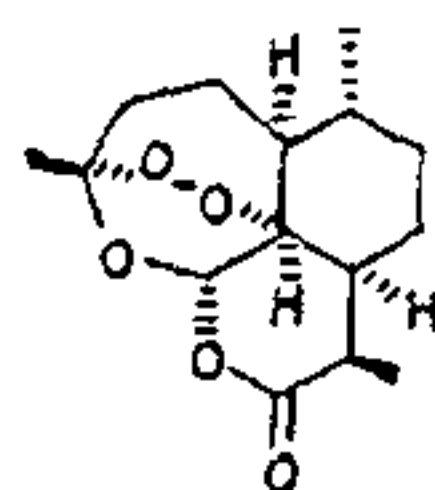


Artemisinin (Qinghaosu)*

T. Ravindranathan

A short and practical synthesis for artemisinin is described and the merits of the chemistry used compared to a few other well-known methods are presented. The synthesis adopts a new philosophy, viz. devising a simple and practical method amenable for preparing large amounts.

ARTEMISININ (1) was discovered to be the essential active principle of an ancient Chinese herbal extract (from *Artemisia* species) used as a grandmother's remedy for common cold, chills and fever. The herbal extract is called 'qinghaosu' and it has entered Chinese medicinal literature right from ancient days¹. Among different species, artemisinin occurs mainly in *Artemisia annua*. Although the claims of artemisinin content are 0.01% and upwards and special horticultural methods and plant tissue culture methods were employed to enhance the artemisinin content, success is not very high. In India, artemisinin is reported to have been isolated to the extent of 0.01% from *Artemisia annua* occurring around Lucknow. The comparative non-abundance of this species and the low content of artemisinin would probably require a good synthetic method for its production and also analogues which may finally be found useful in therapy.



(+) ARTEMISININ (1)

WHO is currently investing substantially in the development of artemisinin and its analogues as antimalarials and this article will deal with our synthetic methodology development adopting a few criteria as the mainstay of synthetic planning, viz., efficiency, practicality and amenability for scale-up. Before the NCL approach is discussed some of the important approaches described in literature are also presented as background and for comparison.

Zhou's approach

One of the earliest syntheses of artemisinin by Zhou *et al.*², started from citronellal (2) and the key reactions employed by him to obtain a stereospecific synthesis was mainly using a chiron approach starting from citronellal. A critical ozonolysis step leads to the formation of keto aldehyde 8 which eventually furnished the enol ether (9) and which providentially sets up the internal ketal peroxide system, surprisingly efficiently. The synthesis is outlined below (Scheme 1).

The key keto aldehyde 8 obtained is converted to artemisinin (1) in about six steps. The synthesis involved a long sequence (22 steps) to obtain the artemisinin structure starting from citronellal. The design of synthesis is mainly the application of general methodologies available for ring formation, usual functional group transformation, selective protections, deprotections, etc. The chirality transfer from the starting chiron was at best satisfactory. But there is a step involving a non-regiospecific dehydration adding to the problems of long sequence of reaction. However, this synthesis is noteworthy not only because this is the first synthesis of artemisinin but it provided a key sub-target, viz. the keto-aldehydes 8 which can become the basis of synthetic design for other workers.

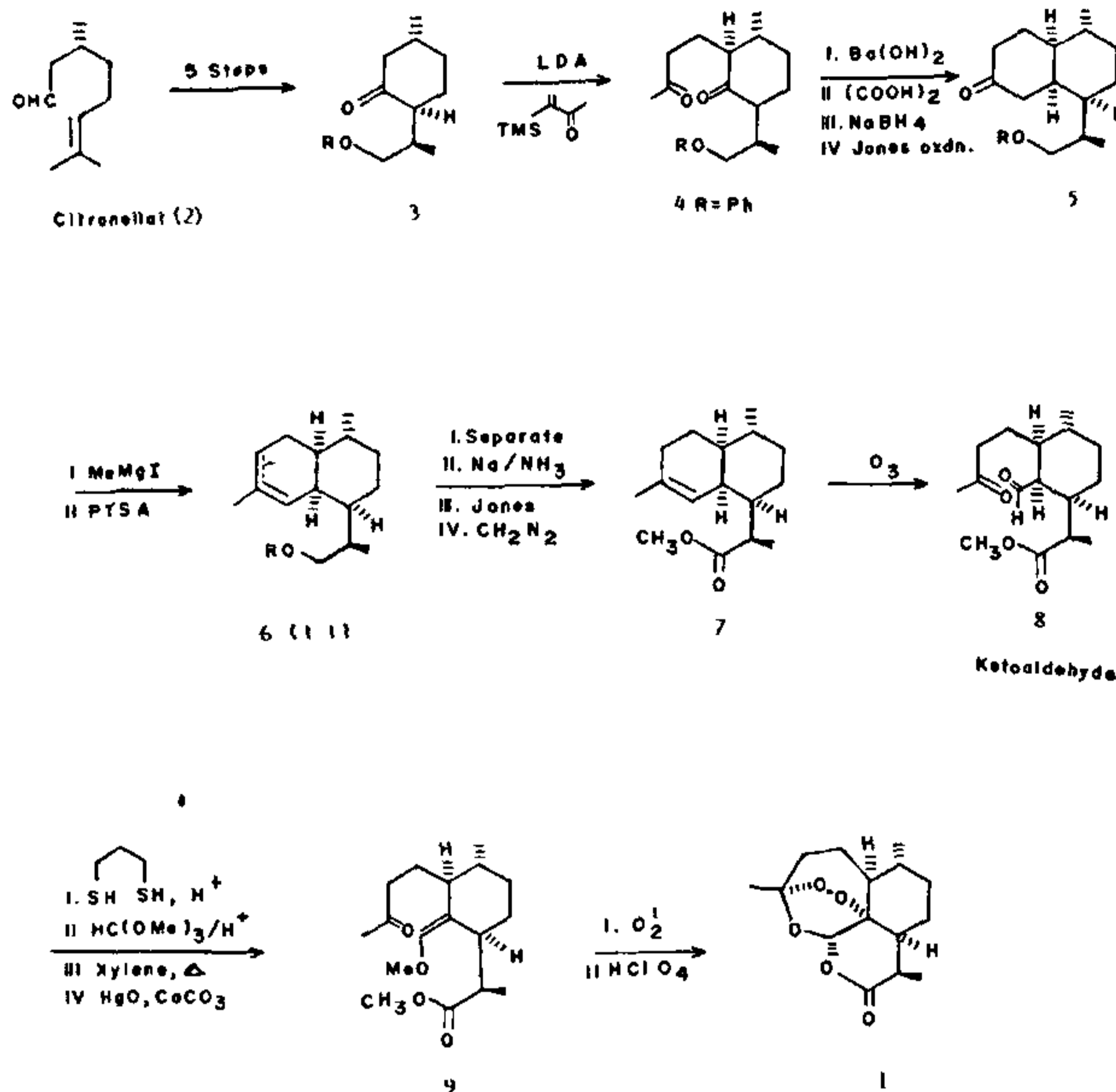
The information generated, i.e. the keto-aldehyde (8) can be easily converted via the enol ether 9 by singlet oxygen to the internal ketal peroxide system 1 with the right asymmetry of carbons and the fact that the seemingly delicate internal ketal peroxide structure is really stable chemically (resistant to borohydride reduction, etc.) and thermally stable allowing it to come out of the final reaction soup in crystalline form in as high as 35% yield was comforting, considering that this key keto-aldehyde (8) has to be taken through synthetic steps for the final internal ketal peroxide formation in the target structure.

Avery's approach

Another synthesis which is again noteworthy was by Avery *et al.*^{3,4}. Avery's approach, starting from R(+)-pulegone, is again a chiron approach. Although in synthetic design in concept, this approach was more

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Scheme 1.

elegant, it definitely lacked in terms of stereospecificity and shortness: in this synthesis R(+)-pulegone (10) was subjected to a base-catalysed epoxidation; exposure of epoxide 11 to sodium thiophenoxide, oxidation of the resulting sulphide led to the formation of sulphoxide 12 to provide optically active 3-methyl cyclohexanone 12, a little laboriously albeit elegantly (as shown below).

Subsequently, the key alkylation was not highly stereospecific, affording a mixture of ketones 13 with $\alpha : \beta$ ratio of 1 : 9. Another key reaction, viz. the addition of trimethylsilylaluminum to 15 in acetic anhydride gave diastereomers A (16) and B (17), of which only one (16), could be converted to the required vinylsilane via Claisen rearrangement. However, his continued studies on this reagent and diastereoselectivity problems and other problems associated with the yield finally helped him to achieve a very elegant synthesis. An interesting key reaction is the unusual ozonolysis of vinylsilane 18 which through the intermediacy of siloxyxetane 20 rearranges to the internal ketal peroxide structure efficiently as explained in scheme 2.

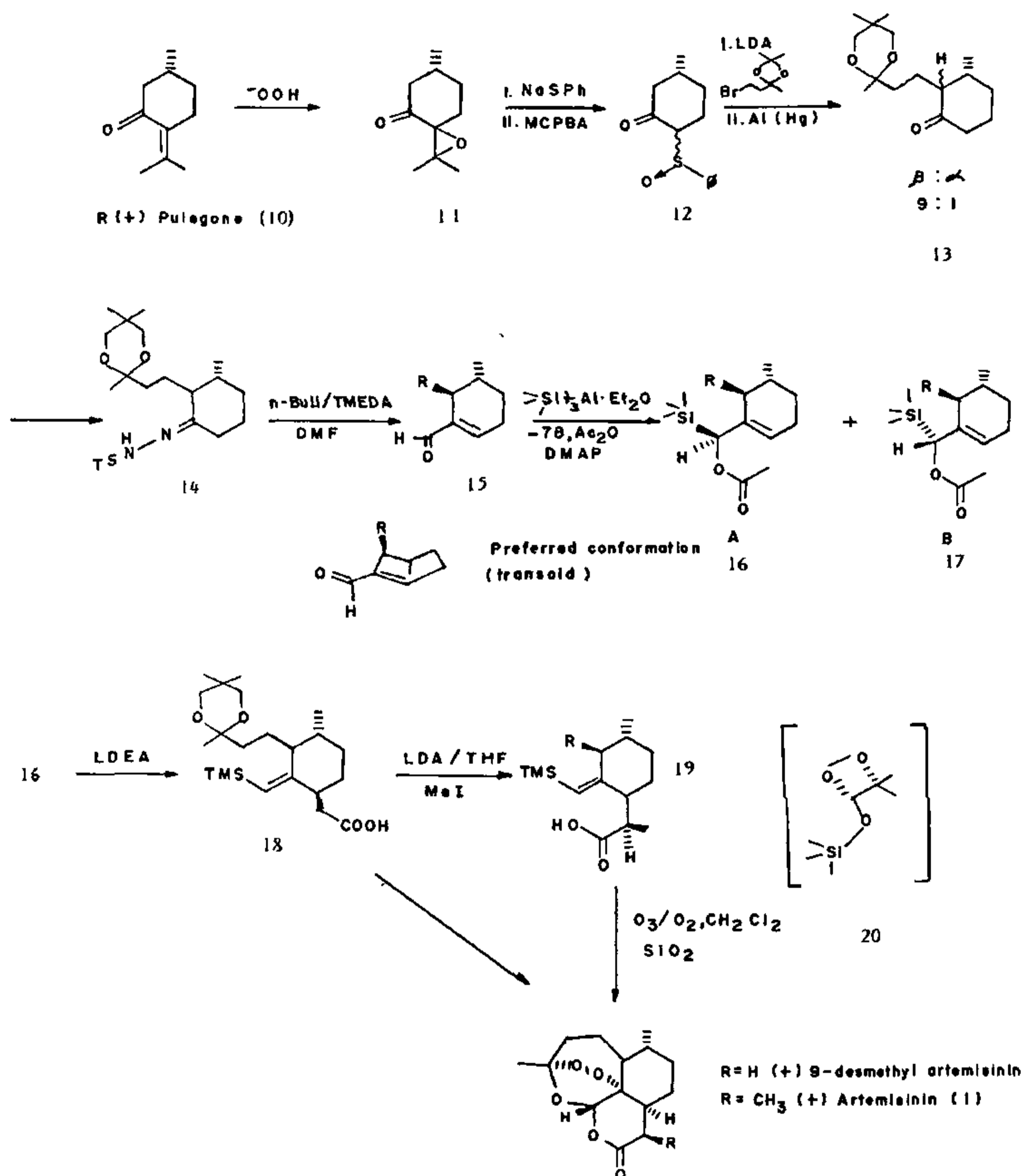
This observation of unusual ozonolysis product and its rearrangement to artemisinin and the realization that the preferred conformation is the transoid form of α, β unsaturated aldehyde system 15 as shown in the

scheme 2 helped Avery to manipulate the addition of trimethylsilylaluminum etherate diastereospecifically to artemisinin. With this modification of the original reaction scheme Avery's method as reported now looks quite promising from a practical point of view.

NCL approach

From the point of view of a practical synthesis of artemisinin (1), a proper selection of starting material has to be made. The material selected should be easily available, cheap and should have suitable functionalities for further elaboration of the structure through simple methods and elaboration of chiral centres, unambiguously. Indigenously available Δ^3 -carene (21) was considered as a material which will fit this bill neatly. Δ^3 -carene (21) is an asymmetric molecule and can be converted into *Menthone* by pyrolysis via menthadiene (isolimonene) (22) (ref. 6). We thought of setting up a Diels-Alder system using this menthadiene and finally lead to Zhou's ketoaldehyde 8 (scheme 1). This synthetic idea is presented briefly in scheme 3.

Although the diene-dienophile partners are not necessarily reactive ones in 23, we thought the basic nature of Diels-Alder reaction being concerted and going

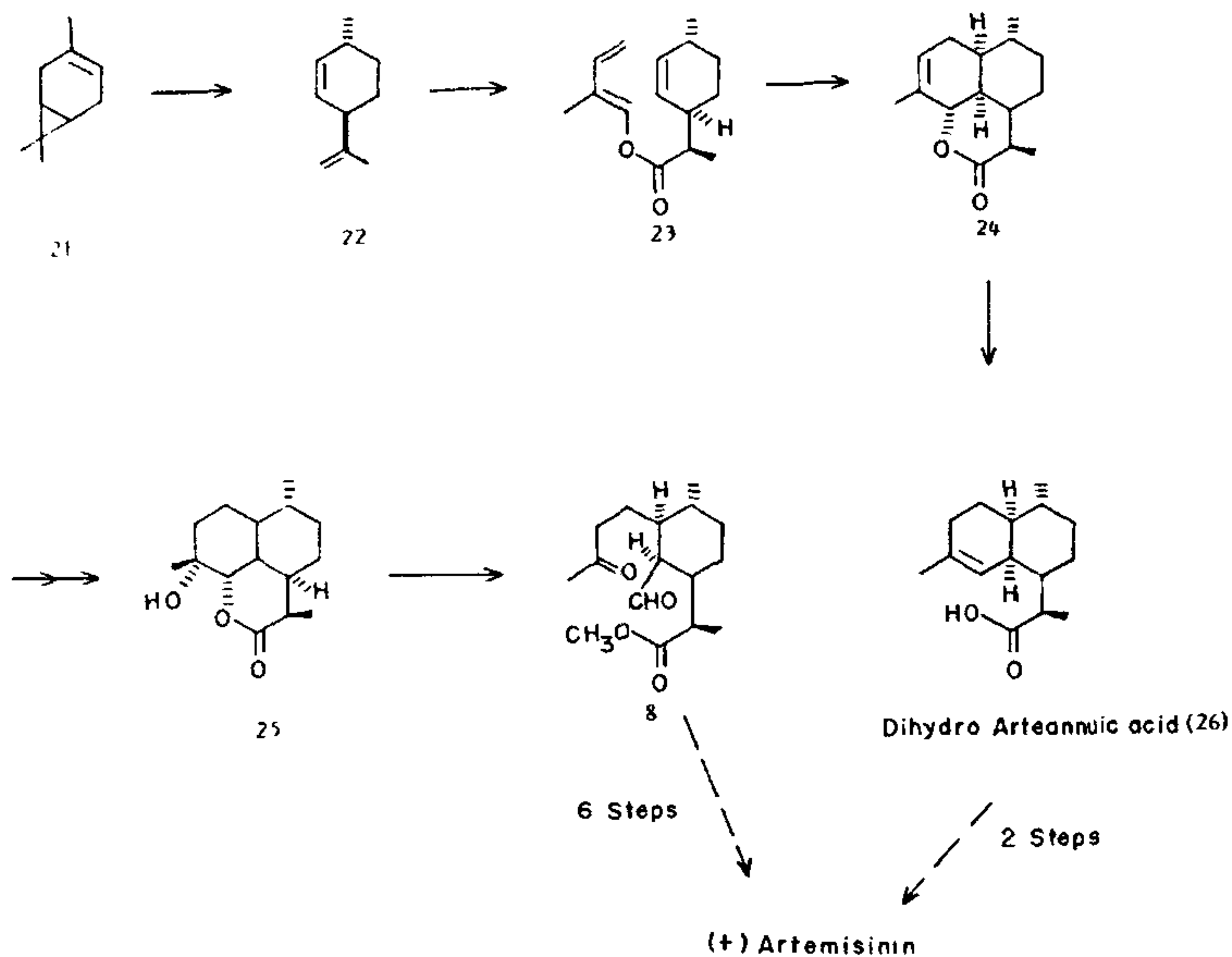


Scheme 2.

through a transition state which is highly stereo-regulated and capable of producing in certain situations as many as 4 chiral centres, we should make use of Diels–Alder reaction. Once the ketoaldehyde **8** is obtained, it will constitute a formal synthesis of artemisinin although by further known sequence of reactions in 6 steps as done by Zhou. Alternately, if the lactone product obtained after Diels–Alder addition can be isomerized to dihydroarteannuic acid (**26**), synthesis of artemisinin (**1**) can again be achieved through further conversion by a shorter sequence involving only two steps⁷. At this time we have to pay special attention to the possible transition state involved in the Diels–Alder reaction itself and

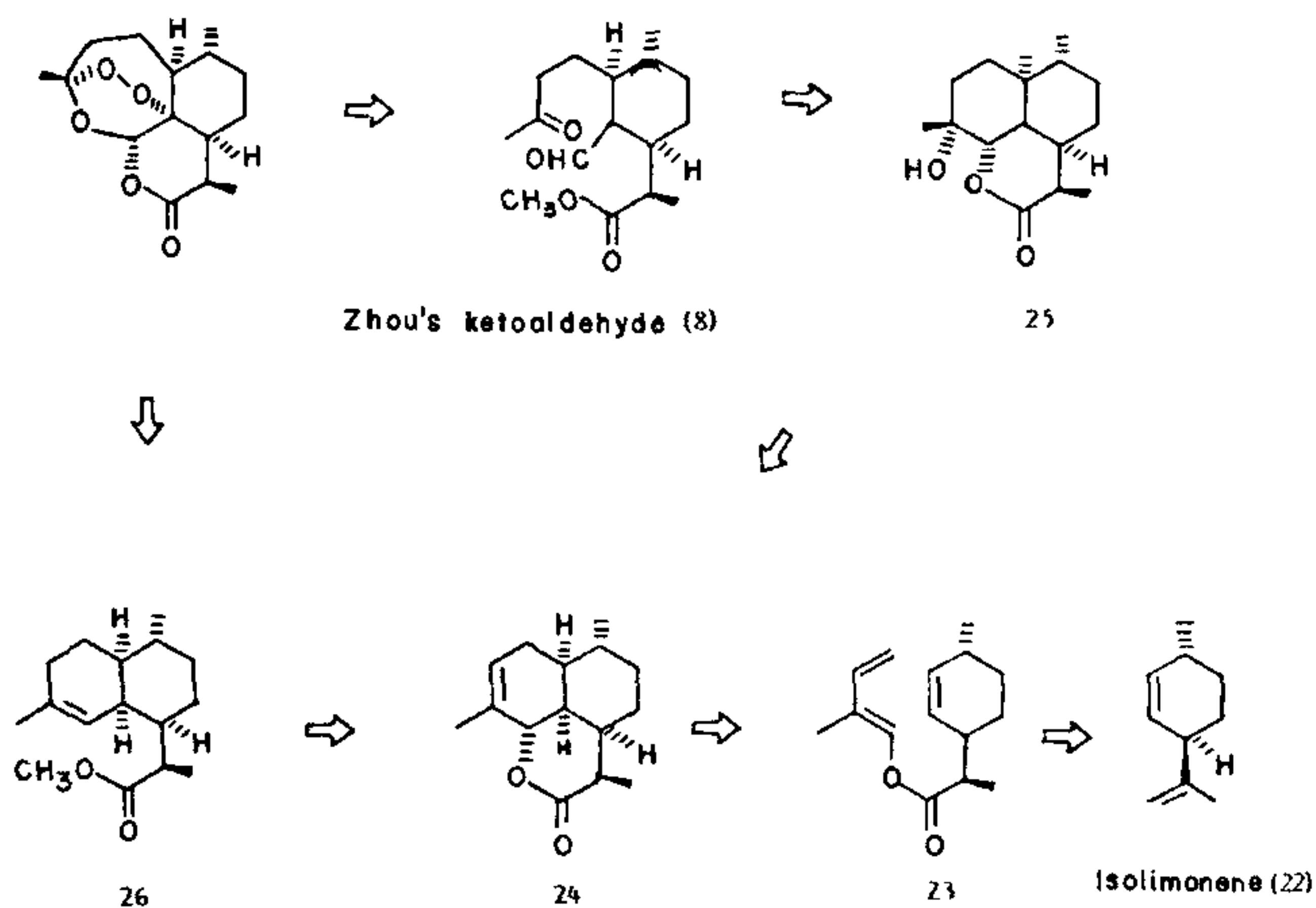
check on the possible outcome as far as the stereo-selectivity questions are concerned.

With the above framework of ideas of custom design for (+)artemisinin, we wanted to elaborate the complete synthetic strategy from the basics. Necessarily the basic structural features to be taken into account before doing this job are: (i) Sesquiterpene lactone peroxide, internal acetal; (ii) Polycyclic: Condensed tetracyclic framework; and (iii) 7 Asymmetric centres: Array of contiguous carbon centres. Although the structure seems to be complicated by features which are not simple, considerations of a possible synthesis and therefore a retro-synthesis gave the pathway shown in scheme 4.



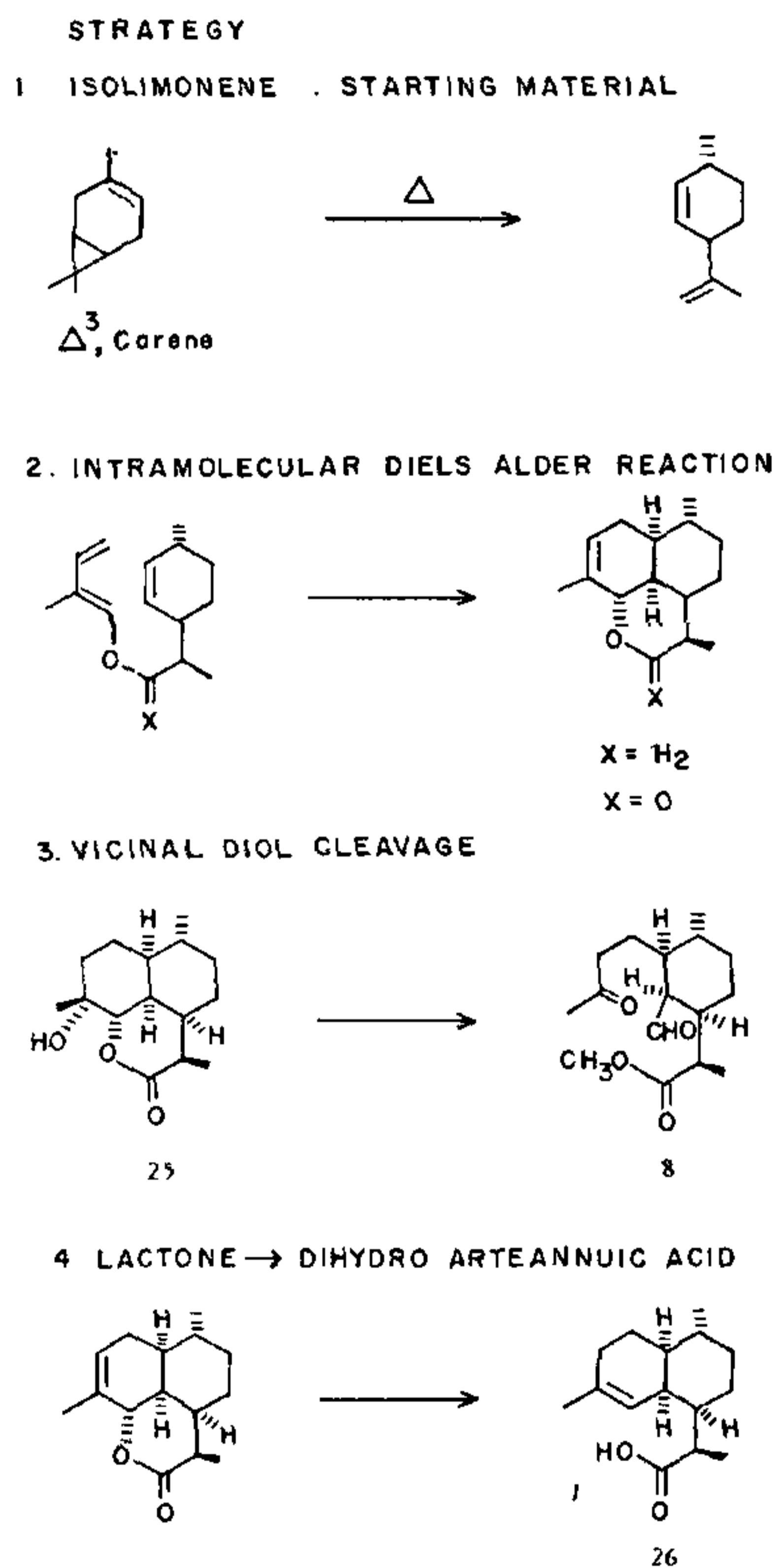
Scheme 3.

RETROSYNTHESIS AND STRATEGY



Scheme 4.

To sum up the basic strategy (scheme 5): (1), one will have to start from menthadiene from Δ^3 -carene which has a right chirality for elaboration and thus can be a useful chiron (2). Next one has to set up an intramolecular Diels–Alder system (23) and (3) the adduct (24) has to be manipulated chemically to a vicinal diol (25) which on cleavage would provide the ketoaldehyde 8. Alternately, the lactone adduct can be isomerized to dihydro arteannuic acid (26) to obtain a still shorter synthesis for the same ketoaldehyde (8) as well as its conversion to artemisinin in two steps.



Scheme 5.

Before the work on total synthesis of artemisinin was taken up, a close look for designing a proper intramolecular Diels–Alder system was made by careful

analysis of molecular models. The intramolecular approach of the diene towards the dienophile showed us that β -side approach of the diene will lead to exo-product, and the likely outcome would be an overall stereoselectivity of different chiral centres, compared to any other approaches, as shown in scheme 6.

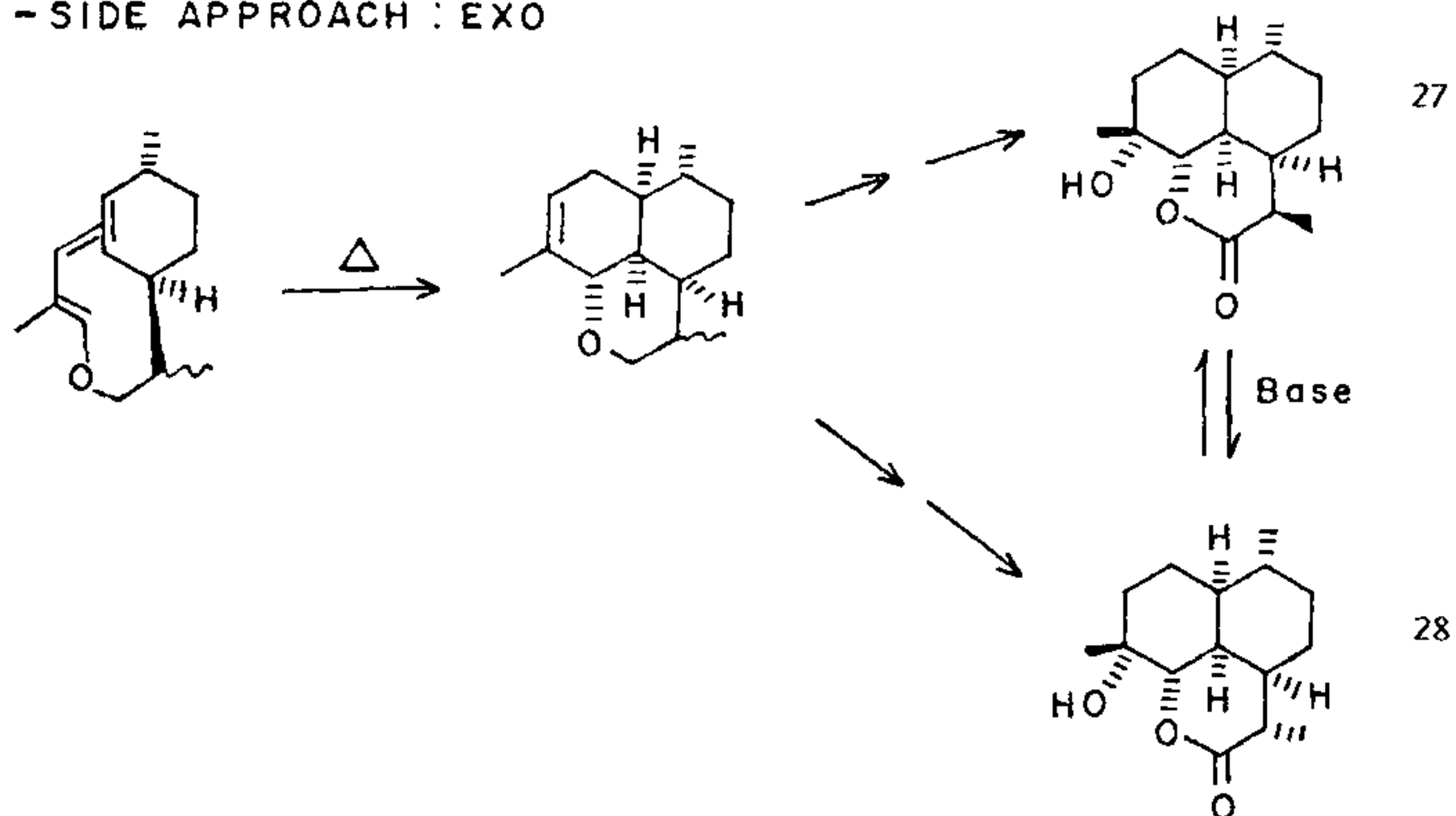
The β -side exo approach can possibly give two isomers, (27 & 28) differing in the configuration of the methyl α to the carbonyl, which can be easily equilibrated using a suitable base. All the above considerations led us to believe that the Diels–Alder adduct obtained also will undergo stereospecific α -epoxidation which should ultimately give the required vicinal diol system 25 useful for cleavage into Zhou's ketoaldehyde 8.

The experimentation for the synthetic steps using the above mentioned strategies was taken up and the results were obtained as shown in scheme 7. One would see that the internal Diels–Alder system set up using the dienyl ester failed to undergo Diels–Alder reaction whereas the corresponding dienyl ether system not only underwent Diels–Alder addition, but gratifyingly also with complete stereoselectivity, except for the 'methyl' mentioned earlier. Further epoxidation also was stereoselective, leading to a diol system. Oxidation of the cyclic ether using NaIO₄/RuCl₃ not only gave the lactone but made the methyl function equilibratable. We found that the unrequired α -isomer could be equilibrated and the β -methyl product separated efficiently by chromatography. This constituted a formal total synthesis of artemisinin which is the first completely stereoselective approach reported. Further, the expectation of the efficiency of stereocontrol was better than anticipated. In fact at one stage, the intermediate lactone had surplus number of chiral carbons (total 7) than even present in Zhou's ketoaldehyde. Further elaboration of Zhou's ketone to artemisinin by an improved method as shown by Avery recently or the alternate method of isomerisation to arteannuic acid and elaboration to artemisinin remains to be achieved shortly.

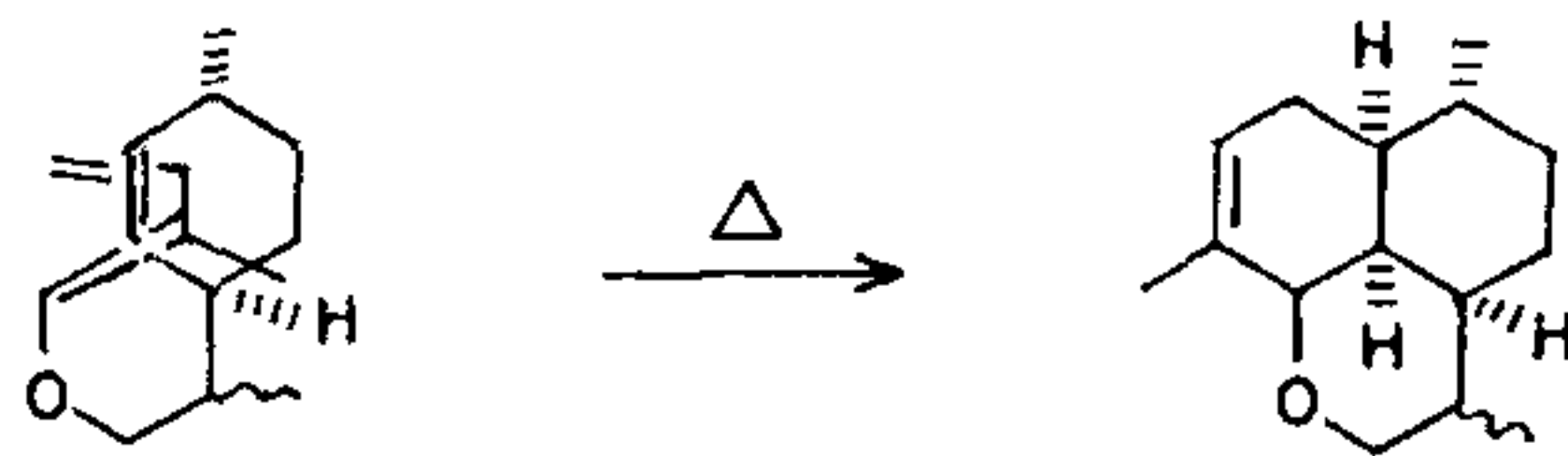
It is only pertinent now to see the status of our synthetic method compared to other methods, particularly that of Zhou's and Avery's methods. Compared to Zhou's method involving 16 steps for his ketoaldehyde (8), we have now a completely stereospecific method in 8 steps and also our method for artemisinin will now be only 14 steps instead of 22 steps compared to Zhou's method. There is no stereoselectivity problem as in Zhou's method and if the conversion of the intermediate lactone to dihydro arteannuic acid is done our synthesis will lead to a still shorter (11 steps) method for artemisinin. This will then compare favourably with Avery's method not only in terms of number of steps (12 steps for Avery's method) but also in terms of simplicity and practicality. We still believe that further work can be done on refining the design of artemisinin synthesis to make our method simpler and practical and

DESIGN OF INTRAMOLECULAR 4 + 2 REACTION

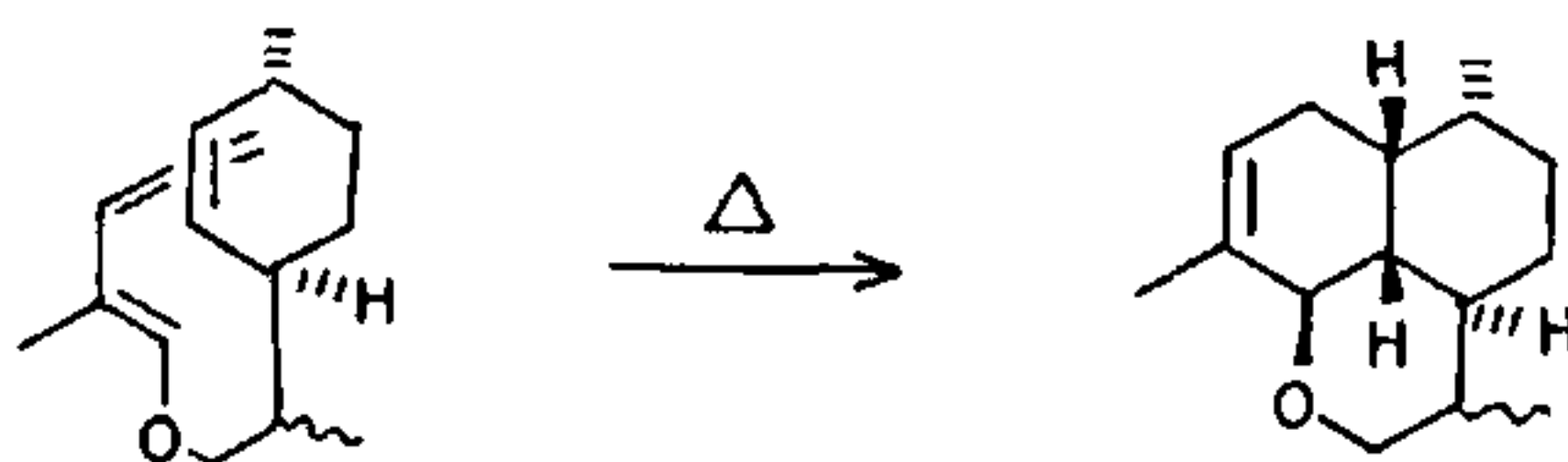
β -SIDE APPROACH : EXO



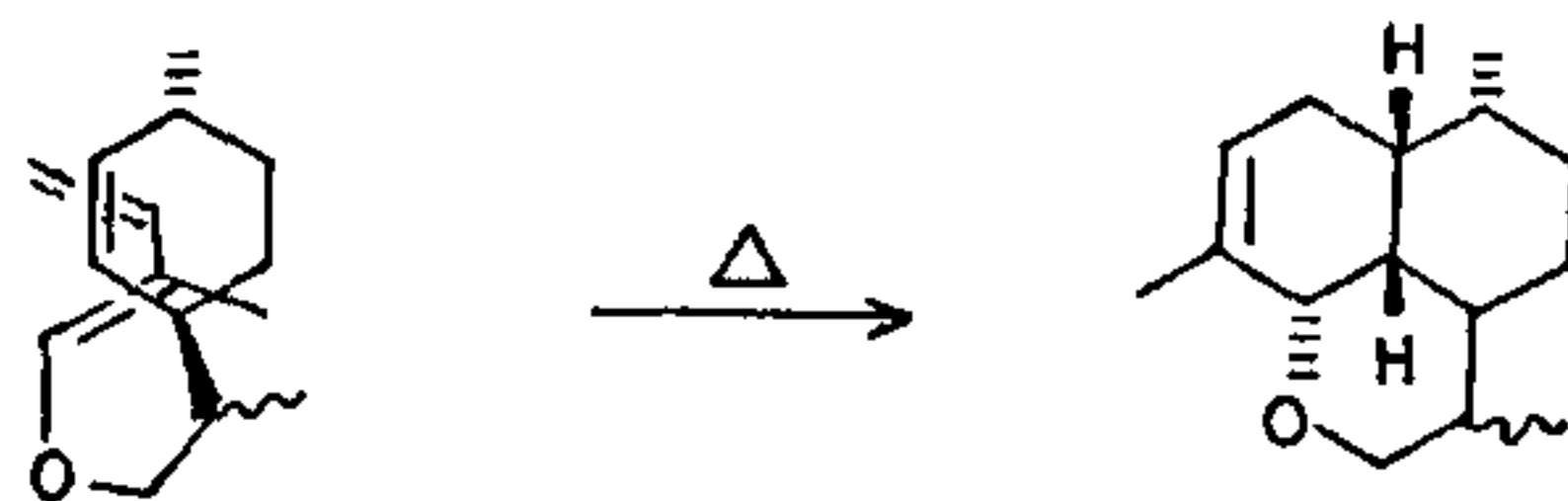
β -SIDE APPROACH : ENDO



α -SIDE APPROACH : EXO

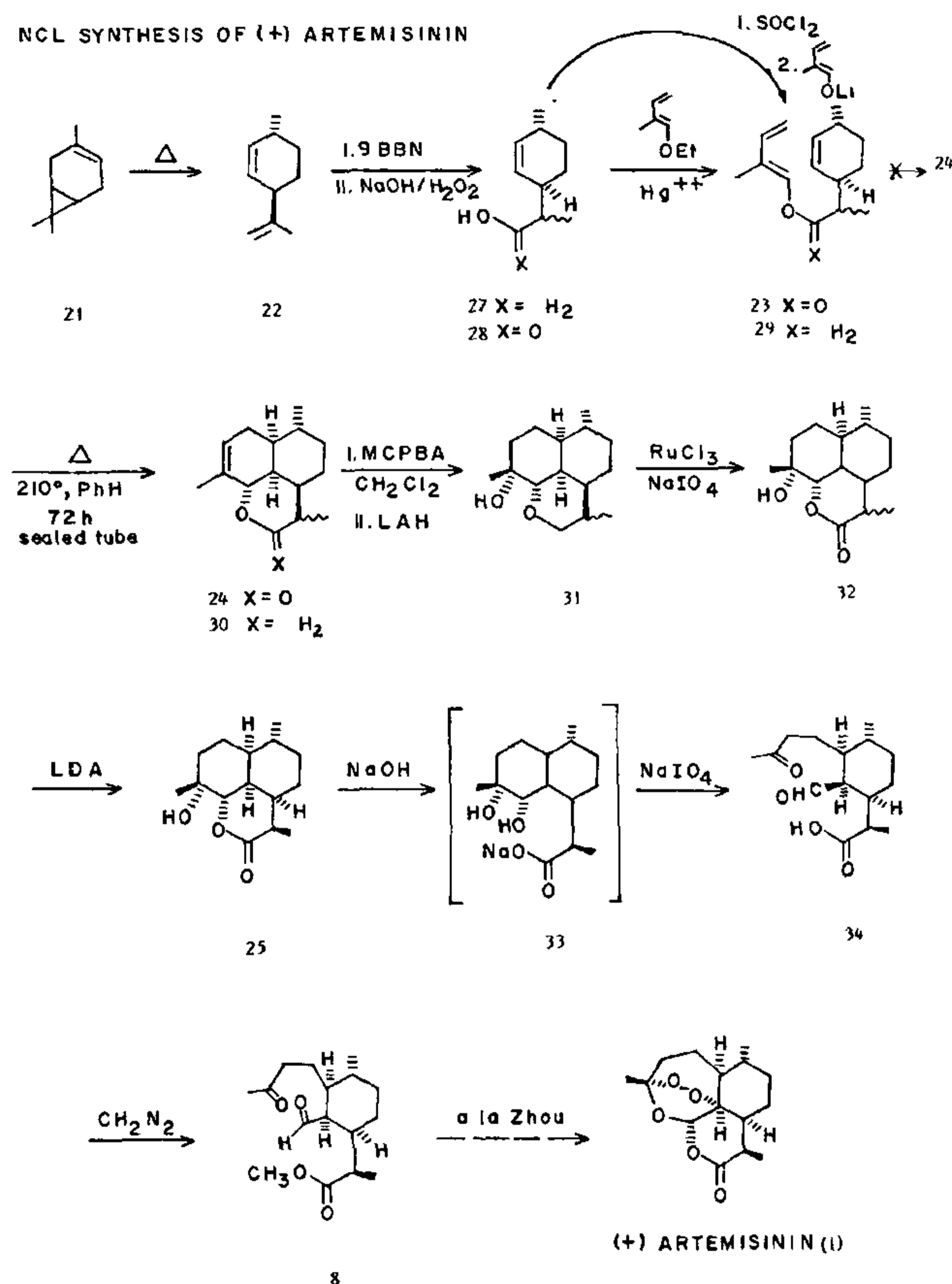


α -SIDE APPROACH : ENDO



Scheme 6.

NCL SYNTHESIS OF (+) ARTEMISININ



Scheme 7.

therefore, conversion of the chemistry described here to a technology for producing the useful artemisinin and its derivatives is not too far.

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