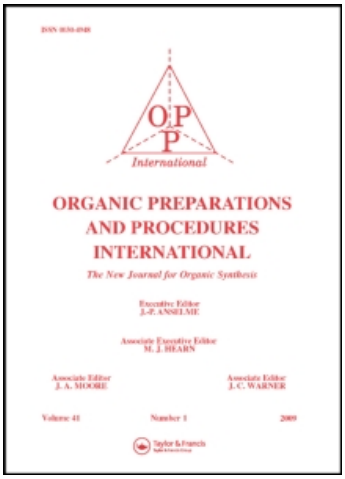

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THE SYNTHESIS OF SUCCINIC ACIDS AND DERIVATIVES. A REVIEW

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THE SYNTHESIS OF SUCCINIC ACIDS AND DERIVATIVES. A REVIEW

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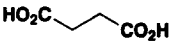
INTRODUCTION

Succinic acid (**1**) (mp 185-187°) is one of the simplest organic diacids. Its pKa_1 is 4.16 while pKa_2 is 5.61. It is recognized as an intermediate in the Krebs acid cycle, and occurs as colorless crystals that are monoclinic and have an acidic taste.

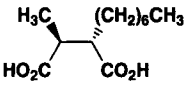


1

The intent of this review is to cover the strategies for the synthesis of substituted succinic acid derivatives. Very few surveys on this topic have been published,[1-3] and they are limited to the discussion of several types of carboxylic acids and esters, with only a portion focused on diacids and diesters. For the purposes of this review, we have divided the synthetic strategies into four main groups – formation from two 2-carbon units, from one 3-carbon and one 1-carbon unit, modification of an existing 4-carbon unit, and modification of an existing 5-carbon unit.

I. USES OF SUCCINIC ACIDS AND DERIVATIVES

Succinic acid and its many derivatives have a very broad spectrum of uses. Succinic acid itself is obtained from anaerobic bacteria as a fermentation by-product.[4] Other naturally occurring butanedioic acids include sphaeric acid (**2**), roccellic acid (**3**), and pedicellic acid (**4**).[5]



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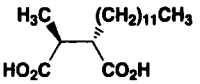

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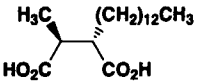

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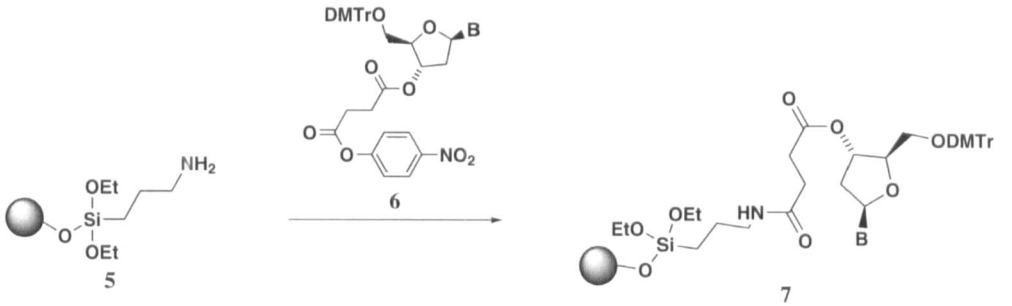
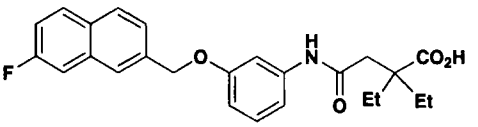
Succinic acid is a precursor for a variety of industrially important starting materials that include *N*-methylpyrrolidone, 1,4-butanediol, γ-butyrolactone, adipic acid, tetrahydrofuran, and linear aliphatic acids.[6] A review on the uses of products derived from succinic acid has recently been published.[7] This diacid is used extensively in the polymer industry. An advantage of butanedioic acid-derived polymers is their biodegradable nature, therefore offering environmentally friendly materials.[8]

Succinate derivatives are used as linkers to attach oligonucleotides[9] and peptides[10] to solid support for automated syntheses as shown in *Scheme 1*. After the appropriate number of coupling steps, the desired oligonucleotide or peptide is obtained by cleavage of the linker from the solid support using aqueous ammonium hydroxide.[11]



Scheme 1

Succinic acids are often used as intermediates in the synthesis of medicinal agents. However, there are examples of compounds such as the LTD_4-antagonist CGP57698 that has a 3,3-diethylsuccinate monoamide fragment necessary for activity.[12] This compound has been discussed as a possible treatment for human bronchial asthma.

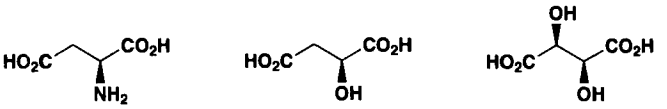


CGP57698

Matrices for MALDI mass, IR and UV spectroscopy have used succinic acids.[13] Several studies have investigated the use of succinates as a possible treatment for non-insulin diabetes. It was shown that in rats, these diesters have the ability to stimulate biosynthetic activity in the pancreas.[14]

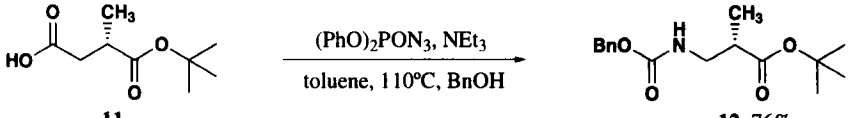
1. Uses as Synthetic Intermediates

The availability of enantiomerically pure substituted succinate derivatives has resulted in a plethora of uses for these molecules. Naturally occurring succinic acid derivatives that have been used as starting materials for total syntheses include aspartic acid (**8**),[15, 16] malic acid (**9**),[17, 18] and tartaric acid (**10**).[19]



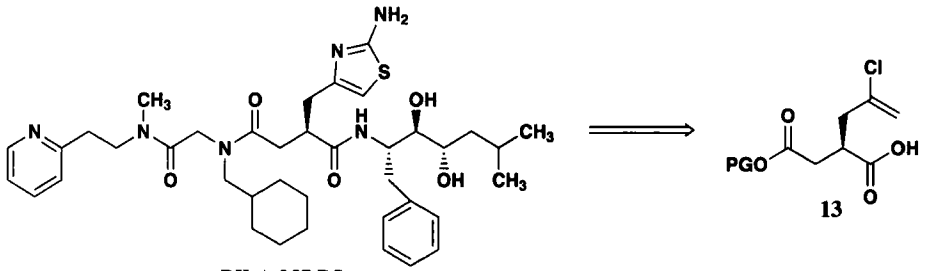
An important aspect concerning the use of succinic acids as synthetic intermediates is the selective modification of one carboxylate group. For example, in *Scheme 2*, a Curtius rearrangement of acid **11** leads to β-amino acid **12**.[20, 21] β-Amino acids have been used to study protein structure[16]

and peptides' resistance to enzymatic degradation.[22] They have also been used as precursors to β-lactam antibiotics,[16] and other natural products.

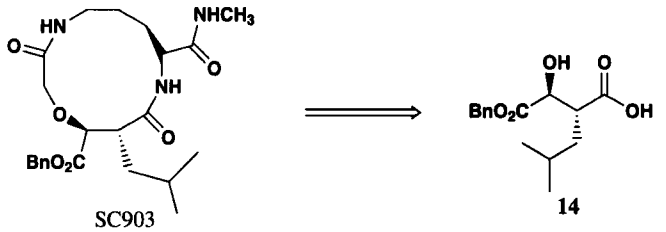


Scheme 2

Another common use of enantiomerically pure succinic acid fragments is the synthesis of enzyme inhibitors. Two recent examples include the synthesis of BILA 257 BS, a potent and optically active renin inhibitor,[23] and SC903, a matrix metalloproteinase inhibitor.[24]



BILA 257 BS



SC903

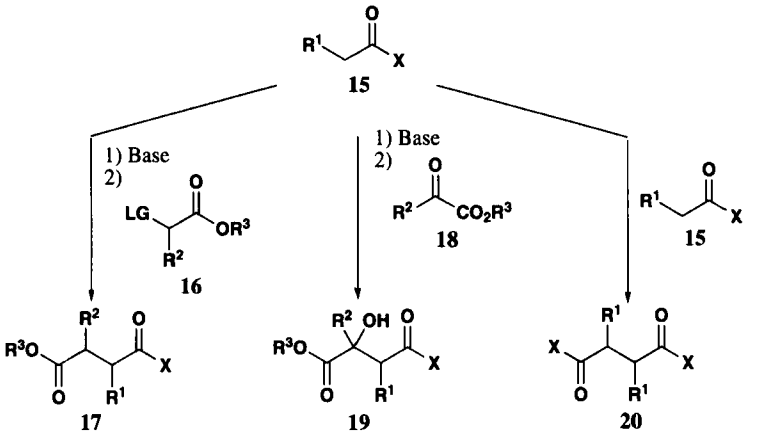
The search for methods for the synthesis of substituted succinates has been difficult. This is in large part due to the fact that most approaches for substituted succinate synthesis are contained in papers describing their further transformations. We have no doubt missed some work, but we hope that we have provided a reasonable overview of strategies to prepare substituted succinic acid derivatives.

We have organized the methods for the preparation of succinic acid derivatives into four general categories. These categories are organized by the number of carbons in the starting materials leading to the 4-carbon diacid or diacid derivative. We should also note that we have tried to include all routes that produce succinic acids, esters, amides as well as nitriles and even succinaldehydes in our discussion as these functional groups can be readily interconverted. Our four general categories are the synthesis of the 4-carbon succinic acid derivative from a) two 2-carbon pieces, b) from one 3-

carbon and one 1-carbon piece, c) modification of a single 4-carbon unit, and d) synthesis from a 5-carbon or larger molecule.

II. SYNTHESIS OF SUCCINATES FROM TWO 2-CARBON UNITS

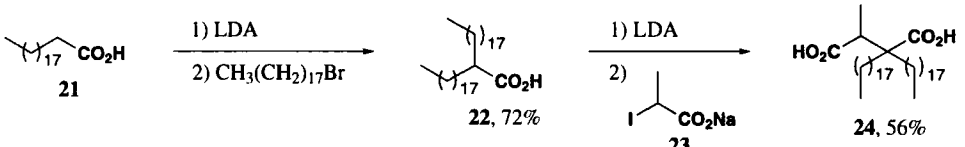
The synthesis of succinic acids and their derivatives from two 2-carbon units is a very useful strategy (*Scheme 3*). This synthetic route includes the reaction of an enolate with an electrophile (**15** and **16** forming **17**, or **15** and **18** forming **19**) as well as the dimerization reactions of esters (**15** and **15** forming **20**). The most common electrophiles used are acetic acid derivatives containing a leaving group on carbon-2 and α-ketoesters giving rise to hydroxysuccinates (malates).



Scheme 3

1. Reaction of Enolates with Acetate Derivatives

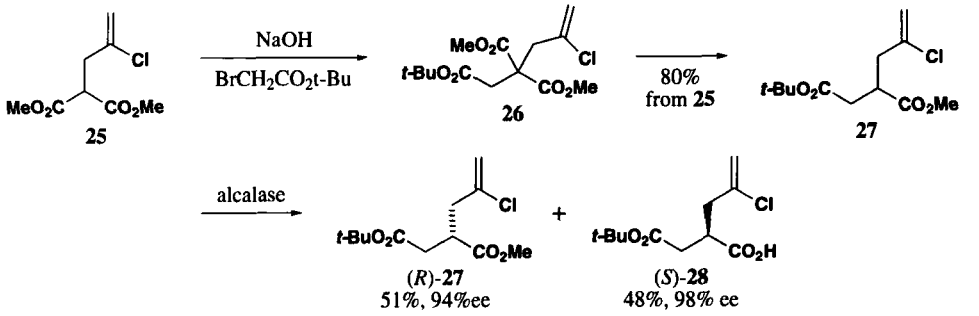
The reaction of an enolate with a two-carbon electrophile is one of the most frequently used routes to succinates. Usually this electrophile is a bromoacetate ester. This approach has the advantages of well known chemistry, control of stereochemistry and good accessibility of starting materials. The natural product fomentaric acid (**24**) was synthesized in two steps from eicosanoic acid (**21**). The first step gave octadecyleicosanoic acid (**22**) in 72% yield, with 23% of **21** being recovered. The second alkylation gave fomentaric acid in 56% yield, with 39% of compound **22** recovered.[25] Other examples include a synthesis of the alkaloid quebrachamine[26] as well as the synthesis of 2,2-disubstituted succinimides.[27]



Scheme 4

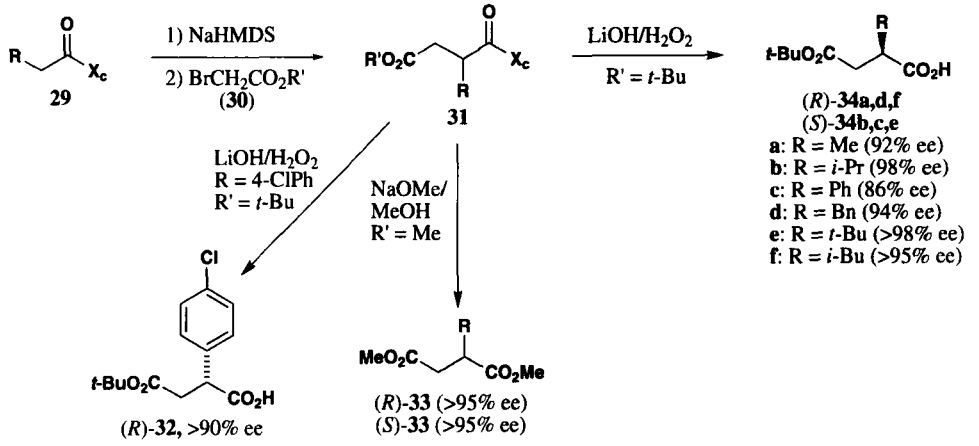
The alkylation of a malonate followed by decarboxylation has been used to prepare substituted succinic acids.[23, 28] In a very straightforward approach, diester **25** was deprotonated with NaOH and alkylated with *t*-butyl bromoacetate to provide triester **26**.[23] This process was followed by hydro-

lysis and decarboxylation to give diester **27** in 80% yield over the two steps. The racemic methyl ester was then hydrolyzed enzymatically to provide (*S*)-**28** in 48% yield. The remaining (*R*)-**27** was then recycled to get back to the racemic succinate (**27**).



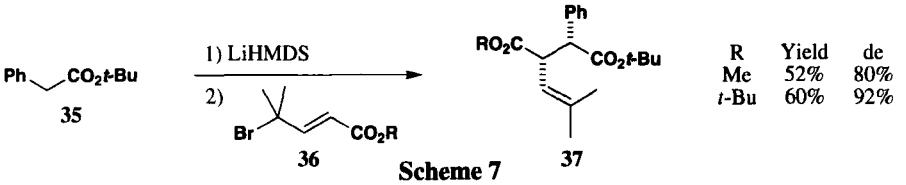
Scheme 5

The most widely used approach for the preparation of enantiomerically pure monosubstituted succinates is the use of a chiral auxiliary on the enolate. This strategy has been utilized to prepare 2-substituted succinates diastereoselectively (*Scheme 6*). The alkylation of the enolate of **29**



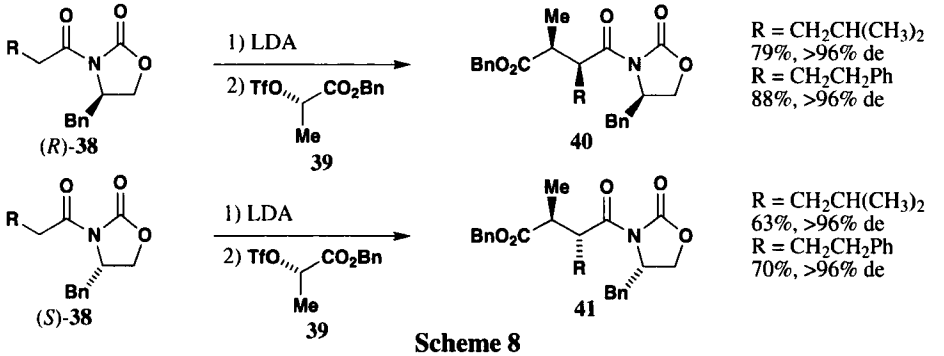
Scheme 6

with bromoacetate **30** provided the 2-alkylsuccinate derivative **31** in 72-89% yield with >95% diastereomeric excess in most cases.[21, 29-31] The chiral auxiliary can be removed to give the monoacid (**32, 34**)[21, 29, 31] or the diester (**33**).[30] Control over relative stereochemistry in the preparation of 2,3-disubstituted succinates has been achieved using the enolate of **35**. Deprotonation of **35** with LiHMDS, followed by an S_N2' alkylation with **36** gave the succinates (**37**) in moderate yield with 80-92% diastereomeric selectivity.[32]



Scheme 7

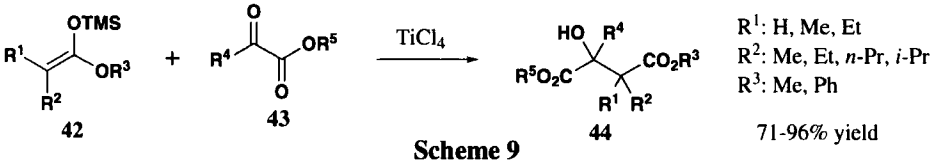
A major limitation of these methods is the moderate diastereoselectivity associated with the preparation of 2,3-disubstituted succinates. A partial solution to this problem is the use of a chiral acetate derivative[33, 34] to prepare 2,3-disubstituted succinates enantioselectively (*Scheme 8*). Deprotonation of **38** with LDA, followed by alkylation with benzyl lactate triflate (**39**), gives the disubstituted succinate derivative in good yields and with excellent stereoselectivity. The only limitation of this approach is the availability of the desired lactate triflate.[33]



Scheme 8

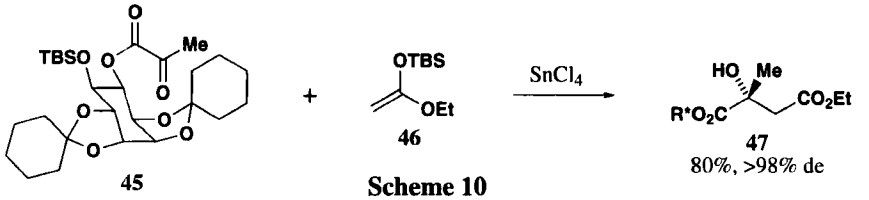
2. Reaction of Enolates with Keto Esters

The reaction of an ester enolate with an α-ketoester will give a 2-hydroxysuccinate (malate). This is a fairly general approach to the synthesis of hydroxysuccinates with numerous examples. The overall process is shown in *Scheme 9*. The reaction of a ketene acetal (**42**) with an α-ketoester (**43**)



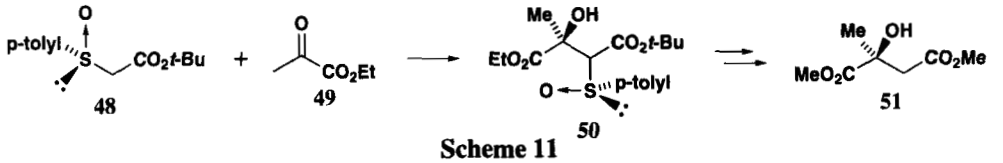
Scheme 9

gives a variety of hydroxysuccinate derivatives in 71-96% yield.[35] As the synthesis of enantiomerically pure hydroxysuccinates is of interest, three different methods have been used to synthesize homochiral hydroxysuccinate derivatives. The three options are the use of a chiral auxiliary linked to the ketoester, a chiral auxiliary linked to the enolate portion, or to use a chiral catalyst. Chiral auxiliaries linked to the ketoester component include both menthyl[36] and 8-phenylmenthyl.[37] These auxiliaries give the desired hydroxysuccinates with only moderate stereoselectivity. However, ketoester **45**,



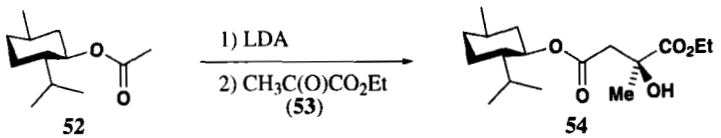
Scheme 10

in which the chiral auxiliary is a pseudosugar, reacts with ketene acetal **46** to provide a hydroxysuccinate (**47**) in good yield (80%) and with excellent stereoselectivity (>98% de). The chiral auxiliary can also be attached to the enolate. For example, the reaction of chiral sulfoxide **48** with ethyl pyruvate (**49**) provided the hydroxysuccinate **50** in good yield but poor diastereoselectivity (8.5% de). This compound was then converted to citramalic ester **51**.[38]



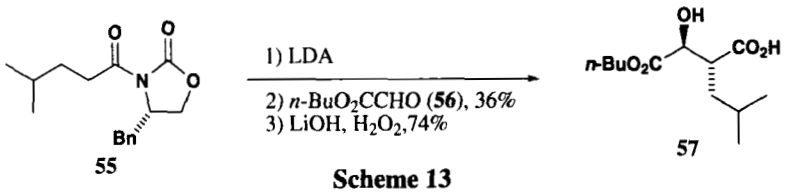
Scheme 11

A similar approach to the method shown in *Scheme 11* involved the generation of the lithium enolate of (-)-menthyl acetate (**52**) and its reaction with ethyl pyruvate (**53**). A 75% yield of the citramalate (**54**) was achieved in slightly better stereoselectivity (26% de).[39] Use of a more sterically hindered base, combined with the use of (-)-bornyl acetate gave, at best, 45% ee of the corresponding citramalate.[40]



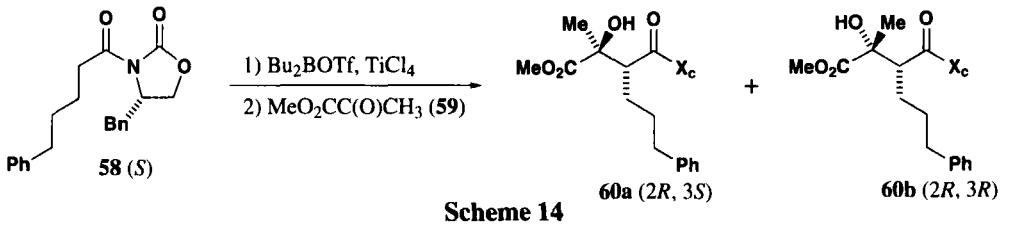
Scheme 12

A more common strategy is the use of a chiral oxazolidinone (*e.g.* **55**) in an aldol reaction to provide the hydroxysuccinate. In a synthesis of cyclic inhibitors of matrix metalloproteinases, the enolate of **55** was reacted with butyl glyoxylate (**56**), to eventually give 2-hydroxy-3-isobutylsuccinate (**57**) in 50% de.[24]



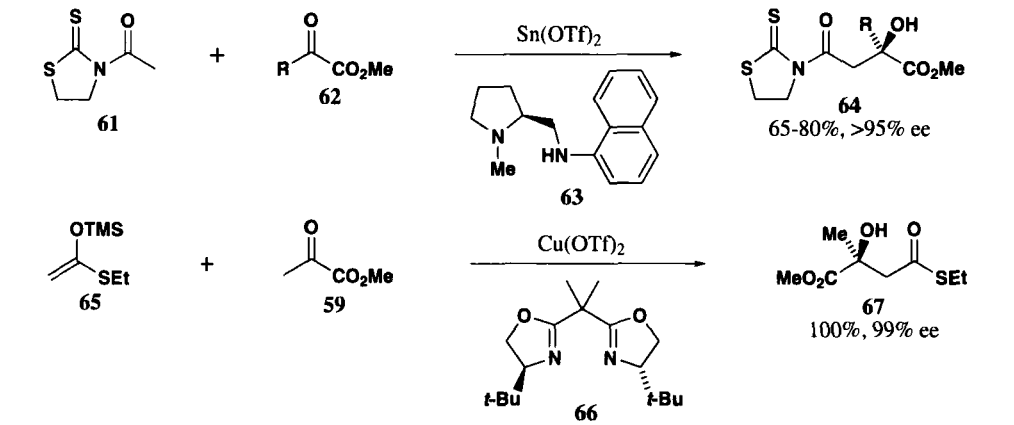
Scheme 13

The oxazolidinone auxiliaries have also been utilized in the synthesis of all four diastereomers of hydroxysuccinate derivative **60**. The boron-enolate of **58** was reacted with methyl pyruvate (**59**). When the (*S*)-oxazolidinone was used, **60a** and **60b** were produced in 65% yield, with **60a** being the major product (in a 4:1 ratio). When the (*R*)-oxazolidinone was used, the (2*S*, 3*R*) and (2*S*, 3*S*)-enantiomers were produced in 72% yield with the (2*S*, 3*R*) being the major diastereomer (3.8:1 ratio).[41] In general, this route does not provide particularly good diastereoselectivity.



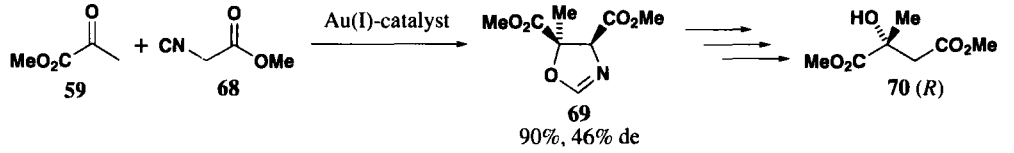
Scheme 14

The third option for the synthesis of enantiomerically pure hydroxysuccinates is to use a chiral catalyst for the reaction. The use of a proline-derived diamine and a Lewis acid has been shown to be an effective method for inducing asymmetry.[42, 43] Acetate-derivative **61** and an α-ketoester (**62**, where R is larger than Me) were coupled in the presence of diamine **63** to provide hydroxysuccinate derivative **64** in good yield, with excellent stereoselectivity.[42] The use of a chiral copper catalyst has been reported recently.[44, 45] This has allowed for the synthesis of citramalate-derivative **67** in 100% yield with 99% ee.



Scheme 15

In a very interesting catalytic process, a five-membered oxazoline ring (**69**) has been constructed using a chiral ferrocenyl-gold catalyst. This reaction proceeds via a cycloaddition reaction between the carbonyl of **59** and the isonitrile of **68**. In order to confirm the absolute stereochemistry, this ring was then converted into (*R*)-citramalate **70** in several steps.[46]



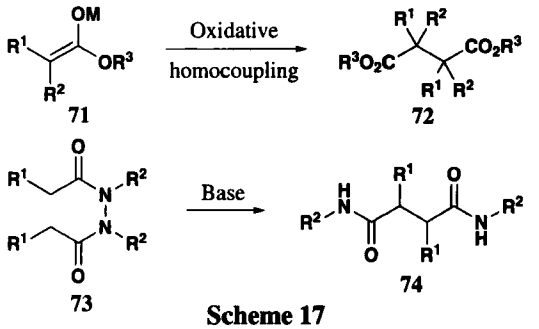
Scheme 16

The chiral catalyst route to hydroxysuccinate derivatives has proven to be quite effective in terms of yields although the diastereoselectivity is variable, ranging from 46% (**69**) to 99% ee (**67**). As

with all synthetic routes to the hydroxysuccinates, the preparation of diastereomerically pure 2,3-disubstituted succinates is difficult.

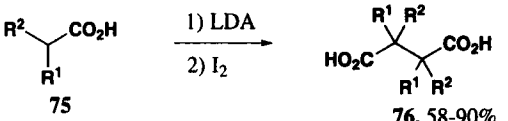
3. Dimerizations of Esters and Acids

The most common dimerization routes to succinates are intermolecular oxidative homocoupling, as well as anionic intramolecular [3,3]-rearrangements (*Scheme 17*). Both ester enolates and



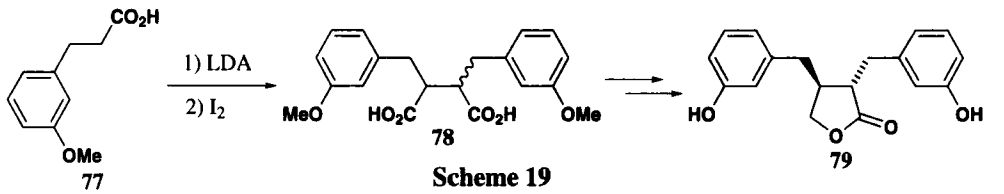
Scheme 17

carboxylic acid dianions can be used for oxidative homocoupling, although the ester enolates tend more towards self-condensation giving β-ketoesters. Several examples of this reaction,[47, 48] including a review of the reactions of anions of carboxylic acids and ester enolates,[49] have been reported. As shown in *Scheme 18*, the preparation of a dianion of a carboxylic acid (**75**) with 2 equivalents of LDA,



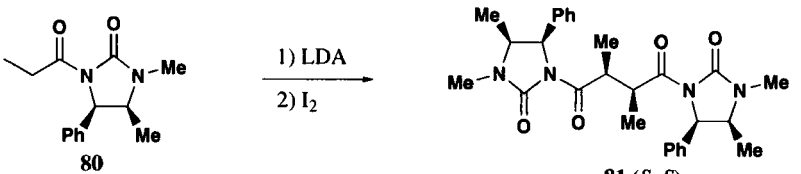
Scheme 18

followed by addition of 0.5 equivalents of iodine gave succinic acids **76** in 58-90% yield. When the starting acid was monosubstituted (R^2 = H), the yields of the disubstituted succinic acid were 70-90%.[50] This strategy has been used to prepare lignans,[51] such as enterolactone (**79**), where intermediate **78** was prepared in 85% yield and 64% de (*Scheme 19*).[52]



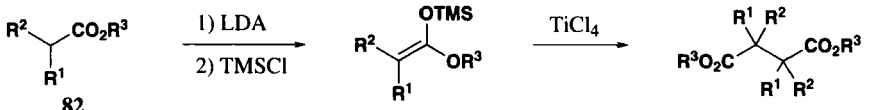
Scheme 19

A few groups have utilized chiral auxiliaries to induce absolute stereoselectivity in this reaction.[53, 54] One of the most stereoselective examples is shown in *Scheme 20*.[55] In this example an imidazolidinone was used as the chiral auxiliary to provide compound **81** in >98% ee. Copper(II)



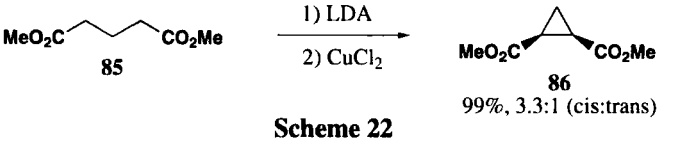
Scheme 20

pentanoate could also be used as the oxidant to give **81** with a similar ee, but a slightly lower yield (66%). Silyl ketene acetals can also be coupled to provide the succinates. Upon treatment of **83** with $TiCl_4$, di- and tetrasubstituted succinates (**84**) were obtained in 52-98% yields (*Scheme 21*).[56, 57]



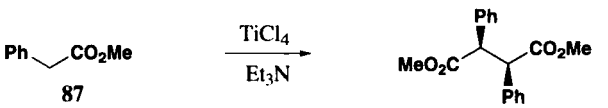
Scheme 21

Similar homocouplings have been carried out using $CuBr_2$,[58] CuI/O_2,[59] $FeCl_3$,[60] and 2,3-dibromo-2,3-dimethylbutane.[61] Intramolecular oxidative couplings, such as that of dimethyl glutarate (**85**) to give the cyclopropane derivative **86** in 99% yield, have been reported (*Scheme 22*). However, only moderate diastereoselectivity is observed.[62] Both copper(II) chloride[62, 63] and copper(II) triflate[64] can be used as the oxidant in these reactions.



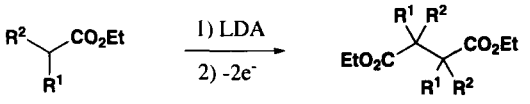
Scheme 22

The oxidative coupling can also be accomplished in the presence of $TiCl_4$ and a weak base.[65, 66] The use of Et_3N in the coupling of methyl phenylacetate (**87**) gave disubstituted succinate **88** in 83% yield and with 98% de (*Scheme 23*).[66] Electrochemical oxidation is another way to achieve the



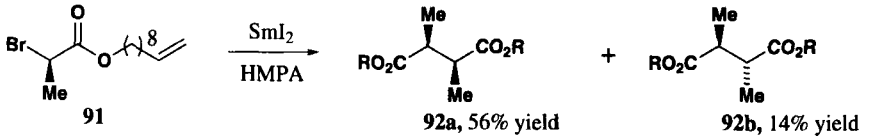
Scheme 23

coupling. Most monoalkyl derivatives (R^1 = H) gave poor yields (8-45%), the only exception being phenylacetate (R^1 = H, R^2 = Ph), which gave a quantitative yield. Only one example of a dialkyl derivative was reported ($R^1 = R^2$ = Me) which provided **90** in 82% yield (*Scheme 24*).[67]



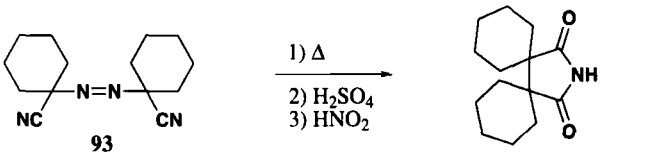
Scheme 24

A recently reported method eliminates the use of a base in the coupling. Samarium(II) iodide in the presence of HMPA promotes the coupling of bromopropionate **91**, presumably through a radical mechanism. This reaction gives **92a** in 56% yield and the minor component **92b** in 14% yield (*Scheme 25*).[68] An earlier report used $CuCl_2/Zn$ for this type of coupling.[69]



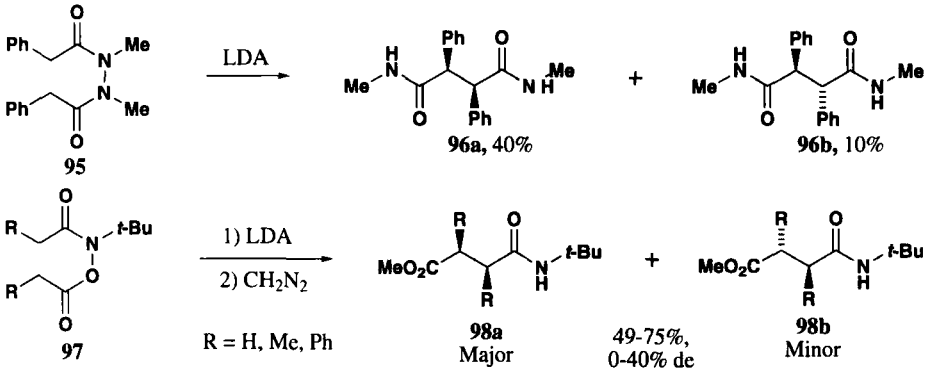
Scheme 25

An example of a similar type of coupling, even though it does not involve a direct oxidation, is the radical reaction of azonitrile **93** to provide succinimide **94** in 85% yield (*Scheme 26*).[70] The



Scheme 26

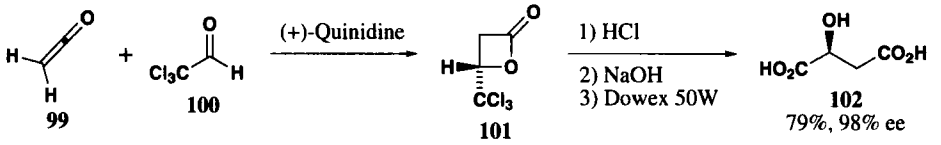
preparation of succinic diamides or monoamides is also possible through an anionic hetero [3,3] rearrangement.[71-74] Compound **95** will rearrange in the presence of LDA to give a 40% yield of **96a** (*syn*) and 10% of **96b** (*anti*).[71] The unsymmetrical compound **97** will also rearrange and with the addition of diazomethane, the monoester monoamide is isolated (*Scheme 27*).[73] A diamide (*e.g.* **95**) can also give the disubstituted succinimide directly by reaction with a silyl triflate.[75]



Scheme 27

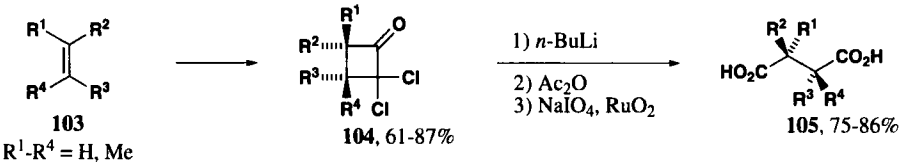
4. 2+2 Cycloaddition

Two routes have been reported for the preparation of succinates through the use of a 2+2 cycloaddition. One of those methods involves the reaction of ketene (**99**) with trichloroacetaldehyde (**100**), catalyzed by (+)-quinidine, to give β-lactone **101**. Careful hydrolysis of the lactone affords (*S*)-2-hydroxysuccinic acid (malic acid) in 79% yield with 98% ee.[76]



Scheme 28

The other 2+2 cycloaddition route makes use of the cycloadduct between dichloroketene and a di-, tri- or tetrasubstituted alkene (**103**). An enol acetate of cyclobutanone **104** is formed and then oxidized using sodium periodate-ruthenium dioxide to yield the substituted succinic acid (**105**) in 75-86% yield (*Scheme 29*). The cyclization is stereospecific, **104** being the only product formed.[77]

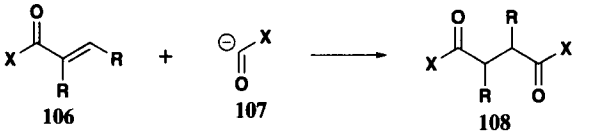


Scheme 29

The preparation of substituted succinates from two 2-carbon pieces is a well studied strategy with numerous methods. By far the most straightforward (and probably most used) is the reaction of an enolate with some type of substituted acetic acid electrophile. None of the other strategies can really compete in terms of generality and applicability.

III. SYNTHESIS OF SUCCINATES FROM ONE 3- AND ONE 1-CARBON UNIT

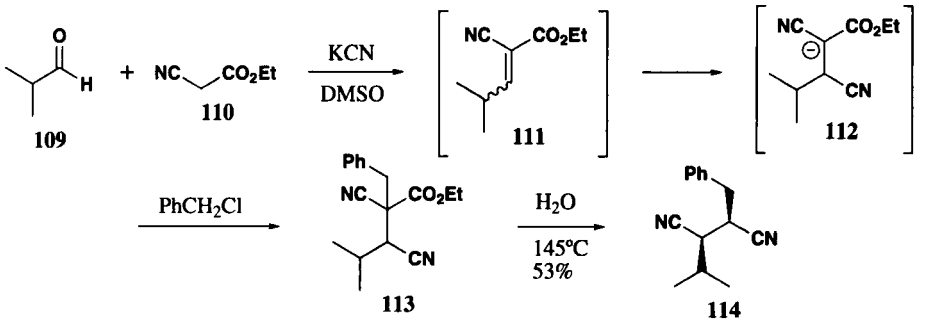
The addition of a one-carbon segment to a three-carbon segment to form the four-carbon succinic acid skeleton is a rarely used strategy. Conceptually one would add a carbonyl anion synthon **107** to an α,β-unsaturated ester, aldehyde, or nitrile **106**. In practice there are few examples of this process. The reported examples make use of cyanide as the carbonyl anion synthon.



Scheme 30

The first example of this route to prepare succinic acids is found in Organic Syntheses.[78] In this procedure, the reaction of benzaldehyde, phenylacetonitrile, and KCN provides 2,3-diphenyl-succinonitrile as the *meso* isomer in approximately 70% yield. Only symmetrical disubstituted succinonitriles can be prepared by this method.

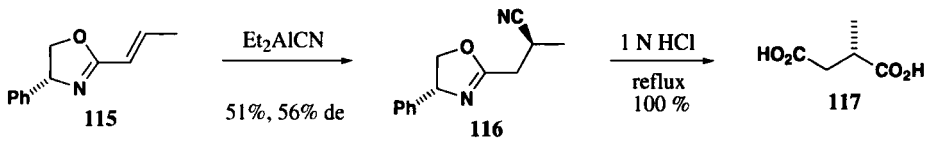
A more useful variant of this reaction is shown in *Scheme 31*,[79] where an aldehyde is condensed with ethyl malononitrile (**110**) to provide the intermediate α,β-unsaturated ester **111**.



Scheme 31

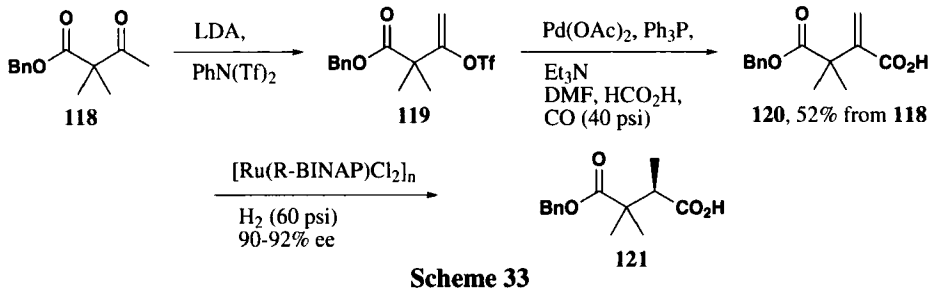
Subsequent addition of cyanide provides the stabilized anion **112** which can then react with an alkyl halide to provide the dinitrile **113**. Water is then added to the reaction mixture and the temperature is increased to induce hydrolysis and decarboxylation. In this manner, the unsymmetrical succinonitrile **114** is produced in 17-70% yield. In general there is very little stereoselectivity associated with this process. The reactants shown in *Scheme 31* give only the *syn*-isomer and provide the best result in terms of diastereoselectivity. The major advantage of both of these reactions is that they can be carried out in one-pot.

Cyanide is also used as the nucleophile in the reaction shown in *Scheme 32*.[80] This reaction makes use of a chiral oxazoline as the α,β-unsaturated electrophile. Treatment of oxazoline **115** with Et_2AlCN in toluene provides the nitrile **116** in modest yields and only moderate diastereoselectivity. Concomitant hydrolysis of the oxazoline and nitrile in aqueous HCl provides the monosubstituted succinic acid **117** in excellent yield and with no loss of optical purity.



Scheme 32

A potentially very useful method which does not involve a conjugate addition of cyanide is the palladium-catalyzed carbonylation of an enol ether (*Scheme 33*).[81] This technique converts ketone **118** to the enol triflate **119**. The crude enol triflate (**119**) was subjected to a palladium-catalyzed

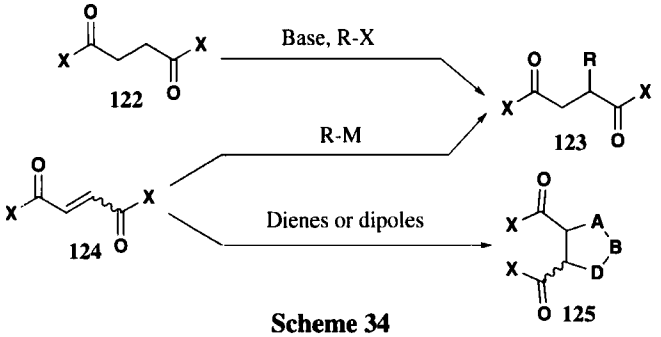


Scheme 33

carbonylation to provide the α,β-unsaturated acid **120** in 52% yield (from **118**). This intermediate is similar to the Stobbe condensation products described in the following section. Hydrogenation of the olefin then provides the succinate in 90-92% ee. Reviews of similar palladium catalyzed carbonylations have been published.[82, 83] While potentially a very useful route to substituted succinic acid derivatives, very little work has been done on this method. It is thus difficult to make general predictions regarding its usefulness or wider applicability.

IV. SYNTHESIS OF SUCCINATES FROM ONE 4-CARBON UNIT

The synthesis of succinates from a 4-carbon unit is conceptually the most straightforward method for the preparation of substituted succinic acid derivatives. All of these routes utilize the functionalization of either a succinic acid or maleic/fumaric acid derivatives to prepare more highly substituted succinic acid derivatives. There are three general types of disconnections that are typically used for the synthesis of succinates from a single 4-carbon unit (*Scheme 34*). The first is simply the alkylation of a succinic acid derivative. Such reactions include alkylation of ester enolates as well as



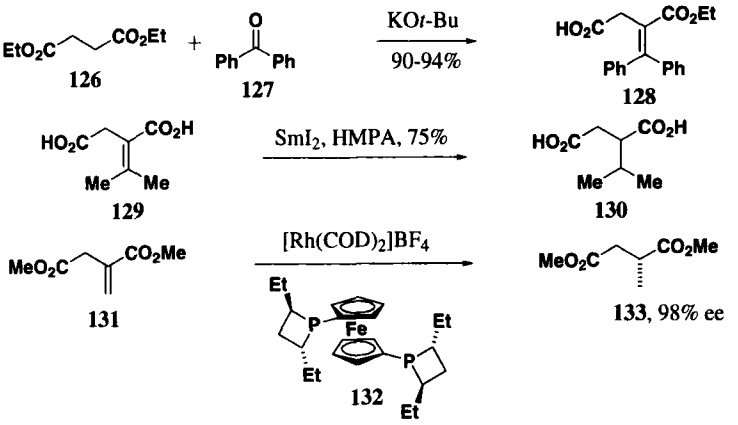
Scheme 34

Stobbe condensations. A second method for modifying a succinic acid derivative is the conjugate addition to a maleic or fumaric acid derivative. The final route to substituted succinates also involves a maleic or fumaric acid *via* a Diels-Alder reaction.

1. Stobbe Condensation

Probably the oldest method for the preparation of substituted succinic acids is the Stobbe condensation followed by hydrogenation. The classic Stobbe condensation involves the reaction of a

diester of succinic acid with a carbonyl compound in the presence of an alkoxide.[84] As shown in *Scheme 35*, the reaction between diethyl succinate (**126**), benzophenone (**127**) and an excess of

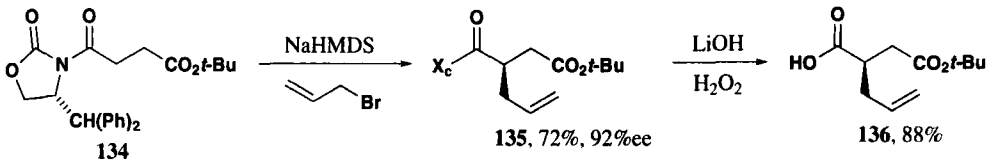


Scheme 35

KO*t*Bu provides the half ester **128** in 90-94% yield. While there have been numerous examples of the Stobbe condensation in the literature, only one novel variation on the standard reaction conditions has been reported.[85] These Stobbe products can be reduced readily to the succinic acid derivatives using both catalytic hydrogenation and metal reducing agents (*e.g.* **129** → **130**).[86] Recently there has been considerable interest in the asymmetric reduction of the Stobbe condensation products.[87-91] For example, the reduction of dimethyl itaconate (**131**) using a rhodium catalyst and the chiral ligand **132** provides **133** in quantitative yield and with 98% ee.[92]

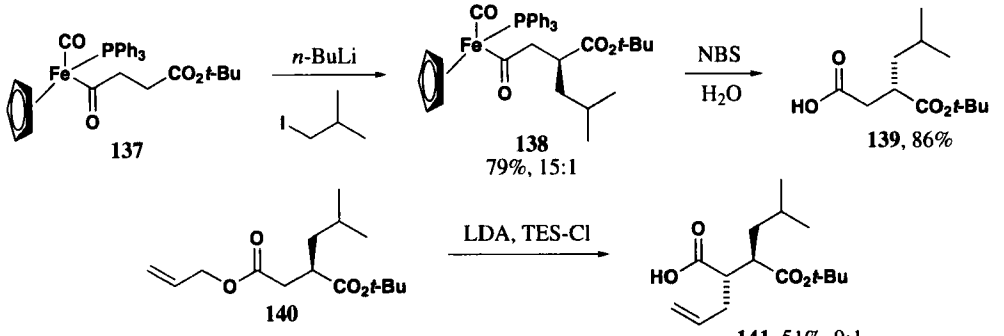
2. Alkylation of Succinates

The alkylation of a succinic acid derivative is a relatively well known route for the preparation of substituted succinic acids. Depending upon the type of succinic acid derivative utilized, one can prepare and use a monoanion (single enolate), a dianion (single enolate), or a dianion (dienolate) in the alkylation step. The use of a monoanion is a strategy that has not been extensively investigated. The general idea is to take a succinate diester (or equivalent) and prepare and alkylate the monoenolate.[93, 94] The example shown in *Scheme 36* is a particularly useful example for the synthesis of enantiomerically pure monosubstituted succinic acids.[95] The sodium enolate of **134** was prepared and alkylated with a number of alkyl halides to provide the succinate derivative **135** in generally good yield and good diastereoselectivity. The chiral auxiliary was cleaved to provide the monosubstituted monoester **136**.



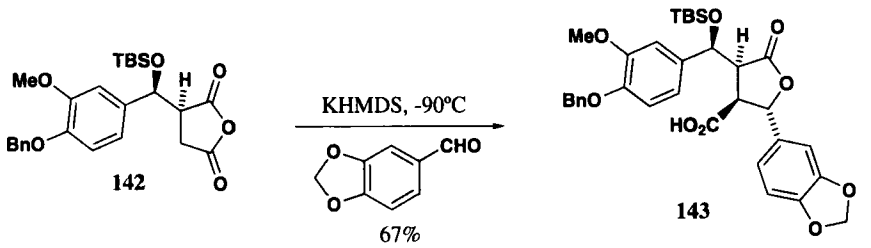
Scheme 36

Two particularly intriguing examples that use a monoanion are shown in *Scheme 37*. The first one uses a chiral ferrocene derivative **137** in an alternate route to enantiomerically pure monosubstituted succinates.[96] Compound **137** is treated with *n*-BuLi to generate the enolate which is then alkylated to provide **138** in excellent yield as a single diastereomer after chromatography; the iron is removed to provide monoester **139**. Another very useful method that provides a disubstituted succinic acid derivative makes use of an Ireland-Claisen rearrangement to form the disubstituted succinate **141** in moderate yield and good diastereoselectivity.[97] This method is significant in that it provides a stereo-controlled route to 2,3-disubstituted succinates.



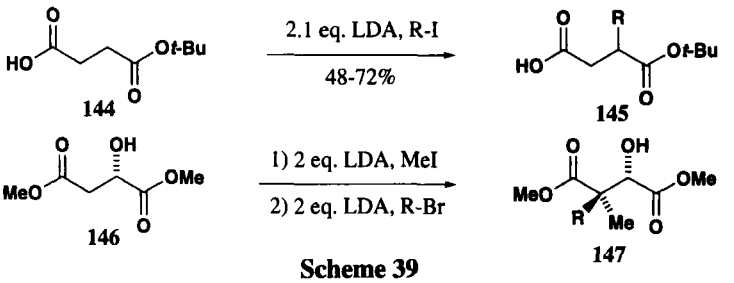
Scheme 37

One additional type of monoanion actually prepares the enolate of succinic anhydride.[98] The substituted succinic anhydride **142** is treated with KHMDS at –90° and the enolate quenched by the addition of an aldehyde. This reaction does not provide the anhydride product but rather the lactone **143** *via* attack of the resulting alkoxide on the anhydride. Even given its limitations (*e.g.* only nonenolizable aldehydes, -90° reaction temperature) this method is unique in utilizing the enolate of succinic anhydride.



Scheme 38

A general problem with the monoanion approach is the sensitivity of the substrate to the reaction conditions, leading to self condensation and dialkylation. An alternate approach to the synthesis of substituted succinic acids via alkylation is the generation and alkylation of a dianion. One such approach uses a monoester of succinic acid (*Scheme 39*).[99, 100] We have recently reported the use



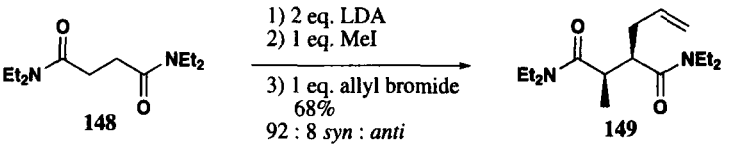
144 145 146 147

Scheme 39

of the dianion of mono-*t*-butylsuccinate **144** as a facile route to monosubstituted succinic acids **145**.[101] In this case the alkylation takes place at the carbon α to the ester. Yields are generally quite reasonable. A method to prepare 2,3-disubstituted succinic acids using this approach has also been reported, and provides a 10 : 1 mixture of the *anti*:*syn* isomers.[102]

Another method for the generation of a dianion with a single enolate is exemplified by the conversion of **146** to **147**.[103-106] In this example, compound **146** is deprotonated to form the dianion and then alkylated sequentially to provide the 2,2-disubstituted malic acid derivative **147**.[105] Compound **147** was subsequently deoxygenated to provide the 2,2-disubstituted succinic acid. A nice feature of this approach is the ability to prepare the 2,2-disubsituted succinate.

Dianions, in which both anions are enolates, have also been used to prepare substituted succinic acid derivatives.[94, 107-111] A nice example is the preparation of the dienolate of the succindiamide **148**.[108] Reaction of **148** with 2 equivalents of LDA provides the dienolate. Subsequent reaction with two different electrophiles provides primarily the *syn* isomer **149** in generally good to excellent yields and very good diastereoselectivity. This method is significant in that it provides a general route for the stereo-controlled synthesis of 2,3-disubstituted succinates.

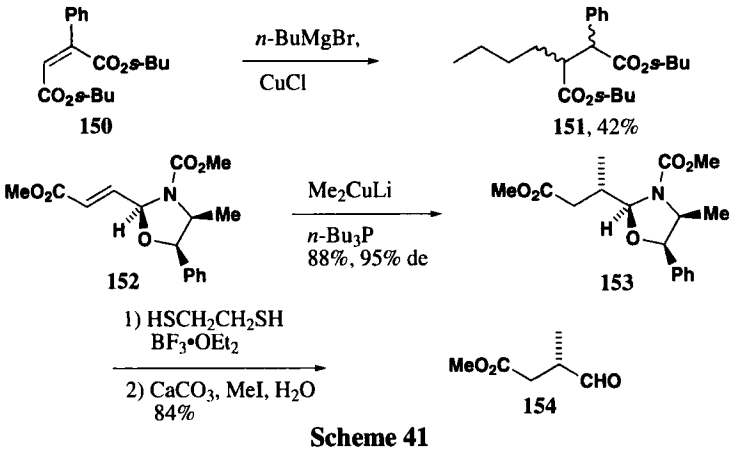


148 149

Scheme 40

3. Conjugate Additions

The conjugate addition of both heteroatom[112-114] and carbon nucleophiles[98, 115-119] to fumaric and maleic acid derivatives has proven to be a very useful route to mono-substituted succinic acid derivatives. What would seem to be a simple example of this strategy is the copper catalyzed addition of a Grignard reagent to maleic or fumaric acid. However, we have been able to find only one example of this reaction.[116] As shown in *Scheme 41*, the addition of nBuMgBr to 2-phenylmaleic ester (**150**) provides only 42% of the 1,4 addition product **151**. Products resulting from addition of the Grignard reagent at the 2-position as well as reduction of the double bond were also obtained. A modified



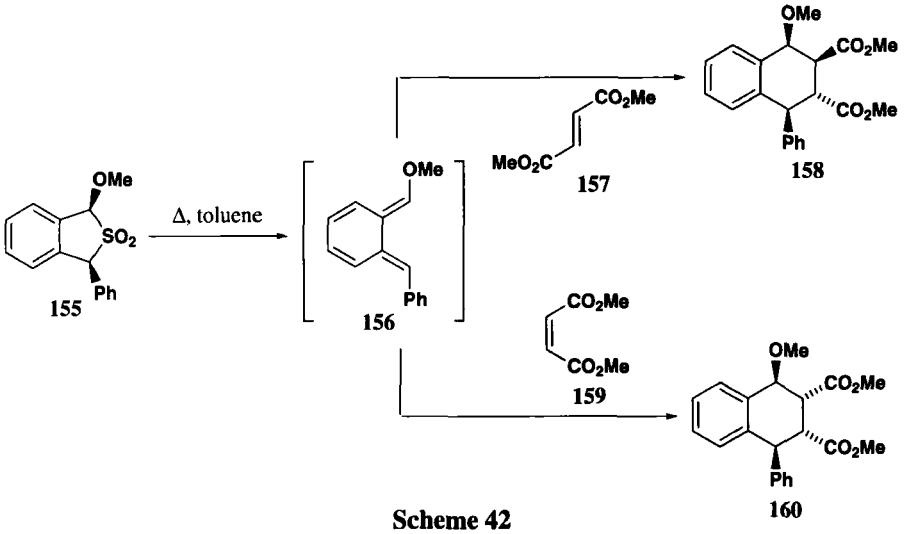
Scheme 41

version of this general strategy has been reported in which one of the esters has been reduced to an aldehyde and protected as an oxazolidine.[117-119] In this example the aldehyde functional group of a succinaldehyde ester is protected as chiral oxazolidine **152** (derived from norephedrine). Addition of Me_2CuLi provides **153** in 88% yield with a ratio of 98:2. Removal of the oxazolidine is effected *via* a two step process of thioacetal formation/thioacetal hydrolysis to provide aldehyde **154** in 84% yield. In a similar type of reaction the anion of a cyanohydrin has been added to dimethyl maleate.[98]

4. Diels-Alder Reaction

Since the Diels-Alder reaction has been reviewed extensively,[120-123] its wide use for the synthesis of di-, tri-, and tetrasubstituted succinic acids will not be discussed in any great detail. Maleic and fumaric acids and esters as well as maleic anhydride are quite reactive dienophiles and many examples are found in the literature. Many novel methods for carrying out a Diels-Alder reaction are initially examined using maleic anhydride and maleimide derivatives as classic examples of dienophiles. Indeed, the Diels-Alder reaction of cyclopentadiene and maleic anhydride is a common undergraduate laboratory experiment.[124] This strategy is useful because of the regio- and stereocontrol of cycloaddition reactions, and the availability of *cis* and *trans* starting materials. The example shown in *Scheme 42* is typical of the utility of Diels-Alder reactions to provide cyclic 2,3-disubstituted succinic acids.[125]

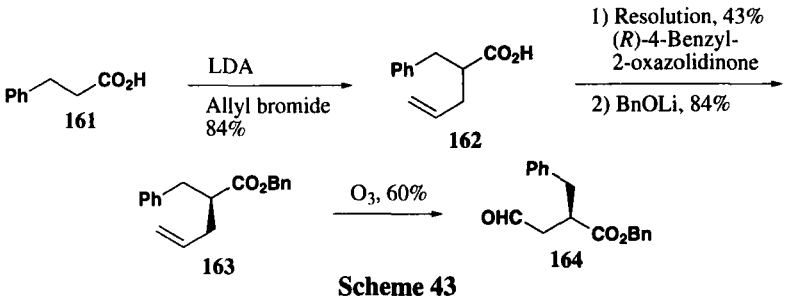
The formation of substituted succinates from a single 4-carbon piece is a well studied strategy. The choice of a method will of course depend upon the products desired, but the alkylation of either monoesters or diesters appears to be very general and, for the preparation of monosubstituted succinates, quite useful. The Diels-Alder reaction is undoubtedly the method of choice for the preparation of cyclic succinates, especially when control of relative stereochemistry is important.



Scheme 42

V. SYNTHESIS OF SUCCINATES FROM A 5-CARBON OR LARGER UNIT

The synthesis of succinates from 5 or more carbons is a difficult synthetic strategy to generalize. There are a variety of synthetic routes to succinic acid derivatives from precursors containing 5 or more carbons. What these routes usually have in common is the oxidation of an olefin or aromatic ring to provide one of the carboxylic acid functional groups. Many of these oxidative routes are variations on routes previously discussed in Sections II-IV.[126-129] The synthesis shown in *Scheme 43* is a

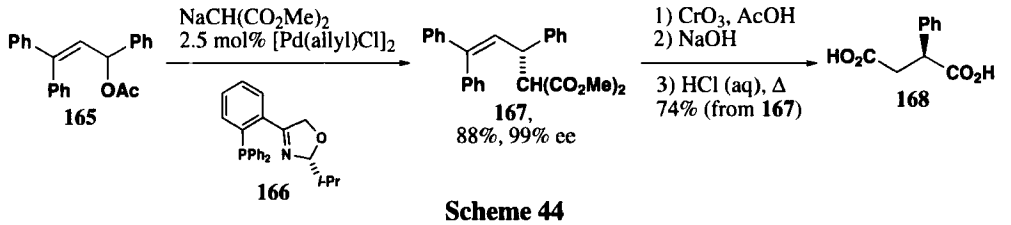


Scheme 43

good example of a variation on the alkylation of a monoester of succinic acid. An advantage of this type of strategy is that any side-reaction associated with a carboxylic acid functionality is effectively avoided.[126] The carboxylic acid **161** is alkylated with allyl bromide to provide acid **162**. A resolution and subsequent esterification provides the enantiomerically pure ester **163**. The olefin is then converted to the aldehyde (**164**) by ozonolysis. This compound was examined as an inhibitor of carboxypeptidase A.

There are a number of examples of oxidations of 5-carbon (or larger) compounds to prepare succinates from compounds which are not completely analogous to those used in previously discussed

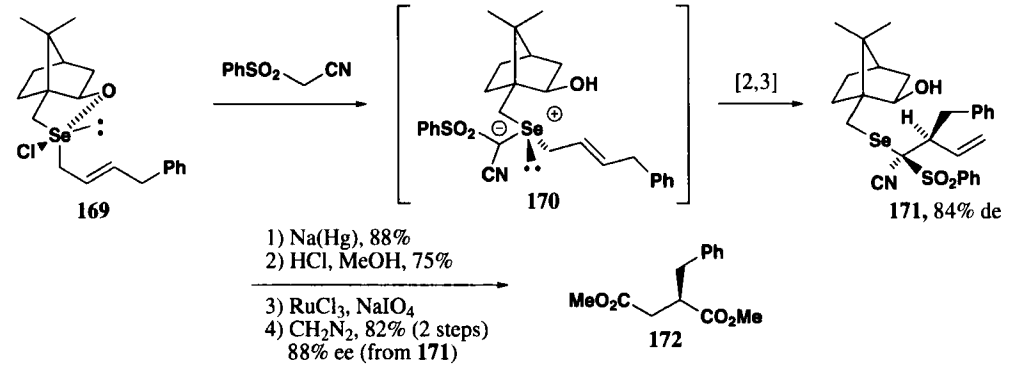
methods. An example of what is formally a 2-carbon plus 2-carbon synthesis of a succinate is shown in *Scheme 44*.[130] This reaction makes use of a malonate addition to a π-allyl palladium intermediate to



Scheme 44

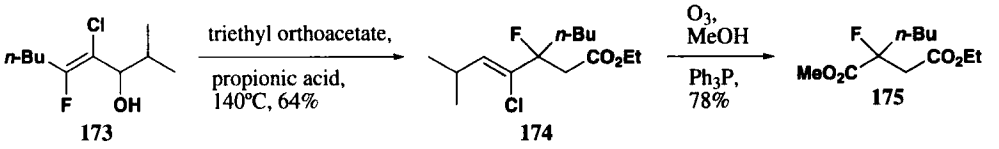
form the backbone of the succinate. Addition of a malonate anion to the allylic acetate **165** in the prescence of Pd and a chiral ligand (**166**) provides substituted malonate **167** in 88% yield and 99% ee. This compound is readily converted to succinate **168** by olefin cleavage followed by a decarboxylation. This is a very good route to enantiomerically pure monosubstituted succinic acids and allows for the preparation of both aliphatic and aromatic substituted succinic acids.

Another method which is formally the addition of a malonate-type anion to an allylic system is shown in *Scheme 45*.[131] The chiral chloroselenurane **169** is treated with the anion of (phenylsulfonyl)acetonitrile to form an intermediate selenonium ylide **170**. This ylide undergoes a [2,3] sigmatropic rearrangement to produce selenide **171** in 78% yield. Reductive removal of both the selenium and phenylsulfone moieties provides the succinate precursor. The nitrile is then hydrolyzed and the olefin oxidatively cleaved to give the diacid. Treatment with diazomethane yields succinate diester **172**.



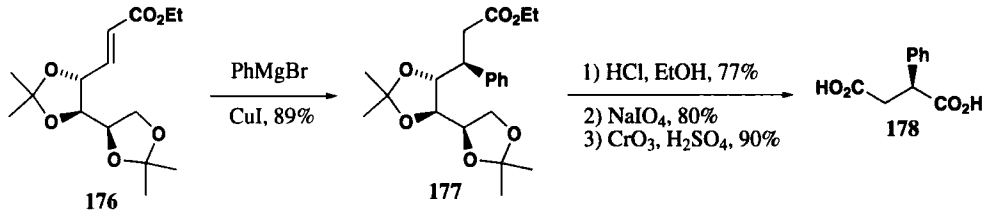
Scheme 45

A potentially quite useful procedure which has been used for the synthesis of a fluoro-substituted succinic acid is shown in *Scheme 46*.[132] Fluoro-allylic alcohol **173** was subjected to Johnson-Claisen conditions to provide the olefinic ester **174** in 64% yield. Ozonolysis of the olefin in methanol provides the methyl ester **175** directly.



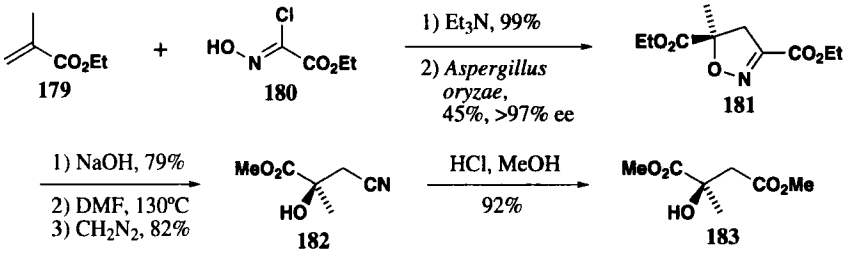
Scheme 46

The conjugate addition of an organocuprate to a carbohydrate derivative provides an example of a formal modification of a 4-carbon unit to provide a succinic acid.[133] The α,β-unsaturated ester **176** (prepared from arabinose) is treated with a copper catalyzed Grignard reagent to provide ester **177** as a single diastereomer. Removal of the acetonides, cleavage of the sugar portion and oxidation of the aldehyde provides the monosubstituted succinic acid **178** in excellent yield. This is a very nice way to carry out what is essentially a conjugate addition to a fumaric acid derivative in an enantiomerically pure fashion.



Scheme 47

One synthesis of a succinate from a 5-carbon or larger unit which does not involve the oxidative cleavage of an olefin is shown in *Scheme 48*.[134] In this method the conversion of the 5-carbon compound to a succinate involves a decarboxylation to form a nitrile. Nitrile oxide cycloaddition is used to prepare isoxazole **181** in 99% yield. An enzymatic resolution of this diester provides



Scheme 48

the enantiomerically pure diester in >97% ee. A three step sequence of ester hydrolysis, decarboxylation and re-esterification provides the hydroxysuccinonitrile derivative **182**. Methanolic hydrolysis of the nitrile yields enantiomerically pure dimethyl citramalate **183**.

The synthesis of succinic acids from a 5-carbon or larger unit provides a number of interesting synthetic strategies. In general the scope and limitations associated with these strategies are the same as those for the synthesis of the related 4-carbon syntheses. An additional limitation is of course the final oxidative cleavage of the olefin or aromatic ring.

VI. CONCLUSIONS

As we have seen, the syntheses of substituted succinic acid derivatives comprise a wide and interesting array of methods. The choice of synthetic approach is both substrate and product dependent. Even with this limitation there are often several strategies to choose from. This wide range of methodology provides the synthetic chemist with a great deal of flexibility in the design and planning of synthetic schemes. One area that still has not been well defined is the synthesis of di-, tri-, and tetrasubstituted succinic acid derivatives. While many procedures can provide monosubstituted succinates and sometimes disubstituted succinates, the stereocontrolled syntheses of highly substituted succinates is still an area where contributions can be made.

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