# RADICAL CYCLIZATIONS IN THE SYNTHESIS OF NATURAL PRODUCTS

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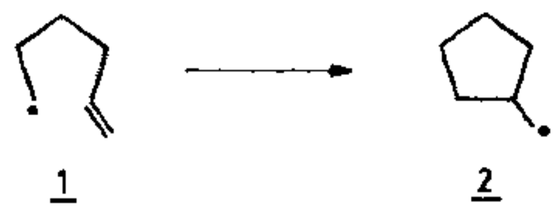
## ABSTRACT

Organic chemists have begun to use intramolecular radical addition reactions i.e. radical cyclizations to develop useful synthetic transformations. The mild reaction conditions and the observed selectivities made these radical cyclizations a viable alternative to the conventional polar reactions. Application of radical cyclization strategy to various natural products like sesquiterpenes (sativenes, agarofurans, hirsutene, capnellenes, silphiperfolene, seychellene, patchouli alcohol), marine diterpene isoamijiol, pyrrolizidine alkaloids (dehydrohastanecine, heliotridine, hastanecine), by various organic chemists demonstrates the versatility of this relatively new area in organic synthesis.

THE use of free radical intermediates in ring formations has until recently been limited to studies of a more mechanistic bias. In the past, the mild reaction conditions and high selectivities of radical cyclizations have often been overlooked. However, the last few years have witnessed a rapid development in the use of radical-mediated reactions in organic synthesis[1,2]. Organic chemists have begun to use intra and intermolecular free radical addition reactions to develop useful synthetic transformations. This is mainly due to the fact, that because of the mechanistic studies in the last three decades, the main features of the radical reactions are now known; radicals have been generated from nearly every important functional group; radical chains can be constructed and controlled in which reactions between radicals and nonradicals occur with high selectivities. Radicals exhibit high chemoselectivity i.e. they react with different functional groups with different rates. Furthermore, functional groups like –OH and $–NH_2$ can be tolerated without protection as these groups are attacked by the radicals so slowly. Carbon-centred radicals can add on to electron-rich or electron-poor alkenes, allenes and acetylenes. The versatility of the radical cyclizations enhanced because of the ease of generation of quarternary carbons and also the formation of unusual bonds quite contrary to the polar reactions[3]. Radical rearrangements are much less common when compared to the rearrangements of cations. Similarly the clevage of a $\beta$C–X bond is less pronounced in comparison with those of anions. This means that during radical reactions the adjacent chiral centres survive. Intramolecular cyclization and intermolecular reactions of cyclic radicals impressively demonstrate that even the stereochemistry of radical reactions can be high. However, for non-cyclic radicals much work has yet to be done to improve the stereoselectivity.

By far the most studied cyclizations are those of 5-hexenyl radicals (1→2) It has been shown that initial radical structure, steric effects resulting from olefin substitution patterns and geometric constraints on the chain linking the olefin and radical are factors in governing cyclization regiochemistry.



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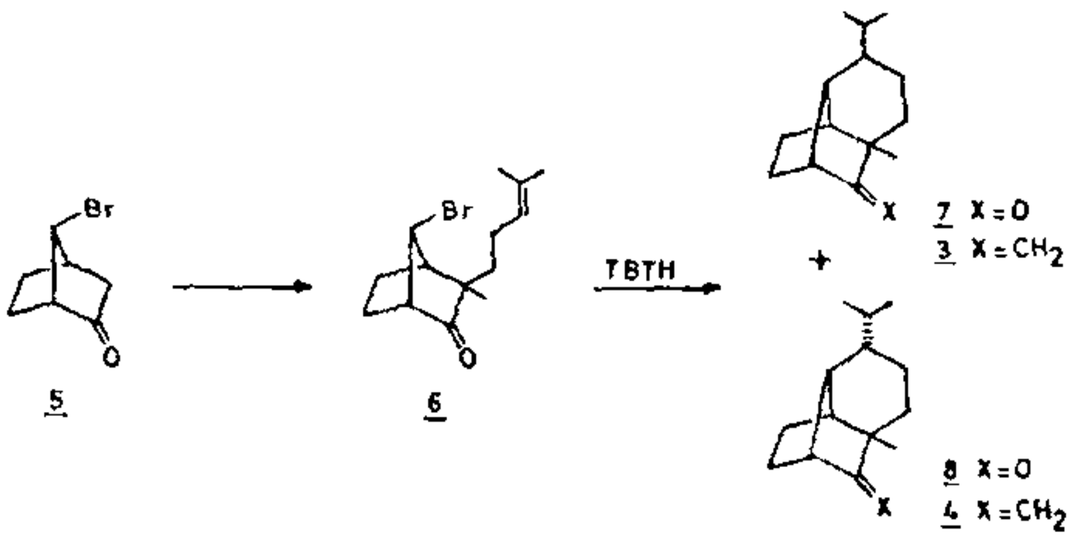
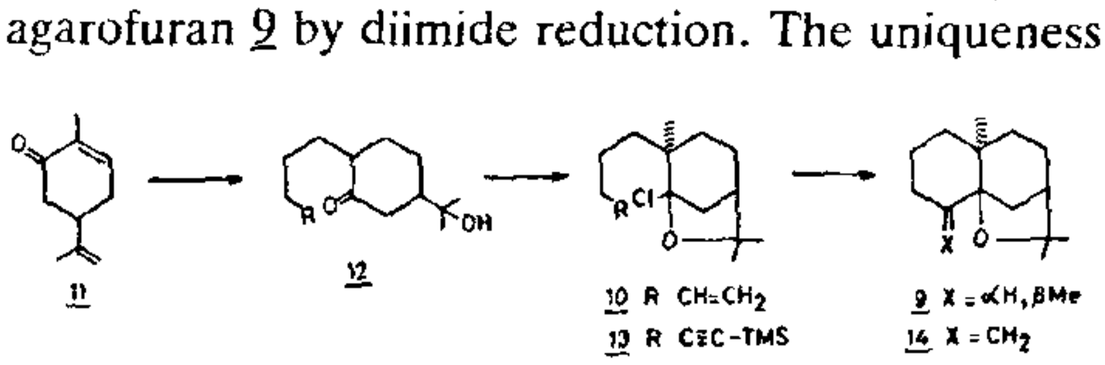
In spite of the promising work done during the last three decades, radical cyclizations did not find its well-deserved place in the synthesis of natural products until the beginning of this decade. Much activity has been initiated during the last 4 or 5 years mainly by Stork, Curran, Pattenden and their coworkers. Only a couple of scattered examples of radical cyclization derived synthesis of natural products appeared in the late seventies. The purpose of this article is to initiate much more activity in utilizing radical cyclizations in the synthesis of natural products.

In 1976 Bakuzis and coworkers[4] reported the synthesis of sesquiterpenes sativene (3) and its epimer capocamphene (4) via the ketones 7 and 8, which perhaps is the first example of the utilization of the radical cyclization as the key step in the synthesis of natural products. The key cyclization precursor, bromo olefin 6 was obtained from the readily available bromo norbornanone 5. However, the radical generated by treatment with tributyl tin




**Scheme 1.**

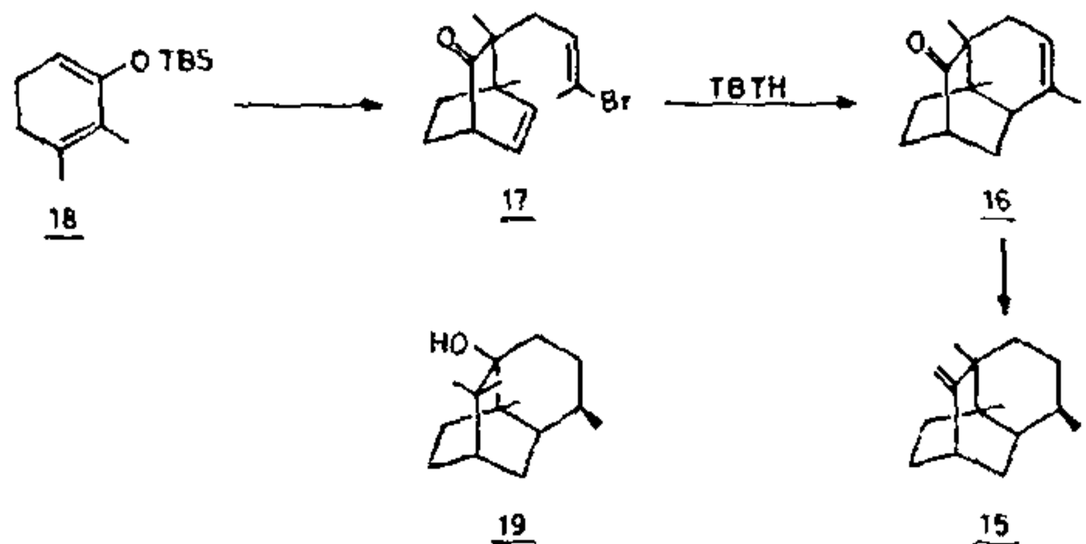
hydride (TBTH) showed poor stereoselectivity in the cyclization and ketones 7 and 8 were formed in a ratio of 3:2. Buchi in his chiral synthesis of dihydroagarofuran (9) encountered similar stereochemical problems[5]. The chiral intermediate chloro vinyl ether 10, obtained from (−) carvone (11) via 12, on treatment with TBTH cyclized to dihydro agarofuran 9 and its epimer in a ratio of 5:2. This was circumvented by using terminal acetylene in place of terminal olefin. Thus, cyclization of the chloro acetylene 13 followed by protiodesilylation generated the olefin 14. This was transformed to dihydroagarofuran 9 by diimide reduction. The uniqueness




**Scheme 2.**

of this method is the construction of ring A onto preformed oxa bicyclo (3.2.1) octane system, contrary to the other methods of constructing the tetrahydrofuran ring at the end. This establishes the versatility of radical cyclizations in the formation of unusual bonds.

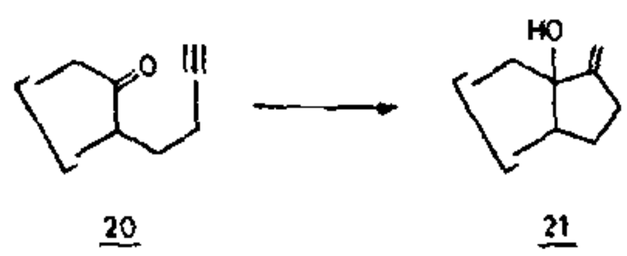
More systematic work in utilizing radical cyclization in the synthesis of natural products started in the beginning of this decade. Prof. Stork[6] after establishing a variety of synthetically useful radical mediated transformations, applied the methodology to the synthesis of sesquiterpene hydrocarbon seychellene 15 via the ketone 16 as outlined in scheme 3. He used a combination of Diels-Alder reaction and selective enolate alkylations to generate the necessary vinyl bromide 17 starting from the enol ether 18. The vinyl radical generated from the bromide 17 cyclises regiospecifically to give norseychellenone 16 in over 70% yield. He has also synthesized the sesquiterpene alcohol patchouli




**Scheme 3.**

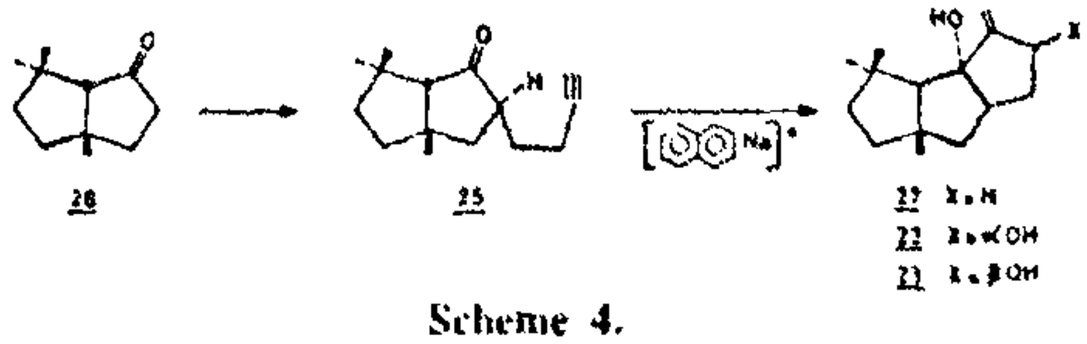
alcohol 19 using a similar vinyl radical cyclization strategy, except that he uses a terminal acetylene to generate vinyl radical[7].

Radicals generated from different origin were also exploited in ring formations. Pattenden and coworkers used ketones as radical sources. Radical anions generated from alkynyl ketones, 20, either by electrochemical means or by titration with naphthalene-sodium anion radical, was found to cyclize to form allylic alcohols 21. Even the allenyl ketones were found to cyclize to give predominantly cyclopentanols. This methodology was successfully

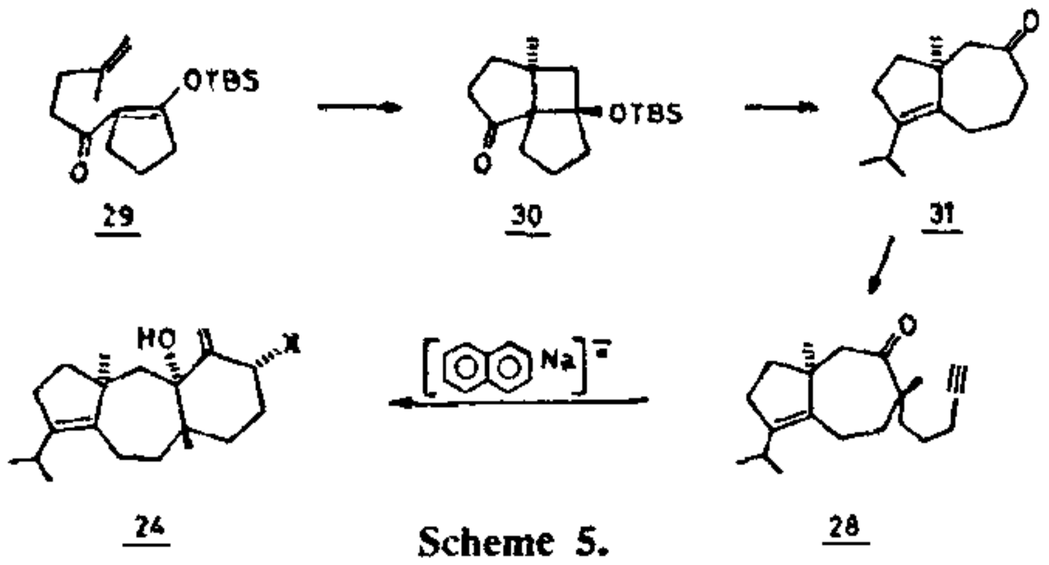



applied first in the synthesis of capnellen-8α-10α-diol (22) an isomer of the marine sesquiterpene capnellene-8β-10α-diol (23) in 1982 and more recently to the synthesis of marine metabolite isoamijiol (24). Titration of the acetylenic ketone 25, obtained by stereospecific alkylation of the bicyclic ketone 26, with sodium-naphthalene radical anion furnished the triquinane 27 in a moderate yield[9]. This was oxidized to the diol 22. Later this was transformed to the natural capnellen using potassium superoxide[10].

Synthesis of the dolestane skeleton, a 5-7-6 ring system, present in the molecule isoamijiol (24) widens the scope of this methodology[11]. Starting from cyclopentanone enamine required acetylenic



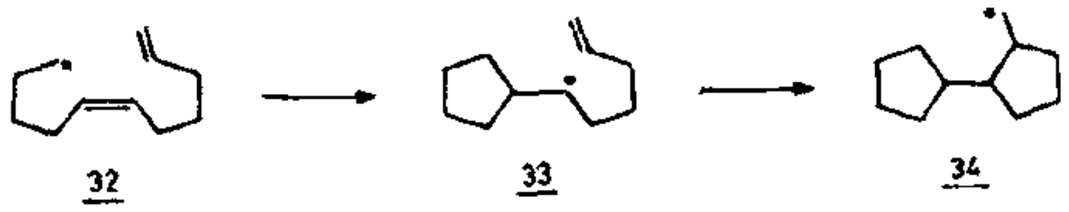

**Scheme 4.**



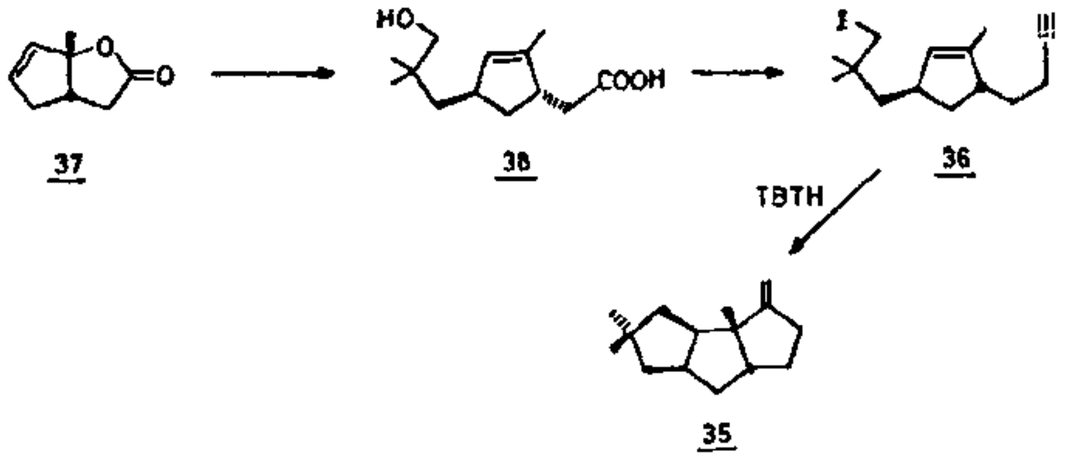

Scheme 5.

ketone 28 was prepared via the intermediates 29, 30, 31, using 2+2 cycloaddition and retroaldol reactions. Treatment of the acetylenic ketone 28 with sodium-naphthalene converts smoothly to desoxyisoamijiol 32, which was oxidized to isoamijiol 24 using selenium dioxide.

It is readily recognized that if the initial cyclized radical produce again hex-5-enyl radicals, subsequent cyclization can occur (32→33→34). Basing on this concept of tandem radical cyclizations, Curran and coworkers developed a general radical-mediated polyolefinic cyclization to polycyclopentanoids, analogous to cation mediated polyolefin

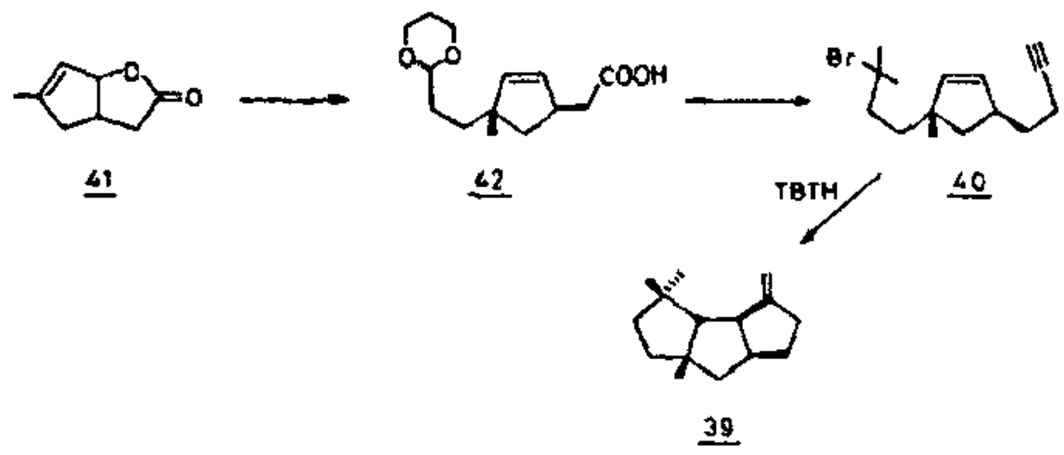



cyclizations to steroids. First he demonstrated the utility of this tandem radical cyclization sequence to the synthesis of linear triquinane sesquiterpene hirsutene (35)[12] as outlined in scheme 6. The




Scheme 6.

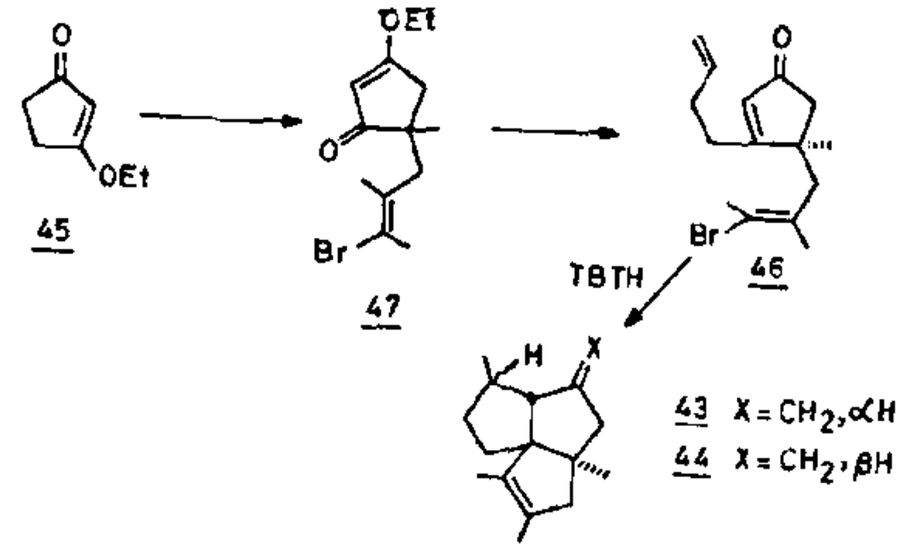
requisite iodo en-yne 36 was obtained from the bicyclic lactone 37 via 38 using a combination of cuprate chemistry and functional group manipulation. Treatment of 36 with TBTH in benzene furnished hirsutene (35) with complete regio and stereochemical control. He extrapolated[13] this methodology to yet another linear triquinane of




Scheme 7.

marine origin, capnellene (39) via the tertiary bromide as outlined in scheme 7. Bromide 40 was obtained analogous to the iodide 36, via $S_N2'$ cuprate opening of bicyclic lactone 41 to the acid 42. Capnellene (39) was formed smoothly from bromide 40 under standard radical conditions, however it is interesting to note that it took a different course with the corresponding iodide.

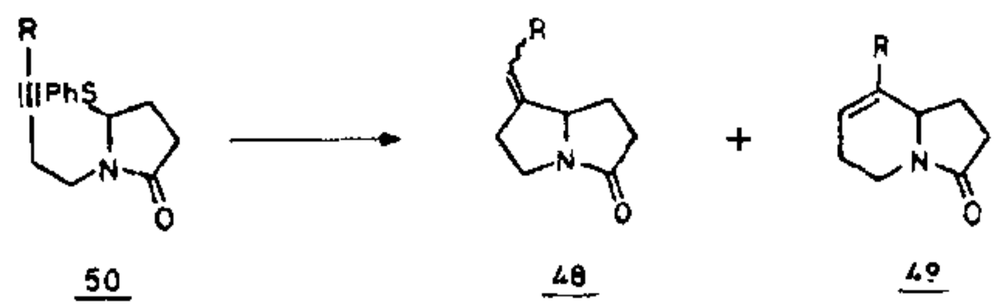
In an attempt to demonstrate that this tandem cyclization methodology can be applied to a variety of polyquinanes he synthesized the angular triquinane, silphiperfol-6-en (43) and its 9-epimer 44 starting from 3-ethoxy cyclopentenone (45) (scheme 8)[14]. The vinyl radical precursor 46 was obtained in a



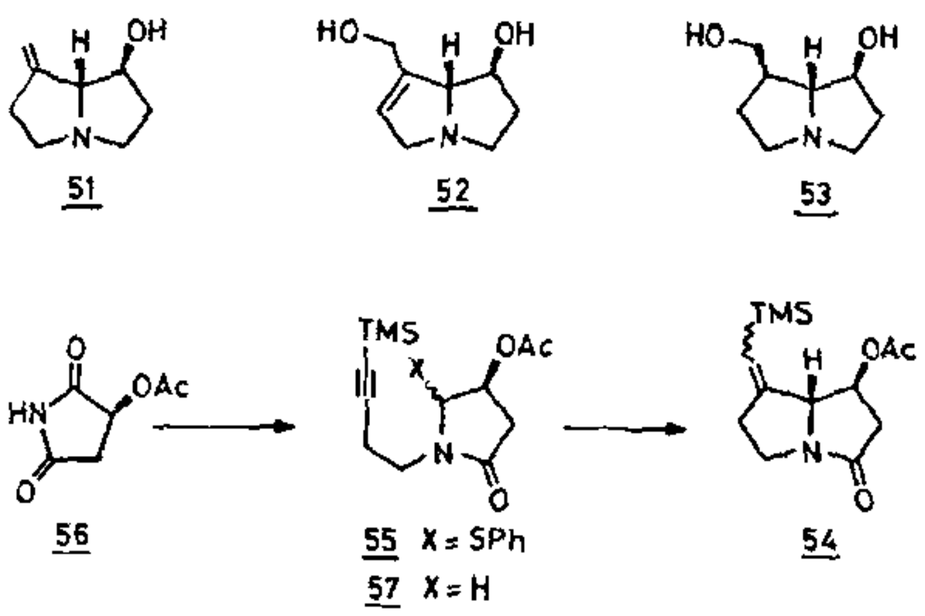

Scheme 8.

straightforward manner via 47. Treatment of vinyl bromide 46 with TBTH followed by Wulff-Kishner reduction resulted silphiperfolenes 43 and 44 in an unfavourable ratio of 1:3. The ratio can be altered to a more reasonable 5:2 by protecting the ketone in 46 as its ethylene ketal and by making use of the steric bulk so produced.

Application of this radical cyclizations is not restricted to carbocycles. Hart and coworkers[15] after



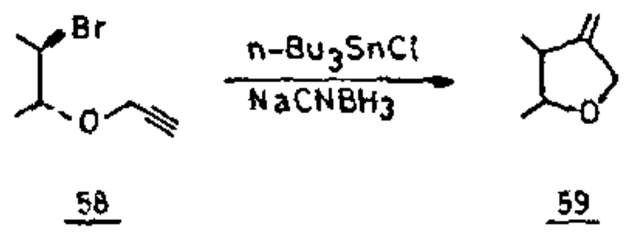
exploring the generation of pyrrolizidines 48 and indolizidines 49, structural subunits of a large number of alkaloids, starting from the acetylenic sulphide 50, and detailed study of the effect of the substituent R in cyclizations, they applied this strategy to the chiral synthesis of pyrrolizidine alkaloids (−)-dehydrohastanecine (51), (+)-heliotridine (52), (+)-hastanecine (53) via common intermediate 54[16]. The sulphide 55 required for the construction of 54 was obtained from the chiral succinimide 56. Cyclization of 55 under standard



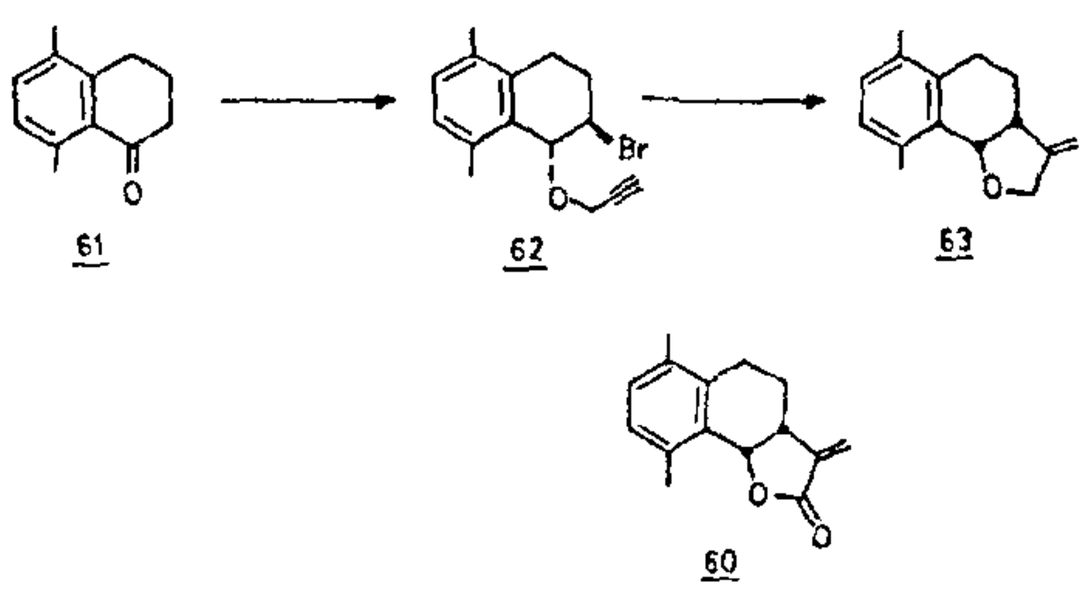

**Scheme 9.**

radical conditions generated geometric isomers 54 in over 70% yield along with the reduction product 57 (18%). 54 was transformed to alkaloids 51, 52 and 53, thus constituting their chiral synthesis.

As part of our interest in utilizing radical cyclization reactions in the synthesis of natural products, in our laboratories, we have developed a methodology




to construct $\alpha$-methylene-$\gamma$-butyro lactone, a widely occurred biologically important moiety, basing on the cyclization of propargyloxy ethyl bromides 58 to 3-methylene tetrahydrofurans 59. As an application




**Scheme 10.**

of this methodology an analog of santonin, 11, 13-dehydro isohyposantonin 60 was synthesized starting from the readily available 5, 8-dimethyl tetralone (61) via bromide 62 and methylene tetrahydrofuran 63 as outlined in the scheme 10[17]. We are further exploiting the radical cyclization methodology to variety of cyclopentanoid natural products.

In conclusion, we have tried to present in this article examples which illustrate the recent development and application of radical cyclizations in the synthesis of natural products. It is clear that this kind of carbon-carbon bond forming reactions has much to offer and it is expected that the organic chemists would use much more of this chemistry to tackle the problems in organic synthesis, especially in the area of natural product synthesis.

4 November 1986

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# NEWS

## LEPROSY—PROGRESS IN SIGHT

For the first time the multidrug therapy (MDT) has provided opportunities for effective control programmes. Although expensive, it has reduced the treatment period and proved its capacity to overcome drug resistance. Most countries and voluntary organizations have adopted MDT, albeit slowly, because of cost constraints and inadequate health infrastructures.

During the past 3–4 years, over 5,00,000 patients from different countries have been put on MDT and the role of the World Health Organization's in leprosy control is not only to assist in the development of new technology, but also to promote, coordinate and support leprosy control through the new strategy of MDT.

The WHO Leprosy Control Programme is receiving strong support from several bilateral, multilateral and voluntary organizations and from generous foundations. For many years, it has greatly benefited from generous donations made by the Japan Shipbuilding Industry Foundation (JSIF), headed by 87-year-old Mr Ryoichi Sasakawa.

The results on the efficacy of the leprosy vaccine are expected to be available within the next 5–10 years through ongoing field trails in Venezuela and Malawi. Other trails are being contemplated.

With WHO's current new thrust in leprosy control through MDT and its investment in an effective leprosy vaccine for the future, major reductions in the prevalence of leprosy are foreseeable in the near future with a possible perspective on elimination of the disease in the distant future. Therefore, this calls for further intensified efforts to mobilize the additional resources required to implement the programme as well as to strengthen health services at different levels. (WHO Press Release/23, 25 November 1986. World Health Organization Media Service, 1211, Geneva 27, Switzerland).

## BLOOD CELLS TELL THE DIAGNOSIS

Blood cells of both humans and animals are capable of changing their shape. Studies in this sphere have been carried out at Moscow's Institute of Biological Tests of Chemical Compounds. The experiments consisted in sieving blood through film with minute holes. The blood of healthy people passes even through a close-meshed sieve, the blood cells being highly flexible, while the sick persons' cells lose their flexibility and will be retained on the sieve.

The established inter-relationship between the shape of the red blood cells and the state of the organism is expected to help in the early diagnosing of a broad range of disorders. Even cardio-vascular diseases reduce cell flexibility.

A variety of sieves for medical purposes is being currently developed. The materials used are mostly synthetic.

(*Soviet Features*, Vol. XXVI, No. 34, March 19, 1987, p. 2; Information Department, USSR Embassy in India, P. B. 241, 25 Barakhamba Road, New Delhi 110 001).