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Synthesis of optically active steroids—achievements and aspirations

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Abstract

Different approaches to obtain steroids in high optical purity have been discussed. Utility of syntheses from natural precursors, resolution of intermediates and selective derivatizations using chiral reagents have been highlighted. The mechanisms of different asymmetric syntheses have been reviewed. A mechanism involving bifunctional catalysis has been proposed for amino acid catalyzed asymmetric cyclization reactions on the basis of available literature data.

Key words: Optically active steroids, optical resolution, thermodynamically controlled asymmetric derivatizations, asymmetric synthesis, diastereomeric transition states, intramolecular asymmetric induction, chiral recognition, bifunctional catalysis.

1. Introduction

Steroids have engaged the attention and activities of a large number of synthetic chemists all over the world for the past few decades.[1(a,b)] The unique tetracyclic skeleton with definite stereochemical arrangement of this class of molecules had always been a challenge for the synthetic chemist, the inspiration being further intensified by the immense medicinal potential of these molecules. They have initiated a new era in contraception and added a new dimension to chemotherapy.

However, 'absolute specificity for a particular stereoisomer of a given compound is a common biological phenomenon'*, and steroids are no exception to this. We find that most of the biologically active steroids have 'natural configuration' (Fig. 1). Synthesis of natural steroids and analogs with natural configurations, thus, necessitates the preparation of compounds in enantiomerically pure form. The scarcity of natural sources has prompted many countries to market totally synthetic steroids and steroid analogs to meet their requirements. But most of these total syntheses yield steroids

* *Molecular asymmetry in biology*, Vol. 1, R. Bentley, Academic Press, N.Y., 1969.

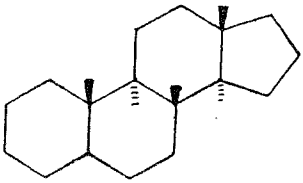


FIG. 1

as a racemic mixture and separation of the required enantiomer at a late stage of multi-step synthetic scheme obviously brings down the efficiency of the process by more than 50%.

Studies have been directed, however, towards synthesis of steroids in the optically pure form[2] and to date, a wide variety of strategies have been adopted to realize the goal. A systematic analysis of these strategies* will reveal the stage of art of synthesizing a chiral molecule of medicinal importance, *viz.*, steroids, with desired absolute configuration and enable us to compare the different strategies in terms of their efficiency and practicability. A review of this subject may, optimistically, contribute to: (*a*) the development of improved methodologies, (*b*) identification of potential but as yet unexplored areas of research, and (*c*) understanding of the all-pervading biological phenomenon called 'chiral recognition' in course of discussion of asymmetric catalysis as a promising synthetic technique.

2. Use of optically active natural products as precursors

To synthesize a chiral molecule of natural occurrence in optically pure form, an obvious choice of starting material had been the more abundant natural products which are structurally related to the target compound. Plant sapogenins, *e.g.*, diosgenin[3], hecogenin[4,5], etc., served the purpose and were adopted for industrial preparation of steroids. They enjoy a distinct advantage as raw material for steroid manufacture since they possess the same stereochemical configuration as the steroids; mere functional group transformations can bring about variations at the periphery of the rigid tetracyclic skeleton to yield natural and modified steroids with moderate ease. A delightfully imaginative route from (−) camphor to optically active steroid intermediate has recently been published[6] (Fig. 2).

3. Resolution of intermediates

For a totally synthetic route, stereo-controlled reaction sequences can at the most lead to the production of racemic steroids. To economize the entire operation, intermediates

* The coverage of literature is illustrative rather than exhaustive and is up to 1979.

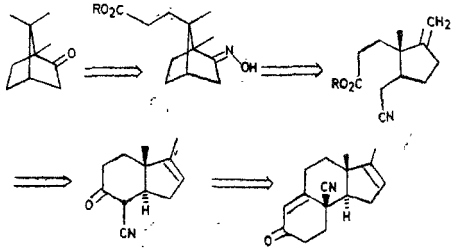


FIG. 2

were resolved at different stages[7–11] (Fig. 3) in different synthetic schemes and the desired enantiomers were subsequently elaborated to steroids.

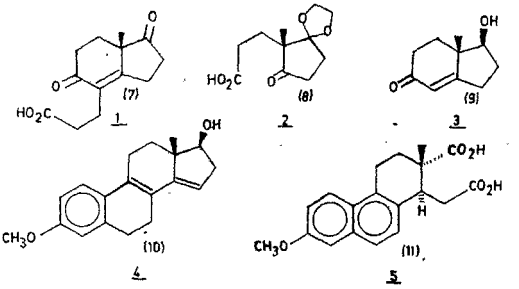


FIG. 3

Chromatographic techniques have been recently developed to separate enantiomers, either indirectly *via* diastereomeric derivatives, or directly with optically active mobile or stationary phase[12]. Thus, separation of amines, alcohols, acids, etc., has been realized. The technique provides the advantages of easy operation and scaling-up, recycling and regeneration of reagents, etc., which are relevant for large-scale production. The possibilities of this technique have not been exploited so far for routine resolution of steroid intermediates.

4. Selective derivatizations with asymmetric reagents

A classical resolution which has been perfected to give hundred per cent recovery of one enantiomer still suffers from a loss of fifty per cent of the total material. Thermodynamically controlled asymmetric transformations of stereochemically labile

diastereoisomers is a remarkable improvement over the classical method of resolution in terms of yield and efficiency. An intermediate with a prochiral centre is derivatized to give predominantly one particular enantiomer *via* a thermodynamically controlled process[13], as shown in Fig. 4.

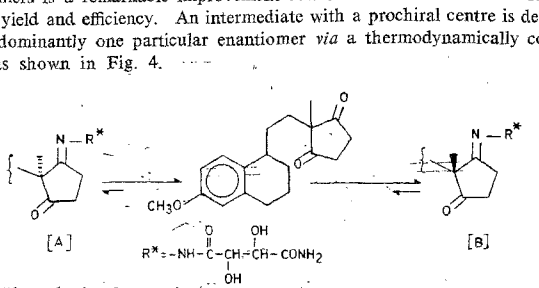


FIG. 4

Fortuitously, the required derivative precipitates out of the solution and the equilibrium is driven to the right to give more of the required derivative (84%). The derivative is cyclized and hydrolyzed in a single step with dioxan-HCl to give the pentaenone in high optical and chemical yield.

An analogous approach has been reported by Pappo[14] using an optically active hydroxylamine. Saucy[15] used an optically active Mannich base to condense with 2-methyl-cyclopentane-1, 3-dione to obtain an optically active intermediate (Fig. 5).

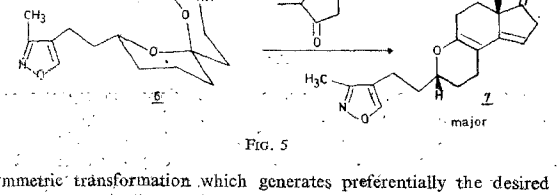


FIG. 5

An asymmetric transformation which generates preferentially the desired chirality in a molecule is strategically superior because it obviates the necessity of resolution and resulting loss of material.

5. Asymmetric syntheses

By definition[16], an asymmetric synthesis is "a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant in a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts." To put

it in more explicit terms, if an achiral centre in a molecule is converted by a reaction into a chiral centre, a pair of enantiomers will be formed if the original molecule was achiral; a pair of diastereoisomers will be formed if the original molecule was chiral. Ordinarily, the two stereoisomers will be produced in equal amounts. An asymmetric synthesis, by definition, will lead to an unequal distribution of stereoisomeric products.

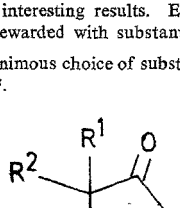
Unlike the selective thermodynamically controlled derivatizations of molecules containing prochiral centres (described above), asymmetric syntheses are kinetically controlled. The substrate and reagent form diastereomeric transition states which differ in energy $\triangle G^{\ddagger}$. The greater the difference in $\triangle G^{\ddagger}$ between the two transition states, the more stereoselective is the process.

Although the basic idea in designing an asymmetric synthesis is to maximize the $\triangle\triangle G^{\ddagger}$, it is not at all straightforward[17]. It is, however, appropriate to choose an early stage for an asymmetric synthesis in a multi-step synthetic scheme and give careful consideration to choice of substrate or reagent (or both) which shows maximum transition state interactions.

There are two alternatives in designing an asymmetric synthesis: (1) the asymmetry in one part of the substrate molecule can be utilized to induce asymmetry in another part so that diastereoisomers are produced in unequal amounts; and, (2) the substrate molecule containing a prochiral group can be converted selectively to one of the enantiomers of the resulting chiral molecule with the help of an asymmetric reagent or catalyst.

Various research groups of Hoffmann-La Roche and Schering, which are actively engaged in asymmetric synthesis of steroids for the past two decades, have come up with very interesting results. Exploration of both the approaches mentioned above has been rewarded with substantial success.

The unanimous choice of substrate was (8) (Fig. 6) with variations at the substituents R^1 and R^2.



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a: $R^1 = CH_3$, C_2H_5
$R^2 = CH_2CH_2COCH_3$
b: $R^1 = CH_3$
$R^2 = -(CH_2)_2\ CO\ (CH_2)_2\ CO_2CH_3$
c: $R^1 = CH_3$
$R^2 = (CH_2)_2\ CO\ (CH_2)_2\ C_6H_4-OCH_3$ (m)

FIG. 6

The configuration of the quarternary carbon C–13 in natural steroids is 'S'. Once that centre is fixed, the task of synthesis of optically pure steroids is more than half done. In most of the stereoselective total syntheses reported in literature for racemic steroids, the relative stereochemistry of C–14, C–8 and C–9 could be fixed only with respect to C–13. Since the racemic starting material had equal number of molecules

with 'R' and 'S' configurations at C–13, even after manipulating the other centres to all-trans configuration, the synthesis resulted in a racemic mixture. In Hoffmann-La Roche and Schering approach, first the configuration at C–13 was attempted to be fixed as 'S' by an asymmetric synthesis, followed by elaborating the rest of the steroid. Since the centre C–13 is never involved in any subsequent reactions directed towards obtaining the complete tetracyclic steroid skeleton, this could act as an anchor for the rest of chemical transformations on the molecule, providing the handle for stereoselectivity.

Saucy[18] has reported asymmetric induction at C–13 with the help of asymmetry at C–5 (Fig. 7). The product-like transition states for the formation of two possible diastereoisomers indicate the steric interactions responsible for energy differences in the diastereoisomeric transition states.

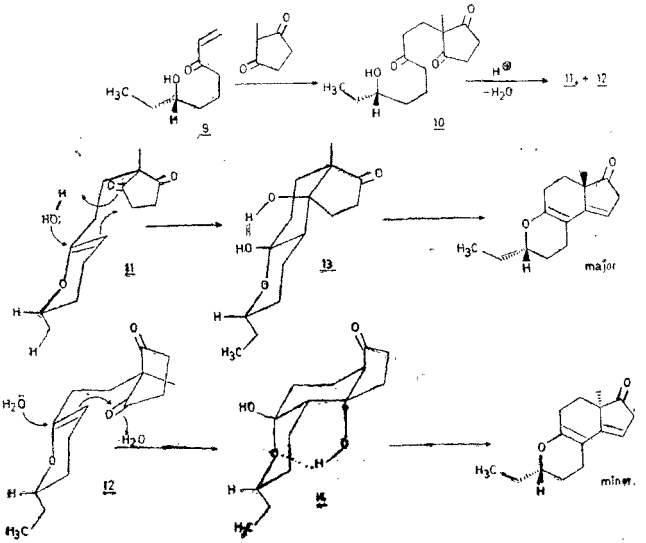


FIG. 7

The newly formed C-C bond is equatorial with respect to the pyran ring in (13) and is in energetically unfavourable axial position in (14). This accounts for the observed stereoselectivity.

Asymmetric induction at C–13 by C–11 has been reported by Daniewski and Kocor[19,20]. The reaction of (11·S) (–) α-acetoxydiazoketone (15*a*) with tris [2-(3-methoxyphenyl)-

1-ethyl] borane, followed by oxidation yielded tricyclic ketol (16*a*) in more than 95% enantiomeric excess. Similarly, the (11·S) (—)-*α*-chloro analog (15*b*) yielded (16*b*) in enantiomerically pure form (Fig. 8).

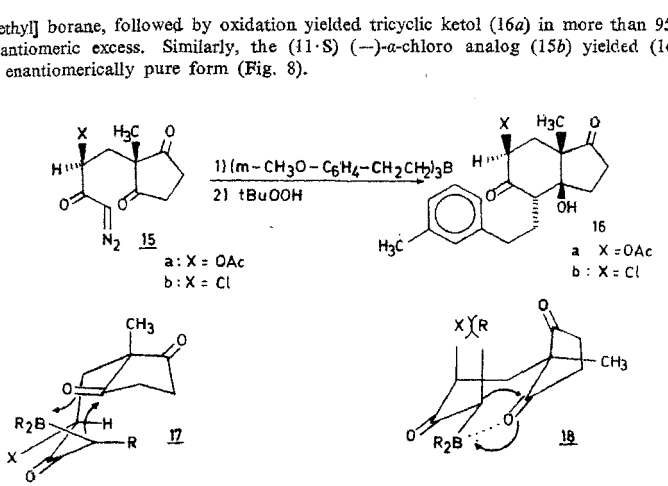


FIG. 8

As can be clearly seen from a study of the more likely transition state conformations (17) and (18) for the process, (18) is energetically unfavourable because of severe 1, 3-diaxial interactions and the role of C–11 substituent is evident.

From the above two examples of asymmetric induction in an intramolecular reaction, one is tempted to impress the importance of product-like transition state, *i.e.*, during the new C–C bond forming process the molecule assumes a conformation which is more like the product than the reactant and the steric interactions which are manifested in the product are also present in the transition state conformation. This makes the design of such asymmetric synthesis relatively more practicable because one now has a definite idea of the type of interactions present in the transition state which determines the ultimate course of stereoselection.

The more product-like the transition state is the more effective will be the manipulation of steric factors to govern a reaction in a particular direction. Extensive studies in biomimetic polyene cyclization at Stanford University by W.S. Johnson[21] and E. E. van Tamelen[22] in the fields of steroids and terpenes respectively, have more or less conclusively indicated that the transition state of squalene-type polyene cyclization is more product-like and the enzyme provides the necessary asymmetric environment to produce selectively one of the enantiomers. By incorporation of an asymmetric centre at a suitable position in the polyene system, Johnson[23] has demonstrated that a very high

degree of asymmetric induction is indeed possible during the concerted polyene-cyclization step (Fig. 9).

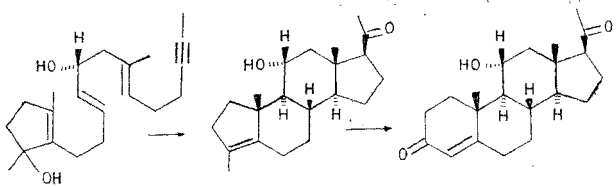


FIG. 9

The alternative approach to asymmetric synthesis, *viz.*, converting a prochiral centre to a chiral one with desired enantioselectivity utilizing an asymmetric catalyst, has been reported independently by two research groups—one at Hoffmann-La Roche and the other at Schering. The general scheme is shown in Fig. 10.

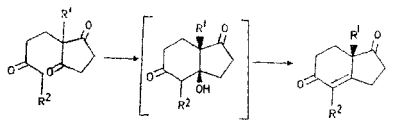
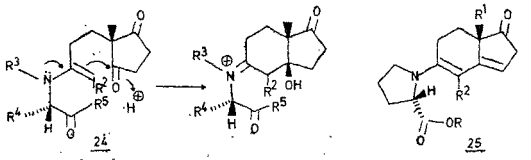


FIG. 10

Eder[24] has carried out this reaction with a series of compounds with varying substituents at R^1 and R^2, in refluxing acetonitrile containing catalytic amount of perchloric acid and molar proportion of different amino acids. Hajos and Parrish[25] have perfected the technique with their substrates ($R^1 = CH_3$ and C_2H_5, $R^2 = H$) using DMF as solvent at room temperature and L-proline as catalyst. They isolated the intermediate ketol and subsequently dehydrated the ketol to the enedione. The reaction is almost quantitative to give the product an optical purity of 94%. Danishefsky[26] has used this strategy to sythesize optically active 19-norsteroids (optical purity 86%).

The extent of asymmetric induction in these amino acid catalyzed cyclizations is remarkable and the stereoselectivity is comparable to that of an enzyme. Though the detailed mechanistic aspects of this reaction are still not available, a few suggestions have been made. For example, an enamine like intermediate (24) has been proposed[27,28] which in turn cyclizes to the bicyclic compound regenerating the amino acid (Fig. 11). Intermediates of this type (25) could be isolated and characterized when amino acid esters or amino alcohols, etc. were used in place of amino acids. No intermediate, however, could be isolated when amino acids themselves were used.

To account for the extremely high degree of stereoselectivity for their compounds, Hajos and Parrish[25] suggested a product like intermediate (26) which has a rigid confor-



24 25

FIG. 11

mational arrangement stabilized by hydrogen bonding and marked by proper juxtaposition of groups so as to give the required stereoisomer (Fig. 12).

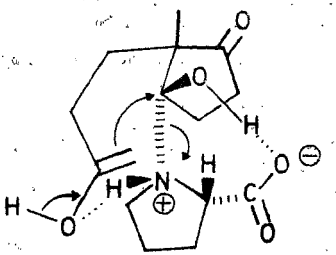


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FIG. 12

Jung[29] in his review has pointed out that the conformational arrangement suggested by Hajos indicates that the reaction 'is formally a substitution reaction proceeding with *retention* which can occur only if there is a large amount of S_Ni character in the reaction'. Hence, he suggested a modification (Fig. 13) which inolves an S_N2-type

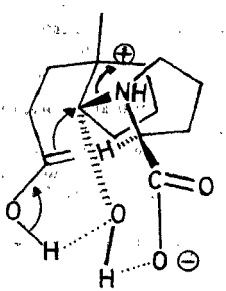

FIG.13

displacement of the proline moiety by the enol with an inversion of configuration. Since a detailed mechanistic study of the reaction is still awaited, we might take a close look at the compatibility of the proposed mechanisms with the data that are already available.

The enamine-type intermediate has been appreciated by Eschenmosher and Dunitz[3a] and they have undertaken a detailed crystal structure analysis to indicate the role of cyclic enamine stereochemistry in determining the course of stereo selection. Although the relevance of crystal structure to dynamic solution conformation of the molecules has not been explicitly mentioned, the authors did recognize that the answer sought for the problem is far from simple. Even after recognising the constraints in cyclic enamine structure, it is difficult to comprehend how the asymmetric induction by other amino acids for related systems can be addressed from this standpoint.

Essentially, the enamine intermediate, as has been pictured by (24), can be viewed in the same line as Saucy's presentation of steric interaction in the product-like transition state, in which case the compound should cyclize only in the required way because the course of reaction is supposed to be dictated by the newly formed C–C bond disposition. But in this case, a tricyclic structure is not formed and hence the consideration can not hold good. The mechanism also fails to implicate the role of the asymmetric carbon and the structural similarity between the amino acid side chain and the side chain R^2 of the substrate[28].

The enamine intermediate isolated (when amino acid derivatives were used) failed to give a high optical yield in spite of the high chemical yield of the product, on subsequent treatment with acid[27], which casts a doubt as to its justification as an intermediate. An intramolecular process guided by an asymmetric centre incorporated in the molecule is expected to give a high optical yield for the product*. In view of the conditions employed for reactions in which enamines were isolated, one can perhaps postulate their formation as a by-product rather than as an intermediate.

The model proposed by Hajos[25] for the intermediate is a better approximation of the real situation because the enzyme-like three-point attachment explains the high enantioselectivity of the reaction. But it does not take into account the variations in the extent of asymmetric induction with variations in the structural features of substrates and amino acids.

Jung's modification[29], however mechanistically appealing, fails to explain the fact that like side chains in the substrate and the amino acid accentuate asymmetric induction, because the side chains are too far apart to visualize any kind of through-space interaction. Moreover, no model of the intermediate can explain why the cyclization is sluggish when the steroid D-ring is six-membered.

* For related observations see reference 23 and (1) T. Kametani *et al*, *Tet. Letts*., 1978, **2**, 2425 ; (2) J. Gutzwiller *et al*, *Helv. Chim. Acta*, 1977, **60**, 2258.

The present authors wish to consider bifunctional catalysis as a simpler and more effective way to explain many facts. The bifunctional catalysis for the process being discussed can be viewed as in Fig. 14.

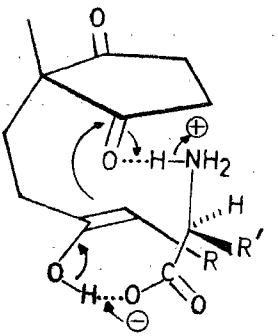

FIG. 14

The essential features of the process are that (1) no intermediate is formed; (2) the transition state is basically product-like except for the asymmetric bias. This will explain the following :

(1) The importance of the carboxyl function is fully realized, the carboxylate anion initiates the cyclization by taking the enol proton. The pH dependence of the reaction is explained since fully protonated carboxylic acid function cannot be efficient in abstracting a proton nor a neutral amino function can part with a proton easily; the Zwitterion must be maintained to realize the full potential of the catalyst. The pH of the system (or the dielectric constant) should be such that a process : amino acid (neutral) → amino acid (Zwitterion), is facilitated, in view of the fact that neutral amino acid is released once the cyclization is over. Such a process is of wide occurrence in enzyme catalysis in bio-systems.

(2) An intermediate for such a process cannot be isolated because no intermediate is formed according to the mechanism. The reaction rate and high asymmetric induction speak volumes of the efficiency of catalysis by free amino acid as compared to their derivatives; the mechanisms of reactions for free amino acids and for amino acid derivatives may as well be different.

(3) Since the amino acids provide only the chiral bias for the reaction, the inherent trend of reactivity of five- and six-membered cyclic diketones towards cyclization is maintained.

(4) The disposition of the side chains R and R^1 of the substrate and the amino acid respectively, in the same direction in space leaves room for considering

non-covalent interaction as a criterion for asymmetric recognition. This explains why an alkyl side chain in the substrate experiences efficient asymmetric induction with valine and alanine while an arylalkyl side chain is recognized by phenylalanine and tyrosine for efficient asymmetric induction. If this conjecture has any validity, this will be an example of chiral recognition accentuated by non-covalent interaction, for small molecules and might be relevant for studies pertaining to origin and propagation of asymmetry in the course of biological evolution.

(5) Asymmetric induction by S-phenylalanine and S-homophenylalanine on the same substrate shows[31] not only opposite chiral sense but also a substantial variation in the degree of induction. With the same substrate for which Hajos had reported 94% optical yield with S-proline, S-phenyl alanine gave an optical yield of 24·7% whereas S-homophenylalanine gave an optical yield of 82·7% but the asymmetry induced is reversed in the chiral sense. A study of molecular models shows that the proximity of the reacting centres assisted by the amino acids can be maintained only in one of the diastereomeric cyclization mode while in the other, the two reacting centres are far away from each other. Hence, in this case, if not for the asymmetric environment alone, the feasibility of the reaction itself has a bias with respect to the steric course of the reaction.

(6) Bifunctional catalysis is of common occurrence in enzyme catalyzed reactions[32]. The catalysis comprises a synchronous flow of electrons and functionalities of amino acids only are exploited. The substrate is frequently recognized by non-covalent and/or electrostatic interactions and the mechanism proposed above, except for the complex structures of enzymes absent, is similar to enzyme-catalyzed reactions in all other aspcts. It also explains the high degree of specificity with appropriate combination of substrate and catalyst. The suggestion of Rose and Hanson[33] for catalytic efficiency in enzyme systems, *viz.*, (*a*) the use of minimum number of acidic and basic groups taking part in catalysis, (*b*) the maximum separation of the catalytic groups, and (*c*) minimum motion of the substrate, is also relevant to the bifunctional catalysis suggested by us. The functional groups of amino acids alone are present at the initiating and terminating points of the electron-flow sequence and the molecule is held in a conformation to allow a facile transition from reactant to product without any appreciable movement involving torsion, etc., or collapse of an intermediate. A study of enzyme models[34] would reveal a wide variety of cases where simpler catalytic systems have been designed to mimick enzymes in cell-free systems. Breslow[35] has demonstrated in his remote functionalization studies the importance of molecular association and also illustrated the role of carboxylic acid dimer to accentuate molecular association which is nothing but manifestation of non-bonded attractive forces.

This last mechanism of bifunctional catalysis proposed, however, remains purely a conjecture. It is an attempt to correlate information available about enzymic catalysis,

enzyme models, and molecular recognition by non-covalent interactions in order to gain a better insight regarding the mechanism of amino acid catalyzed asymmetric cyclization reactions.

6. Conclusion

With the remarkable advancement of synthetic methodology in organic chemistry, industrial production of steroids and related drugs based on totally synthetic methods is no longer a distant possbility. A number of high-yield preparative methods are currently available which call for process development to make them industrially feasible. The methods developed in recent years have bypassed the necessity of resolution or selective derivatizations in equilibrium-controlled reactions. They have been perfected to achieve high chemical yield and chiral economy. They are amenable to large-scale preparations and the asymmetric reagent or catalyst can be profitably recovered and recycled to improve the economy of the process further. With the concurrent advances in chromatographic technique, the day may not be very far when an asymmetric transformation will be carried out in a column where the reagent is incorporated in the column material; the reactant is charged at one end and elution brings out the product through the other.

7. Acknowledgement

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