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# Retrosynthetic Analysis of Centratherolide A

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## Abstract

Centratherolide A is small and permeable, yet it can cause selective irreversible reactions to proteins, including topoisomerase-3$\beta$(TOP3B), the only dual RNA and DNA topoisomerase found in humans. Centratherolide A is mainly cytotoxic because of its $\alpha$-methylene-$\gamma$-lactone ring, a potent Michael Acceptor present in their family of Furanoheliangolides and sesquiterpene lactones. Through the common atom analysis, oxidation level analysis, Michael Addition, and common carbon relationships, Centratherolide A was able to be broken down into 7 parts. Trisecting the main chain seems more plausible than bisecting. Further understanding of different R groups and variations propose a possibility of cytotoxicity against other diseases and cancers.

## Keywords

Centratherolide; Retrosynthesis; Cytotoxicity; Topoisomerase 3$\beta$(TOP3B); Human Colon Carcinoma

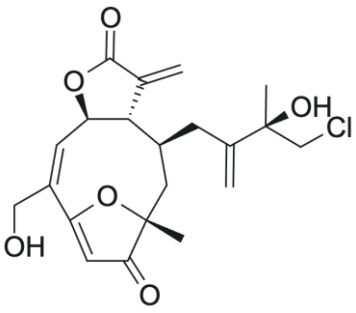


**Figure 1** Original compound Centratherolide A.

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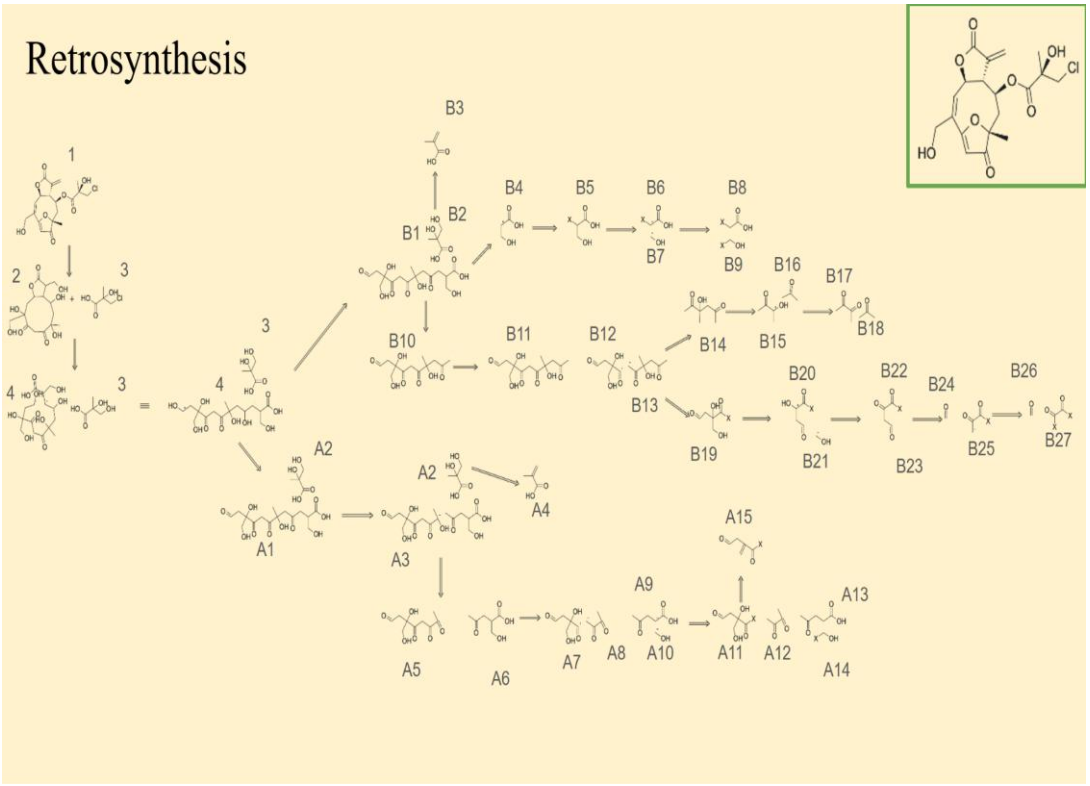


**Figure 2** Full retrosynthesis.

## Introduction

Centratherolide A is a furanoheliangolide, a complex subclass of sesquiterpene lactones that display a variety of bioactivities including anticancer, antimalarial, anthelmintic, anti-inflammatory, antibacterial, and antifungal properties (1). It is small and permeable, yet it can cause irreversible reactions to proteins, enzymes, and redox regulators. It was extracted as a colorless oil from the plant Centratherum punctatum, a common plant with pink button flowers native to Central and South America. The plant was already known for its medicinal capabilities.

The Molecular formula of Centratherolide A is C19H2ClO8 with a molecular weight of 413.0979g. (1) An important structural feature is the $\alpha$-methylene-$\gamma$-lactone ring, a potent Michael Acceptor (Figure 3). These rings are present in Centratherolides and Furanoheliangolides.

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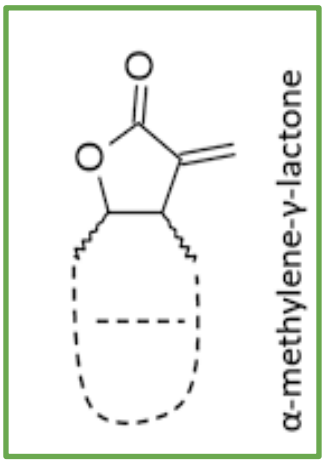


**Figure 3** The *α*-methylene-*γ*-lactone ring, a potent Michael Acceptor

The Michael Reaction using the *α*-methylene-*γ*-lactone ring is the main contributor to Centratherolide A's protein destroying and selective cytotoxicity. It specifically showed this quality through electrophilic covalent interactions against the topoisomerase-3*β(*TOP3B) of human colon cancer HCT116 cells; it did not react to wild-type HCT116 cells.

Topoisomerase-3*β(*TOP3B) is the only dual RNA and DNA topoisomerase found in humans. It is also essential for the replication of all positive single stranded viruses including the recent SARS-CoV-2. (2) By targeting TOP3B, it can stop these diseases and cancers from spreading.

Understanding more about Centratherolides and other furanoheliangolides including its synthesis / retrosynthesis, it could help mankind understand the role of TOP3B in cancer cells. Further discoveries of similar molecules and variations of the R group could lead to molecules of cytotoxic behavior against other diseases (4).

I propose a retrosynthesis method achieved through common atom analysis, oxidation level analysis, the Michael Addition, and common carbon-carbon relationships such as 1, 3 and 1, 5.

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## Methods

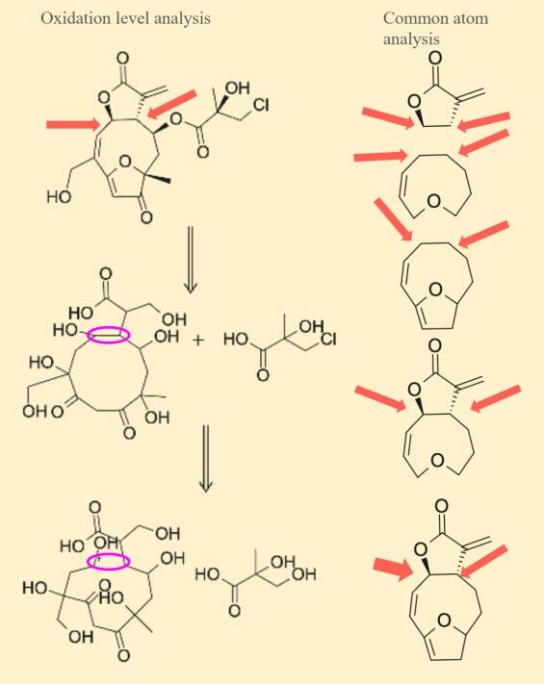


**Figure 4** Common atoms(marked by the arrows) presented in a total of five rings

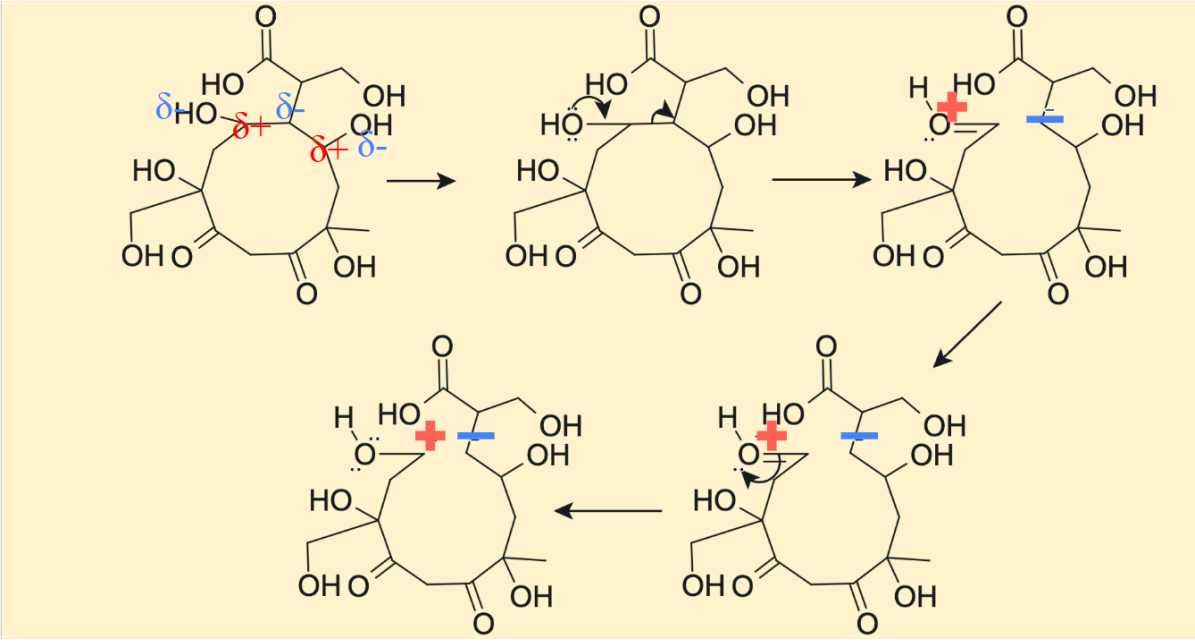

**Figure 5** Mechanism of first bond, partial charges due to the oxygen makes the cleavage / formation plausible

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### *2.1 Early bond disconnections*

The most crucial steps of the retrosynthesis usually come down to the first few bonds. Molecules that may seem synthetically challenging could be simplified drastically within these early stages. If the three rings could be simplified into a single chain, it would make the compound synthetically plausible. To achieve a better understanding of which bond to break, the common atom analysis found two carbons contained in five rings (Figure 4). There were some other atoms present in multiple rings, but the two shown above were the only carbons adjacent to each other, therefore giving me a clear bond to break.

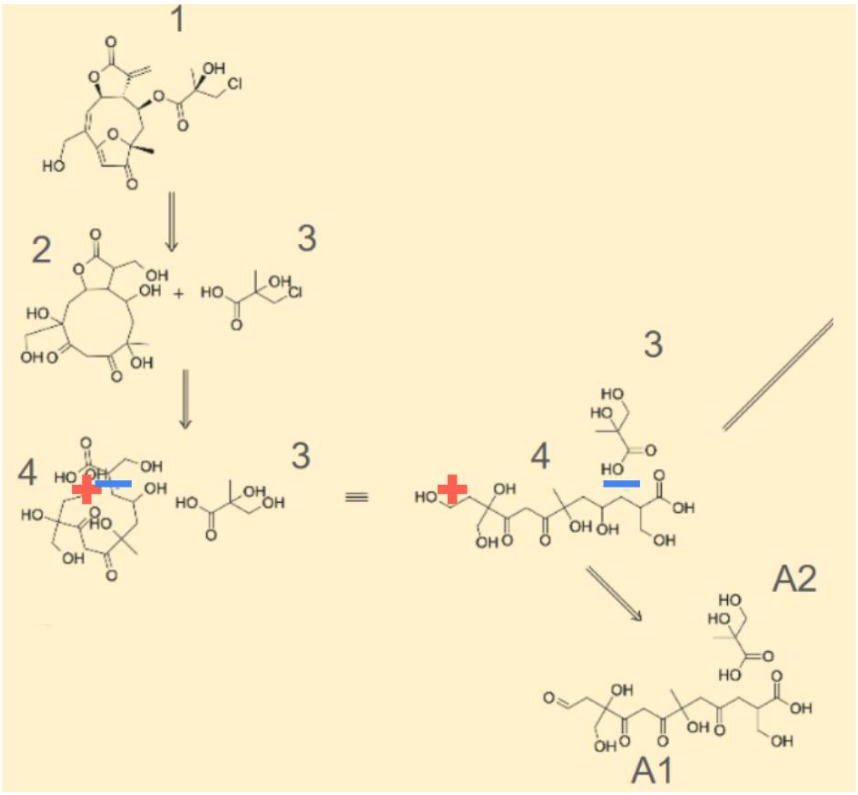


**Figure 6** Early bond disconnections through the common atom analysis and oxidation level analysis.

The oxidation levels of the carbons were analyzed and redrawn as compound 2 and 3. By breaking the bond between the two common atoms found above would turn it into a single chain (Compound 4). To break the bond, the partial charges of the 1, 3 relationship between the two carbons bonded to the alcohols were used (Figure 5). I laid compound 4 out as a single chain and changed the compounds to its synthetic equivalents A1 and A2 (Figure 6).

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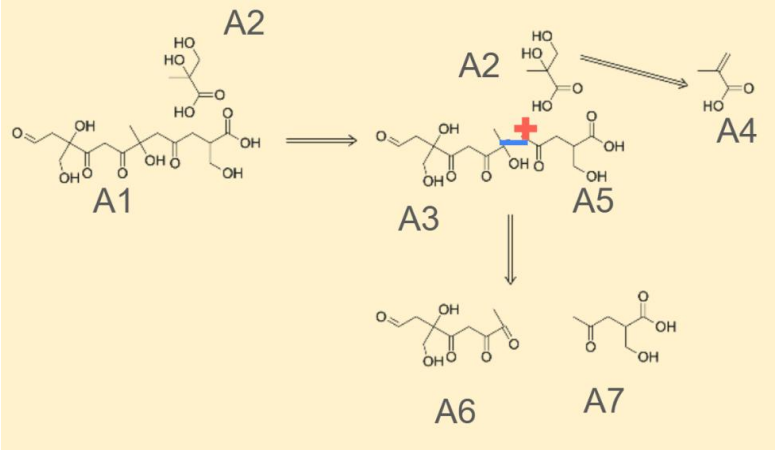


**Figure 7** Bisecting the main chain through 1, 3 relationships

### *2.2 A path bisect*

The main chain is now 12 carbons long. To simplify, I broke the bond between the 1, 3 relationship of the fifth and sixth carbon. The resulting compound was A3 and A5. A2 was dehydrated into A4. A6 and A7 are the synthetic equivalents of A3 and A5 (Figure 7).

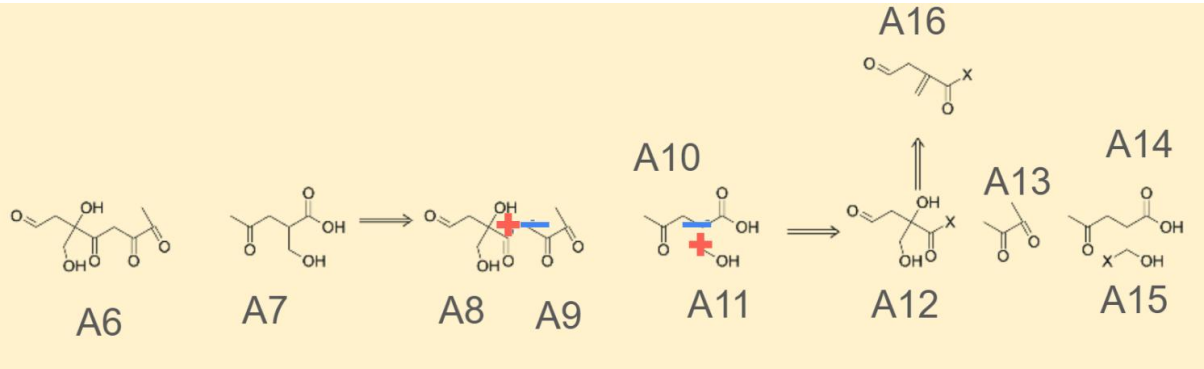


**Figure 8** Lack of plausible disconnections / formations when bisected

A6 was split into A8 and A9. A7 was broken into A10 and A11. A12, A13, A14, and A15 were all turned into their synthetic equivalents A11, A12, A13, and A14 by adding halogens or protons.

However, A12 and A15 are not synthetically plausible. A12 does have a 1, 3 relationship, but the partial charges of the carbons are positive due to the more electronegative oxygens. The advantage of using 1, 3 and 1, 5 relationships was to create these partial positive charges on the carbons directly attached to the oxygens and partial negative charges on the alpha carbon (Same mechanism from A2 to A4) (Figure 13). However, in A12 the oxygen attached to the alpha carbon pulls electrons to itself, making the alpha carbon partially positive. It is hard to break these C-C bonds without partial charges to distribute the formal charges. A15 doesn't have any plausible bonds to break either (Figure 8).

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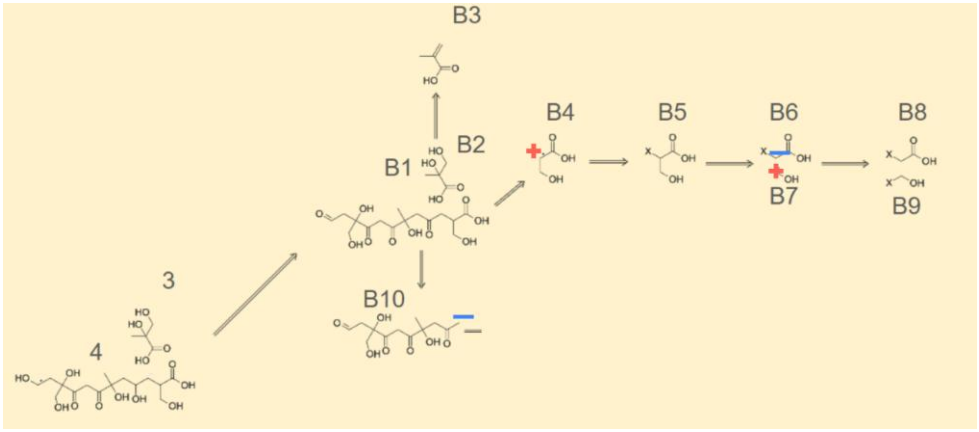


**Figure 9** Trisecting the main chain using the Michael Addition and more common carbon relationships

### *2.3 B path trisect*

Instead of bisecting, breaking the compound into three seems more plausible. The R group, B2 is simplified to its alkene version B3. B4 can be formed using the Michael Addition reaction using the alpha-beta unsaturated carbons. This reaction was mentioned as a crucial characteristic of cytotoxicity in Centratherolides earlier. The bond contains the alpha carbon of the original compound and another unsaturated carbon connected to the cyclodecane, which also happens to be one of the common atoms from the first bond broken. B5 is B4's synthetic equivalent, formed by adding a halide to the carbocation. This carbocation is also secondary, making it a more stable carbocation compared to having the positive charge on B1 which would make it a primary carbocation. A1, 3 relationship was then used forming B6, B7. Their synthetic equivalents are B8 and B9 (Figure 9).

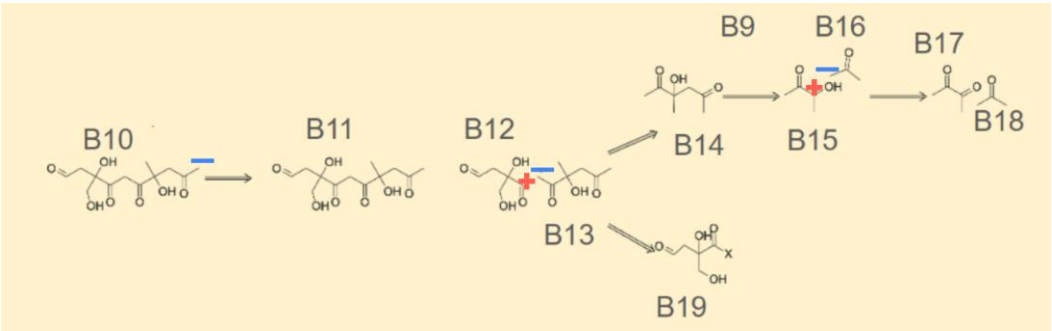


**Figure 10** Retrosynthesis of B12.

B10's synthetic equivalent is B11. I used 1, 3 relationships to disconnect B11 to B12 and B13. B14 is B13's synthetic equivalent and I used another 1, 3 relationship for B15 and B16. The positive charge goes to B15 due to it being a more stable tertiary carbocation. Their synthetic equivalents are B17 and B18 (Figure 10).

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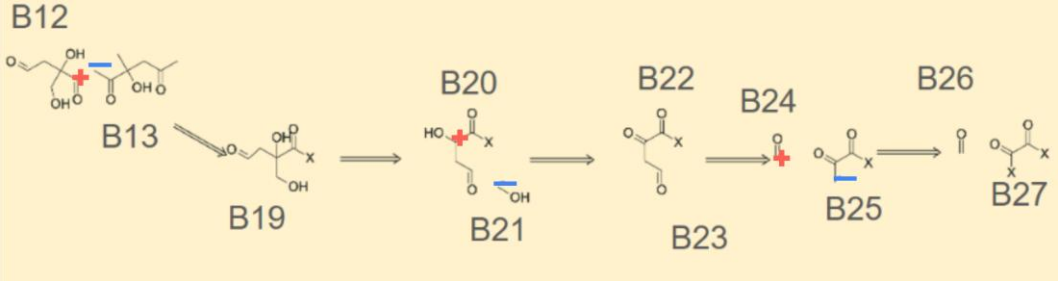


**Figure 11** Retrosynthesis of B12.

B19 is B12's synthetic equivalent and through 1, 3 relationships B20 and B21 were formed. The negative charge goes to B21 due to the oxygen directly attached to the carbon being able to distribute the negative charge away from the carbon. B21 would also have nowhere to distribute the positive charge if given. It's a primary carbocation and the only heteroatom is oxygen. B22 and B23 are their synthetic equivalents (B23 is water) B22 was further simplified to B24 and B25 using another 1, 3 relationship and their synthetic equivalents are B26 and B27. (Figure 11).

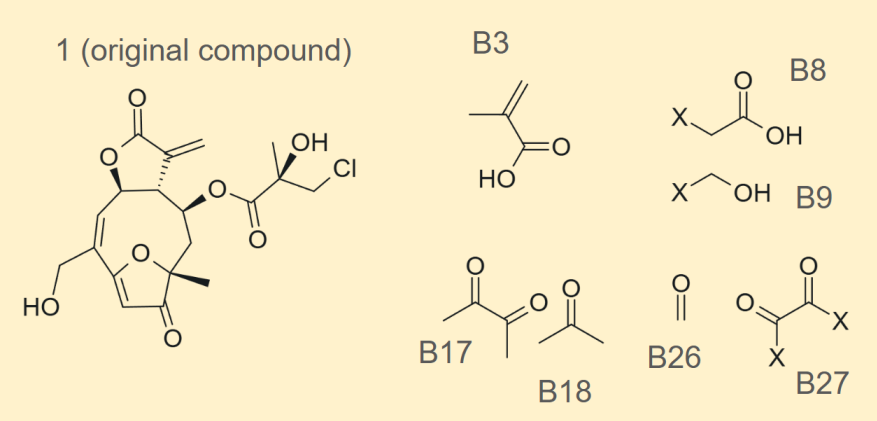


**Figure 12** Final results, the original compound and its building blocks

## Results and Discussion

There are three key points to implementing this retrosynthesis into its synthesis. The first point comes down to the $\alpha$-methylene-$\gamma$-lactone ring that characterizes sesquiterpene lactones. As mentioned earlier, they are the top contributor for Centratherolide A's cytotoxic behavior. It most likely uses the ring as a Michael Acceptor and reacts with thiols in proteins and enzymes, in this case, TOP3B. When it goes through the Michael Addition, it will form irreversible covalent bonds. The Centratherolide could clog or shield the activation site and hinder enzyme and protein function.

However, the same extremely reactive $\alpha$-methylene-$\gamma$-lactone ring is going to show its extremely reactive characteristics to other carbon chains. B4, the compound that will soon become the $\alpha$-methylene-$\gamma$-lactone ring,

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needs to bond with B10 and not any other compound. The connection will be crucial to forming the main chain. When B4 eventually switches its alcohol to an alkene there needs to be something stopping it from undergoing the Michael Reaction with something else. The same could happen to most steps since most of these reactions are reversible.

The second concern involves the R group. Centratherolide A is a compound with a specific R group from the Centratherolides with a chlorine attached to the end. There probably will be other R groups that perform better than Centratherolide A but to get this specific compound it needs to be made sure that B3, the R group, bonds with the main chain instead of a random hydrogen or other compounds. The chlorine has to eventually be brought in as well. Although eventually isolated independently, Centratherolides were originally found in many of its forms in the plant Centratherum Punctatum (1). When synthesized, it will be most likely that there will be multiple variants and R groups, formed as an oil.

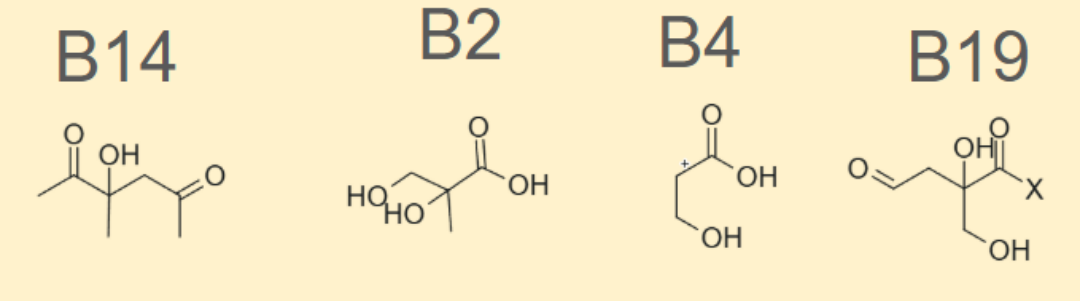


**Figure 13** Four similar compounds of the trisect path.

Lastly, there is a possibility of forming the compound from four identical parts. The R group and the trisected main chains are not identical, but very similar (Figure 13). They all contain three to four oxygens and one to two ketone groups. All could be modified from one ketone and be bonded afterward. It may take more steps but if they all come from an identical compound that is synthetically plausible, it could drastically improve the quality of the synthesis.

The retrosynthesis revolves mainly around common carbon relationships. These relationships are plausible, but they are also mostly reversible. Work up and quenching after each step would be essential for immense quantities.

## Conclusion

The retrosynthesis is deemed plausible through a series of analyzation methods. The common atom analysis and an oxidation level analysis were used to find ideal early bond cleavages. The compound is then broken down into four similar parts, the main chain is trisected and the R group is dehydrated into its synthetic equivalent. Trisecting the main chain resulted in a more plausible retrosynthesis compared to bisecting. The rest of the compound is simplified through common carbon relationships.

The next steps of research would be finding a single compound that could be modified into four similar main components which are the trisected main chain and the R group. It would also be worth experimenting with synthesizing methods found in nature, especially with the *α*-methylene-*γ*-lactone ring. Finding the ideal variation in the compound could lead to a higher hit rate and different targets such as a TOP3B of a different cancer.

Selectively cytotoxic compounds such as Centratherolide A are the future of cancer treatment. Toxicity to healthy cells is dangerous for the patient, especially in an already damaged body due to cancer.

With trial and error, eventually compounds with immense selective cytotoxicity to colon carcinoma, other cancers, viruses, and bacteria will be discovered. I hope this paper could provide inspiration and encouragement for future retrosynthetic and synthetic analyses.

## References

[1] Khong, Q. T.; Marron, L.; Huang, S.-Y. N.; Dalilian, M.; Saha, S.; Goncharova, E. I.; Woldemichael, G. M.; Pommier, Y.; O'Keefe, B. R.; Wilson, B. A. P.; Du, L. Furanoheliangolides from *Centratherum Punctatum* and a General Approach for Stereochemical Assignment of Flexible Chiral Side Chains. *Journal of natural products* **2025**, *88* (6), 1413–1424. https://doi.org/10.1021/acs.jnatprod.5c00329.

[2] Prasanth, K. R.; Hirano, M.; Fagg, W. S.; McAnarney, E. T.; Shan, C.; Xie, X.; Hage, A.; Pietzsch, C. A.; Bukreyev, A.; Rajsbaum, R.; Shi, P.-Y.; Bedford, M. T.; Bradrick, S. S.; Menachery, V.; Garcia-Blanco, M. A. Topoisomerase III-β Is Required for Efficient Replication of Positive-Sense RNA Viruses. *Antiviral Research* **2020**, *182* (104874), 104874. https://doi.org/10.1016/j.antiviral.2020.104874.

[3] Poon, T.; Mundy, B. P.; Shattuck, T. W. The Michael Reaction. *Journal of Chemical Education* **2002**, *79* (2), 264. https://doi.org/10.1021/ed079p264.

[4] Ge, Z.-P.; Gao, Y.; Zhang, Y.; Liu, H.-C.; Zhao, J.-X.; Yue, J.-M. Highly Modified Sesquiterpene Lactones with Cytotoxic Activities from *Strobocalyx Chunii*. *The Journal of Organic Chemistry* **2023**, *88* (15), 11122–11129. https://doi.org/10.1021/acs.joc.3c0110