Chapter 29. Asymmetric Synthesis

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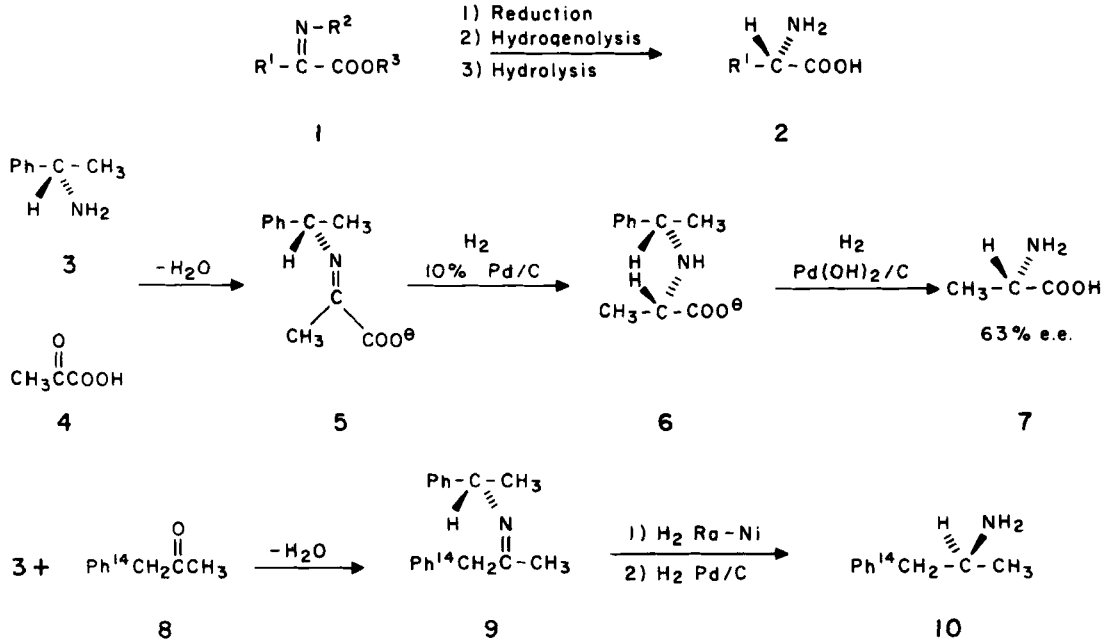
In an asymmetric synthesis an achiral substrate is transformed by a chiral reagent to produce an excess of one enantiomer of the chiral product. Asymmetric synthesis is a lively field whose early promise is being realized in development of several useful processes. Effective use of asymmetric synthesis to obtain a chiral substance requires that a suitable substrate be found which can be transformed to a synthetically useful (typically > 50%) enantiomeric excess (e.e.) of a chiral product which can be fractionated to give pure enantiomer. This article briefly summarizes the best results currently obtainable by asymmetric synthesis using chemical reagents. More detailed treatments are available.[1-4]

Asymmetric transamination (1→2) is a useful route to α-amino acids. Catalytic reduction of imine 1 (R^2 and/or R^3 chiral) to the corresponding amine and hydrogenolysis (R^2 is usually benzylic) gives the amino acid 2. Usually R^2 and R^3 can be chosen so that 2 is obtained in high e.e.[5,6] Typical is synthesis of (S)-alanine 7 in 63% e.e. (4→7).[7] A similar synthesis of amines,[8-14] well suited to preparation of amphetamine derivatives, is available, i.e. 8→10.[14] Replacing amine by hydrazine,[15-18] the best being 11,[17] allows transamination to be achieved without losing the original chiral center, e.g. 11+12→14+15.[17]



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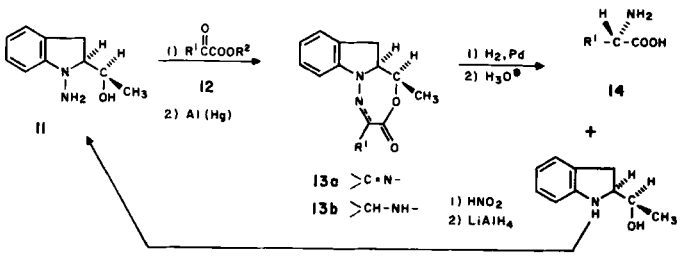
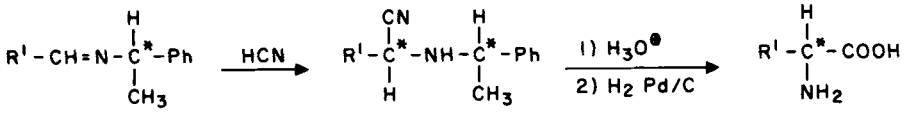
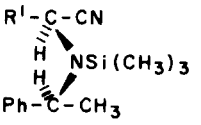


Chiral amines and amino acids have been made via additions of nucleophiles to amines, e.g. asymmetric Strecker synthesis wherein cyanide adds to 16 giving selectively one diastereomeric form of 17. Nitrile hydrolysis and reductive benzyl cleavage complete the synthesis.[19] The amino acids 18 can typically be obtained in only 20-60% e.e. unless it is possible to purify the aminonitrile intermediate by crystallization. Numerous modifications of the basic procedure have been tried without much success[20-23] although improved (61-75%) e.e. of 18 results from Lewis acid catalyzed condensation of imine 16 with trimethylsilylcyanide to give 19 whose acid hydrolysis under mild conditions yields (S,S)-17. Enantioselectivity in conversion of 16 to 19 depends on the catalyst. Zinc chloride is preferred.[24] Use of ephedrine[25] and (S,S)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane[26] as amines for Strecker-type amino acid syntheses have been reported, the former being restricted to preparations of aromatic N-methylamino acids and the latter to preparations of α-methylamino acids. An asymmetric Strecker synthesis is used in commercial synthesis of the antihypertensive agent α-methyl DOPA.[27]

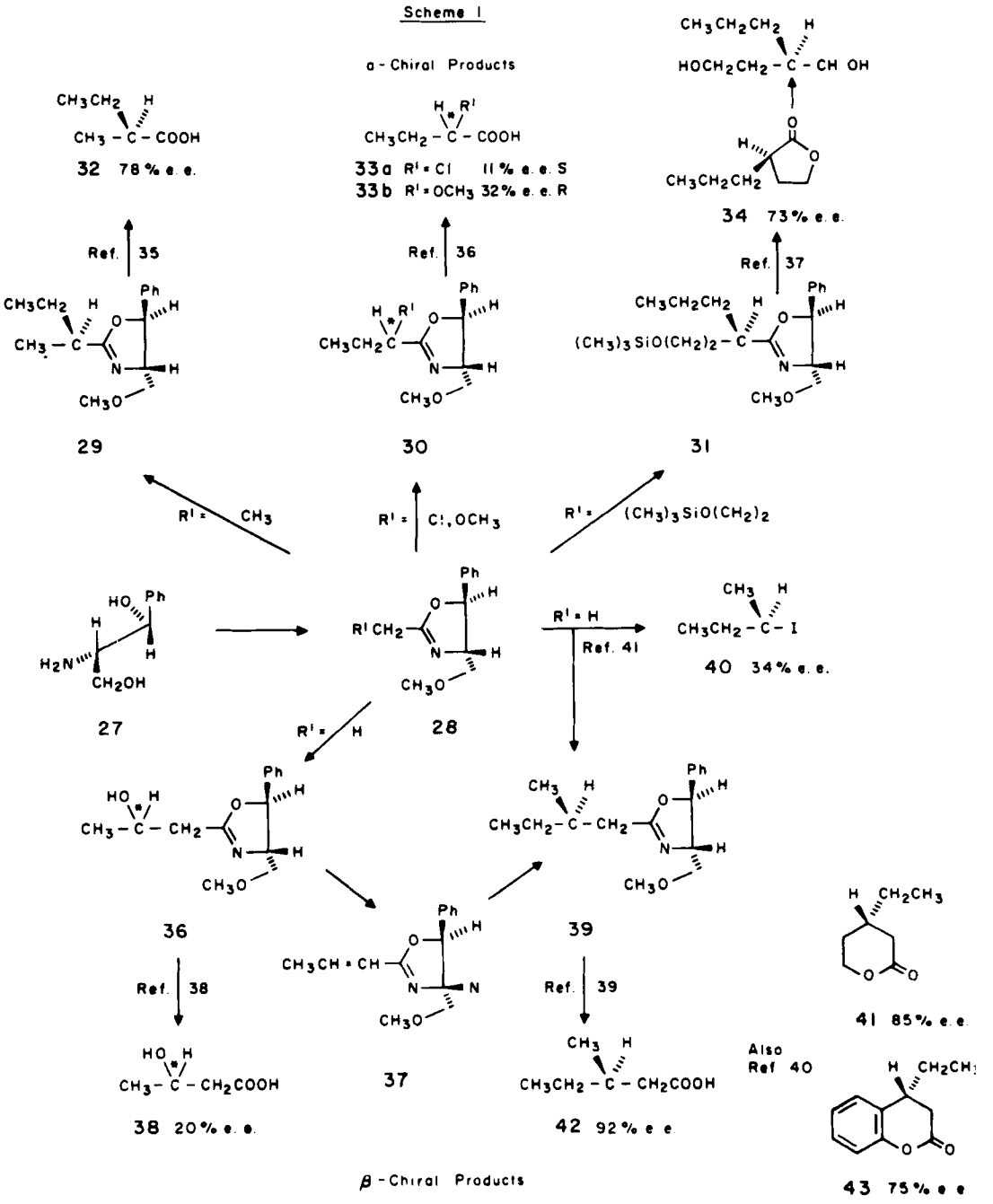


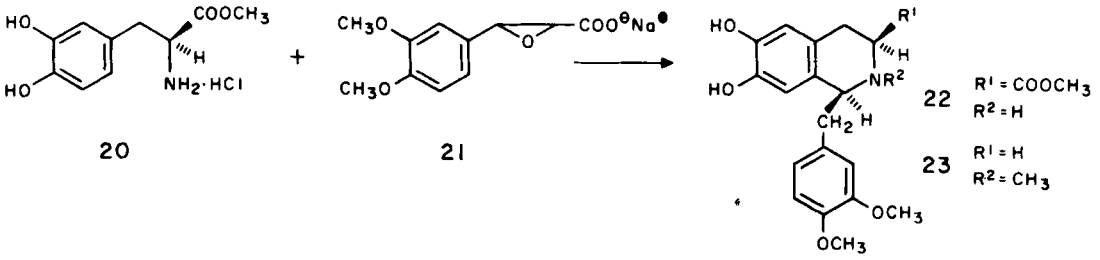
16 17 18



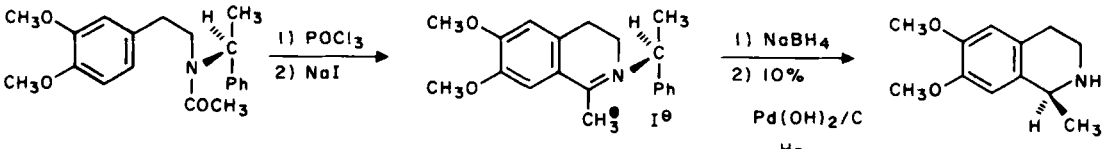
19

The iminium cation intermediate in Pictet-Spengler ring closures is implicated in a 1,3-asymmetric transfer process which gives chiral alkaloids.[28] Condensation of (S)-DOPA methyl ester hydrochloride, (S)-20, with glycidate 21 (3,4-dimethoxybenzaldehyde precursor) gives isoquinoline 22 in 76% e.e. Methylation and 3 step removal of the carbomethoxy group (and thus of the original center of asymmetry) gives (S)-laudanosine (S)-23.[29] The method was used also to prepare (R)-laudanosine,[30] (S)-reticuline[31] and, in modified form, to prepare (+)-maritidine.[32] In a related process, borohydride reduction of 25 followed by hydrogenolysis gives (S)-salsolidine, (S)-26, in 36-44% e.e.[33]


Scheme I
α - Chiral Products
32 78% e. e.
33a R' = Cl 11% e. e. S
33b R' = OCH3 32% e. e. R
34 73% e. e.
Ref. 35
Ref. 36
Ref. 37
29
30
31
R' = CH3
R' = Cl, OCH3
R' = (CH3)3SiO(CH2)2
27
28
R' = H
Ref. 41
40 34% e. e.
R' = H
36
39
Ref. 38
Ref. 39
37
38 20% e. e.
42 92% e. e
41 85% e. e.
Also Ref 40
43 75% e. e
β - Chiral Products



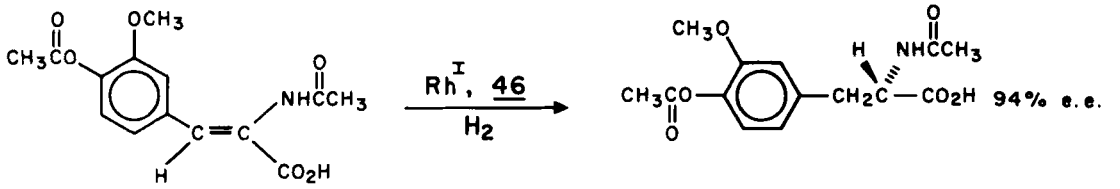
20 21



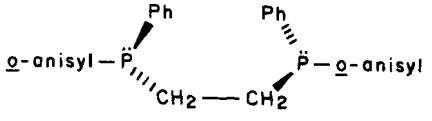
24 25 26

Very useful asymmetric transformations of imine anions, especially anions of oxazoline 28, have been reported.[34] These are practical synthetic procedures which often afford high e.e. products. Some examples of the α- and β-chiral carboxylic acids prepared by this method[34-43] are given in Scheme 1.

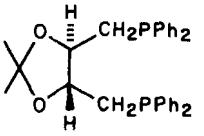
A catalytic asymmetric hydrogenation (reviews: ref. 4,44) of (Z)-44 gives (S)-45 in ca. 95% e.e. when Rh-46[45] catalyst is used. This reaction is the basis for a commercial L-DOPA synthesis.[46] Similar catalysts with phosphine enantiomers ligated to rhodium have been used to transform other enamides, certain prochiral C=C, C=O and C=N chromophores into chiral hydrogenation and hydrosilylation products. Many other useful phosphine ligands have been discovered - the most widely used is DIOP, 47,[44] which often affords good enantioselectivity and has the virtue of being commercially available. It is useful to recognize that substrates which can be hydrogenated with high enantioselectivity at reasonable rates by these catalysts are primarily those which are at least formally able to coordinate to Rh in a bidentate fashion, e.g. 48, (X=O,CHR,NR;Y=O,N,CH_2, etc.).



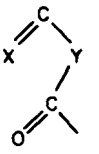
(Z) - 44 (S) - 45



46
(DIPAMP)

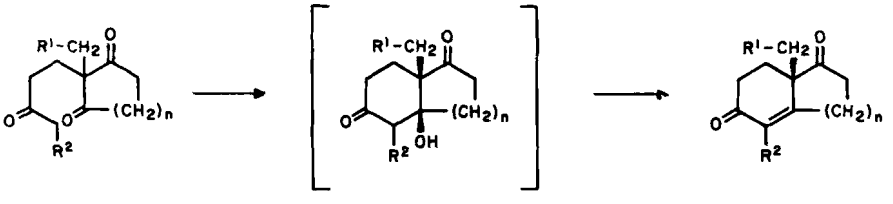


47
(-)-DIOP

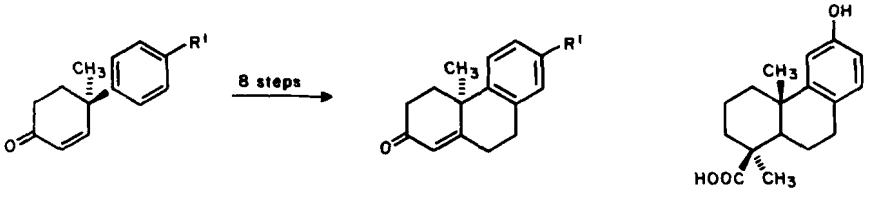


48

An exciting new development is the chiral amine catalyzed cyclization of prochiral triones 49 via 50 which is sometimes isolable, to give enones 51. The scope and applicability of these reactions, which were discovered independently by 2 groups,[47-48] have been reviewed.[49] With amino acids or amino acids and added perchloric acid as catalysts, these reactions afford enones 51 in 60-97% e.e., presumably via enamine intermediates.[49] Enones 51 (n=1), are useful to form the CD ring system in some steroid syntheses while 51 (n=2, R^1=R^2=H) is the chiral Wieland-Miescher ketone[50] which is a steroid AB ring synthon[49] and a valuable starting material for terpene syntheses.

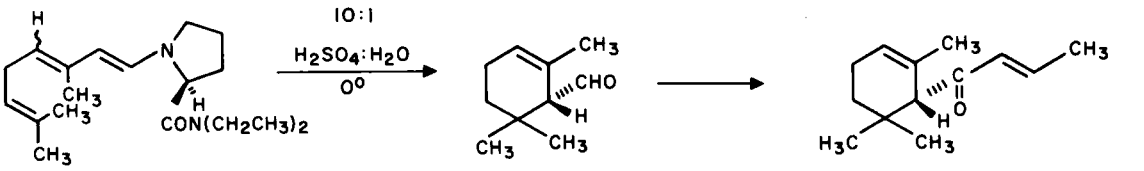


49 n=1,2 50 51



52 53 54 Podocarpic Acid

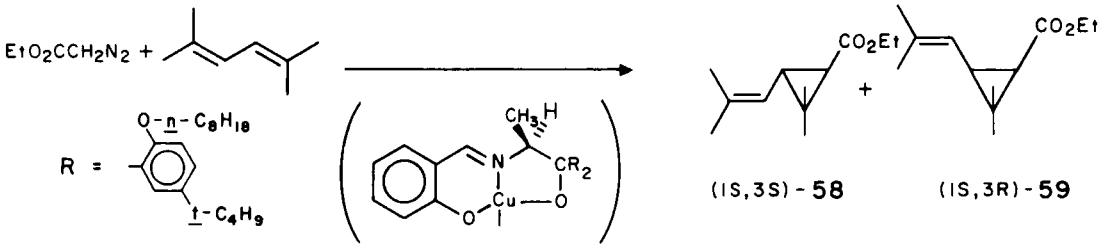
Michael reactions of enamines with methyl vinyl ketone are of special interest since chiral cyclohexenone derivatives may be obtained.[51,52] The utility of the method is illustrated by the preparation of 52, (R^1=H) in 44% e.e.,[53] which is convertible in 8 steps to 53, useful in many natural product syntheses.[54] The enantiomer of 53 (R^1=H), prepared similarly can be converted to natural podocarpic acid.[55] An analogous preparation affords unnatural (+)-mesembrine.[56] The same type of reaction yields (R)- or (S)-$\Delta^{1,9}$-2-octalone.[57] Also, acid catalyzed cyclization of enamine 55 gives (R)-α-cyclocitral, 56, (converted to trans-α-damascone 57) in 33% e.e.[58]

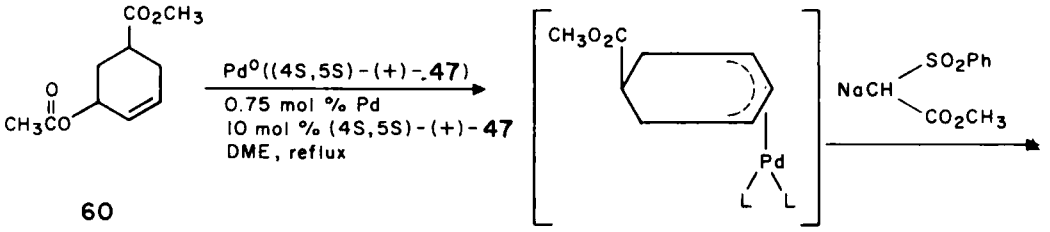


55 56 57

A catalytic asymmetric process with evident potential is decomposition of diazo esters by enantiomeric copper chelates in the presence of olefins, e.g. to prepare optically active chrysanthemates 58 and 59 in about 60% e.e.[59]

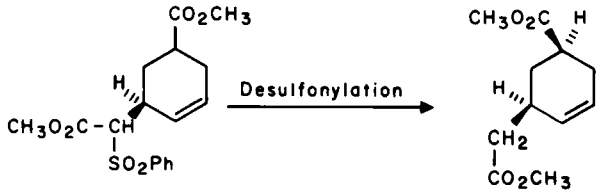
Another promising method which affords chiral centers not otherwise easy to obtain in enantiomeric form is catalytic displacement on allylic acetates, e.g. 60, under the influence of enantiomeric palladium (0) complexes, to give optically active chiral sulfone derivatives 61 in moderate e.e. This reaction proceeds via Pd π-allyl complexes and may also be run stoichiometrically on preformed complex.[60-69]





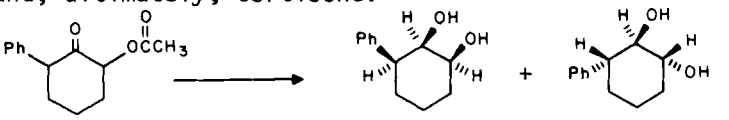
60
cis, racemic

Intermediate
Achiral if L achiral
Chiral if L chiral
2L = (4S,5S)-(+)-47

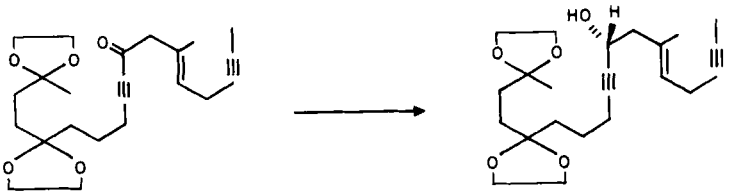


61 (R,R)-62

Use of chirally modified metal hydrides to reduce prochiral ketones continues to be studied actively and some encouragingly high e.e.'s of chiral alcohols have now been reported in individual cases.[70] Careful optimization is probably at least as important as initial reagent selection but the best results have been obtained with an $LiAlH_4$ complex with Darvon alcohol. Reduction of rac.-63 using $LiAlH_4$-(2R,3S) Darvon alcohol gives a 38% yield of 1S,2R,3S-64 (64% e.e.) and 21% yield of 1R,2R,3R-65 (at least 77% e.e.)[71-72] The $LiAlH_4$-Darvon alcohol reagent affords highly enantioselective reductions of prochiral acetylenic ketones. Reduction of 66 gives 67 (84% e.e.).[73] This alcohol is a precursor to 11α-hydroxyprogesterone, and, ultimately, cortisone.[74]

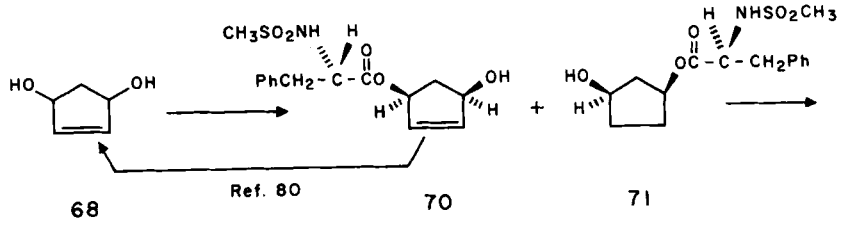


63 64 65

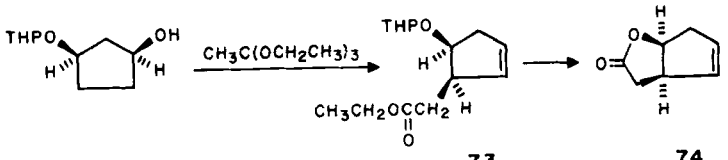


66 67

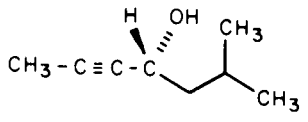
Intramolecular rearrangements, usually proceeding via doubly suprafacial [2,3] or [3,3] sigmatropic pathways, may sometimes be used to transfer asymmetry creating a new asymmetric center while sacrificing one which is easier to obtain. The most useful of these reactions involve Claisen[75] or modified Claisen[76] rearrangements. Both cyclic[77-80] and acyclic systems[81-85] give good results, for instance, the following examples:[86]



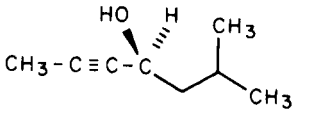
68 70 71



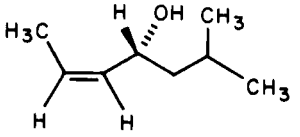
72 73 74



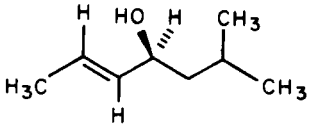
(R) - 75



(S) - 75

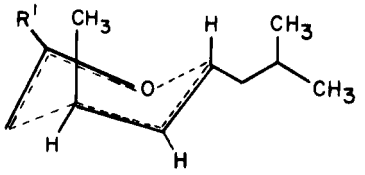


Ref. 82,83

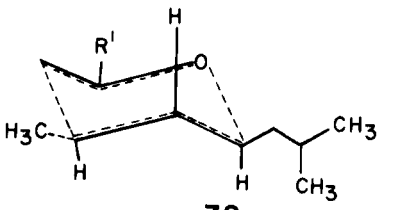


(R) - (Z) - 76

(S) - (E) - 77

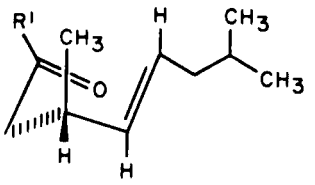


78



79

96.5 - 99.4 %
Transfer of Chirality



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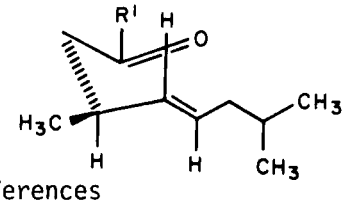

(S) - (E) - 80

a $R^1 = H$

b $R^1 = OCH_2CH_3$

c $R^1 = N(CH_3)_2$

d $R^1 = OH$

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