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α-Lipoic acid chemistry: the past 70 years

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α-Lipoic acid (**ALA**) is a naturally occurring sulfur-containing fatty acid with high antioxidant activity. It is also used to treat diabetes, nerve pain, weight loss, heart disease, and primary mitochondrial disorders. Moreover, numerous therapeutic agents have been studied for managing other clinical conditions, including for anticancer, anti-HIV, anti-inflammatory, and anti-AD treatments. The medicinal importance of **ALA**, especially its biologically active form (*R*-**ALA**), has attracted considerable attention from synthetic chemists in industrial and academic fields. In this review, we discuss synthetic approaches to **ALA** and *R*-**ALA** over the past 70 years (1952 to the present), which will help medicinal chemists further develop novel routes for their synthesis.

1. Introduction

Nature is extremely generous in offering life-saving therapies using diverse natural products. α-Lipoic acid, also known as thioctic acid or **ALA**, is a naturally occurring, sulfur-containing fatty acid of great pharmacological importance. **ALA** was first isolated as an amphipathic molecule from liver tissue in 1951 by Reed *et al.*[1] and was originally identified as an enzymatic cofactor of dihydrolipoate acyltransferase in the mitochondrial tricarboxylic acid cycle that manages gene transcription. Since then, various biological activities of **ALA** have been demonstrated. It is commonly known to function as a powerful antioxidant and is manufactured as a medicine or supplement to prevent aging.[2] In addition, **ALA** is used in antidiabetic treatments because of its excellent glycemic control. It has been approved for the treatment of diabetic polyneuropathy in Germany.[3] Moreover, it has great therapeutic potential in managing numerous clinical conditions, including anti-cancer, anti-HIV, anti-inflammatory, and anti-AD treatments. Some reviews have summarized the biological activities and therapeutic potentials of **ALA**.[4]

ALA is composed of three main structural units (Fig. 1): a disulfide five-membered ring (red), a C2–C5 linkage (black),

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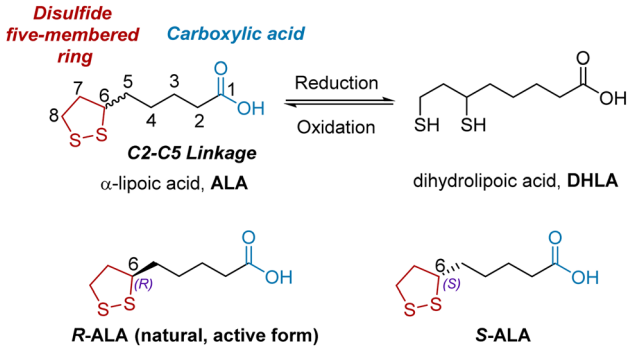

Fig. 1 The chemical structure of racemic ALA, optical isomers of ALA, and its active metabolite DHLA.

and carboxylic acid (blue). **ALA** has a single chiral center at C6, resulting in two enantiomeric forms: ***R***- and ***S*-ALA**.[5] Notably, **ALA** exists in nature as the *R* enantiomer, which is the biologically active form. However, **ALA** is often marketed in its racemic form because ***S*-ALA** shows no significant biological side effects. The reduced form of **ALA** is an active metabolite, called dihydrolipoic acid (**DHLA**), which can be converted to **ALA** under various oxidative conditions such as $FeCl_3/O_2$ and I_2/KI.

The high medicinal importance of **ALA**, especially ***R*-ALA**,[6] has attracted great attention from synthetic chemists in industrial and academic fields. The global **ALA** market size was valued at USD 106.89 million in 2022 and is expected to expand at a CAGR of 3.86 percent during the forecast period, reaching USD 134.15 million by 2028. The extensive demand for **ALA** in global markets 3000–3500 tons per year necessitates the development of efficient synthetic approaches. Over the past 70 years, numerous synthetic approaches have been patented and reported. To the best of our knowledge, only a few reviews have summarized **ALA**'s synthesis approaches. In 1990, Yadav *et al.* published an excellent review of synthetic studies on **ALA**.[7]

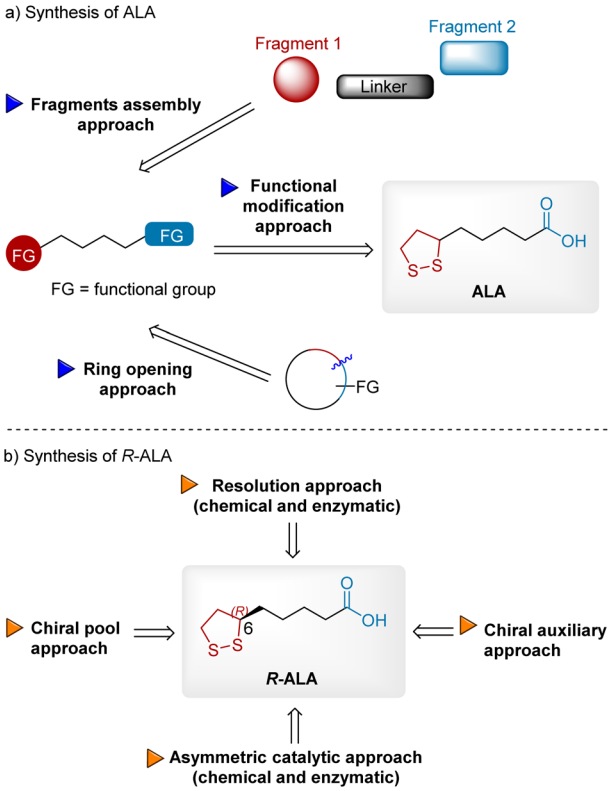

Fig. 2 Synthetic strategies for synthesizing ALA and *R*-ALA. (a) Synthesis of ALA; (b) synthesis of *R*-ALA.

Schaefer *et al.* published another review in 2019 but it was relatively brief.[8] In this review, we provide comprehensive advances in the fields of **ALA** and ***R*-ALA** synthesis to inspire the scientific community to develop innovations (Fig. 2). First, the synthesis of **ALA** is summarized and discussed according to three different approaches: functional modification, fragment

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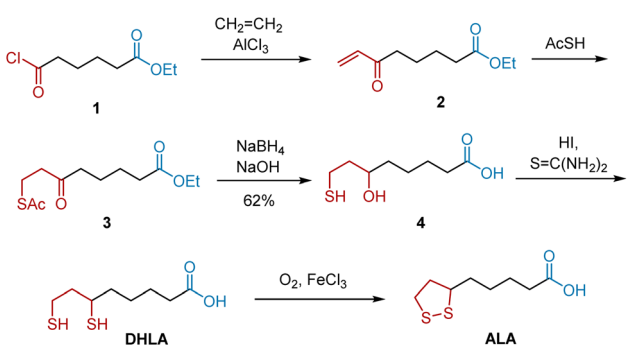
assembly, and ring opening (Fig. 2a). In the functional modification approach, **ALA** can be readily synthesized from precursors bearing inherent C2–C5 linkage and two terminal functional groups. Some of these precursors are commercially available, but some must be synthesized from simple building blocks or cyclic compounds, resulting in fragment assembly and ring-opening approaches. In the second part, stereoselective approaches to ***R*-ALA** are summarized and classified into four sections: chiral resolution (chemical and enzymatic), chiral pool, chiral auxiliary, and asymmetric catalysts (chemical and enzymatic) to introduce chirality into the molecule (Fig. 2b).

2. Synthesis of racemic ALA

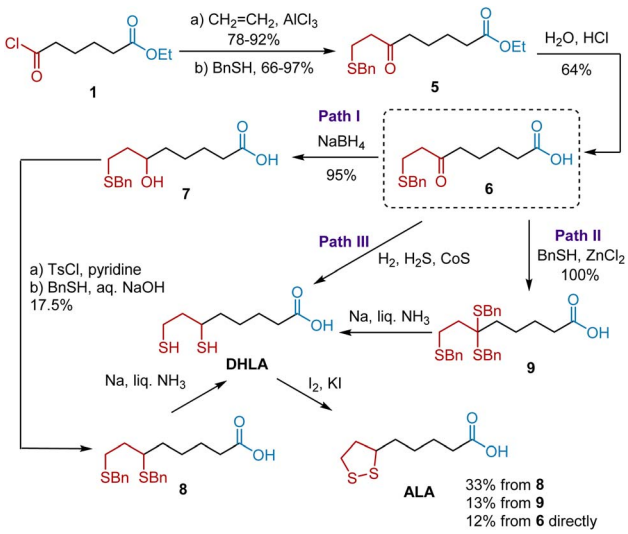
2.1 Functional modification

In 1952, Bullock *et al.* briefly reported the first total synthesis of racemic **ALA**.[9] Later, they published the full article describing their synthetic approach which confirmed the structure of **ALA**.,[10] Dicarbonyl compounds have great potential to be transformed into five-membered disulfide rings and carboxylic acids, which are key moieties in **ALA**. As shown in Scheme 1, compound **1**, ethyl 6-chloro-6-oxohexanoate was selected as the starting material, because its inherent structure could be transformed into that of **ALA** through functional modifications. Initially, the Lewis acid-catalyzed insertion of ethene, followed by the spontaneous elimination of hydrogen chloride, afforded unsaturated ketone **2**. Treatment of **2** with thiolacetic acid afforded compound **3**, whose ketone group was reduced to a tertiary alcohol group. Subsequent hydrolysis delivered compound **4**, which reacted with excess thiourea and hydriodic acid to yield **DHLA**. Finally, **DHLA** was oxidized smoothly in the presence of oxygen and ferric chloride to deliver **ALA**. The yields of most of these steps have not been previously reported.

Inspired by this pioneering work, Soper *et al.* expanded the first generation of synthetic approaches, especially enriching the paths from keto acids, such as compound **6**, to **ALA** (Scheme 2).[11] Keto acid **6** was synthesized from **1** according to Bullock's protocol. Having synthesized keto acid **6**, three divided paths were developed, providing fundamental benefits for the subsequent synthesis. Path I began with the $NaBH_4$-mediated reduction of **6** to yield hydroxy acid **7** with



Scheme 1 Bullock's synthesis of ALA.

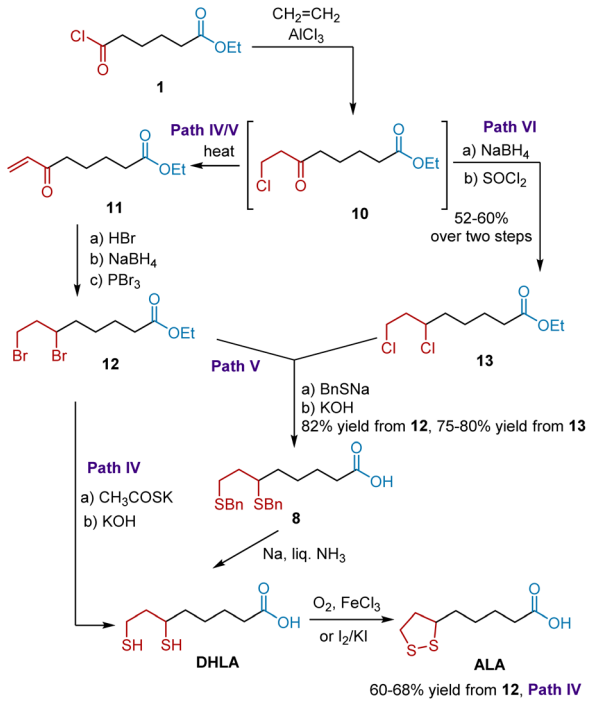


Scheme 2 Soper's synthesis of ALA.

a 95% yield. The esterification of **7** with tosyl, followed by treatment with benzyl mercaptan and a sodium hydroxide solution gave 6,8-dibenzylmercaptoöctanoic acid **8** in 17.5% yield over two steps. After deprotection, the **DHLA** was obtained. The subsequent oxidation of **DHLA** directly delivered **ALA**. Path II was developed using tribenzyl mercaptocaprylic acid **9** as the key intermediate, obtained from **6** in the presence of benzyl mercaptan and anhydrous zinc chloride. The treatment of **9** with liquid ammonia and solid sodium in anhydrous ether afforded **DHLA**, which was then oxidized to **ALA**. Alternatively, they developed a more efficient two-step synthetic route to **ALA** from **6** (path III). Hydrogenation of **6** using a sulfur/cobalt sulfide catalyst in the presence of H_2 followed by the oxidation of **DHLA** afforded **ALA** in 12% yield over two steps.

Since 6,8-dibenzylmercaptoöctanoic acid **8** and **DHLA** are useful intermediates for synthesizing **ALA**, an improved synthesis of **8** and **DHLA** was further developed by Reed *et al.* in 1955.[12] As shown in Scheme 3, the synthesis also commenced with acid chloride **1**, which was transformed into 8-chloro-6-oxoctanoöate **10**. Without purification, compound **10** was transformed into dibromo esters **12** and dichloro esters **13** as key intermediates. The former paths IV and V started from heating **10** to give α,β-unsaturated ketone **11**. The treatment of ketone **11** with anhydrous hydrogen bromide, followed by reduction and bromination, generated dibromo ester **12**, which was readily transformed into **DHLA** and **8**. In path IV, **ALA** was synthesized in 60–68% yields based on **DHLA** *via* thiolation and oxidation. In path V, dibromo ester **12** was converted to **8** in 82% yield by treatment with sodium benzyl mercaptide, followed by alkaline hydrolysis. **ALA** was synthesized in high yield according to Soper's protocol. In addition, path VI readily converted dichloro ester **13** to **ALA**. Later, these paths were widely used to synthesize **ALA** and were published in many patents[13] and in the literature.[14]

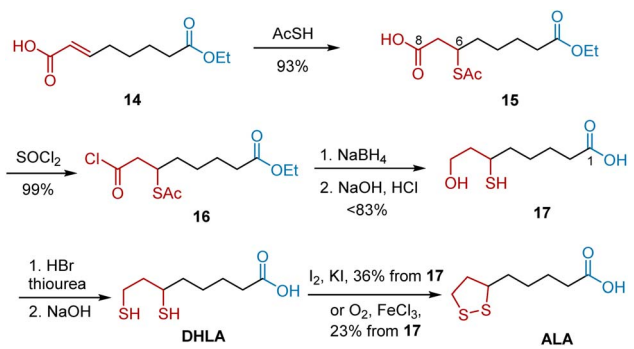
Walton *et al.* reported the synthesis of **ALA** starting from 7-carbethoxy-2-heptenoic acid **14** by introducing a thiol group at



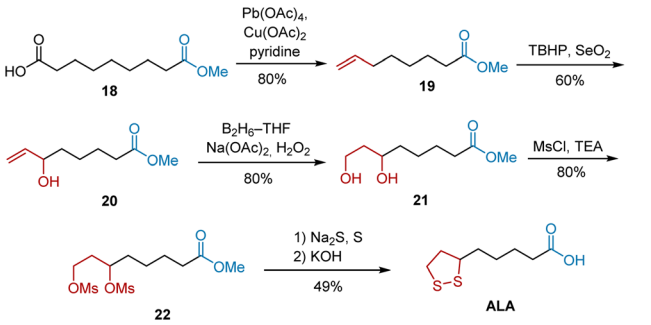
Scheme 3 Reed's synthesis of ALA.

C6, as shown in Scheme 4.[15] The addition of thiolacetic acid to **14** yielded carboxylic acid **15** in 93% yield, which was then converted into its acid chloride **16**. The following two-step reactions involving $NaBH_4$-mediated reduction and alkaline hydrolysis proceeded smoothly to generate 8-hydroxy-6-thioloctanoic acid **17**. The replacement of **17** followed by oxidation gave rise to **ALA**. ***R*-ALA** and ***S*-ALA** were synthesized using the corresponding chiral isomers of **15**.

In 1987, Rao *et al.* developed a highly regioselective allylic oxidation of olefins using *tert*-butyl hydroperoxide (TBHP) and selenium dioxide (SeO_2) to construct a secondary allylic alcohol, followed by the hydroboration–oxidation of the terminal double bond to construct a 1,3-diol system. By using this method, as illustrated in Scheme 5.[16] Olefin methyl 7-octenoate **19** was synthesized from azelaic acid **18** *via* decarboxylative elimination using $Pb(OAc)_4/Cu(OAc)_2$/pyridine. In the presence of selenium dioxide and *tert*-butyl hydroperoxide, the regioselective allylic



Scheme 4 Walton's synthesis of ALA.



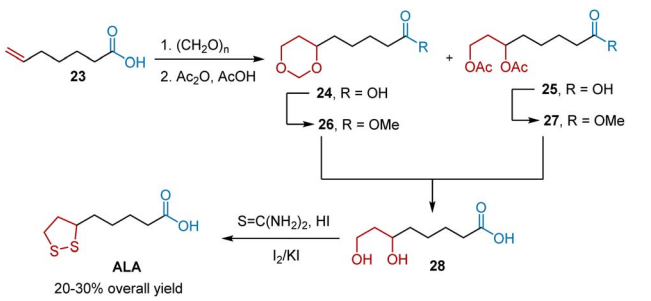
Scheme 5 Rao's synthesis of ALA.

oxidation of **19** afforded secondary allylic alcohol **20** in 60% yield, which was treated with a borane–tetrahydrofuran complex to yield **21**. Finally, the conversion of **21** to dimesylate **22**, reaction with Na_2S/S, and hydrolysis of the ester completed the synthesis of **ALA**.

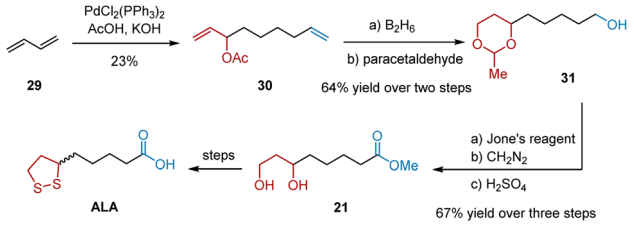
The Prins reaction is an acid-catalyzed condensation of olefins with aldehydes to produce 1,3-diols, 1,3-dioxanes, or unsaturated alcohols. Among them, 1,3-diols and 1,3-dioxanes can be readily transformed into five-membered disulfide rings. In 1956, Braude *et al.* reported a route to **ALA** from hept-6-enoic acid **23** using the Prins reaction as the key step (Scheme 6).[17] The Prins reaction of **23** generated a mixture of 1,3-dioxane **24** and acyl-protected 1,3-diol **25** in a ratio of 5 : 1. The conversions of Prins reaction products **24** and **25** into methyl esters **26** and **27** were performed to avoid lactonization during the synthesis of diol **28**. Diol **28** was transformed into **ALA** as previously described. The authors reported that the overall **ALA** yield was 20–30%.

2.2 Fragments assembly

In 1978, Tsuji *et al.* reported a synthetic route to **ALA** using butadiene telomer **1** as the starting material (Scheme 7).[18] Telomer **30**, bearing the eight-carbon chain necessary for **ALA** synthesis, was synthesized from **29** using $PdCl_2(PPh_3)_2$/AcOH/KOH. Hydroboration of the two terminal double bonds and subsequent protection yielded **31** in 64% yield over two steps. Oxidation of the unprotected terminal alcohol was carried out using the Jones reagent, giving carboxylic acid. Next, it was methylated with diazomethane to prevent lactone formation. After deprotection, 1,3-diol **21** was obtained in 67% yield in



Scheme 6 Braude's synthesis of ALA.

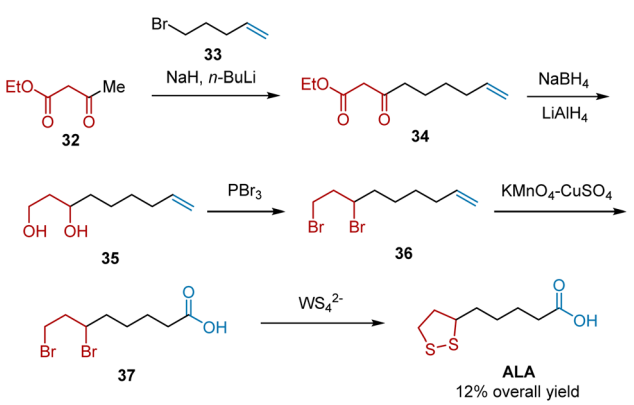


Scheme 7 Tsuji's synthesis of ALA.

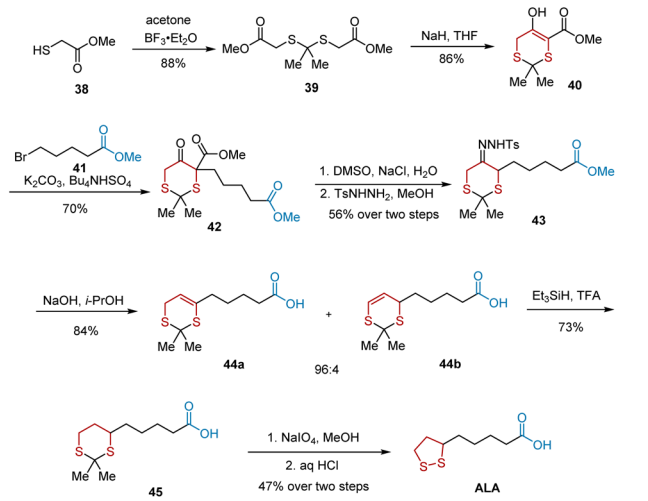
three steps. 1,3-Diol **21** can be transformed into **ALA**, as described in a previously published protocol.

In 1992, Chandrasekaran *et al.* developed a methodology for the construction of cyclic disulfides from alkyl halides using tetrathiometalates (MS_4^{2-}) as sulfur transfer reagents. Subsequently, by employing this reaction as the key step, **ALA** was synthesized (Scheme 8).[19] The synthesis began with the alkylation of ethylacetoacetate **32** and 5-bromopent-1-ene **33**. The obtained intermediate **34** was reduced stepwise to 1,3-diol **35**, whose alcohol groups were brominated to yield 6,8-dibromooctanoic acid **36**. Oxidative cleavage of the terminal double bond in the presence of $KMnO_4$ afforded compound **37** as a precursor to cyclic disulfides. Subsequently, the MS_4^{2-}-mediated sulfur transfer reaction of **37** occurred, generating **ALA** in 12% overall yield.

In 2005, Chavan *et al.* developed the regioselective decomposition of tosylhydrazones to form olefins and utilized this method to accomplish the total synthesis of **ALA**.[20] As illustrated in Scheme 9, the synthesis began with acetonide protection of methyl thioglycolate **38** to give 88% yield of diester **39**, which was subjected to Dieckmann condensation to afford cyclic compound **40** in 86% yield. The *C*-alkylation of **40** was carried out using K_2CO_3 in the presence of Bu_4NHSO_4 as a phase transfer catalyst, leading to the formation of *C*-alkylated product **42** in 70% yield. A two-step sequence involving decarboxylation and tosylhydrazone formation resulted in tosylhydrazone **43**. Using NaOH in isopropyl alcohol, tosylhydrazone **43** was decomposed to olefins **44a** and **44b** with a regioselectivity of 96 : 4 in 84% yield. After the reduction of the mixture of olefins **44a** and **44b**, dithiane acid



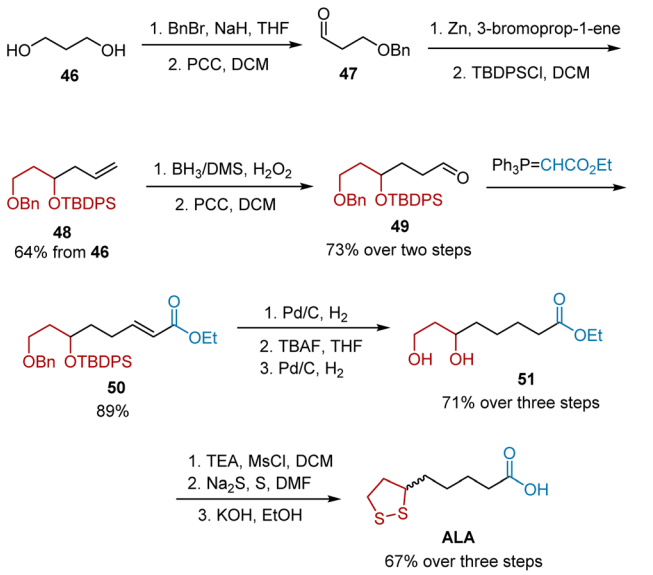
Scheme 8 Chandrasekaran's synthesis of ALA.



Scheme 9 Chavan's synthesis of ALA.

45 was obtained. Subsequent oxidation and treatment with aqueous HCl in benzene culminated in the production of **ALA** in 47% yield.

In 2015, Purude *et al.* reported their efforts to synthesize either racemic **ALA** or its chiral isomers, ***R*-** and ***S*-ALA** (Scheme 10).[21] Selective benzyl protection of commercially available diol **46** and subsequent oxidation afforded aldehyde **47**, which upon treatment with allyl bromide in the presence of Zn, followed by TBDPS protection, yielded terminal alkene **48**. Oxidation and the Wittig reaction gave unsaturated ester **50**, which possesses fundamental functional groups to afford **ALA**. Ester **50** was converted into diol **51** through a three-step sequence, including selective hydrogenation of the double bond and deprotection. Racemic **ALA** was obtained under the known protocol from diol **51**. Using this strategy, the synthesis of ***R*-ALA** and ***S*-ALA** was also accomplished using this strategy.



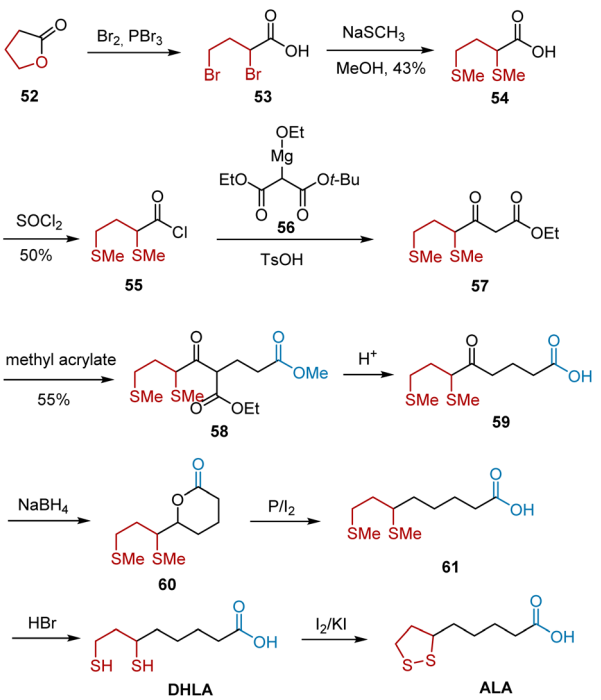
Scheme 10 Purude's synthesis of ALA.

2.3 Ring opening

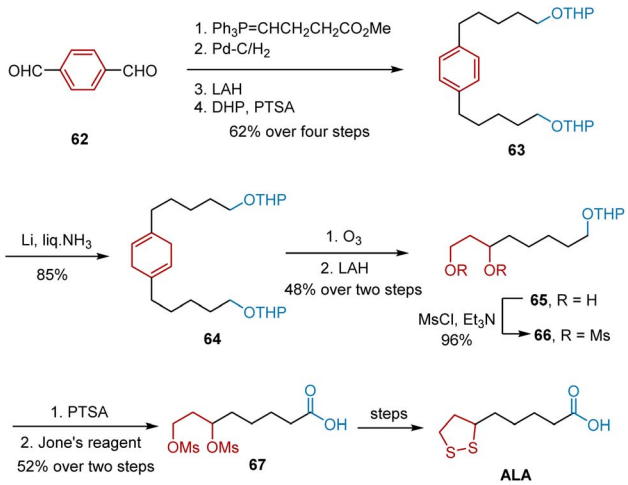
Some cyclic compounds are readily transformed into 1,3-diol, which is a precursor for the formation of five-membered disulfide rings. Thus, efforts were made to synthesize **ALA** from cyclic compounds, followed by introducing the C2–C5 linkage and the carboxylic acid group at any stage of the synthesis.

In 1955, Wagner *et al.* reported a synthesis of **ALA** by adopting γ-butyrolactone **52** as the starting material (Scheme 11).[22] The first sulfur-containing intermediate **54** was synthesized from lactone **52**, which was then converted into its acid chloride **55**. Acylation, elimination of the *t*-butyl group, and decarboxylation in the presence of a catalytic amount of TsOH transformed **55** to **57**, followed by condensation with methyl acrylate. Hydrolysis and decarboxylation of **57** under acidic conditions generated keto acid **59**. The reduction of **59** to **61** was accomplished in two steps. Finally, demethylation and subsequent oxidation occurred, leading to **ALA**. The yields of most of these steps have not been reported in the literature.

Another synthetic work was reported by Rao *et al.* in 1995 using Birch reduction as the key step (Scheme 12).[23] The synthesis commenced with a Wittig reaction of terephthalaldehyde **62** and the ylide obtained from (3-carbomethoxy) propyl triphenylphosphonium bromide to yield an olefinic intermediate. Subsequent Pd–C-mediated hydrogenation, LAH-mediated reduction, and protection of the alcohols with tetrahydropyran gave diTHP ether **63** in 62% yield. The birch reduction of **63** afforded 1,4-diene **64** in 85% yield. Ozonolysis of **64** and quenching of the ozonide with LAH afforded **65** in 48% yield over two steps. The conversion of **65** to its dimesylate **66** was accomplished using triethylamine and mesyl chloride.



Scheme 11 Wagner's synthesis of **ALA**.

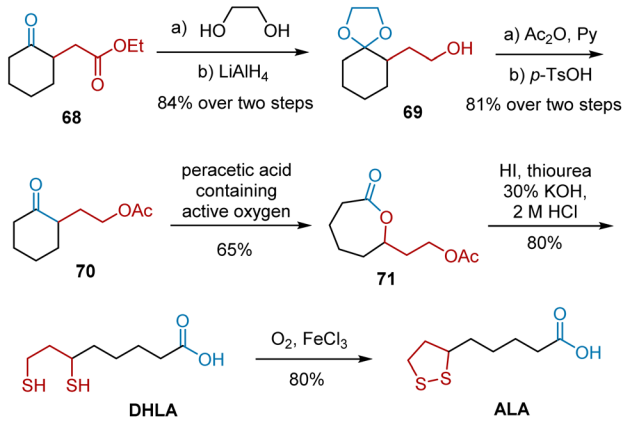


Scheme 12 Rao's synthesis of **ALA**.

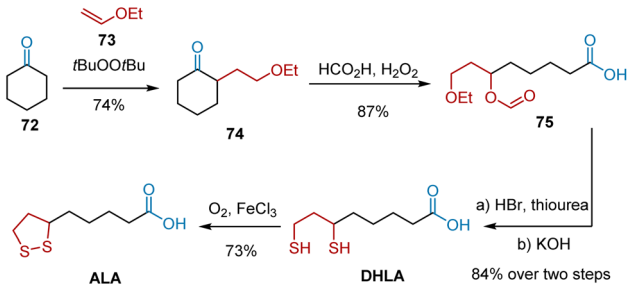
Deprotection of the THP group and oxidation by Jones resulted in the formation of a carboxylic acid group in **ALA**, yielding **67** in 52% yield. In the last stage, **ALA** was synthesized according to a known procedure.

In 1957, Segre *et al.* selected ethyl cyclohexanone-2-acetate **68** as a precursor for **ALA** synthesis (Scheme 13).[24] The synthesis featured the Baeyer–Villiger oxidation as the key step. A series of protection, reduction, and deprotection transformed **68** into ketone **70**, which was then treated with a solution of peracetic acid (containing active oxygen) to produce seven-membered cyclolactone **71** in 65% yield. The treatment of lactone **71** with thiourea in a strong mineral acid *via* alkaline hydrolysis of the isothiuronium salt easily yielded **DHLA**, which afforded the desired **ALA** after oxidation.

In 1999, Paust *et al.* followed the Baeyer–Villiger strategy to develop an optimized synthesis.[25] As shown in Scheme 14, initially, the key intermediate **74** was synthesized in one stage from the base chemicals, cyclohexanone **72** and vinyl ethyl ether **73**, catalyzed by di-*tert*-butyl peroxide. The key Baeyer–Villiger oxidation was performed using performic acid generated *in situ* from formic acid and 30% aqueous hydrogen peroxide. 8-



Scheme 13 Segre's synthesis of **ALA**.



Scheme 14 Paust's synthesis of ALA.

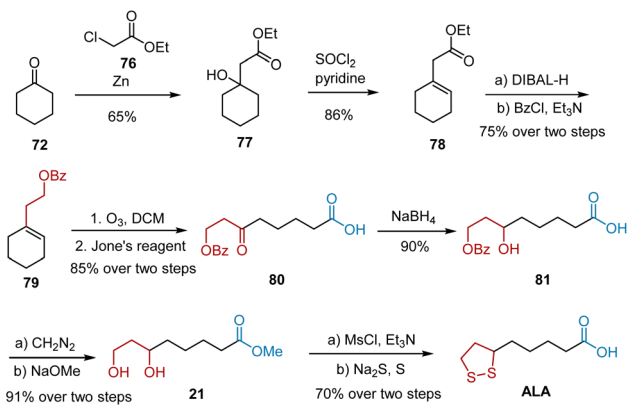
Ethoxy-6-formyloxyoctanoic acid **75** was obtained as the main product in 87% yield. To introduce sulfur at C6 and C8, **75** was heated with 62% hydrohalic acid in the presence of thiourea and hydrolyzed to form **DHLA**, which was oxidized to **ALA** according to an established protocol. This route delivered **ALA** from cyclohexanone **72** at an overall yield of 40%.

Chavan *et al.* have reported the synthesis of **ALA** *via* a modified Reformatsky reaction (Scheme 15).[26] The synthesis commenced with the Reformatsky reaction of cyclohexanone **72** with ethyl chloroacetate **76** in the presence of activated Zn powder, followed by the elimination of the hydroxyl group to give alkene **78**. DIBAL-H-mediated reduction and subsequent protection yielded compound **79**, which was bubbled through O_3 gas, followed by Jones oxidation to generate carboxylic acid **80**. Under $NaBH_4$-mediated reduction conditions, the tertiary alcohol **81** was obtained, which was esterified and treated with sodium methoxide to produce diol **21**. Racemic **ALA** was obtained from diol **21** based on commonly used procedures.

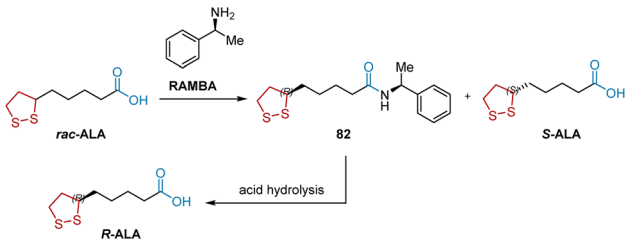
3. Synthesis of *R*-ALA

3.1 Chemical resolution

Currently, the synthesis of ***R*-ALA** on an industrial scale depends on the direct chemical resolution of its racemic mixture, **ALA**, using *R*-(+)-methylbenzylamine (**RAMBA**) as the chiral resolution reagent (Scheme 16).[27] In the initial resolution step, **RAMBA** was added to the racemic **ALA** solution to form **82**, which was separated by crystallization. After acid hydrolysis, ***R*-ALA** was obtained.



Scheme 15 Chavan's synthesis of ALA.

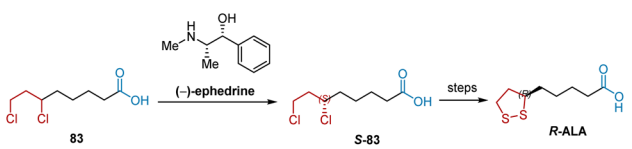


Scheme 16 RAMBA-mediated resolution of ALA to synthesize *R*-ALA.

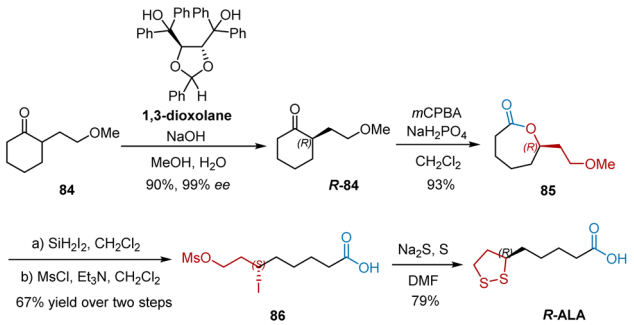
Alternatively, the resolution of racemic intermediates *via* a synthetic route is another method for synthesizing ***R*-ALA**. As shown in Scheme 17, ***S*-83**, a key intermediate for synthesizing ***R*-ALA** can be obtained by the optical resolution of racemic 6,8-dichlorooctanoic acid (DCA) **83** with (−)-ephedrine.[14,28]

The aforementioned studies mainly involved esterification of the carboxylic group located four carbon atoms away from the stereogenic center, which remains a difficult task. In 2010, Kaku *et al.* developed the thermodynamically controlled deracemization of racemic monosubstituted cycloalkanones and utilized this methodology to accomplish the synthesis of ***R*-ALA** (Scheme 18).[29] Using chiral 1,3-dioxolane as the chiral host molecule with sodium hydroxide in aqueous methanol, cycloalkanone **84** was converted into its *R*-isomers ***R*-84** with 99% ee and 90% yield. ***R*-84** was subjected to Baeyer–Villiger oxidation using 3-chloroperoxybenzoic acid and anhydrous sodium dihydrogen phosphate to afford lactone **85** in 93% yield. Ring-opening iodination of **85** and subsequent mesylation afforded **86**, which was transformed into ***R*-ALA** in the presence of sodium sulfide and sulfur in DMF.

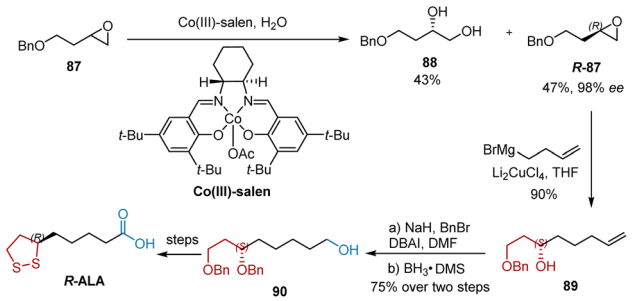
Kinetic resolution is a widely used method that provides easy access to catalysts, separation and recovery of catalysts, high enantiomeric excess, and high practical feasibility. Jacobsen's hydrolytic kinetic resolution (HKR) method uses a readily accessible Co-based chiral salen complex as the catalyst and is an efficient approach for the preparation of highly enantioselective chiral epoxides and diols with high optical purity in excellent yields. In 2006, Bose utilized the HKR of **1** in the synthesis of ***R*-ALA**.[30] As shown in Scheme 19, racemic epoxide **87** was treated with (*R*,*R*)-salen–Co(III)–OAc complex and H_2O at ambient temperature to afford a mixture of 1,2-diol **88** in 43% yield and epoxide ***R*-87** in 47% yield and 98% ee. The regiospecific opening of epoxide ***R*-87** with a Grignard reagent delivered chiral alcohol **89** in 90% yield. Subsequent benzyl protection and borohydride oxidation transformed **89** to **90**, which was used to synthesize ***R*-ALA** by conventionally reported



Scheme 17 (−)-Ephedrine-mediated resolution of DCA to synthesize *R*-ALA.



Scheme 18 Kaku's synthesis of *R*-ALA.



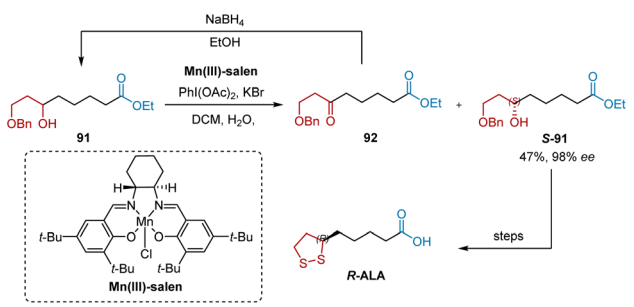
Scheme 19 Bose's synthesis of *R*-ALA.

transformations including oxidation, deprotection, and mesylation.

Mn(III)-salen is the most widely used chiral catalyst in the oxidative resolution of secondary alcohols. In 2015, Kalkote and Chavan reported the use of Mn(III)-salen-catalyzed oxidative kinetic resolution as the key step in obtaining enantiomerically pure ***R*- and *S*-ALA** (Scheme 20).[21] The oxidative kinetic resolution of racemic **91** was performed on Mn(III)-salen to produce ***S*-91** in 98% ee and 47% yield. The construction of ***R*-ALA** was achieved under the aforementioned conditions.

3.2 Enzymatic resolution

Enzyme-catalyzed organic reactions have provided great impetus for organic synthesis owing to several advantages, including mild and environmentally friendly reaction conditions and remarkable chemo-, regio-, and stereoselectivity.

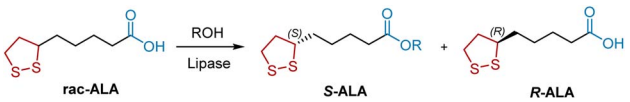


Scheme 20 Kalkote and Chavan's synthesis of *R*-ALA.

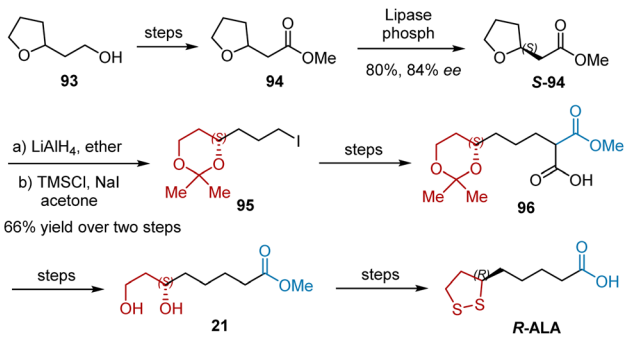
Lipases are routinely used for the treatment of racemic alcohols and carboxylic acids. ***R*-ALA** was synthesized through the resolution of racemic **ALA** by enzymatic esterification of the carboxylic group, which consists of four carbon atoms away from the stereogenic center (Scheme 21). In 1997, Fadnavis *et al.* used the lipase from *Candida rugosa* (E.C.3.1.1.3) to catalyze the enantioselective esterification of racemic **ALA** with aliphatic alcohols in hexane.[31] The enzyme shows enantioselectivity towards the ***S*-ALA** (72% ee). In 2009, Yan *et al.* reported that the lipase from *Aspergillus oryzae* WZ007 is another potential candidate for enzymatic resolution of **ALA**.[32] In 2015, Liu *et al.* combined an ionic liquid co-lyophilized lipase with microwave irradiation to improve enzyme performance in the enantioselective esterification of **ALA**.[33] Under optimal reaction conditions, the ionic liquid co-lyophilized lipase exhibited satisfactory enzyme performance (*E* value, 41.2; enzyme activity, 178.1 μmol h^{-1} mg^{-1}).

Enzymatic resolution involving a remote chiral center is a difficult task. The enzymatic resolution of racemic precursors for ***R*-ALA** is an alternative route. In 1996, Iyengar *et al.* reported a synthetic sequence for the preparation of **21**, the precursor of ***R*-ALA**, using the kinetic resolution of **94** as the key step (Scheme 22).[34] Kinetic resolution of racemic compound **94** with lipase from *Candida cylindracea* afforded ***S*-94** with good enantiomeric purity and good yield (84% ee, 80% yield). Lithium aluminum hydride-mediated reduction and regioselective opening with iodotrimethylsilane gave rise to **95**, the desired six-carbon synthon with a protected diol system. The alkylation of benzyl-methyl malonate with **95** and subsequent debenzylation generated **96**, which was converted into a diol **21** precursor *via* decarboxylation, and deprotection.

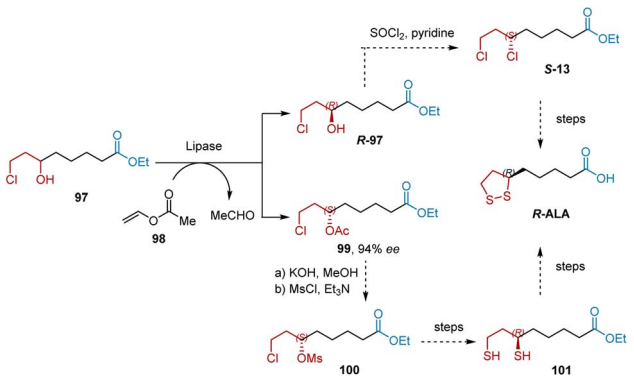
In 2014, Zhou *et al.* developed a lipase-catalyzed transacylation process to resolve ethyl 8-chloro-6-hydroxy octanoate **97** and produced two important chiral precursors, ***R*-97** and **99**, for the synthesis of ***R*-ALA** (Scheme 23).[35] After systematically screening, the optimized condition of optical resolution was



Scheme 21 Lipase-mediated resolution of ALA.



Scheme 22 Iyengar's synthesis of *R*-ALA.



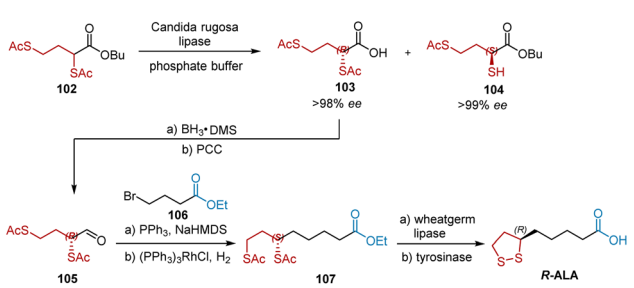
Scheme 23 Zhou's synthesis of *R*-ALA.

determined, resulting in Novozym 435 as catalyst, vinyl acetate as acyl donor, DIPE as solvent. The space-time yield of **99** was 38 g L^{-1} d^{-1} with 94% ee. According to a known procedure, ***R*-ALA** can be synthesized from ***R*-97** or **99**.

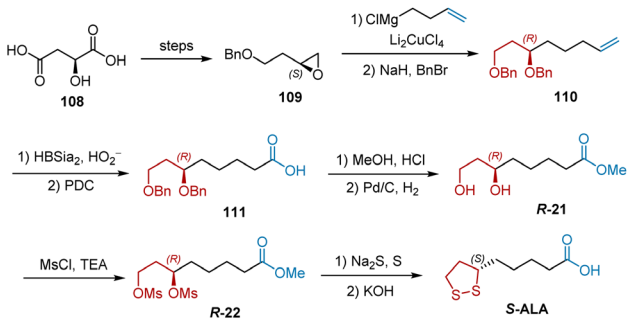
In 1998, Fadnavis *et al.* developed the enantioselective synthesis of pure *R*-2,4-dithioacetyl butyric acid **103** (ee > 98%) and *S*-butyl 2-thio-4-thioacetyl butyrate **104** (ee > 99%) by hydrolysis of the *n*-butyl ester of 2,4-dithioacetyl butanoic acid **102** using the native lipase of *Candida rugosa* (Scheme 24).[36] ***R*-ALA** was synthesized using **103** as the chiral building block. The reduction of **103** with BH_3·DMS provided an alcohol intermediate, which was oxidized by PCC to aldehyde **105**. The subsequent Wittig reaction and hydrogenation afforded ethyl ester **107**, whose ethyl and thioacetyl groups were removed by hydrolysis with the non-enantiospecific enzyme wheat germ lipase in phosphate buffer. ***R*-ALA** was obtained by treating the hydrolyzed product with the oxidative enzyme, mushroom tyrosinase, in the same reaction vessel. The yield of each step is not shown in this study.

3.3 Chiral pool

In 1983, Golding *et al.* selected *S*-2-hydroxysuccinic acid **108** as the starting material to synthesize ***S*-ALA** (Scheme 25).[5] Epoxide **109** was obtained according to a previously published procedure. Treatment of epoxide **109** with 3-butenylmagnesium bromide and Li_2CuCl_4 gave the terminal alkene **110** after protection. Carboxylic acid **111** was generated by double-bond cleavage and PDC-mediated oxidation and was then converted into methyl ester ***R*-21** by esterification and deprotection. The



Scheme 24 Fadnavi's synthesis of *R*-ALA.

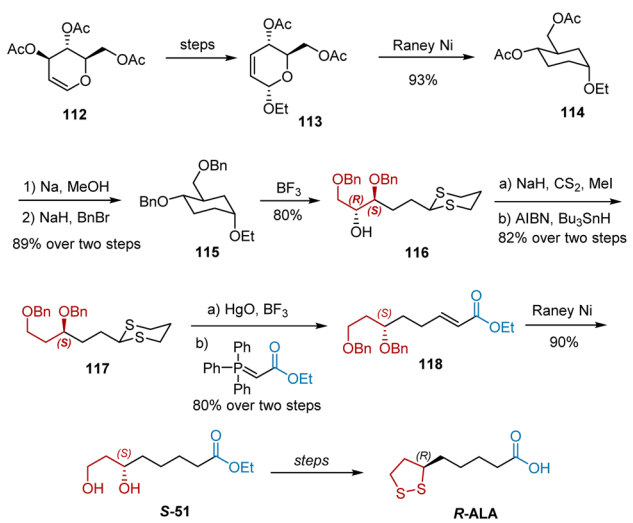


Scheme 25 Golding's synthesis of *S*-ALA.

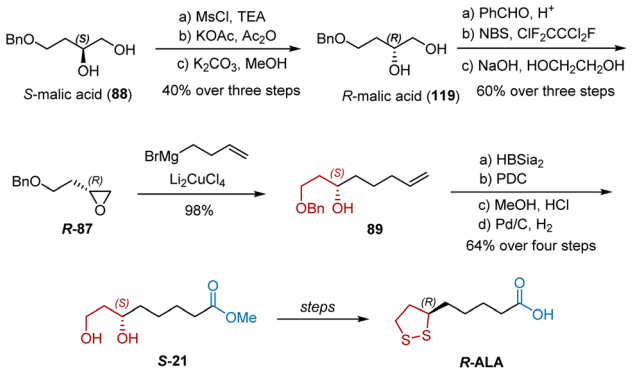
treatment of ***R*-21** with MsCl and Et_3N afforded dimethanesulfonate ***R*-22**. The final two-step transformation of ***R*-22** completed the synthesis of ***S*-ALA**. The yield of each step is not shown in this study.

Rao *et al.* reported an enantiospecific synthesis of natural ***R*-ALA** in 13 steps (Scheme 26).[37] 3,4,6-Tri-*O*-acetyl-D-glucal **112**, a chiral building block, was selected as the starting material and converted into compound **113**, which was smoothly hydrogenated by treatment with RANEY® to give compound **114**. The two acyl groups of **114** were replaced with Bn groups, yielding compound **115**. The treatment of **115** with propanedithiol–boron trifluoride etherate–dichloromethane at room temperature afforded 80% of the dithiane compound **116**. Barton–McCombie deoxygenation of **116** was performed to remove the hydroxyl group. With the compound **117** in hand, hydrolysis of **117** with mercuric oxide–boron trifluoride etherate in aqueous acetone yielded the desired aldehyde, which was converted into unsaturated ester **118** *via* the Wittig reaction. Hydrogenation of **118** over excess RANEY® reduced the double bond and debenzylation gave 90% diol ***S*-51**, which was transformed into ***R*-ALA** following a known strategy.

In 1988, Golding *et al.* revealed their synthesis of ***R*-ALA** and ***S*-ALA** from *S*-malic acid **88**, a member of the "chiral pool"



Scheme 26 Rao's asymmetric synthesis of *R*-ALA.

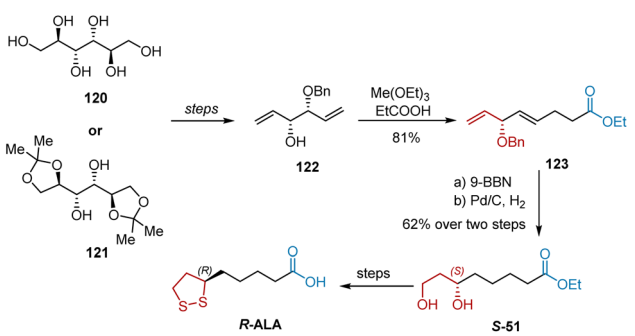


Scheme 27 Golding' synthesis of *R*-ALA.

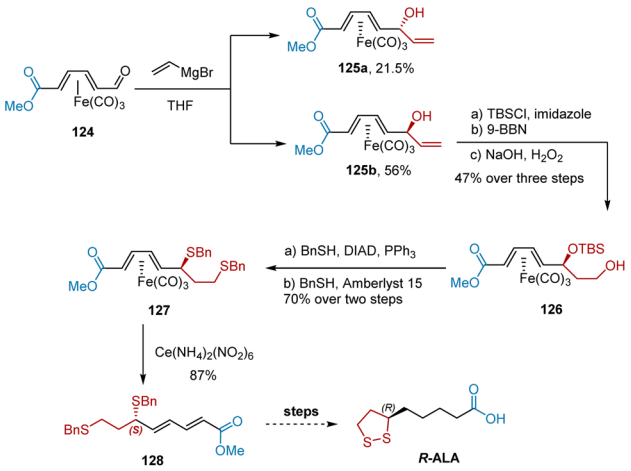
(Scheme 27).[38] Notably, ***R*-ALA** could be directly synthesized from *R*-malic acid **119**. They chose **88** as the starting material because **119** is relatively expensive. The total synthesis commenced with the stereospecific conversion of **88** to **119** using Takano's methodology. Compound **119** was converted into epoxide ***R*-87**, which was allowed to react with the Grignard reagent to give secondary alcohol **89**. The following reaction sequences, including the benzylation of the secondary hydroxy group, hydroboration of the vinyl group, oxidation of the primary hydroxy group, esterification, and hydrogenolysis of the benzyl groups, transformed **89** into ***S*-21** successively. ***R*-ALA** was obtained *via* the known transformations of ***S*-21**. ***S*-ALA** was synthesized using a similar route.

In 1989, Yadav *et al.* reported the synthesis of ***R*-ALA** from D-mannitol **120** and its derivatives **121**, with diene **122** serving as a common intermediate (Scheme 28).[39] With diene **122** in hand, the Claisen ester rearrangement with excess triethyl orthoacetate and a catalytic amount of propionic acid afforded diene ester **123** in 81% yield. Selective hydroboration–oxidation of the terminal double bond in **123** was accomplished with 9-BBN to afford an intermediate, whose hydrogenation proceeded smoothly to give diol ***S*-51**. Finally, the transformation of ***S*-51** into ***R*-ALA** was performed using a previously described procedure.

Tricarbonyl(diene)iron complexes are chiral and have various applications in the asymmetric synthesis of organic molecules. In 1998, Grée *et al.* utilized tricarbonyl(diene)iron



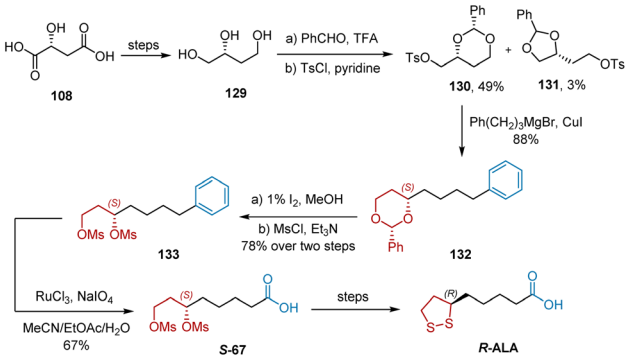
Scheme 28 Yadav's synthesis of *R*-ALA.



Scheme 29 Grée's synthesis of *R*-ALA.

complex **125b** for the formal synthesis of ***R*-ALA**, as shown in Scheme 29.[40] Complex **125b** was obtained in an optically active form after Grignard addition-mediated resolution of **124**. Complex **125b** was used for the subsequent transformation. Subsequent protection of the hydroxyl group and hydroboration–oxidation afforded alcohol **126**. A two-step transformation was performed to obtain compound **127** in high yield. Finally, oxidative decomplexation with ceric ammonium nitrate produced diene **128** in 87% yield, which could be used to deliver ***R*-ALA**.

In 2009, Huang *et al.* developed a synthetic approach to ***R*-ALA** starting from **108** (Scheme 30).[41] The synthesis began with the known compound **129**, which is easily available from **108**. In the presence of trifluoroacetic acid, treatment of **129** with benzaldehyde, followed by Ts-protection, afforded compounds **130** and **131**, which could be readily separated by recrystallization. The subsequent coupling of tosylate **130** with phenylpropyl magnesium bromide in the presence of a catalytic amount of CuI afforded chain elongation product **132**. The acetal groups of dioxane **132** were removed using I_2/MeOH. Bismesylation yielded bismesylate **133**. The oxidative cleavage of the phenyl group into a carboxylic acid group using the developed Sharpless conditions ($RuCl_3$/$NaIO_4$/EtOAc/MeCN/H_2O) furnished ***S*-67** in



Scheme 30 Huang' synthesis of *R*-ALA.

67% yield. Finally, ***R*-ALA** was synthesized using the known transformations.

In 2015, Chavan *et al.* reported the synthesis of ***S*-ALA** from D-glucose (Scheme 31).[42] The key reactions involved in this synthesis were splitting, iodination, and hydrogenation The synthesis commenced with the production of hydroxy aldehyde **135** from D-glucose **134**, according to an established protocol. The following 4-carbon Wittig reaction of hydroxy aldehyde **135** took place to yield an inseparable mixture of *cis* and *trans* isomers, whose double bonds were reduced under the conditions of $Pd/C/H_2$/MeOH to give hydroxyl ester **136** in 84% yield over two steps. The chiral hydroxyl group in **136** was removed to provide **137** *via* a two-step transformation involving iodination and reductive deiodination. Subsequently, the acetal group in ester **137** was deprotected using PTSA in methanol to obtain 1,3-diol ***S*-21**, which was then transformed into ***S*-ALA** according to previously reported steps.

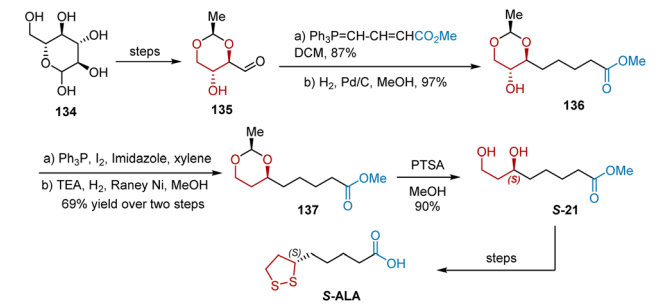
3.4 Chiral auxiliary

In 1984, Johnson and Elliott reported the use of *R*,*R*-2,4-pentanediol (PTSA) as a chiral auxiliary in a $TiCl_4$-catalyzed aldol-type reaction to synthesize aldol esters in excellent yields and high diastereoselectivities.[43] One year later, they extended this work by employing ketene acetal **141** as the nucleophile, and utilized the developed methodology as the key step in the synthesis ***R*-ALA** (Scheme 32).[44] The initial transformation began with the synthesis of aldehyde **139** from cyclohexene **138**. Acetalization of aldehyde **139** with PTSA as the chiral auxiliary proceeded smoothly to give **140** in 84% yield. $TiCl_4$ mediated coupling of **140** with ketene acetal **141** afforded **142** in excellent yield and diastereoselectivity (93% yield, 98 : 2 dr). The following Jone's oxidation and β-elimination afforded chiral alcohol **143** in 95% yield over two steps, which was reduced to diol **144** by $BH_3 \cdot THF$ complex. Following the known procedure, ***R*-ALA** was harvested.

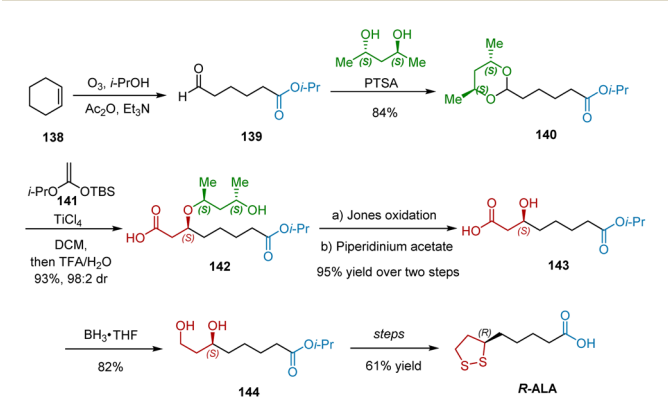
In 1987, a short and highly stereospecific synthesis of ***S*-ALA** using menthone as a recyclable chiral auxiliary was presented by Menon *et al.* (Scheme 33).[45] Dithiane **145**, the starting material, served as the chiral template that controlled the regiochemistry of the subsequent oxidation to provide **146** as a single regioisomer in 80% yield. The stereoselective alkylation of **146** with 5-bromovaleric acid **147** in the presence of lithium diisopropylamide as a base in THF resulted in the carboxylic acid derivative **148**, which was hydrolyzed in aqueous HCl to yield ***S*-ALA**.

3.5 Chemical asymmetric catalysis

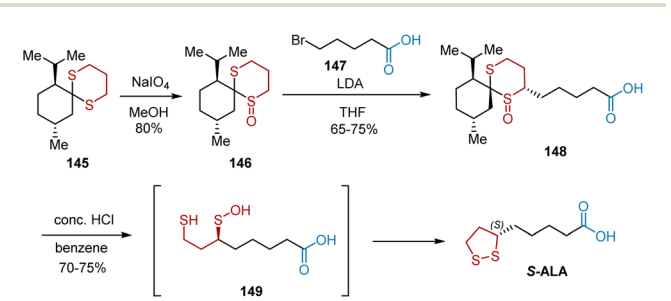
In 1986, Sutherland *et al.* reported the enantioselective synthesis of ***R*-ALA** from achiral precursor **150** using Sharpless asymmetric epoxidation as the key step (Scheme 34).[46] Allylic alcohol **150** was synthesized by alkylation of the lithio-dianion of propargyl alcohol by dissolving the metal reduction of the resultant disubstituted acetylene *in situ*. The sharpless asymmetric epoxidation of **150** was carried out smoothly using Ti(Oi-Pr)$_4$/(+)-DIPT/*t*BuOOH, giving epoxy alcohol **151** in 82% yield and 96% ee. The reduction of **151** with Red-Al resulted in the selective formation of diol ***S*-35** in 89% yield. Under conditions using MsCl/Et_3N, ***S*-35** was sulfonated. Ruthenium tetroxide oxidation of the terminal double bond formed carboxylic acid ***S*-67** in 75% yield over two steps. Finally, the disulfide displacement of the methanesulfonate groups of the potassium salt of ***S*-67** afforded ***R*-ALA** in 52% yield.



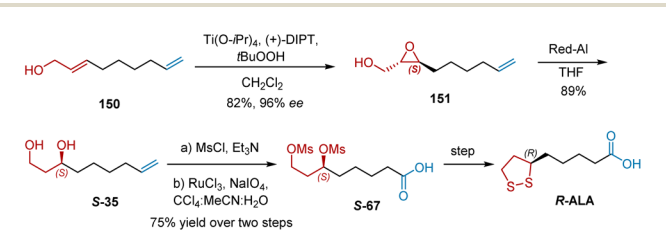
Scheme 31 Chavan' synthesis of *S*-ALA.



Scheme 32 Johnson and Elliott' synthesis of *R*-ALA.



Scheme 33 Menon's synthesis of *S*-ALA.

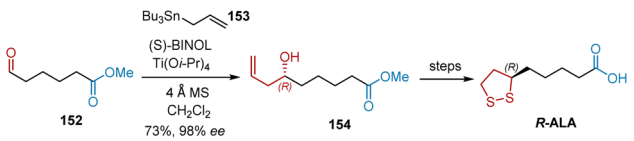


Scheme 34 Sutherland's asymmetric synthesis of *R*-ALA.

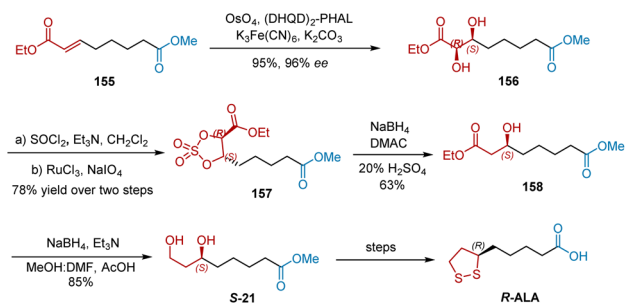
Chiral binaphthol-derived (BINOL) metal species have been widely used as catalysts for enantioselective allylation reactions. In 2000, Zimmer *et al.* used enantioselective allylation as the key step in the formal synthesis of ***R*-ALA** (Scheme 35).[47] Starting with the readily accessible methoxycarbonyl aldehyde **152**, (*S*)-BINOL/Ti(OiPr)$_4$ catalyzed enantioselective allylation was performed with commercially available allyltributylstannane **153**, giving **154** in 73% yield and 98% ee. According to a previously reported protocol, ***R*-ALA** was targeted from **154**.

In 2001, Sudalai *et al.* developed two asymmetric catalytic methods to synthesize ***R*-ALA**, as shown in (Schemes 36 and 37).[48] First, asymmetric dihydroxylation was adopted as the key step in the construction of the chiral center of ***R*-ALA**. Olefinic diester **1** was subjected to OsO_4-catalyzed asymmetric dihydroxylation using hydroquinidine 1,4-phthalazinediyl diether [(DHQD)$_2$–PHAL] as the chiral ligand, affording chiral diol **156** in 95% yield and 96% ee. Diol **156** was then converted into cyclic sulfate **157**, which was reduced to give chiral alcohol **158** in 63% yield. Further selective reduction of one of the ester groups in **158** afforded ***S*-21** in 85% yield, which was converted to ***R*-ALA**, according to a previously reported protocol.

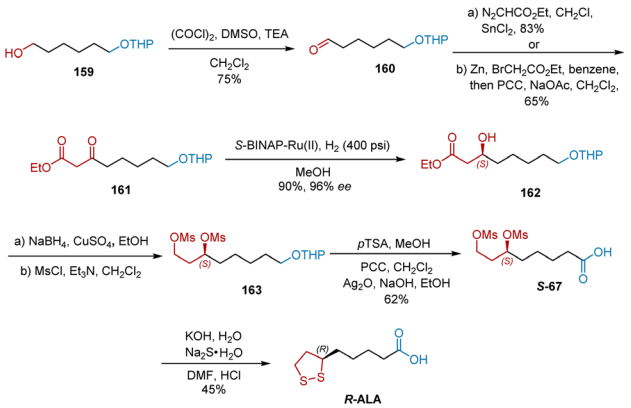
Sudalai developed another synthesis commencing with the Swern oxidation of alcohol **159**, affording aldehyde **160** in 75% yield (Scheme 37).[48] The C–H insertion of ethyl diazoacetate with **160** in the presence of a catalytic amount of anhydrous $SnCl_2$ or the Reformatsky reaction of **160** followed by PCC-mediated oxidation gave keto ester **161** in 65% yield. Under the atmosphere of H_2 (400 psi), *S*-BINAP–Ru-catalyzed asymmetric hydrogenation of **161** proceeded smoothly to generate **162** in 90% yield and 96% ee. The reduction of the ester functional group in **162** using NaBH$_4$–CuSO$_4$ in EtOH yielded the diol intermediate, which was subsequently mesylated under standard conditions to yield **163**. Carboxylic acid ***S*-67** was obtained from **163** in three steps of deprotection and oxidation. Accordingly, the disulfide displacement of ***S*-67** delivered ***R*-ALA**.



Scheme 35 Zimmer's asymmetric synthesis of *R*-ALA.



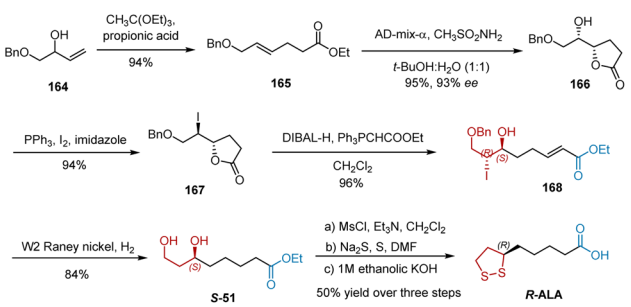
Scheme 36 Sudalai's first asymmetric synthesis of *R*-ALA.



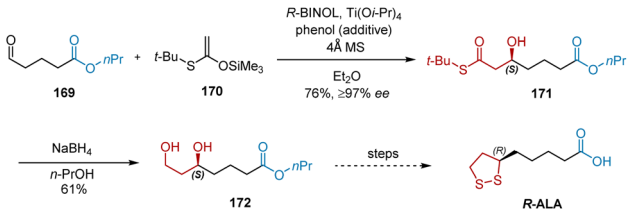
Scheme 37 Sudalai's second asymmetric synthesis of *R*-ALA.

In 2004, Chavan *et al.* reported the synthesis of ***R*-ALA** by employing Claisen orthoester rearrangement and Sharpless asymmetric dihydroxylation as key steps (Scheme 38).[49] Initially, Claisen rearrangement of monoprotected allylic alcohol **159** with triethyl orthoacetate in the presence of catalytic propionic acid afforded unsaturated ester **164** in 94% yield. Sharpless asymmetric dihydroxylation using AD-mix-α and the *in situ* cyclization of **165** furnished hydroxy lactone **166** in 95% yield and 93% ee. Lactone **166** was treated with triphenylphosphine, iodine, and imidazole to give iodolactone **167**, whose reduction was followed by an *in situ* two-carbon Wittig reaction to give unsaturated ester **168**. Under the conditions of W2 RANEY® and hydrogen, the benzyl protection and iodine were removed, and the double bond was reduced in one pot, giving diol ***S*-51** as a known intermediate for the synthesis of ***R*-ALA**. ***R*-ALA** was synthesized according to the established protocol.

In 2002, Zimmer *et al.* developed the asymmetric synthesis of ***R*-ALA** using an enantioselective aldol reaction as the key transformation.[50] As shown in Scheme 39, starting with the easily accessible substrate **169**, enantioselective aldol reactions were performed with *S*-ketene silyl acetal **170** in the presence of *R*-BINOL, Ti(Oi-Pr)$_4$ and phenol, affording chiral alcohol **171** in 76% yield and ≥97% ee. The subsequent NaBH$_4$-mediated reduction of **171** generated the key intermediate **172** in 61% yield, which was converted into enantiopure ***R*-ALA** according to a previously reported protocol.



Scheme 38 Chavan's asymmetric synthesis of *R*-ALA.



Scheme 39 Zimmer's asymmetric synthesis of *R*-ALA.

In 2008, Wang *et al.* unveiled an efficient, highly stereo-controlled formal synthesis of ***R*-ALA** utilizing L-proline-catalyzed, highly enantio- and diastereoselective cross-aldol reaction as the key step (Scheme 40).[51] The L-proline-promoted aldol reaction between ketone **72** and aldehyde **173** afforded chiral aldol adduct **174** in 65% yield with 95% ee and dr of 29 : 1. The regioselective Baeyer–Villiger oxidation of ketone **174** gave lactone intermediate **175**, which could be reduced to chiral compound **176**. Finally, treatment of **176** with sodium methoxide in methanol afforded chiral diol ***S*-21** in 91% yield. The target ***R*-ALA** was obtained using known synthetic sequences.

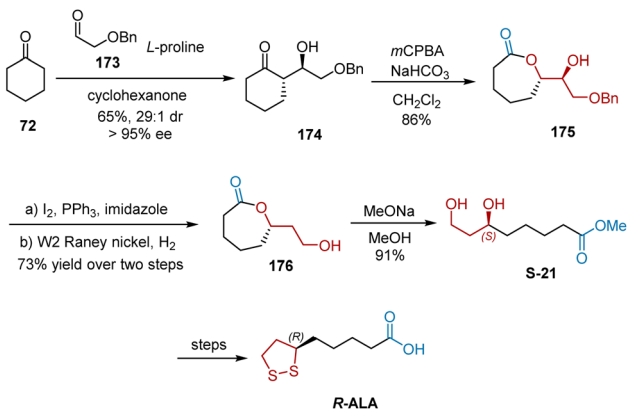
In 2010, Kalkote *et al.* reported an organocatalytic enantioselective approach for the synthesis of ***R*-ALA** using an L-proline-catalyzed sequential aminoxylation–HWE olefination reaction of aldehydes as the key step.[52] The synthesis began with commercially available diol **46** as shown in Scheme 41. The mono-hydroxyl protection of diol **46** and subsequent oxidation provided aldehyde **177** in 74% yield in two steps. Aldehyde **177** was subjected to the following L-proline-catalyzed aminoxylation/HWE olefination/hydrogenation sequence to yield chiral hydroxyester **178** in 58% yield and 97% ee. After the protection of **178**, ester **179** was then reduced to aldehyde **180** with DIBAL-H and subjected to HWE olefination to obtain α,β-unsaturated ester **181**, which was hydrogenated to afford saturated ester **182**. Finally, ***R*-ALA** was synthesized from **182** according to a previously reported protocol.

3.6 Enzymatic asymmetric catalysis

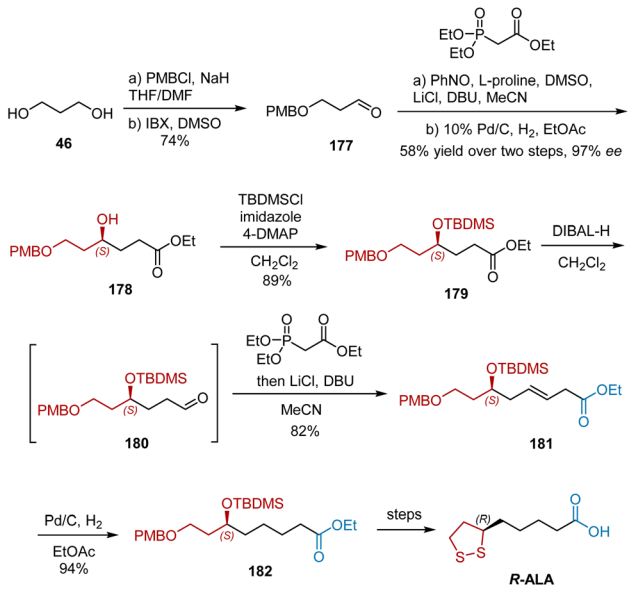
The reduction of functionalized β-keto esters by baker's yeast may be a valuable procedure for the preparation of a variety of chiral trifunctional synthons. In 1989, Gopalan *et al.* utilized baker's yeast reduction to obtain a valuable synthetic intermediate that could be converted to ***R*-ALA** in a short sequence of steps.[53] As shown in Scheme 42, substrate **185** for baker's yeast was prepared by the alkylation of the dianion from alkyl acetoacetate **183** with 4-iodobutyronitrile **184** The Baker's yeast-catalyzed asymmetric reduction of **185** was performed to yield chiral alcohol **186** in 77% yield and 82% ee, which could be transformed into ***R*-ALA** *via* a published route.

In 1990, Gopalan *et al.* also reported their studies on the baker's yeast reduction of readily prepared β-keto esters **187** and applied it to accomplish the total synthesis of ***R*-ALA** (Scheme 43).[54] The keto ester **187** was reduced to the chiral alcohol **188** in 55% yield 85% ee using baker's yeast. Subsequent reduction, acetal protection, alkylation and deprotection generated the diol ***S*-51**, which was in turn converted into ***R*-ALA** following published procedures.

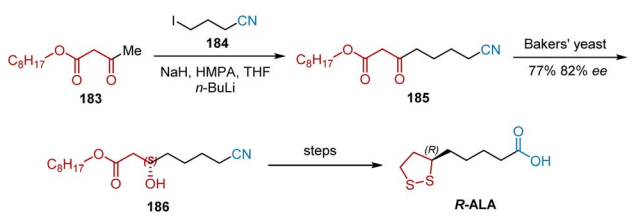
In 1990, Dasaradhi *et al.* reported the stereo-controlled reduction of keto acetals by baker's yeast immobilized on calcium alginate beads to synthesize ***R*-ALA** (Scheme 44).[55] The Cu-catalyzed bromoform addition of **190** followed by treatment with potassium acetate and 18-crown-6 initiated the synthesis of ***R*-ALA**, yielding compound **191** in 68% yield over two steps. The subsequent hydrolysis of **191** in the presence of K_2CO_3 in



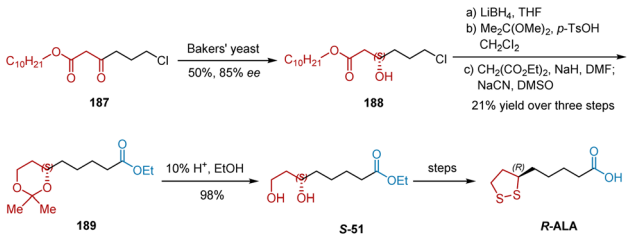
Scheme 40 Wang and Duan's asymmetric synthesis of *R*-ALA.



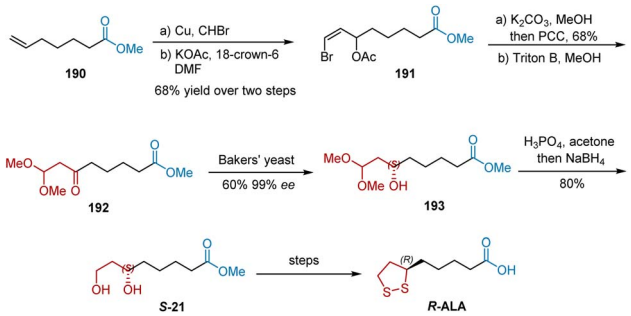
Scheme 41 Kalkote's asymmetric synthesis of *R*-ALA.



Scheme 42 Gopalan's asymmetric synthesis of *R*-ALA.



Scheme 43 Gopalan's asymmetric synthesis of *R*-ALA.

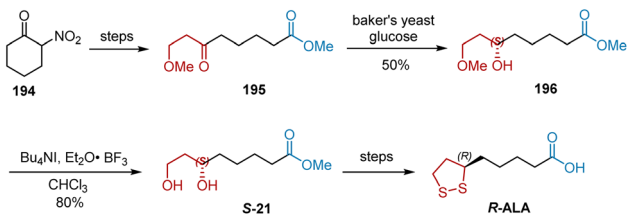


Scheme 44 Dasaradhi's asymmetric synthesis of *R*-ALA.

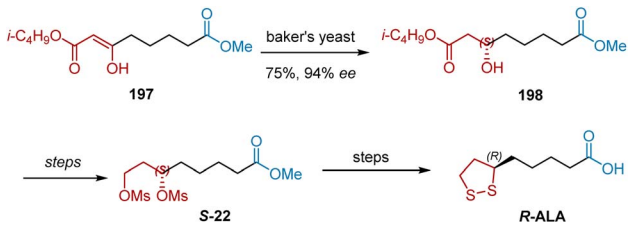
methanol and oxidation with pyridinium chlorochromate afforded ketovinyl bromide, which was then transformed into ester **192** using Triton B in methanol. Ester **192** was enantiospecifically reduced using a glucose solution containing Baker's yeast (*Saccharomyces cerevisiae* NCIM 3044) immobilized on calcium alginate beads to generate crude product **193** in 60% yield and 99% ee. ***R*-ALA** was obtained after deprotection, $NaBH_4$ reduction, mesylation, and hydrolysis ***R*-ALA** was achieved.

In 1996, Bezbarua *et al.* reported the synthesis of ***R*-ALA** by employing the baker's yeast reduction of ketones as a key step.[56] As shown in Scheme 45, the substrate of baker's yeast reduction, ketone **195**, was obtained from 2-nitrocyclohexanone **194**. Ketone **195** was enantiospecifically reduced using Baker's yeast to yield chiral alcohol **196**. The selective hydrolysis of **196** with tetrabutylammonium iodide in $CHCl_3$ afforded chiral diol ***S*-21** in 80% yield, which was converted to ***R*-ALA** according to a previously reported approach.

In 1999, Bringmann *et al.* reported an approach to gain ***R*-ALA** by exploiting 3-oxodiesters **197** as a starting material (Scheme 46).[57] The reduction of **197** took place using baker's



Scheme 45 Bezbarua's asymmetric synthesis of *R*-ALA.

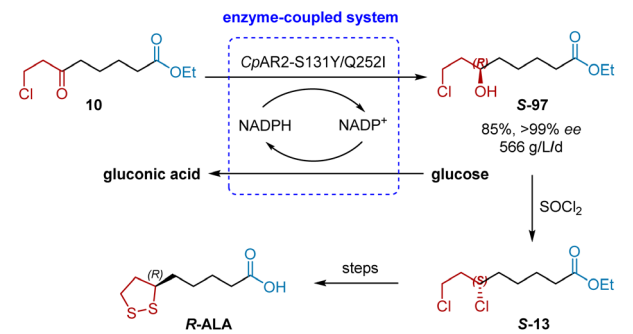


Scheme 46 Bringmann's asymmetric synthesis of *R*-ALA.

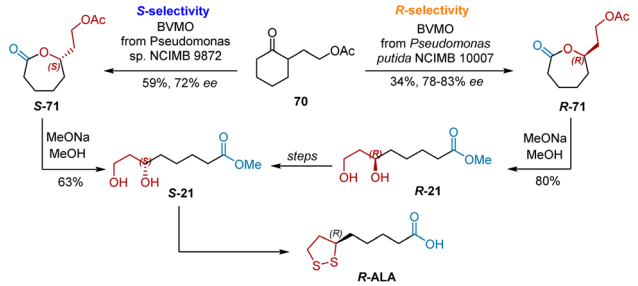
yeast, giving chiral alcohol **198** in 75% yield and 94% ee. ***R*-ALA** was achieved from **198** by using previously reported methods.

In 2015, Xu and Zheng *et al.* discovered a ketoreductase *Cp*AR2 from *Candida parapsilosis* that was able to highly stereoselective reduce ethyl 8-chloro-6-oxooctanoate **1** to (*R*)-8-chloro-6-hydroxyoctanoate **2** (in 85% yield with >99% ee), an advanced chiral intermediate to ***R*-ALA**, with a space-time yield of 530 g L^{-1} d^{-1} (Scheme 47).[27a] However, high biocatalyst loading (10 g L^{-1} of dry *E. coli* cells coexpressing *Cp*AR2 and a glucose dehydrogenase BmGDH) is required. Generally, the biocatalyst loading should be less than 5 g L^{-1} for a green and economical chemical process. Thus, a directed evolution approach was adopted to increase the enzyme activity and thermal stability simultaneously.[58] By using error-prone PCR, the combined mutant S131Y/Q252I was obtained, resulting improved activity (214 U mg^{-1} *versus* 120 U mg^{-1} for wild-type enzyme) and the half-deactivating temperature (T50, for 15 min incubation, increased by 2.3 °C). Gratifyingly, as low as 2 g L^{-1} of the lyophilized *E. coli* cells coexpressing *Cp*AR2S131Y/Q252I and GDH was sufficient to completely reduce 110 g L^{-1} of **1** and achieve the higher space-time yield (566 g L^{-1} d^{-1}), affording the desired **2** in 85% yield with >99% ee.

Enzymatic Baeyer–Villiger Oxidations of ketone provide chiral lactones which are precursors to readily construct chiral alcohol and carbonyl groups *via* ring-opening. Two Baeyer–Villiger monooxygenases were used in the synthesis of ***R*-ALA**, resulting in different stereoselectivities. As shown in Scheme 48, Adger *et al.* used Baeyer–Villiger monooxygenase from *Pseudomonas putida* NCIMB 10007 to catalyze the oxidation of 2-substituted cycloalkanone **70**, yielding ***R*-71** with good enantioselectivities (78–83% ee).[59] Reductive ring opening was performed to yield ***R*-21**. Inversion by the Mitsunobu reaction



Scheme 47 Xu and Zheng's asymmetric synthesis of *R*-ALA.



Scheme 48 Adger and Willetts's asymmetric synthesis of *R*-ALA.

afforded ***S*-21**, which was transformed into ***R*-ALA** according to a published procedure. Willetts *et al.* found that the Baeyer–Villiger oxidation of **70** was preferentially carried out to yield ***S*-21** by monooxygenases from *Pseudomonas* sp. NCIMB 9872.[60] Likewise, the reductive ring opening of ***S*-71** yielded ***S*-21** directly, which was the precursor for the synthesis ***R*-ALA**.

4. Conclusions

This study demonstrates significant progress made over the past 70 years in the field of total **ALA** synthesis. Diverse routes and methods for synthesizing **ALA** have been described in the literature, including racemic synthesis, chemical and enzymatic resolution synthesis, asymmetric chiral pool synthesis, asymmetric chiral auxiliary synthesis, enzyme-catalyzed asymmetric synthesis, chemical-catalyzed asymmetric synthesis. While these methods generally focus on basic scientific research, few of them have proposed synthetic pathways for industrial production.

Accordingly, with the ever-growing demand for **ALA**, practical, concise, and general synthetic strategies and advanced technologies will continue to be explored and exploited. For example, continuous-flow chemistry, enzyme engineering, and other new technologies could have broadly applications in the total synthesis of **ALA** to achieve efficient, economical, and energy-saving industrial production. The ability to combine new technologies advances numerous possibilities for creating cheaper and higher quality products to fulfill the needs of the population. The development of these new technologies will undoubtedly benefit future applications. Furthermore, new technologies and strategies will be implemented in the synthesis of **ALA** to provide ideas and insights for scientific researchers and peers, associated with these realms and aspects in the long run.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 L. J. Reed, B. G. DeBusk, I. C. Guusalus and C. S. Horuberger Jr, Crystalline α-Lipoic Acid: A Catalytic Agent Associated with Pyruvate Dehydrogenase, *Science*, 1951, **114**, 93.

2 (*a*) D. Han, G. Handelman, L. Marcocci, C. K. Sen, S. Roy, H. Kobuchi, H. J. Tritschler, L. Flohé and L. Packer, Lipoic acid increases de novo synthesis of cellular glutathione by improving cystine utilization, *Biofactors*, 1997, **6**, 321–338; (*b*) A. Gorąca, H. Huk-Kolega, A. Piechota, P. Kleniewska, E. Ciejka and B. Skibska, Lipoic acid–biological activity and therapeutic potential, *Pharmacol. Rep.*, 2011, **63**, 849–858.

3 D. Ziegle, M. Reljanovic, H. Mehnert and F. A. Gries, Alpha-lipoic acid in the treatment of diabetic polyneuropathy in Germany: current evidence from clinical trials, *Exp. Clin. Endocrinol. Diabetes*, 1999, **107**, 421–430.

4 Selected reviews: (*a*) S. Ghibu, C. Richard, C. Vergely, M. Zeller, Y. Cottin and L. Rochette, Antioxidant Properties of an Endogenous Thiol: Alpha-lipoic Acid, Useful in the Prevention of Cardiovascular Diseases, *J. Cardiovasc. Pharmacol.*, 2009, **54**, 391–398; (*b*) K. P. Shay, R. F. Moreau, E. J. Smith, A. R. Smith and T. M. Hagen, Alpha-lipoic acid as a dietary supplement: molecular mechanisms and therapeutic potential, *Biochim. Biophys. Acta*, 2009, **1790**, 1149–1160; (*c*) P. M. Bingham, S. D. Stuart and Z. Zachar, Lipoic acid and lipoic acid analogs in cancer metabolism and chemotherapy, *Expert Rev. Clin. Pharmacol.*, 2014, **7**, 837–846; (*d*) F. A. Moura, K. Q. de Andrade, J. C. F. dos Santos and M. O. F. Goulart, Lipoic Acid: Its Antioxidant and Anti-Inflammatory Role and Clinical Applications, *Curr. Top. Med. Chem.*, 2015, **15**, 458–483; (*e*) B. Salehi, Y. B. Yılmaz, G. Antika, T. B. Tumer, M. F. Mahomoodally, D. Lobine, M. Akram, M. Riaz, E. Capanoglu, F. Sharopov, N. Martins, W. C. Cho and J. Sharifi-Rad, Insights on the Use of α-Lipoic Acid for Therapeutic Purposes, *Biomolecules*, 2019, **9**, 356; (*f*) S. Jeffrey, P. I. Samraj and B. S. Raj, *Curr. Diabetes Rev.*, 2021, **17**, e011821190404; (*g*) D. Kaur, T. Behl, A. Sehgal, S. Singh, N. Sharma, S. Chigurupati, A. Alhowail, A. Abdeen, S. F. Ibrahim, C. Vargas-De-La-Cruz, M. Sachdeva, S. Bhatia, A. Al-Harrasi and S. Bungau, Decrypting the potential role of α-lipoic acid in Alzheimer's disease, *Life Sci.*, 2021, **284**, 119899; (*h*) D. P. Theodosis-Nobelos, G. Papagiouvannis, P. Tziona and E. A. Rekka, Lipoic acid. Kinetics and pluripotent biological properties and derivatives, *Mol. Biol. Rep.*, 2021, **48**, 6539–6550; (*i*) H. Xie, X. Yang, Y. Cao, X. Long, H. Shang and Z. Jia, Role of lipoic acid in multiple sclerosis, *CNS Neurosci. Ther.*, 2022, **28**, 319–331; (*j*) B. Fasipe, A. Faria and I. Laher, Potential for Novel Therapeutic Uses of Alpha Lipoic Acid, *Curr. Med. Chem.*, 2023, **30**, 3942–3954.

5 M. H. Brookes, B. T. Golding, D. A. Howes and A. T. Hudson, Proof that the absolute configuration of natural α-lipoic acid is R by the synthesis of its enantiomer [(S)-(−)-α-lipoic acid] from (S)-malic acid, *J. Chem. Soc. Chem. Commun.*, 1983, **19**, 1051–1053.

6 (*a*) A. Marshall, R. Graul, M. Y. Morgan and S. Sherlock, Treatment of alcohol-related liver disease with thioctic acid: a six month randomised double-blind trial, *Gut*, 1982, **23**, 1088–1093; (*b*) N. Ramakrishnan, W. W. Wolfe and G. N. Catravas, Radioprotection of Hematopoietic Tissues in Mice by Lipoic Acid, *Radiat. Res.*, 1992, **130**, 360–365; (*c*) S. Stoll, H. Hartmann, S. Cohen and W. Müller, The potent free radical scavenger α-lipoic acid improves memory in aged mice: putative relationship to NMDA receptor deficits, *Pharmacol., Biochem. Behav.*, 1993, **46**, 799–805; (*d*) A. Faust, V. Burkart, H. Ulrich, C. H. Weischer and H. Kolb, Effect of lipoic acid on cyclophosphamide-induced diabetes and insulitis in non-obese diabetic mice, *Int. J. Immunopharmacol.*, 1994, **16**, 61–66; (*e*) P. Ou, H. J. Tritschler and S. P. Wolff, Thioctic (lipoic) acid: a therapeutic metal-chelating antioxidant?, *Biochem. Pharmacol.*, 1995, **50**, 123–126; (*f*) S. Golbidi, M. Badran and I. Laher, Diabetes and alpha lipoic acid, *Front. Pharmacol*, 2011, **2**, 69.

7 J. S. Yadav, S. V. Mysorekar and K. Garyali, Synthesis of α-lipoic acid-A highly useful biologically active compound, *J. Sci. Ind. Res.*, 1990, **49**, 400–409.

8 R. Ramachanderan and B. Schaefer, Lipoic acid, *ChemTexts*, 2019, **5**, 18.

9 M. W. Bullock, J. A. Brockman Jr, E. L. Patterson, J. V. Pierce, H. vonSultza, F. Sanders and E. L. R. Stokstad, *J. Am. Chem. Soc.*, 1952, **74**, 3455.

10 M. W. Bullock, J. A. Brockman Jr, E. L. Patterson, J. V. Pierce, H. vonSultza, F. Sanders and E. L. R. Stokstad, Syntheses in the Thioctic Acid Series, *J. Am. Chem. Soc.*, 1954, **76**, 1828–1832.

11 (*a*) Q. F. Soper, W. E. Buting Jr, J. E. Cochrau and A. Pohland, Syntheses of DL-α-Lipoic Acid, *J. Am. Chem. Soc.*, 1954, **76**, 4109–4112; (*b*) D. S. Acker and W. J. Wayn, Synthesis of Racemic, Optically Active and Radioactive α-Lipoic Acids, *J. Am. Chem. Soc.*, 1957, **79**, 6483–6484.

12 (*a*) L. J. Reed and C. Niu, Syntheses of DL-α-Lipoic Acid, *J. Am. Chem. Soc.*, 1955, **77**, 416–419; (*b*) R. C. Thomas and L. J. Reed, Synthesis and Properties of High Specific Activity DL-α-Lipoic Acid-S_2[35], *J. Am. Chem. Soc.*, 1955, **77**, 5446–5448.

13 (*a*) D. S. Acker and C. W. Todd, *US Pat.* US2752374, 1956; (*b*) L. J. Reed, *US Pat.* US2980716, 1961; (*c*) H. Ose and K. Yoshida, *US Pat.* US3223712, 1965.

14 D. S. Acker and W. J. Wayne, Synthesis of Racemic, Optically Active and Radioactive α-Lipoic Acids, *J. Am. Chem. Soc.*, 1957, **79**, 6483–6487.

15 E. Walton, A. F. Wagner, F. W. Bachelor, L. H. Peterson, F. W. Holly and K. Folkers, Synthesis of (+)-α-Lipoic Acid and its Optical Antipode, *J. Am. Chem. Soc.*, 1955, **77**, 5144–5149.

16 A. V. R. Rao, S. V Mysorekar and J. S. Yadav, Synthesis of 1,3-Diols: Its Application to the Synthesis of α-Lipoic Acid, *Synth. Commun.*, 1987, **17**, 1339–1347.

17 E. A. Braude, R. P. Linstead and K. R. H. Wooldridge, 594. A new synthesis of 6:8-thioctic acid, *J. Chem. Soc.*, 1956, 3074–3078.

18 J. Tsuji, H. Yasuda and T. Mandai, Synthesis of dl-.alpha.-lipoic acid from a butadiene telomer, *J. Org. Chem.*, 1978, **43**, 3606–3607.

19 P. Dhar, N. Chidambaram and S. Chandrasekaran, Piperidinium tetrathiotungstate as sulfur transfer reagent: synthesis of cyclic disulfides, *J. Org. Chem.*, 1992, **57**, 1699–1702.

20 S. P. Chavan, R. R. Kale and K. Pasupathy, A Facile Regioselective Decomposition of Tosylhydrazones: An Application towards the Synthesis of α-Lipoic Acid, *Synlett*, 2005, **7**, 1129–1132.

21 A. N. Purude, K. P. Pawar, N. B. Patil, U. R. Kalkote and S. P. Chavan, Total synthesis of (R)-lipoic acid and (S)-lipoic acid via an Mn (III)-salen-catalyzed oxidative kinetic resolution, *Tetrahedron: Asymmetry*, 2015, **26**, 281–287.

22 A. F. Wagner, E. Walton, C. H. Hoffman, L. H. Peterson, F. W. Holly and K. Folkers, Synthesis of DL-Dimethyldihydro-α-lipoic Acid, *J. Am. Chem. Soc.*, 1955, **77**, 5140–5143.

23 B. V. Rao and A. S. Rao, A Common Strategy for the Synthesis of (+)-Hepialone and (±)-α-Lipoic Acid, *Synth. Commun.*, 1995, **25**, 1531–1543.

24 A. Segre, R. Viterbo and G. Parisi, A New Synthesis of 6-Thioctic Acid (DL-α-Lipoic Acid), *J. Am. Chem. Soc.*, 1957, **79**, 3503–3505.

25 F. Balkenhohl and J. Paust, A Short and Productive Synthesis of Racemic α-Lipoic Acid, *Z. Naturforsch.*, 1999, **54**, 649–654.

26 S. P. Chavan, K. Shivsankar and K. Pasupathy, Simplistic Expedient and Practical Synthesis of (±)-α-Lipoic Acid, *Synthesis*, 2005, **8**, 1297–1300.

27 (*a*) Y. Zhang, W. Zhang, G. Zheng and J. Xu, Identification of an ε-Keto Ester Reductase for the Efficient Synthesis of an (R)-α-Lipoic Acid Precursor, *Adv. Synth. Catal.*, 2015, **357**, 1697–1702; (*b*) B. Zehnpfennig, P. Wiriyasermkul, D. A. Carlson and M. Quick, Interaction of α-Lipoic Acid with the Human Na^+/Multivitamin Transporter (hSMVT), *J. Biol. Chem.*, 2015, **290**, 16372–16382.

28 Y. Numbu and T. Endo, Stereoselective Reduction of Racemic N-hydroxyamino Acid by Optically Active Thiols-iron(II), *Chem. Lett.*, 1985, **14**, 999–1002.

29 (*a*) T. Tsunoda, H. Kaku, M. Nagaku and E. Okuyama, Deracemization of 2-Alkylcyclohexanones Utilizing Host-Guest Molecular Association with Optically Active Host Compounds in Basic Suspension Media, *Tetrahedron Lett.*, 1997, **38**, 7759–7760; (*b*) H. Kaku, N. Okamoto, T. Nishii, M. Horikawa and T. Tsunoda, Enantioselective Total Synthesis of (R)-α-Lipoic Acid: An Application of Thermodynamically Controlled Deracemization of (±)-2-(2-Methoxyethyl) Cyclohexanone, *Synthesis*, 2010, **17**, 2931–2934.

30 L. S. Bose, L. Fatima and S. Rajender, An Efficient, Highly Enantioenriched Route to L-Carnitine and α-Lipoic Acid via Hydrolytic Kinetic Resolution, *Synthesis*, 2006, **11**, 1863–1867.

31 N. W. Fadnavis and K. Koteshwar, Remote control of stereoselectivity: lipase catalyzed enantioselective

esterification of racemic α-lipoic acid, *Tetrahedron: Asymmetry*, 1997, **8**, 337–339.

32 H. Yan, Z. Wang and L. Chen, Kinetic resolution of α-lipoic acid via enzymatic differentiation of a remote stereocenter, *J. Ind. Microbiol. Biotechnol.*, 2009, **36**, 643–648.

33 N. Liu, L. Wang, Z. Wang, L. Jiang, Z. Wu, H. Yue and X. Xie, Microwave-Assisted Resolution of α-Lipoic Acid Catalyzed by an Ionic Liquid Co-Lyophilized Lipase, *Molecules*, 2015, **20**, 9949–9960.

34 Y. R. S. Laxmi and D. S. Iyengar, Chemoenzymatic Synthesis of Methyl(6S)-(-)-6,8-Dihydroxyoctanoate: A Precursor to (R)-(+)-α-Lipoic Acid, *Synthesis*, 1996, **5**, 594–596.

35 W. Zhou, Y. Ni, G. Zheng, H. Chen, Z. Zhu and J. Xu, Enzymatic resolution of a chiral chlorohydrin precursor for (R)-α-lipoic acid synthesis via lipase catalyzed enantioselective transacylation with vinyl acetate, *J. Mol. Catal. B: Enzym.*, 2014, **99**, 102–107.

36 N. W. Fadnavis, R. L. Babu, S. K. Vadivel, A. A. Deshpande and U. T. Bhalerao, Lipase catalyzed regio- and stereospecific hydrolysis: chemoenzymatic synthesis of both (R)- and (S)-enantiomers of α-lipoic acid, *Tetrahedron: Asymmetry*, 1998, **9**, 4109–4112.

37 (*a*) A. V. R. Rao, M. K. Gurjar, K. Garyau and T. Ravindranatha, Enantiospecific synthesis of (R-(+)-α-lipoic acid from d-glucose, *Carbohydr. Res.*, 1986, **148**, 51–55; (*b*) A. V. R. Rao, A. V. Purandare, E. R. Reddy and M. K. Curjar, Synthesis of R-(+)-α-lipoic acid, *Synth. Commun.*, 1987, **17**, 1095–1102.

38 M. H. Brookes and B. T. Golding, Syntheses of α-(R)- and α-(S)-Lipoic Acid from (S)-Malic Acid, *J. Chem. Soc., Perkin Trans. 1*, 1988, 9–12.

39 J. S. Yadav, S. V. Mysorekar, S. M. Pawar and M. K. Gurjar, Synthesis of (3R, 4R)-1, 2-Divinylglycol and its Unsymmetrical Derivatives: An Application to the Synthesis of R-(+)-α-Lipoic Acid, *J. Carbohydr. Chem.*, 1990, **9**, 307–316.

40 C. Crévisy, B. Herbage, M. Marrel, L. Toupet and R. Grée, A New Iron-Mediated Strategy for the Synthesis of α-Lipoic Acid and Analogues, *Eur. J. Org Chem.*, 1998, 1949–1954.

41 Z. Wei, H. Lan, J. Zheng and P. Huang, New and Concise Approach to (R)-α-Lipoic Acid, *Synth. Commun.*, 2009, **39**, 691–701.

42 S. P. Chavan, K. P. Pawar, C. Praveen and N. B. Patil, Chirality induction and chiron approaches to enantioselective total synthesis of α-lipoic acid, *Tetrahedron*, 2015, **71**, 4213–4218.

43 W. S. Johnson, C. Edington, J. D. Elliott and I. R. Silverman, Asymmetric Synthesis via Acetal Templates. 10. 1 Aldol-Type Reactions. Preparation of a Nonactic Acid Intermediate, *J. Am. Chem. Soc.*, 1984, **106**, 7588–7591.

44 J. D. Elliott, J. Steele and W. S. Johnson, Asymmetric synthesis via acetal templates. 12. Highly diastereoselective coupling reactions with a ketene acetal. An efficient, asymmetric synthesis of R-(+)-α-lipoic acid, *Tetrahedron Lett.*, 1985, **26**, 2535–2538.

45 R. B. Menon, M. A. Kumar and T. Ravindranathan, Stereospecific synthesis of α-lipoic acid, *Tetrahedron Lett.*, 1987, **28**, 5313–5314.

46 P. C. B. Page, C. M. Rayner and I. Sutherland, Enantioselective Synthesis of R-(+)-α-Lipoic Acid, *J. Chem. Soc., Chem. Commun.*, 1986, **18**, 1408–1409.

47 R. Zimmer, U. Hain, M. Berndt, R. Gewald and H. Reissig, Enantioselective synthesis of (S)- and (R)-6-hydroxy-8-nonene-carboxylates by asymmetric catalysis: a formal synthesis of (R)-α-lipoic acid and its (S)-antipode, *Tetrahedron: Asymmetry*, 2000, **11**, 879–887.

48 T. T. Upadhya, M. D. Nikalje and A. Sudalai, Asymmetric dihydroxylation and hydrogenation approaches to the enantioselective synthesis of R-(+)-α-lipoic acid, *Tetrahedron Lett.*, 2001, **42**, 4891–4893.

49 S. P. Chavan, C. Praveen, G. Ramakrishna and U. R. Kalkote, Enantioselective synthesis of R-(+)-α and S-(-)-α-lipoic acid, *Tetrahedron Lett.*, 2004, **45**, 6027–6028.

50 R. Zimmer, A. Peritz, R. Czerwonka, L. Schefzig and H. Reißig, Optimisation, Scope and Limitations of Enantioselective Aldol Reactions of an S-Ketene Silyl Acetal with Aliphatic Aldehydes under (R)-BINOL-Titanium(IV) Catalysis Conditions, *Eur. J. Org Chem.*, 2002, 3419–3428.

51 S. Zhang, X. Chen, J. Zhang, W. Wang and W. Duan, An Enantioselective Formal Synthesis of (+)-(R)-α-Lipoic Acid by an L-Proline-Catalyzed Aldol Reaction, *Synthesis*, 2008, **3**, 383–386.

52 S. P. Panchgalle, G. F. Jogdand, S. P. Chavan and U. R. Kalkote, Enantioselective synthesis of (R)-(+)-α-lipoic acid via proline-catalyzed sequential α-aminoxylation and HWE olefination of aldehyde, *Tetrahedron Lett.*, 2010, **51**, 3587–3589.

53 A. S. Gopalan and H. K. Jacobs, Stereochemical control of yeast reductions: synthesis of R-(+)-α-lipoic acid, *Tetrahedron Lett.*, 1989, **30**, 5705–5708.

54 A. S. Gopalan and H. K. Jacobs, Bakers' Yeast Reduction of Alkyl6-Chloro-3-oxohexanoates: Synthesis of (R)-(+)-α-Lipoic Acid, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1897–1990.

55 L. Dasaradhi, N. W. Fadnavis and U. T. Bhalerao, A Novel Enantiospecific Synthesis of (S)-(-)-Methyl 6,8-Dihydroxyoctanoate, a Precursor of (R)-(+)-α-Lipoic Acid, *J. Chem. Soc., Chem. Commun.*, 1990, **10**, 729–730.

56 M. Bezbarua, A. K. Saikia, N. C. Barua, D. Kalita and A. C. Ghosh, A Short Enantioselective Formal Synthesis of Methyl (S)-(-)-6,8-Dihydroxyoctanoate: A Key Intermediate for the Synthesis of R-(+)-α-Lipoic Acid, *Synthesis*, 1996, **11**, 1289–1290.

57 G. Bringmann, D. Herzberg, G. Adam, F. Balkenhohl and J. Paust, A Short and Productive Synthesis of (R)-α-Lipoic Acid, *Z. Naturforsch.*, 1999, **54**, 655–661.

58 Y. Xu, Q. Chen, Z. Zhang, J. Xu and G. Zheng, Co-evolving the Activity and Thermostability of an ε-Ketoester Reductase for Better Synthesis of (R)-α-Lipoic Acid Precursor, *ChemBioChem*, 2020, **21**, 1341–1346.

59 B. Adger, M. T. Bes, G. Grogan, R. McCague, S. Pedragosa-Moreau, S. M. Roberts, R. Villa, P. W. H. Wan and A. J. Willetts, Application of Enzymic Baeyer-Villiger Oxidations of 2-Substituted Cycloalkanones to the Total Synthesis of (R)-(+)-Lipoic Acid, *J. Chem. Soc., Chem. Commun.*, 1995, **15**, 1563–1564.

60 (*a*) M. T. Bes, R. Villa, S. M. Roberts, P. W. H. Wan and A. Willetts, Oxidative biotransformations by microorganisms: production of chiral synthons by cyclopentanone monooxygenase from Pseudomonas sp. NCIMB 9872, *J. Mol. Catal. B: Enzym.*, 1996, **1**, 127–134; (*b*) B. Adger, M. T. Bes, G. Grogan, R. McCague, S. PedragosaMoreau, S. M. Roberts, R. Villa, P. W. H. Wan and A. J. Willetts, The Synthesis of (R)-(+)-Lipoic Acid using a Monooxygenase-Catalysed Biotransformation as the Key Step, *Bioorg. Med. Chem.*, 1997, **5**, 253–261.