Recent applications of radical reactions in natural product synthesis

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Abstract: Recent progress in the development of new strategies and tactics for natural products synthesis is described. An emphasis is placed on the development of new sequences of radical reactions. A new approach to the crinipellin family of tetraquinanes and a recently completed formal total synthesis of camptothecin are highlighted.

We recently compiled a review to bring together recent advances in "Radical Reactions in Natural Products Synthesis." This paper will summarize some of our recent progress in developing new strategies for the use of radical reactions in the synthesis of natural products. Often, the implementation of these new strategies will require the development of new reactions.

Most synthetic applications of radical methods conduct only one key reaction in between generation of a radical and its removal. Starting from our earliest work in this field, one of our major themes has been the sequencing of radical reactions. Radical reactions are naturally suited to sequencing because the product of every radical reaction is a radical. We define a tandem radical reaction as a sequence of radical reactions which has more than one step between radical generation and radical removal. Chemoselectivity is a big issue in tandem sequences, and a variety of powerful strategies have emerged to solve selectivity problems.

One of the simplest, yet most powerful, strategies is to plan only rapid intramolecular radical reactions between radical generation and removal. In this way, it is often as easy to form two or three bonds as it is to form one. This tandem cyclization strategy has been an early and continuing theme in our work. Figure 1 uses a new radical notation to summarize tandem radical strategies to two large, important classes of triquinane sesquiterpenes: linear and angular. Though the two ring systems are quite different, the strategies are closely related. Each case calls for a central cyclopentene ring bearing two side chains: one with a radical donor and one with a radical acceptor. The tandem cyclization then occurs through the middle of the cyclopentene ring. The only difference between the two strategies is where the two side chains are located on the central ring.

Figure 1. Tandem Cyclization Strategies for Linear and Angular Triquinanes

Figure 2 summarizes the key tandem radical cyclization steps in our early syntheses of hirsutene (a typical linear triquinane) and silipherfolene (a typical angular triquinane). These syntheses are exceptionally short and efficient. To show that these strategies were general, we also synthesized an isomer of hirsutene, capnellene, and two more highly oxygenated hirsutanes, coriolin and hypnophilin. Finally, to round out the triquinane family, we recently completed both tandem and non-tandem syntheses of the angular triquinane modhephene.

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The strategies in Figure 1 and the syntheses in Figure 2 nicely illustrate that a double bond is the natural equivalent of a vicinal radical acceptor/radical donor. But how can we implement a strategy where the radical acceptor and radical donor are not vicinal? One way to do this is to conduct a non-tandem sequence, as we did with modhephene. In such sequences, the radical for the second cyclization is not formed in the first one. Therefore, donors and acceptors can literally be anywhere. Yet there are also simple ways to use tandem cyclizations to form non-vicinal C–C bonds.

We first thought about the problem of forming two C–C bonds in a 1,4 orientation in the context of a planned synthesis of the tetraquinane crinipellin A,12,13 Figure 3a shows one way of thinking about crinipellin; the B, C, and D rings are an "angular triquinane" not unlike silphiperfolene. However, when we applied our silphiperfolene strategy to the model compound shown in Figure 3b, strategy a, we quickly diagnosed two major problems. First, the required precursor 1 is an unsymmetrically substituted tetraalklycyclopentadiene; a class of molecules that is difficult to make. Second, and of more concern, the projected radical cyclization would surely fail. There are two possible sites of 5-exo cyclization for the initial radical formed from 1, and it would almost certainly add to the less substituted end of the cyclopentadiene rather than the more substituted one. Strategy b looks more attractive. Though the two forming C–C bonds are not vicinal, they are rendered "vinyllogously vicinal" by the double bond. This plan calls for a tandem cyclization through the middle of the diene; in one end and out the other. Now the precursor 2 is a symmetrically substituted tetraalklycyclopentadiene. This facilitates the synthesis of 2 and solves the regiochemical problem because the two ends of the diene are equivalent.

Figure 2. Hirsutene and Silphiperfolene

Figure 3a. Crinipellin Structure

Figure 3b. Crinipellin Strategies
Figure 4 shows the first successful model reaction and a proposed mechanism. This model reaction and several other related ones encouraged us to continue the development of this strategy. To solve problems of precursor preparation and relative stereochemistry of the iso-propyl bearing carbon, we have invested significant time to retool the early steps of our synthesis. Coupled with this, we have reversed the direction of the tandem cyclization; in other words, the end of the molecule that was the acceptor is now the donor, and vice versa.

![Chemical structure](image)

Figure 4. Crinipellin Model Study

Figure 5 shows the latest of several successive generations of this approach, which is now looking very good. Readily available ketal 3 is reacted with bis-silyloxy acyloin 4 and excess BF$_3$-Et$_2$O according to a modification of Kuwajima’s aldol/pinacol rearrangement sequence. This forms key cyclopentanediene 5 in one step in about 50% yield. Bis-Wittig reaction followed by careful double bond migration with HI has proved to be a reliable, high-yielding way to prepare the functionalized cyclopentadiene 6. Now iodination and tin hydride reduction form triquinane 7 in 75% yield. We are hoping to use the reactions shown in Figure 5 as a springboard to finish the rest of the synthesis; however, no member of the crinipellin family has yet been synthesized and major obstacles clearly remain.

![Chemical structure](image)

Figure 5. Current Strategy for Crinipellin

Conducting rapid cyclizations in tandem is one of the easiest ways to sequence radical reactions. Conducting a radical cyclization before an addition is one notch up in difficulty, and conducting an addition before a cyclization is a notch above that. This last sequence—a radical annulation—is also especially interesting because it forms a ring from two acyclic precursors. It is also especially challenging because the initial radical must undergo radical addition (not chain transfer) and the final radical must participate in chain transfer (not addition). Because both of these reactions are bimolecular, the initial and final radicals can be difficult to differentiate by using the tin hydride method (because many radicals react with tin hydride at similar rates).
We have found that the atom transfer method\textsuperscript{18} is one of the most powerful methods for conducting radical annulations.\textsuperscript{19} With appropriate pairings, annulations of both nucleophilic and electrophilic radicals can be conducted, and Figure 6 shows one example of each.

\[ \text{Yields 40-60\%} \]

These 3 + 2 radical annulations once again use an alkene as a vicinal radical acceptor/radical donor. A couple of years ago, we were taken by the idea of developing 4 + 1 radical annulations, and Figure 7 illustrates our original idea; however, the results that we obtained were not the expected ones.\textsuperscript{20}

\[ \text{Idea} \]

Figure 8 shows the actual result of the experiment. Early reactions of iodopentene and phenyl isonitrile provided very low yields (2\% in the first experiment) of a highly UV-active product soon identified as (cyclopenta)quinoline 8. With 8 in hand, we formulated the mechanism shown in Figure 8. Radical addition and cyclization had apparently occurred to give 9 as planned; however, cyclization of the vinyl radical 9 to the phenyl ring\textsuperscript{21} was clearly much faster than iodine transfer. Rearomatization\textsuperscript{22} of the so formed cyclohexadienyl radical then produced the quinoline 8. Systematic variation of the reaction conditions raised the yield of 8 from 2\% to about 63\%. In the optimum conditions, a 0.025M benzene solution of iodopentene, 5 equiv of phenyl isonitrile, and 1.5 equiv of hexamethylditin was sealed, heated to 150°C, and irradiated with a sunlamp for 5-24 h. The rate dropped significantly if the temperature was lowered or if the mixture was not irradiated.

\[ \text{Figure 8. A (Cyclopenta)quinoline Synthesis} \]
We surveyed about a dozen examples of this reaction under the optimum conditions, varying both the isonitrile and the alkyne substituents. Isolated yields ranged from 50-70%. Figure 9 summarizes our observations with p-substituted isonitriles. From these reactions we isolated two products: a major unarranged product 10 and a minor rearranged one 11. In the rearranged product 11, the aromatic substituent that was para to the nitrogen atom bond is now meta to it. A related rearrangement had been observed and studied by Tundo and coworkers.23 From their work and ours, it appears that the unarranged product 10 arises from a 1,6-cyclization to give 12, while the rearranged product 11 arises from a 1,5-cyclization to give 13 followed by ring opening to an iminyl radical and reclosure.

Figure 9. 4 + 1 Annulation—Regiochemistry

Our general interest in natural products chemistry soon attracted us to the structure of camptothecin, which is shown in Figure 10a. Initial synthetic excitement culminated in a number of total syntheses of racemic camptothecin during the decade of the 70s.24 Oncological and medicinal interest in camptothecin was resuscitated in the mid 80s when details about camptothecin’s unique mechanism of action began to unfold.25 Camptothecin acts on DNA through the intermediacy of the enzyme topoisomerase I.26 Camptothecin, often called a “topoisomerase poison”,27 is now being touted as an unusually important lead in cancer chemotherapy.25-28

Camptothecin is an “azacyclopepta”-fused quinoline, and is a prime target for synthesis by a 4 + 1 radical annulation. Such an approach requires addition of a pyridone radical to an isonitrile, and the strategy is summarized in Figure 10 along with the result of a key model reaction. Dibromopyridine was hydrolyzed and then propargylated to give model D ring precursor 14. Reaction of 14 with phenyl isonitrile succeeded at 80°C, and crystalline 1529 was isolated in 40% yield. A mechanism analogous to that in Figure 8 is proposed for the formation of 15.

Figure 10a. 4 + 1 Strategy for Camptothecin.
Figure 10b. Camptothecin Model Reaction.

Figure 11 shows our recently completed formal total synthesis of camptothecin.\textsuperscript{30} The synthesis of the bromopyridone 17 is a significant modification of a known chloropyridone synthesis,\textsuperscript{31} and it starts with Doebner condensation of cyanoacetic acid and dimethyl acetone dicarboxylate. This reaction occurs in 70% distilled yield (10 g scale). Saponification gives diacid 16, which is reacted in one pot with PCl\textsubscript{5}, then gaseous HBr. After methanol quench and workup, bromopyridone 17 is isolated in 62% yield. N-Propargylation (70%) followed by alkylation (95%) gives 18. The key radical annulation of 18 with phenyl isonitrile now works well, and we isolate the known tetracycle 19 in 40-45% yield. Hydroxymethylation (35%) and oxidation (quantitative) complete the synthesis of racemic camptothecin.\textsuperscript{32}

This "first-generation" synthesis of tetracycle 19 takes only six steps from dimethyl acetone dicarboxylate, and the overall yield is about 13%. We hope to improve the synthesis and also to prepare optically active camptothecin. In the long run, our goal is to develop a practical synthesis not only of camptothecin itself but also of important derivatives.

As evidenced by the camptothecin work, our applications of radical reactions to organic synthesis have now moved a long way from triquinane natural products. Indeed, one of the main goals of research in the field has now become the extension of radical reactions beyond "established" systems (like cyclopentanes) into completely new structural motifs. We hope that our results and ideas will help in the attainment of this goal.

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REFERENCES

27. See editorial "Chemotherapy: Topoisomerases as Targets" in: Lancet 1990, 335, 82.