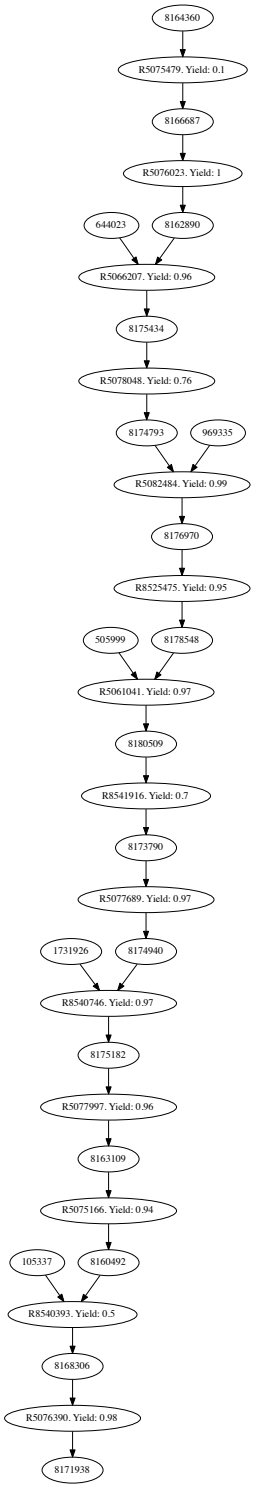
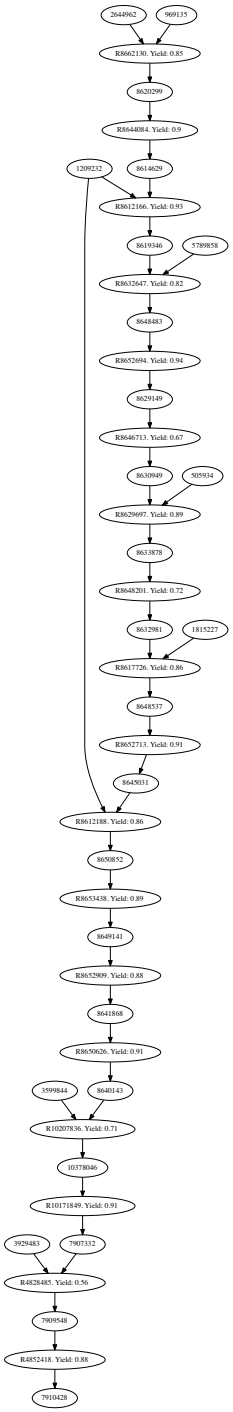
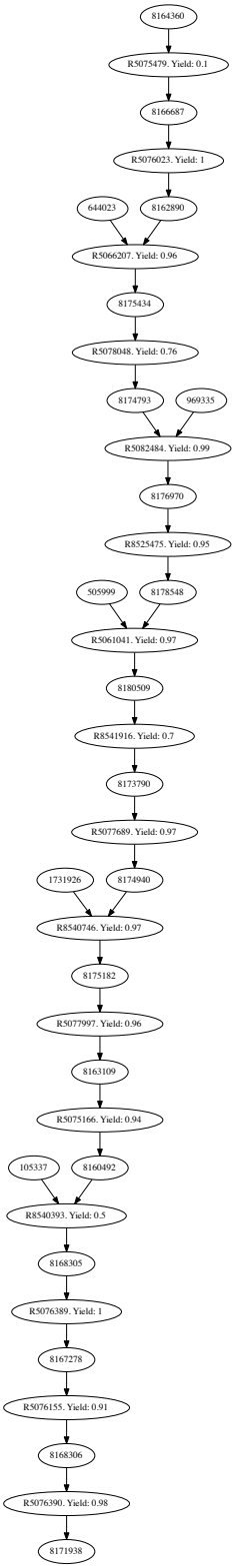


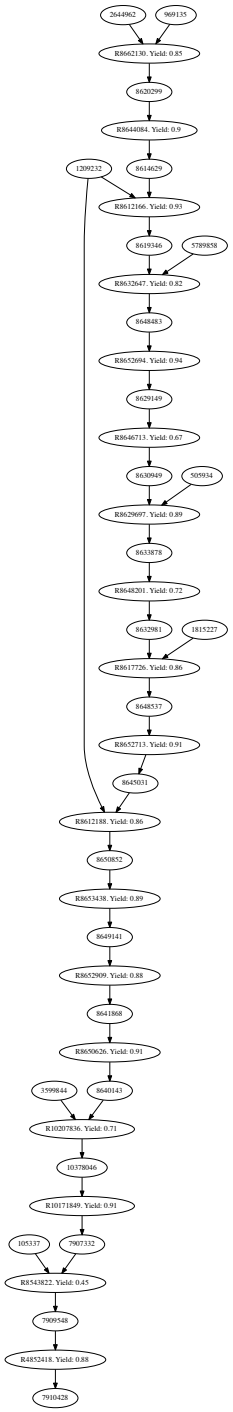
C.29 Dysidiolide plan 8



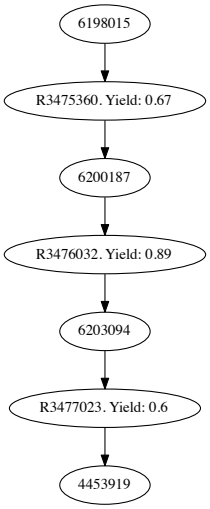
C.30 Dysidiolide plan 9



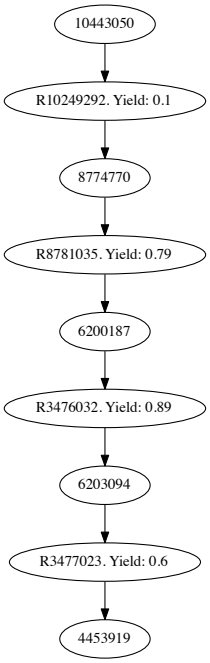
C.31 Dysidiolide plan 10



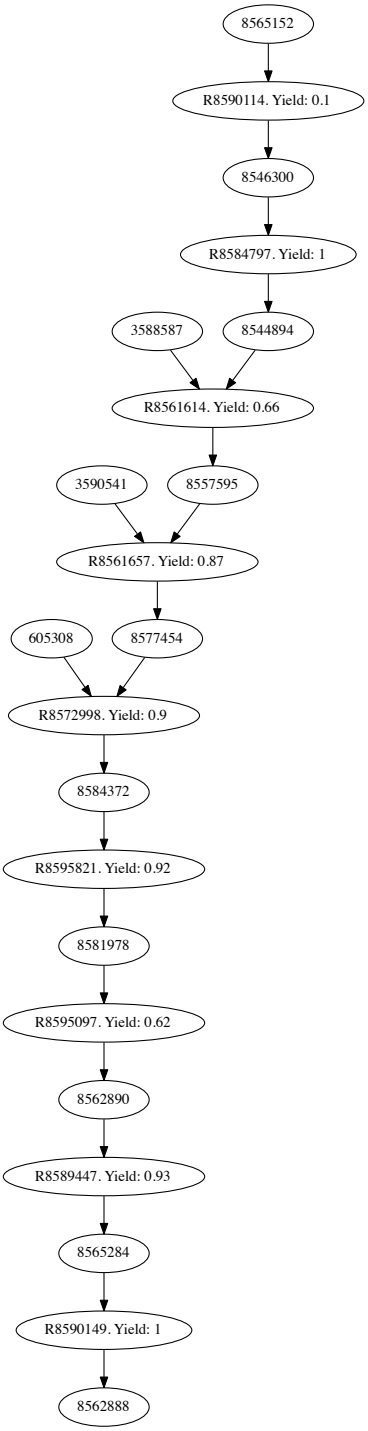
C.32 Asteriscanolide plan 1



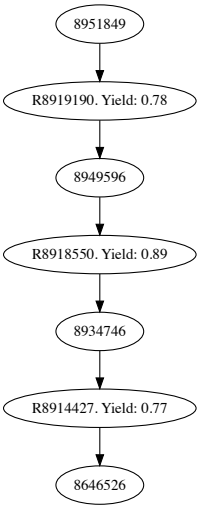
C.33 Asteriscanolide plan 2



C.34 Asteriscanolide plan 3



C.35 Lepadiformine plan 1



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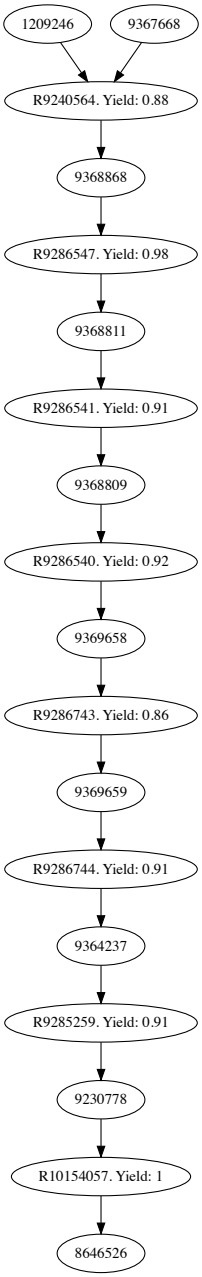
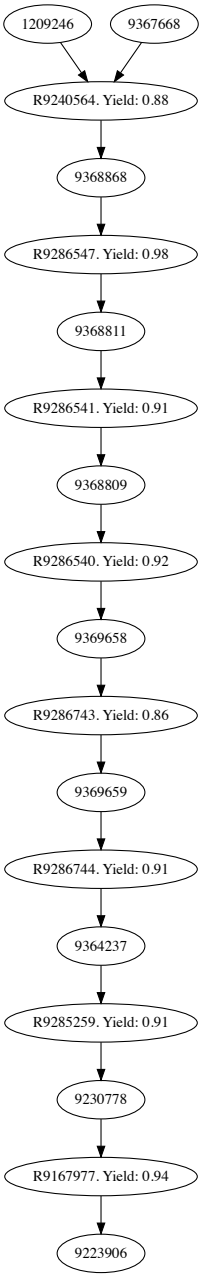
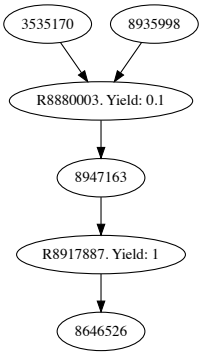


C.37 Lepadiformine plan 3



C.38 Lepadiformine plan 4



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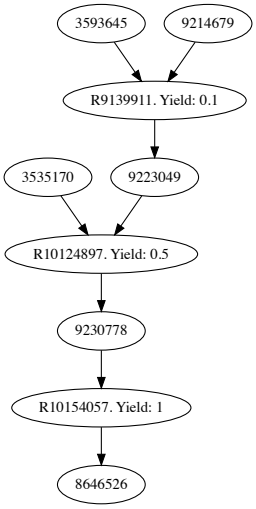

C.40 Lepadiformine plan 6