Asymmetric Induction in 19-Norsteroid Total Synthesis

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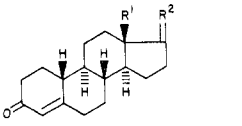
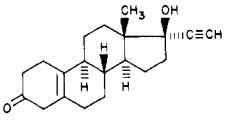
An inherent, practical problem in steroid total synthesis[1] involves the production of optically active compounds. This difficulty arises because the useful biological properties of most steroidal drugs (e.g., antiinflammatory, progestational agents) are confined to only one enantiomer. Whereas partial synthesis from natural products (diosgenin, sterols) leads to the required chiral compounds, total synthesis generally produces their racemic counterparts. Thus, a realistic approach to steroid total synthesis requires either removal of the unwanted antipode at the end of the sequence by chemical[2] or microbiological[3] resolution or, far more efficiently, the avoidance of its formation altogether. The latter goal can be achieved through the resolution of a relatively simple intermediate, early in the synthetic scheme[4] or by means of an asymmetric transformation.[5]

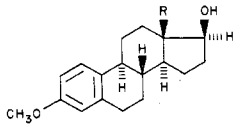
By offering the theoretical possibility of creating a new chiral center in 100% enantiomeric excess, asymmetric syntheses possess the greatest potential for the efficient construction of chiral molecules.[6] In practice, however, useful results are seldom attained. It is pertinent to note, therefore, that in few other areas of organic synthesis have asymmetric transformations been applied as effectively as in steroid total synthesis. The achievements of greatest significance along these lines have arisen, for the most part, out of studies aimed at the progestational 19-nor steroids, norethindrone (**1a**),[7] norgestrel (**1b**),[8] and norethynodrel (**2**),[7] as well as their synthetic precursors **1c,d**[1] and **3a,b**.[1] Compounds **1a,b** and **2** occupy a central role in human contraception.[7]





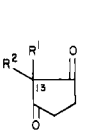
1a ; $R^1 = CH_3$, R^2 = OH and ≡C≡CH
1b ; $R^1 = C_2H_5$, R^2 = OH and ≡C≡CH
1c ; $R^1 = CH_3$, R^2 = O
1d ; $R^1 = C_2H_5$, R^2 = O

2



3a ; R = CH_3
3b ; R = C_2H_5

Work carried out in the early 1960's and directed toward the total synthesis of these 19-nor steroids produced certain schemes having considerable practical potential.[1,4,9,10] These approaches, as well as several developed somewhat later, share a convergent strategy[11] in which the steroid molecule is assembled starting from a D-ring synthon in the form of a 2-alkyl-1,3-cyclopentanedione. Involved in most of these schemes are intermediates having the generalized structure **4**, the



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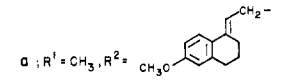


a ; $R^1 = CH_3$, R^2 =
b ; $R^1 = C_2H_5$, R^2 as in **4a**
c ; $R^1 = CH_3$, $R^2 = CH_3O_2C(CH_2)_3CO(CH_2)_2-$

prochiral[12a] nature of which presents the opportunity for an asymmetric transformation (introduction of chirality at C-13[13]) at an early stage. Such a process, if efficient, would allow a direct synthesis of optically active steroids without the requirement of, and disadvantages associated with, classical resolution procedures.

(1) For comprehensive discussions of steroid total synthesis see: (a) A. A. Akhrem and Yu. A. Titov, "Total Steroid Synthesis", Am. ed, Plenum Press, New York, N.Y., 1970; (b) R. T. Blickenstaff, A. C. Ghosh, and G. C. Wolf, "Total Synthesis of Steroids", Academic Press, New York, N.Y., 1974; (c) R. Pappo in "The Chemistry and Biochemistry of Steroids", N. Kharasch, Ed., Vol. 3, No. 1, Intra-Science Research Foundation, Santa Monica, Calif., 1969, pp. 123–140; (d) G. Saucy and N. Cohen, *MTP Int. Rev. Sci., Ser. One*, **8**, 1–26 (1973).

(2) (a) G. C. Buzby, Jr., D. Hartley, G. A. Hughes, H. Smith, B. W. Gadsby, and A. B. A. Jansen, *J. Med. Chem.*, **10**, 199 (1967); (b) C. H. Kuo, D. Taub, and N. L. Wendler, *J. Org. Chem.*, **33**, 3126 (1968); (c) F. Riehl, *J. Prakt. Chem.*, **311**, 694 (1969).

(3) G. Greenspan, L. L. Smith, R. Rees, T. Foell, and H. E. Alburn, *J. Org. Chem.*, **31**, 2512 (1966).

(4) (a) L. Velluz, G. Nominé, G. Amiard, V. Torelli, and J. Cérède, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **257**, 3086 (1963); (b) R. Bucourt, M. Vignau, and W. Weill-Raynal, *ibid.*, **265**, 834 (1967).

(5) For excellent reviews of asymmetric synthesis, see: (a) J. W. Scott and D. Valentine, Jr., *Science*, **184**, 943 (1974); (b) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971.

(6) "Chiral Economy"; cf. A. Fischli, *Chimia*, **30**, 4 (1976).

(7) P. D. Klimstra and F. B. Colton in "Contraception: The Chemical Control of Fertility", D. Lednicer, Ed., Marcel Dekker, Inc., New York, N.Y., 1969, Chapter 3, and references cited therein.

(8) Compound **1b** was originally marketed as the racemate. However, as with most progestational agents of this type, the biological activity is concentrated in the "natural", *d* enantiomer, having the absolute configuration shown.[7]

(9) G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, 5072 (1963).

(10) I. V. Torgov, *Pure Appl. Chem.*, **6**, 525 (1963).

(11) A convergent synthesis is one in which two fairly well-developed portions of the target molecule are formed and subsequently combined at a late stage in the overall synthetic scheme. This approach offers substantial cost, yield, and logistical advantages relative to a linear approach in which a single fragment is continually elaborated. Cf. L. Velluz, J. Valls, and G. Nominé, *Angew. Chem., Int. Ed. Engl.*, **4**, 181 (1965).

(12) (a) In the present context, a prochiral molecule is most easily described as an achiral one of the type $CXYZ_2$ containing a mirror plane. Replacement or modification of one of the ligands Z leads to a chiral compound. Cf. K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1966). (b) Enantiotopic ligands are those such as Z in $CXYZ_2$ which can be interchanged only by a rotation–reflection operation, and not simply by a rotation, to give a structure indistinguishable from the original—see the reference cited in ref 12a.

(13) Throughout this Account, steroid numbering will be used for convenience, even when describing intermediates which are not steroids. The numbering, therefore, anticipates the position a given center will occupy in the ultimate steroid product.

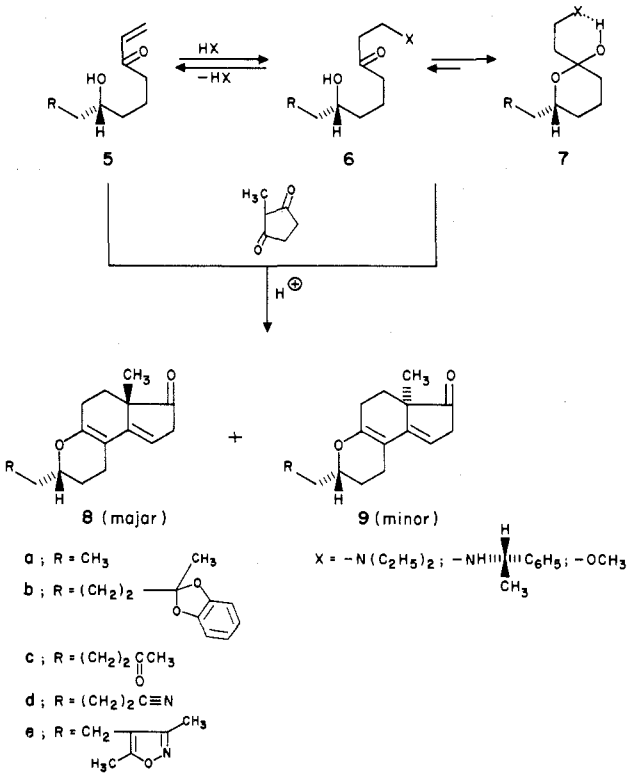
Noal Cohen was born in Rochester, N.Y., in 1937 and received the B.S. degree from the University of Rochester in 1959. After spending 2 years at Eastman Kodak Co., he undertook graduate studies at Northwestern University and received the Ph.D. degree in 1965. A 2-year postdoctoral position at Stanford University followed, and in 1967, Dr. Cohen joined the Chemical Research Department of Hoffmann-La Roche, Inc., where his present position is that of Research Fellow. His principal research interests involve synthesis of biologically important substances, especially natural products, and the development and application of methods for the efficient construction of chiral molecules.

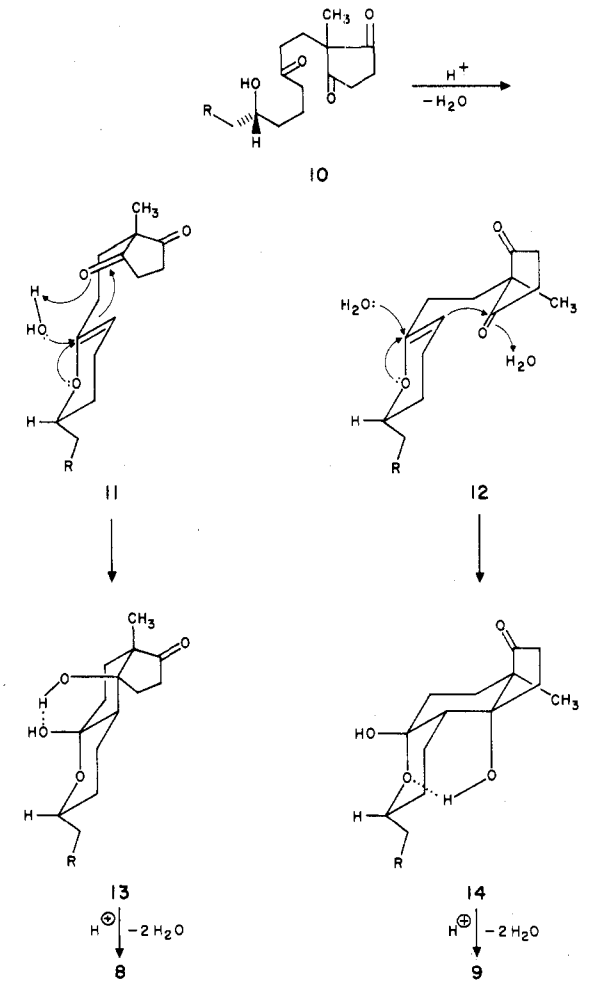
Initial efforts toward this goal[14-16] (and recent variations thereof[17,18]) concentrated on modification of the diketones **4a–c** with external, chiral reagents; these reagents may be either chemical[16-18] or microbiological (enzymatic)[14,15] and are capable of differentiating between the enantiotopic[12b] carbonyl groups. In this manner, optically active products having predominantly or totally the desired 13β configuration were obtained. More recently, alternative processes based upon *intra*molecular induction of chirality at C-13[19] have been developed and found to be quite effective in the construction of optically active steroids. It is the purpose of this Account to survey several of the more successful applications of such processes. In addition, certain new and striking examples of *inter*molecular asymmetric induction using amino acid reagents will be reviewed.

Induction at C-13 by C-5

In one well-developed approach involving intramolecular induction of asymmetry, chiral vinyl ketone annulating agents of the type **5**, or the derived amine or alcohol adducts **6** and **7**, were treated with 2-methylcyclopentane-1,3-dione; in the resulting mixture of the dienes **8** and **9** the desired 13β epimer predominated.[20a-f] In general, these condensations were carried out in refluxing toluene–acetic acid under which conditions an **8**:**9** ratio of 3–4:1 was observed. In series **b**,[20c] **c**,[20d] and **d**,[20e] recrystallization provided the pure 13β epimer **8** in 55, 61, and 37% yields, respectively. On the other hand, because the diene epimers in series **a**[20a,b] and **e**[20f] could not be separated, an optical purification later in the synthetic sequence was required.

The dienes **8** and **9** arise *via* initial formation of the Michael adduct, triketone **10**, a variation of the archetypal intermediate **4** possessing, besides the prochiral center destined to become C-13, a reactive chiral center at C-5. The reaction sequence most likely first involves acid-catalyzed elimination of water from **10**, leading to an enol ether intermediate which can exist in two significant conformational forms, namely **11** (*pro*-13β) and **12** (*pro*-13α). The crucial C-8–C-14 bond formation can now take place with participation of water, producing the tricyclic diols **13** and **14**. Elimination of two molecules of water then yields the observed dienes **8** (major) and **9** (minor), respectively.





The observed stereoselectivity (asymmetric induction) can be rationalized if one assumes a product-like transition state in the key carbon–carbon bond-forming step. Thus, it would be expected that the formation of

(14) (a) H. Kosmol, K. Kieslich, R. Vössing, H.-J. Koch, K. Petzoldt, and H. Gibian, *Justus Liebigs Ann. Chem.*, **701**, 198 (1967); (b) C. Rufer, E. Schröder, and H. Gibian, *ibid.*, **701**, 206 (1967); (c) C. Rufer, H. Kosmol, E. Schröder, K. Kieslich, and H. Gibian, *ibid.*, **702** 141 (1967).

(15) P. Bellet, G. Nominé, and J. Mathieu, *C. R. Hebd. Seances Acad. Sci., Ser. C.* **263**, 88 (1966).

(16) R. Bucourt, L. Nédélec, J.-C. Gasc, and J. Weill-Raynal, *Bull. Soc. Chim. Fr.*, 561 (1967).

(17) G. Haffer, U. Eder, G. Sauer, and R. Wiechert, *Chem. Ber.*, **108**, 2665 (1975).

(18) R. Pappo, R. B. Garland, C. J. Jung, and R. T. Nicholson, *Tetrahedron Lett.*, 1827 (1973).

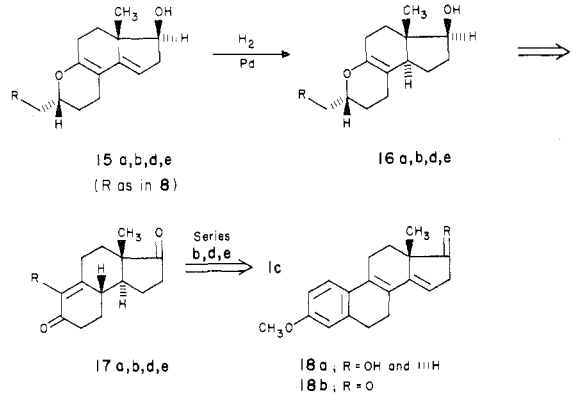
(19) Diastereoselective syntheses—cf. Y. Izumi, *Angew. Chem., Int. Ed. Engl.*, **10**, 871 (1971). In the present context, such processes involve substrates or intermediates possessing a chiral center in addition to the prochiral center destined to become C-13.

(20) (a) G. Saucy and R. Borer, *Helv. Chim. Acta*, **54**, 2121 (1971); (b) G. Saucy and R. Borer, *ibid.*, **54**, 2517 (1971); (c) M. Rosenberger, A. J. Duggan, R. Borer, R. Muller, and G. Saucy, *ibid.*, **55**, 2663 (1972); (d) G. Saucy, B. Banner, R. Borer, N. Cohen, W. Eichel, S. Kwoh, D. R. Parrish, M. Rosenberger, and R. D. Youssefyeh, *J. Steroid Biochem.*, **6**, 183 (1975); (e) N. Cohen, B. Banner, R. Borer, R. Mueller, R. Yang, M. Rosenberger, and G. Saucy, *J. Org. Chem.*, **37**, 3385 (1972); (f) J. W. Scott, R. Borer, and G. Saucy, *ibid.*, **37**, 1659 (1972); (g) N. Cohen, B. L. Banner, J. F. Blount, M. Tsai, and G. Saucy, *ibid.*, **38**, 3229 (1973).

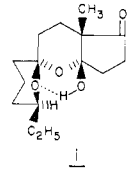
13 from 11 should have a lower energetic requirement than the corresponding formation of 14 from 12 because of the relative number of 1,3-diaxial interactions present in the resultant diols (and reflected in the transition states). Specifically, it can be seen that the newly formed bond in 14 occupies an axial position relative to the pyran ring, whereas the corresponding bond in 13 assumes the less encumbered equatorial conformation. On this basis, diene 8 would be expected to, and does, predominate. The importance of the chirality at the carbinol center in the starting material can also readily be seen, since the Michael adduct having the antipodal configuration at this center will lead to a preponderance of the dienol ether enantiomeric with 8.

Evidence for the above mechanistic postulations comes from the following observations.[20b] Under the reaction conditions which produced the dienes 8 and 9, 2-methyl-1,3-cyclopentanedione when treated with methyl vinyl ketone gave only the Michael adduct with no ring closure. This result strongly suggests the involvement of the hydroxyl group in the transformation of 10 to the dienol ether products. Furthermore, it was found that treatment of **10a**[21] with *p*-toluenesulfonic acid at room temperature for a brief period of time gave mainly a keto diol with spectral and chiroptical properties consistent with the proposed intermediate **13a.** On further mild acid treatment, this intermediate gave the mixture of dienes **8a** and **9a** in a 20:1 ratio, respectively.

In addition to the substantial asymmetric induction observed in their formation, the dienes 8 proved to be especially desirable intermediates with regard to introduction of the required CD-trans ring fusion stereochemistry, a classical problem encountered in many approaches to steroid total synthesis.[1,22] Thus, it was observed that catalytic hydrogenation of the 14,15-conjugated double bond in the derived 17β alcohols **15a,b,d,e** occurred almost exclusively from the α face of the molecules, giving the CD-trans-fused enol ethers



(21) This material could be isolated when **5a** was reacted with 2-methylcyclopentane-1,3-dione in *tert*-butyl alcohol–water at 50 °C.[20b] An x-ray crystallographic analysis of (±)-**10a** (carried out by Dr. J. Blount) confirmed the intriguing, tricyclic, internally hydrated structure, i, which this compound possesses, in the solid state.



i

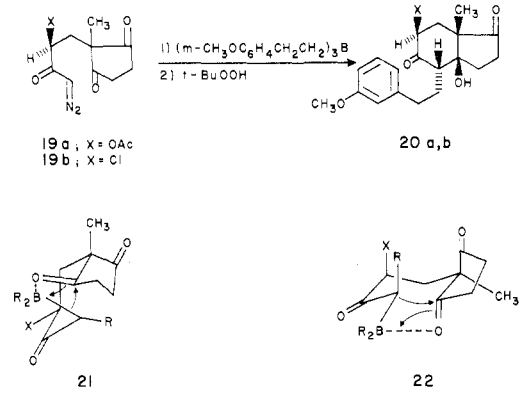
(22) (a) T. C. McKenzie, *J. Org. Chem.*, **39**, 629 (1974); (b) G. Nominé, G. Amiard, and V. Torelli, *Bull. Soc. Chim. Fr.*, 3664 (1968).

16a,b,d,e in high yield. These results are, therefore, analogous to those observed upon catalytic hydrogenation of the 8,14-dienol **18a,**[9,10,14b,16,18] an intermediate to which the dienes **15** bear a structural resemblance.[23]

The rather facile production of the intermediates **16** having the necessary 13β,14α stereochemistry rendered the syntheses of the key BCD-tricyclic enediones **17b,d,e,** and ultimately the target steroid **1c,** highly stereoselective processes.[20c,e,f] Variations of these schemes allowed the preparation of optically active aromatic steroids (i.e., **3a**) as well.[20d,g] It is interesting to note that in the overall transformation of **10** to **17,** the original, chiral, hydroxyl center (C-5), having accomplished its required task of inducing asymmetry at C-13, is ultimately destroyed.

Induction at C-13 by C-11

In a fruitful application of organoborane chemistry to steroid total synthesis, the (11*S*)-(−)-α-acetoxy diazo ketone **19a,** upon reaction with tris[2-(3-methoxyphenyl)-1-ethyl]borane, followed by oxidation of borate intermediates, yielded the 13β-ACD-tricyclic ketol **20a** in *an enantiomeric excess of at least 95%*.[24a] In a similar manner, the (11*S*)-α-chloro analog **19b** gave rise to **20b** *in optically pure form.*[24b] The seco intermediates **20** could be efficiently transformed[24] into either 11-substituted aromatic steroids or the important dienone **18b**[14b,16,18] (obtained in 56% overall yield based on **19b**). In view of the ready availability of the chiral substrates **19** (derived initially from 2-methyl-1,3-cyclopentanedione and methyl α-chloroacrylate[24a]) and the substantial asymmetric induction observed in their conversion into **20,** this scheme appears to offer a facile route to aromatic and 19-nor steroids, especially those containing 11 functionality. Of special strategic interest is the novel utilization of the incipient 11 substituent for the early and highly efficient introduction of chirality at C-13.



A possible rationale for the pronounced asymmetric induction observed in the transformations of **19** to **20** is apparent if one assumes that the crucial C-8–C-14 bond formation occurs via an intermediate α-ketoborane.[24a] Such an intermediate can exist in a number of conformations, in which substantial rigidity should be

(23) Catalytic hydrogenations of closely related intermediates (with similar results) have been reported. Cf. (a) U. Eder, G. Sauer, J. Ruppert, G. Haffer, and R. Wiechert, *Chem. Ber.*, **108**, 2673 (1975); (b) U. Eder, H. Gibian, G. Haffer, G. Neef, G. Sauer, and R. Wiechert, *ibid.*, **109**, 2948 (1976); U. Eder, G. Sauer, G. Haffer, J. Ruppert, R. Wiechert, A. Fürst, and W. Meier, *Helv. Chim. Acta*, **59**, 999 (1976).

(24) (a) A. R. Daniewski, *J. Org. Chem.*, **40**, 3135 (1975); (b) A. R. Daniewski and M. Kocor, *ibid.*, **40**, 3136 (1975).

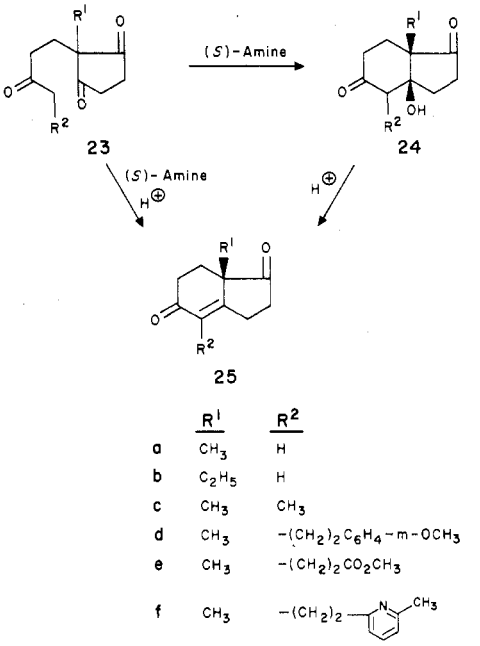
imposed by the expected coordination of boron with one of the carbonyl oxygens. On the basis of molecular models, the most favorable (chairlike) transition states for ring formation appear to arise from species **21** and **22** (X = Cl, OAc; R = *m*-$CH_3OC_6H_4CH_2CH_2$), which are analogous to the enol ether conformers **11** and **12** discussed above. The influence of the 11*S* substituent is now evident since, in the *pro*-13β form **21**, this substituent occupies an equatorial position, but must assume the more energetic axial arrangement in the *pro*-13α conformer **22**. Thus, compounds **20a,b**, which are derived from **21**, would be expected to predominate.

Asymmetric, Amino Acid Mediated Aldol Cyclizations

One of the most significant recent developments with regard to the total synthesis of optically active steroids has been the exploitation of asymmetrically biased, intramolecular aldol cyclizations.[25-28] The key breakthrough in this area occurred with the discovery that prochiral triketones such as **23**, upon exposure to optically active amino acids, are converted into the ketols **24**[25] or the enediones **25**[26] in excellent chemical yield, and, in certain cases, with *close to 100% enantiomeric excess*. Clearly, such processes are advantageous because the required chirality at C-13 is introduced with high efficiency at an early stage of the synthetic sequence.

A conceptual distinction between these processes and those discussed above should be noted. Whereas the conversions of **10** to **8** and **19** to **20** are basically stereoselective reactions[19] in which the new chirality is derived from a preexisting asymmetric center, the formation of **24** or **25** from **23** constitutes a true asymmetric synthesis[5] in which an achiral substrate is converted, selectively, into a chiral one via a regenerable, chiral reagent.

A variety of conditions have been employed for carrying out these transformations, and the results obtained from various laboratories are summarized in Table I. From the data, certain generalizations emerge. (1) Amino acids (or their derivatives) of *natural configuration* (*S*) induce the desired 13β-alkyl configuration (cf. entries 16, 36, and 38). (2) Amino acids are much more effective than their amide or ester derivatives or simple chiral amines in terms of producing high optical yields (entries 11–14, 17–26, 31). (3) The quantity of amino acid employed does not appear to be critical with regard to the extent of chiral induction and can frequently be catalytic (entries 2, 15, 27, 35, 36). The use of larger quantities of chiral reagent mainly affects the reaction time.[26] Apparently, in the case of amino acid esters and amides, a molar equivalent is required. (4) For the substrates where R^2 = H, a secondary amino acid, (*S*)-proline, is preferred (entries 1, 2, 15, 27). However, when R^2 is larger than H, as in **23c–f**, improved chemical and optical yields are obtained when



	R^1	R^2
a	CH_3	H
b	C_2H_5	H
c	CH_3	CH_3
d	CH_3	$-(CH_2)_2C_6H_4$-m-OCH_3
e	CH_3	$-(CH_2)_2CO_2CH_3$
f	CH_3	$-(CH_2)_2$-(N, CH_3)

a primary amino acid, preferably (*S*)-phenylalanine, is employed in conjunction with a mineral acid (entries 30, 33, 35). The only tertiary amino acid employed was totally ineffective (entry 10). (5) The use of amino acids in polar, aprotic solvents at room temperature allows isolation of the aldols **24a,b** in high chemical and optical yield (entries 1, 2, 27). However, addition of mineral acids in small quantities leads directly to the enones **25** with somewhat reduced but nonetheless quite satisfactory optical yields (entries 15, 28). Amino acid ester and amide derivatives apparently produce only the enone products. (6) High optical yields are obtained when polar, aprotic solvents such as dimethylformamide (DMF) and CH_3CN are employed in the amino acid catalyzed reactions. In contrast, the most favorable chiral induction produced by amino acid esters and amides is observed in the relatively nonpolar solvent, toluene (entries 17–26). (7) Substantial asymmetric induction (64%) by amino acids is observed even at 120 °C (entry 32), indicating that temperature is not a critical factor. On the other hand, the induction exhibited by (*S*)-proline pyrrolidide is increased (although not to a practical level) by lowering the reaction temperature to 0 °C (entry 25).

The mechanistic aspects of these asymmetric transformations are intriguing, although not yet clearly defined. Interaction of the chiral amine component with the substrate **23** can conceivably occur via attack at either the side chain carbonyl or at one of the enantiotopic cyclopentanedione carbonyls. In the former case, one can envision formation of an enamine **26**,[27b,28a,29,30] an intermediate similar to the enol ethers **11** and **12** discussed above. The crucial cyclization, forming the C-8–C-14 bond, can then take place, producing the immonium species **27**, which upon hydrolysis (with regeneration of the chiral amine reagent) yields the observed products **24** or **25**, depending on the reaction conditions. When esters and amides of amino acids are employed, intermediates of the type **26** have, in fact, been isolated and shown to cyclize, giving first a dienamine of the type **28**, which then affords the ene-

(25) (a) Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, **39**, 1615 (1974); (b) Z. G. Hajos and D. R. Parrish, German Patent 2102623 (Hoffmann-La Roche) (July 29, 1971); *Chem. Abstr.*, **75**, 129414r (1971).

(26) U. Eder, G. Sauer, and R. Wiechert, *Angew. Chem., Int. Ed. Engl.*, **10**, 496 (1971).

(27) (a) S. Danishefsky and P. Cain, *J. Am. Chem. Soc.*, **97**, 5282 (1975); (b) S. Damishefsky and P. Cain, *ibid.*, **98**, 4975 (1976). The author is grateful to Professor S. Danishefsky for providing data prior to publication.

(28) (a) K. Nagasawa, H. Takahashi, K. Hiroi, and S. Yamada, *Yakugaku Zasshi*, **95**, 33 (1975); (b) K. Nagasawa, K. Hiroi, and S. Yamada, *ibid.*, **95**, 46 (1975).

(29) G. Sauer, U. Eder, and G.-A. Hoyer, *Chem. Ber.*, **105**, 2358 (1972).

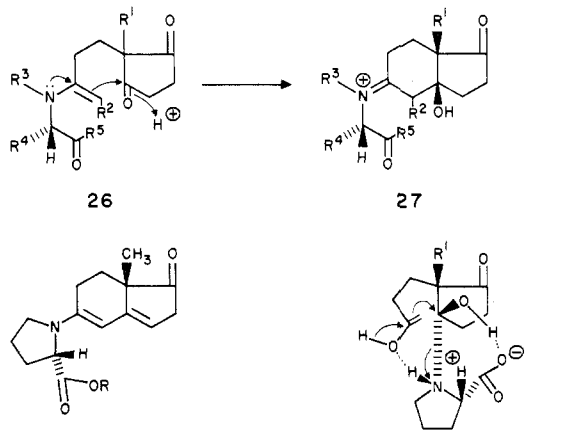
(30) J. Ruppert, U. Eder, and R. Wiechert, *Chem. Ber.*, **106**, 3626 (1973).

Table I
Asymmetric Aldol Cyclizations

Entry	Substrate	Amine or amino acid and additive (mol equiv)	Solvent	Temp, °C	Time	Product	Chemical yield, %	Optical yield, %	Ref
1	**23a**	(*S*)-Proline (1)	CH_3CN	20	6 d	**24a**	97	97	25a
2		(*S*)-Proline (0.03)	DMF	20	20 h	**24a**	100	93	25a
3		(*S*)-Proline (1)	EtOH	20	3–4 d	**25a**	NA[a]	28	25a
4			*n*-BuOH	20	3–4 d	**25a**	NA[a]	32	25a
5			*i*-PrOH	20	3–4 d	**25a**	NA[a]	61	25a
6			*t*-BuOH	20	3–4 d	**25a**	NA[a]	84	25a
7		(*S*)-Azetidine-2-carboxylic acid (0.03)	CH_3CN	20	6 d	**24a**	51	64	25a
8		(*S*)-Phenylalanine (1)	*i*-PrOH	20	7 d	**24a**	37	19	25a
9		(2*S*)-*trans*-4-Hydroxyproline (1)	*i*-PrOH	20	26 d	**24a**	12	73	25a
10		(*S*)-Hygrinic acid (1)	*i*-PrOH	20	18 d		0[b]	0	25a
11		Ethyl (*S*)-prolinate (1)	CH_3CN	20	20 h	**25a**	18	6	25a
12		(*S*)-Prolinol (1)	CH_3CN	20	3 d	**24a**	59	17	25a
13		(−)-Ephedrine (1)	C_6H_6[c]	80	16 h	**25a**	71	15	25a
14		(*S*)-α-Methylbenzylamine[d]	CH_3CO_2H	100	2 h	**25a**	81	45	26
15		(*S*)-Proline (0.5), 1 N $HClO_4$ (0.27)	CH_3CN	80	22 h	**25a**	87	84	26
16		(*R*)-Proline,[d] 1 N $HClO_4$[d]	CH_3CN	80	20 h	*ent*-**25a**	75	67	26
17		Methyl (*S*)-prolinate (1)	CH_3CN[e]	25	3 h	**25a**	78	12	28a
18			EtOH[e]	25	3 h	**25a**	73	17	28a
19			THF[e]	25	3 h	**25a**	84	15	28a
20			Toluene[e]	25	3 h	**25a**	80	17	28a
21		(*S*)-Proline pyrrolidide (1)	CH_3CN[e]	25	3 h	**25a**	79	19	28a
22			EtOH[e]	25	3 h	**25a**	81	19	28a
23			THF[e]	25	3 h	**25a**	86	20	28a
24			Toluene[e]	25	3 h	**25a**	79	24	28a
25			Toluene[e]	0	6 h	25a	76	40	28a
26			Toluene[e]	60	1 h	**25a**	83	5	28a
27	**23b**	(*S*)-Proline (0.3)	DMF	20	20 h	**24b**	71	100	25a
28		(*S*)-Proline,[d] 1 N HCl[d]	DMF	100	7 h	**25b**	76	80	26
29	**23c**	(*S*)-Alanine,[d] 1 N $HClO_4$[d]	CH_3CN	80	70 h	**25c**	69	NA[f]	26
30	**23d**	(*S*)-Phenylalanine,[d] 1 N $HClO_4$[d]	CH_3CN	80	43 h	**25d**	60	92[g]	26
31		(*S*)-Proline pyrrolidide (1)	Toluene[e]	25	6 h	**25d**	60[h]	31[h]	28b
32	**23e**	(*S*)-Phenylalanine[d]	CH_3CO_2H	120	4 h	**25e**	55	64	26
33	**23f**	(*S*)-Phenylalanine (1.2), 1 N $HClO_4$ (0.5)	CH_3CN	80	40 h	**25F**	82	86	27a,b
34		(*S*)-Proline (1.2), 1 N $HClO_4$ (0.25)	CH_3CN	80	10 d	**25f**	67	26	27b
35		(*S*)-Tyrosine *O*-methyl ether (1.2), 1 N $HClO_4$ (0.25)	CH_3CN	80	60 h	fb25f	82	84	27b
36		(*S*)-Tryptophan (1.2), 1 N $HClO_4$ (0.25)	CH_3CN	80	3 d	*ent*-**25f**	70	78	27b
37		(*S*)-Serine (1.2), 1 N $HClO_4$ (0.25)	CH_3CH	80	5 d	**25f**	77	35	27b
38		(*S*)-Valine (1.2), 1 N $HClO_4$ (0.25)	CH_3CN	80	4 d	*ent*-**25f**	72	21	27b

[a] Yield not reported. [b] 60.3% of starting triketone recovered; 20% of a racemic, bridged ketone obtained. [c] Reaction initially produced a mixture of two diastereomeric spirooxazolidines (ca. 3:2) which were hydrolyzed to **25a** with 1 N HCl, in a separate step. [d] Molar ratio not reported. [e] 4A Molecular sieves added to remove water; initially formed dienamine hydrolyzed with 10% HCl to give the enedione **25.** [f] Optical yield not available since the $[\alpha]_D$ of optically pure **25c** is unknown. [g] Optical yield based on an observed $[\alpha]^{RT}_D$ +181° [26] and $[\alpha]^{25}_D$ +196° (C_6H_6) later reported for optically pure **25d.**[20g] [h] Yields based on isolation of the dienone **18b** obtained by polyphosphoric acid cyclization of **25d** which, itself, was not analyzed.

dione **25** on hydrolysis.[28a] On the other hand, intermediates derived from amino acids themselves have yet to be characterized. Some experimental evidence obtained during a study of the (*S*)-proline-catalyzed cyclization of **23a** has led to the suggestion of an alternative mechanism involving the species **29,** derived from interaction of the amino acid with one of the cyclopentanedione carbonyls.[25a,31]



What seems to be most significant, based on the experimental data available thus far, is the beneficial effect upon the asymmetric induction of a free, α-carboxyl moiety in the chiral amine reagent. The high optical yields observed with amino acids, as well as the observed solvent effects (suggestive of intramolecular H bonding), strongly implicate the carboxyl group as playing a key role in the transition state. Its function could involve either intramolecular protonation of the incipient

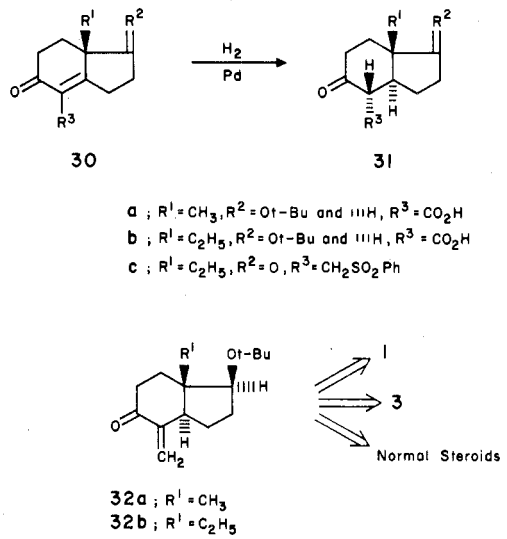
(31) A mechanism involving a carbinolamine intermediate closely related to **29,** but which allows ring formation to give **24a** via a backside displacement of the proline moiety by the enol function (S_N2 type process), has recently been proposed. Cf. M. E. Jung, *Tetrahedron,* **32,** 3 (1976).

tertiary hydroxyl group, as in the cyclization of **26** to **27**, or the enforcement, via H bonding, of a rigid, asymmetrically biased arrangement. At any rate, the definitive mechanistic details of these fascinating and most useful reactions must await more detailed studies.

Although the mechanistic aspects of these asymmetric aldol cyclizations may not be fully understood at present, little doubt exists as to the importance and utility of these processes in steroid total synthesis. Among the optically active, 8-substituted bicyclics **25** obtainable in this manner, the pyridyl intermediate **25f** has recently been employed in an efficient synthesis of *d*-(+)-estrone (13% overall yield from 2-methyl-1,3-cyclopentanedione).[27] However, the simplest CD-bicyclic synthons, **25a** and **25b**, have served most expeditiously for the preparation of useful steroids. An important consideration is the ready accessibility and relatively low cost of the prochiral precursors **23a,b**, which are simply Michael adducts of methyl vinyl ketone with 2-methyl- and 2-ethyl-1,3-cyclopentanedione, respectively.[25a,32]

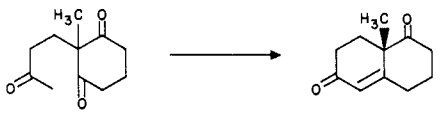
The successful use of the CD-bicyclics **25a,b** in steroid total synthesis is dependent upon their facile conversion into intermediates possessing the required CD-trans ring fusion.[1,22] Thus, a significant breakthrough was achieved with the discovery that catalytic hydrogenation of the unsaturated keto acids **30a,b** (prepared in three stages from the enones **25a,b**) gave the desired CD-trans products **31a,b** almost exclusively.[33a] The high stereoselectivity of these reductions is probably a result of conformational factors conferred upon the keto acid substrate via H bonding of the carboxyl proton with the ketone carbonyl.[33a] A similar result was recently noted when the unsaturated diketo sulfone **30c**, (available by treatment of **25b** with paraformaldehyde–benzenesulfinic acid–acetic acid) was hydrogenated over palladium on charcoal, under acidic conditions, to produce the trans-fused product **31c** in 75% yield.[34]

Because the keto acids **31a,b** were readily available, it was now possible to introduce, regioselectively, the A and B rings of the steroid molecule by exploiting the activation at C-8 provided by the carboxyl substituent. To this end, the keto acids **31a,b** were subjected to a facile decarboxylative Mannich reaction[33b] by treatment with formaldehyde and piperidine catalyst in Me_2SO, a procedure which yielded the α-methylene ketones **32a,b** in excellent yield.[33c] These intermediates are conveniently functionalized for facile introduction of AB-ring synthons via conjugate addition processes. In this manner, it was possible to obtain optically and chemically pure 19-nor steroids **1c** and **1d**, in overall yields of 27 and 18%, respectively (based on starting 2-alkyl-1,3-cyclopentanedione).[33c] The high overall efficiency observed in this approach stems from several factors, including: (1) the early introduction of chirality (**23a,b** → **25a,b**); (2) high stereoselectivity throughout (a result of the facile introduction of the CD-trans ring fusion stereochemistry); (3) convergence; and (4) the requirement of only a minimal amount of intermediate purification. The versatility of the enones **32a,b** was demonstrated by their conversion into aromatic steroids[35] as well as potential corticoid intermediates.[36]



Conclusions

From the foregoing discussion, it should be apparent that the application of asymmetric induction processes to the preparation of 19-nor steroids now allows total synthesis, in a most efficient manner, of a variety of medicinally important, optically active compounds. Space limitations preclude consideration in detail of the asymmetric transformations which have been utilized for the synthesis of normal steroids. Nonetheless, it should be noted that the (*S*)-(+)-enedione **34**, a potential AB-ring synthon,[30,37] can now be made available by cyclization of the triketone **33** with (*S*)-



proline[26,30] and its derivatives[28a] (asymmetric synthesis). In addition, mention must be made of the elegant approaches to progesterone[38a,b] and 11-substituted progesterones[38c,d] using biomimetic polyolefin cyclizations, in which substantial asymmetric induction at several chiral centers is observed (diastereoselective syntheses). The successful utilization of asymmetric transformations demonstrated in the steroid field defines the potential of such processes and bodes well for their equally successful application in other areas of natural product synthesis.

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