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Since the original isolation of 30 mg of R-(+)-LA crystals by Reed in 1951 from an estimated 10 tons of beef liver, RLA has been a favorite target of organic chemists. Dozens of papers and patents have been published over the last 57 years for preparation on both the laboratory and industrial scales. This book is a comprehensive review of all the known methods for production of LA with special emphasis on modern adaptations of existing protocols to build the chiral center at C6. Many of the reported processes are expensive and/or use dangerous reagents or catalysts and suffer severe disadvantages on the industrial scale. In 2008, the bulk of the world's rac-LA and RLA are produced by Friedel-Crafts acylation of ethylene, a process first described in 1954 and which produces large amounts of waste (E factor =40). Due to recent advances in asymmetric synthesis and improved resolution strategies, as well as the commercial availability of chiral synthons, it is now possible to produce RLA and R-DHLA free of residual solvents with high chemical and enantiomeric purities on the MT scale, cost effectively with minimal environmental impact.

Introduction:

Since the original isolation of 30 mg of yellow R-(+)-Lipoic Acid (RLA) crystals by Reed in 1951 from an estimated 10 tons of beef liver, RLA has understandably been a favorite target of organic chemists.

While the first generation (1951-1965) research and industrial lipoic acid chemists* were quite thorough in investigating most of the possible methods of building the racemic compound, the technology of the day was limited by inefficient resolution strategies of both the key intermediates and rac-LA, which limited the availability of enantiomerically pure RLA and SLA. It was known as early as 1954 that rac-LA, RLA and SLA were not bioequivalent.

The absolute configuration of dextro (+)-LA was predicted in 1954 by Mislow and Meluch and confirmed by Brookes and Golding in 1983 through synthesis of SLA from L-malic acid.

After a quiet period in research and industrial development from the mid 1960's to early 1980's, Ulrich of DeGussa/Asta Medica (1983) generated a resurgence of interest in lipoic acid due to his newly discovered differences in the biological effects of the enantiomers (RLA was demonstrated to be primarily anti-inflammatory and SLA primarily anti-nociceptive), second generation chemists

improved the practical resolution strategies and devised new asymmetric approaches to the targets.

Due to an exponential increase in interest after the publications generated by the DeGussa/Asta Medica group and Packer's team at UC Berkeley, rac-LA became a highly sought after medicine for treatment of diabetic neuropathy in Europe and as a dietary "antioxidant" and potential "anti-aging" compound in the US.

LA (through its redox partner DHLA) is considered a key component of the "antioxidant network" along with Vitamin C, Vitamin E, and CoQ10 due to its ability to maintain these dietary ingredients in their active, reduced form. With the publication of the rejuvenating effects of RLA and ALCAR by Ames and Hagen, RLA became a highly prized compound amongst Life Extension enthusiasts as having potential at slowing or reversing several markers of age-related decay. Despite growing demands for RLA, there were numerous practical challenges to overcome in order to produce RLA on an industrial scale.

Since 2001, when the Nobel Prize in chemistry was awarded for advances in asymmetric catalysis, numerous new commercially available synthons and methods have appeared and have increased the possible approaches of constructing RLA and SLA on the metric ton scale using simple catalysts, straight forward reactions and eco-friendly reagents and solvents.

Commercial interest in RLA and R-DHLA as a nutraceutical over the last 10 years has led to considerable improvements in solvent-free RLA with both high chemical purities and high enantiomeric excess (>99%).

As of 2000, RLA was not commercially available in bulk. Since that time there has been significant interest and exponential growth of the RLA market. The current world supply of rac-ALA is >800MT/yr whereas the supply of RLA is now ~30 MT/yr and growing.

New models, identification of stereospecific targets, published research from many groups and human clinical trials indicate RLA and R-DHLA are the eutomers (the pharmacological and physiologically superior forms) of LA for human supplemental and therapeutic uses.

Overview of Lipoic Acid Synthetic Methods; Part 1

The bulk of the world's 800 MT annual supply of rac-LA and the 30 MT supply of RLA are made by Friedel-Crafts acylation of ethylene by ethyl adipoyl chloride, a process first reported in 1954 and utilized by many groups. The high-yielding process (overall yield=60% in 6 steps) is hampered by the need for disposal of as much as 40 MT of aluminum waste per MT of rac-ALA (E factor = 40). A truly catalytic (and recyclable) FC catalyst is needed.

Although numerous papers and patents have appeared over the last 20 years claiming improved processes for manufacturing RLA and SLA, most have not been able to compete in terms of cost or efficiency with classical resolution strategies involving the fractional crystallization of the diastereomeric salt pairs formed between RLA and RAMBA or SLA and SAMBA.

This paper provides a comprehensive overview of synthetic methods of manufacturing ALA and RLA with special emphasis on recent advances and future directions.

General Synthetic Approaches to Lipoic Acid

A-four carbon synthons

- 1-butyrolactones
- 2-furans
- 3-1, 3-butadiene
- 4-malic acid

B-five carbon synthons

- 1-glutaric acid derivatives
- 2-cyclopentanone derivatives
- 3-valerolactones
- 4-dihydropyrans

C-six carbon synthons

- 1-adipic acid derivatives
- 2-cyclohexene and cyclohexanone derivatives
- 3-ε-caprolactones
- 4- Tricarbonyl (n⁵ pentadienyl) iron complexes

D-seven carbon synthons

- 1-cycloheptanone
- 2-alkyl 6-heptenoate

E-eight carbon synthons

1-octenoic and suberic acids and esters

2-cyclooctene

3-cyclooctadienes

A-1,5-cyclooctadiene

B-1,3-cyclooctadiene

4-alkyl 6-hydroxy-8-halocaprylate

5-alkyl 6, 8-dichlorocaprylate

6-alkyl cyclohexene acetate

F-nine carbon synthons

1-azelaic acid

2-alkyl 6-oxo-8-nonenoate

G-fragmentation of longer carbon chains from long chain fatty acids

Preparation of Lipoic Acid Enantiomers: Part 2

1) Resolution Strategies

A. selective crystallization and hydrolysis of diastomeric salt pairs and esters

1-alkyl 6-hydroxy-8-chlorooctanoate

2-alkyl 6, 8-dichlorocaprylate

3-alkyl 7-carbethoxy-3-acetyl-thioheptanoic acid

4-rac-ALA

B. kinetic resolution relies on different rates of reaction of the 2 enantiomers and is directed by a chiral catalyst (limited to a theoretical 50% yield)

1-alkyl 6-oxo-7-octenoate

2-alkyl 2,3-octen-1ol

C. Dynamic Kinetic Resolution (DKR) different rates of reaction of the 2 enantiomers and the opposite/undesired enantiomer is inverted to the desired enantiomer (theoretically 100% conversion)

2) Chiral Templates & Chiral Pool Synthons

A. Chiral Templates induce chirality in a substrate through interaction with a ligand.

B. Chiral Pool (the "Chiron approach") act as source of optically active starting materials that become incorporated into the structure of the target molecule with retention or inversion of configuration and optical purities preserved through the entire reaction sequence.

- 1-L-maltose
- 2-D-glucose
- A-3,4,6-tri-O-acetyl-D-glucal
- 3-D-menthone
- 4-L-homocysteine
- 5-D-ribose
- 6-D-Arabinose
- 7-L-malic acid

C. Other (Pro)-Chiral Synthons

- 1-cis-1,4-butene diol
- 2-[2-phenylmethoxy]ethyl oxirane
- 3-Tosyl hydrazones
- 4-beta hydroxy esters
- 5-2S,3S-epoxynon-8-en-1-ol
- 6-1,6,8-octanetriol and 1,6,8-octanetrithiol
- 7-Tricarbonyl (n5 pentadienyl) iron complexes
- 8-caprolactones
- 9-R-6-(2R, 4R-4-hydroxypentan-2-yloxy)-non-8-enenitrile

3) Asymmetric synthesis

A. enzymatic oxidation (monooxygenases)

- 1-selective oxidation of either an R or S-secondary alcohol

B. enzymatic reduction (bovine liver acetone, baker's yeast, lipases)

C. chiral reduction catalysts/asymmetric hydrogenation (ie RuBINOL/BINAP, oxazaborolidines and borohydride modifiers)

- 1-ketones & beta-keto esters
- 2-thioketones
- 3-sulfoxides

D. Asymmetric c-c bond formation

- 1- allyl stannylation

- 2- Aldol reaction
 - A-Beta-hydroxy thioesters
- 3- Reformatsky reaction
- 4- Knoevenagel Reaction
- 5- Cope Reaction
- 6- Selective Alkylation
 - A-chiral acetals

E. Asymmetric C-O bond formation

- 1- Sharpless Asymmetric Epoxidation? chiral episulfides/thiaranes
- 2- acetoxylation

F. Asymmetric C-X bond formation

- 1- allylic halogenation

G. Asymmetric C-S bond formation

H. enzymatic esterification, acylation

I. enzymatic saponification

4) Bioengineered processes

5) Catalytic and "Green" processes

6) Solvent and reagent recycling

7) Polymerization

8) Bioavailability

9) Radioactive LA

10) LA analogs & Pro-drugs

11) Synthesis of LA metabolites

A-BisnorLA and derivatives

B-TetranorLA and derivatives

C-BMOA

12) Chiral analysis of LA & Metabolites

• Research Foundation of New York, Eli Lilly, E Merck, Dupont, American Cyanamid/Lederle Laboratories, Takeda, Fujisawa, Daiichi Seikaku, Yamanouchi, Rohto and Farmaco-Cutolo-Calosi.

