The Enantioselective Synthesis of Conformationally Constrained Cyclic β-Amino Acids

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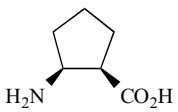
Abstract: Enantiomerically pure and conformationally constrained cyclic β-amino acids have been the subject of a vast amount of research across the chemical, biological, and medicinal disciplines. These valuable molecules are synthetic precursors for a wide variety of useful compounds that include natural products and modified peptides. Many methods have been developed to prepare chiral cyclic β-amino acids in high optical purity. This mini-review will discuss some of the most recent and successful approaches.

Keywords: β-amino acids, cyclic β-amino acids, enantioselective synthesis, conformationally constrained, peptides, asymmetric synthesis.

I. INTRODUCTION

The enantioselective synthesis of β-amino acids has recently attracted considerable attention due to their interesting structural properties, significant pharmacological activities, location within natural products, and utility as chiral auxiliaries and building blocks [1-3]. Although much less abundant than their α-analogs, β-amino acids are also present in nature. For example, a β-amino acid structure can be found in the anticancer agent taxol (paclitaxel), which was originally isolated from the bark of *Taxus brevifolia*, commonly known as the Pacific yew tree [4]. Due to their antibiotics such as β-lactams and (–)-cispentacin ((1*R*,2*S*)-2-aminocyclopentanecarboxylic acid, ((1*R*,2*S*)-2-ACPC, Fig. (**1**), **1**), the later being extracted from either *Bacillus cereus* or *Streptomyces setonii*. The antibiotic properties and the syntheses of cispentacin have recently been highlighted by Fülöp [6]. The cispentacin subunit is also a critical component of the natural antibiotic amipurimycin, **2** [7].

Having an extra carbon atom between the amine and the carboxylic acid termini, β-amino acids have a much greater potential for structural diversity than mono-substituted α-amino acids. In addition, β-amino acids are generally more



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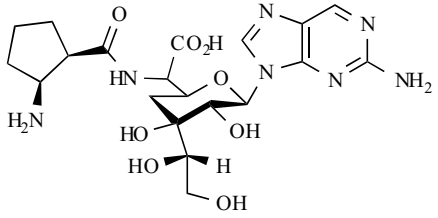
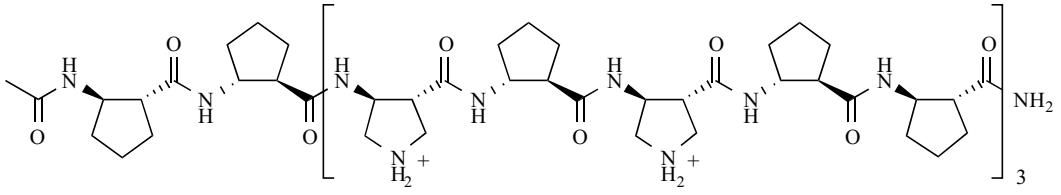


2 - amipurimycin



3 - β-17 synthetic peptide

Fig. (1). The importance of cyclic β-amino acids: natural products cispentacin and amipurimycin and the synthetic peptide β-17.

pharmacological potential, conformationally constrained cyclic β-amino acids have been a topic of great interest in recent years [5]. These compounds are also found in numerous natural products like macrocyclic peptides and metabolically stable to hydrolysis than their α-amino counterparts [8] and, as a result, have been widely used in the preparation of modified peptides [9-11]. In particular, the non-natural cyclic *trans*-cyclohexyl and *trans*-cyclopentyl β-amino acids (Fig. (**2**), *trans*-**4** and *trans*-**5** respectively), which restrict conformational mobility have been successfully incorporated into many β-peptide designs. One example is the peptide β-17 (**3**), which was developed by the Gellman laboratory and contains *trans*-five-member β-

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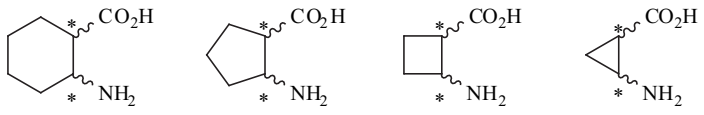


Fig. (2). Alicyclic β-amino acid derivatives.

amino acids [12, 13]. This particular synthetic peptide has been found to be active against four species of bacteria, including vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus* [14].

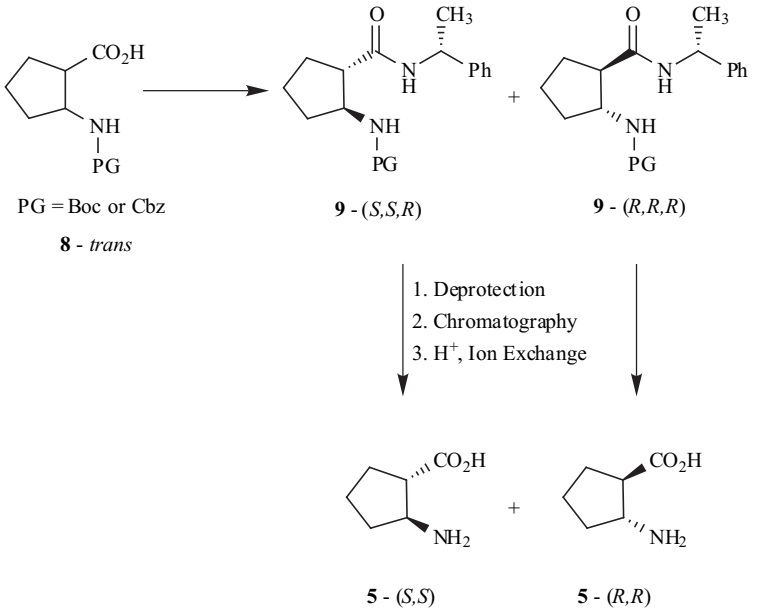
Given the significance of this class of molecules, a number of novel methods for the synthesis of conformationally restricted optically pure β-amino acids (Fig. (**2**), **4-7**) have emerged. These methods include techniques such as classic resolutions, diastereomeric salt formations and separations, biocatalyzed transformations, enantioselective synthesis, and, more recently, asymmetrically catalyzed chiral induction reactions. These cyclic molecules have limited conformational mobility, which allows for carefully controlled placement of functional groups, making them interesting and much-sought-after substrates for application purposes.

II. CHIRAL CYCLOHEXYL AND CYCLOPENTYL β-AMINO ACIDS

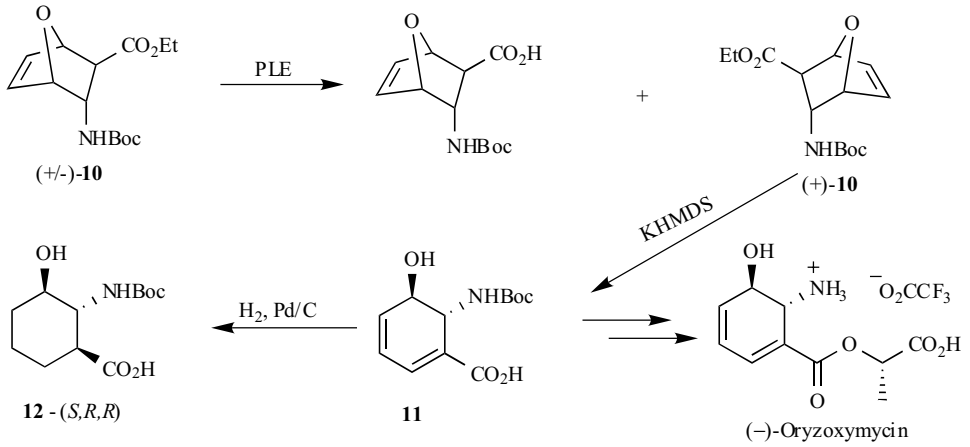
Resolution Methods

Of the known cyclic β-amino acids, 2-aminocyclohexanecarboxylic acid (2-ACHC, **4**) and 2-aminocyclopentanecarboxylic acid (2-ACPC, **5**) have been the most commonly investigated derivatives. The most frequent preparative methods for the optically pure five- and six-member rings have employed resolution techniques. The cinchona alkaloids quinine and quinidine have been used to resolve cyclic β-amino acid derivatives through desymmetrization reactions [15, 16]. *Cis*- and *trans*-2-ACPC and the corresponding diastereomers of 2-ACHC have been successfully separated into their enantiomers through diastereomeric salt formation with chiral derivatives such as (–)-ephedrine [17] and cinchonine [18] followed by fractional crystallization and subsequent desalting. Chiral auxiliaries have also been employed for the resolution of the larger cyclic β-amino acids through diastereomeric pair formation. For instance, the groups of Goodman [17] and Fülöp [19] have separated the two enantiomers of *trans*-2-ACPC by coupling the racemic compound **8** with *R*-(+)-α-methylbenzylamine (Scheme **1**). The diastereomers **9**-(*S,S,R*) and **9**-(*R,R,R*) were *N*-deprotected and could then be easily separated *via* column chromatography. Subjection to strong acid to cleave the chiral amine auxiliary and subsequent anion exchange afforded either chirally pure *trans*-β-amino acid enantiomer **5**-(*S,S*) or **5**-(*R,R*). Other groups have also used similar chiral auxiliary strategies and reductive amination procedures to produce optically pure five- and six-member analogs [20-23].

Enzymatic resolutions have also been used to produce enantiomerically enriched cyclopentyl and cyclohexyl β-amino acids. Kanerva *et al.* resolved all four enantiomers of both 2-ACPC and 2-ACHC based on lipase PS-mediated acylation in organic solvents [24]. Likewise, lipase AK has also proven to be successful in controlling the selective acylation of *cis*-2-ACPC precursors, thus allowing for the resolution and formation of diastereomers. The diastereomers were easily separated and, after further derivitization, furnished (*S,R*)-*cis*-**5** with an enantiomeric excess (ee) of 98% and (*R*,*S*)-*cis*-**5**, the previously mentioned (–)-cispentacin (**1**), in 90% ee [25]. Recently, the Fülöp and



Scheme 1. Resolution of *trans*-2-ACPC using *R*-(+)-α-methylbenzylamine.



Scheme 2. PLE-mediated synthesis of (–)-oryzoxymycin.

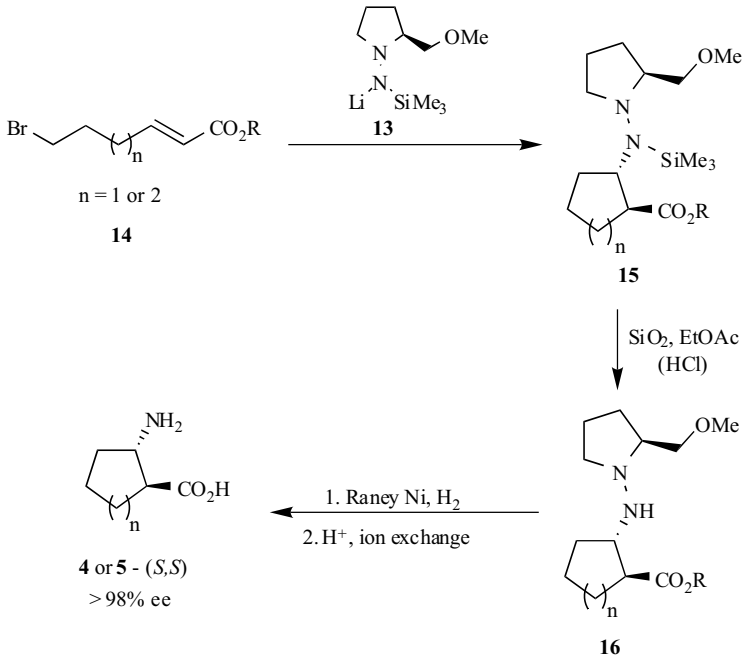
Kazlauskas laboratories have utilized lipase B (from *Candida antarctica*) to enantioselectively ring open racemic β-lactams. Using this methodology, the five-, six-, seven-, and even the eight-member products have been synthesized in very high enantiomeric excess [26, 27].

Another application of enzymatic resolution for the synthesis of β-amino acid derivatives is the more recent synthesis of (–)-oryzoxymycin by the Steel laboratory [28]. The cyclic β-amino acid, **12**-(*S,R,R*), was produced from a precursor (**11**) of the aforementioned natural product (Scheme 2). A bicyclic amino ester, (±)-**10**, derived from a Diels-Alder reaction between furan and a β-nitroacrylate, was resolved through enzymatic hydrolysis mediated by pig liver esterase (PLE). Following the kinetic resolution, base-promoted fragmentation of (+)-**10** with potassium hexamethyldisilazane (KHMDS) afforded the carboxylic acid derivative **11**, which, through subsequent steps, led to the desired natural product. Hydrogenation of the synthetic intermediate **11** over Pd/C in methanol led to the production of the enantiopure γ-hydroxyl cyclic β-amino acid derivative, **12**.

Asymmetric Synthesis and Catalysis

While resolution of racemic mixtures has been shown to have a viable route to optically pure **4** and **5**, enantiomers are simply separated, not selectively produced. As a result, half of the starting material is left unused as the opposite enantiomer. For example, in the synthesis of (–)-oryzoxymycin (Scheme **2**) the PLE-mediated enzymatic hydrolysis step renders the hydrolyzed enantiomer as an unneeded side product. Enantioselective synthesis, on the other hand, is a more efficient technique for the selective production of a single enantiomer in higher yields.

An elegant example of the asymmetric synthesis of five- and six-member cyclic β-amino acids was developed by the Enders laboratory [29] and further applied by O'Brien and co-workers [30]. This synthesis entailed the addition of the



Scheme 3. TMS-SAMP-mediated synthesis of optically pure five- and six-member cyclic β-amino acids.

chiral ammonia-equivalent (*S*)-(–)-2-methoxymethyl-1-trimethylsilylaminopyrrolidine (TMS-SAMP, **13**) to a bromo-substituted enolate (**14**) yielding diastereomerically pure **15** (Scheme **3**). After desilyation of **15**, reductive N-N bond cleavage and ester hydrolysis of **16**, followed by ion-exchange chromatography, produced (*S,S*)-*trans*-cyclic β-amino acids **4** or **5** with over 98% ee.

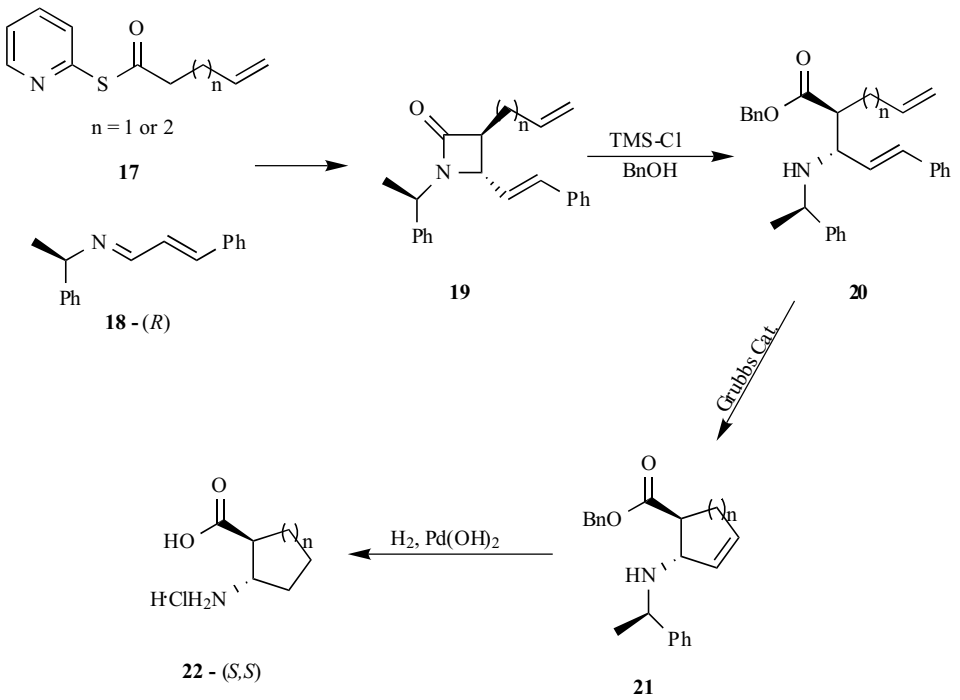
A number of other synthetic approaches targeting chirally pure **4** and **5** have been developed in which chiral starting materials transfer their optical purity into the final products. Intramolecular nitrone-olefin cycloaddition starting from an (*R*)-aldehyde has proven to be an effective route to (–)-cispentacin, **1** [31], while both enantiomers (+ and –) of α-pinene have been reacted with chlorosulfonyl isocyanate to afford β-lactam intermediates, which were ring-opened to give rise to derivatives of **4** with ee's greater than 99% [32]. Similarly, chlorosulfonyl isocyanate can be added regio- and stereoselectively to (+)-3-carene to yield an enantiopure β-lactam, which was also ring-opened to afford the corresponding cyclic β-amino acid derivatives [33]. The Davies [34] and Price [35] laboratories have also successfully produced derivatives of **4** and **5** with high enantioselectivities from substituted cycloalkene carboxylates using optically pure lithium (α-methylbenzyl)benzylamide as chiral nucleophiles.

More recently, Aggarwal and co-workers have developed a method in which an enantiomerically pure ketene dithioacetal bis(sulfoxide) was used as a "chiral controller" to produce (–)-cispentacin, **1** [36, 37]. This reaction proceeded by stereospecific intramolecular 1,3-dipolar nitrone cycloaddition onto the ketene with a three-carbon tether. Using this method, the Aggarwal group has also successfully synthesized other optically pure analogs of **5** in high enantiomeric excess.

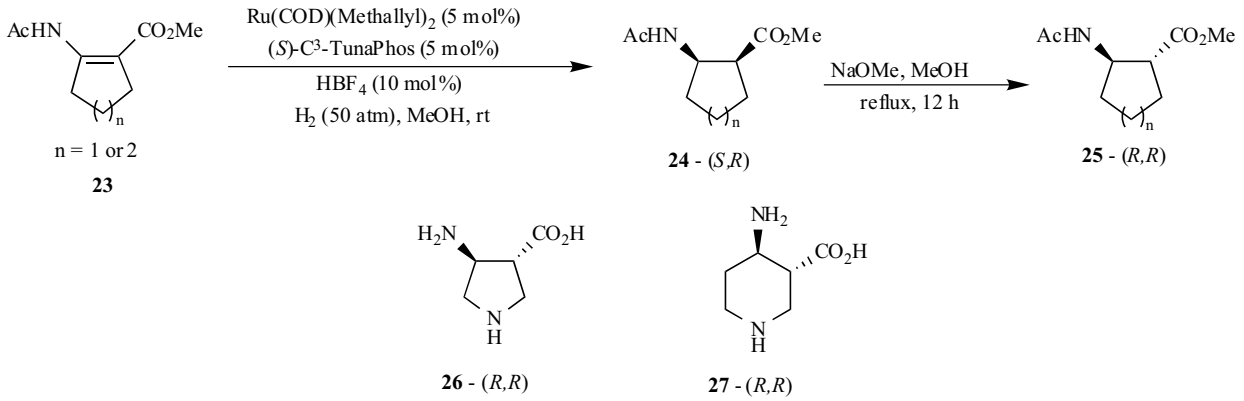
Chiral epoxides have also been used as starting materials for the synthesis of cyclic β-amino acids. Vaccaro and co-workers have recently reported the use of a one-pot copper-catalyzed synthesis of *anti*-α-hydroxy *cis*-**4**, one member of an important class of α-hydroxy-β-amino acid compounds [38]. The reaction proceeded by azidolysis of an α,β-epoxycarboxylic acid followed by *in-situ* reduction of the resulting β-azido-α-hydroxycarboxylic acid. A key aspect of this reaction process is that the same copper catalyst is responsible for both the oxirane ring-opening by sodium azide and the subsequent azido group reduction process. Another benefit of this high-yielding reaction pathway is the use of water as a solvent, as opposed to an organic reaction medium. Vaccaro's group has also scaled-up this reaction to produce gram quantities of the product while completely recovering and reusing the active catalyst.

Ring-closing olefin metathesis (RCM) has received recent attention as a means to five- and six-member cyclic β-amino acids. The Perlmutter laboratory has shown that the nucleophilic addition of chiral imine **18** to pyridyl thioester **17** in the presence of a tin(IV) chloride Lewis acid furnished the asymmetric β-lactam intermediate **19** (Scheme **4**) [39]. Ring-opening of the β-lactam with chlorotrimethylsilane in a solution of benzyl alcohol gave **20**, a suitable RCM substrate. Treatment of **20** with the Grubbs ruthenium metathesis catalyst, $(PCy_3)_2Cl_2Ru{=}CHPh$, produced cyclic compounds **21** (n = 1 or 2), which after $Pd(OH)_2$-catalyzed hydrogenation, afforded the amine-hydrochloride protected salt in the (*S,S*) conformation (**22**).

The Davies laboratory has also utilized Grubbs catalyst to form conformationally constrained β-amino acids *via* RCM [40]. Chiral dienes suitable for RCM were synthesized *via* the diastereoselective conjugate addition of an (*S*)-lithium amide to a variety of α,β-unsaturated acceptors.



Scheme 4. Synthesis of cyclic five- and six-member β-amino acids *via* ring-closing metathesis.



Scheme 5. Asymmetric hydrogenation of β-amino acid precursors.

Using this method, the Davies group has prepared the optically pure five-member ring compound **22**, also in the (*S,S*) conformation. Other work completed in the Davies laboratory has also produced similar high-yield RCM methods for the synthesis of (*S*)-homopipecolic acid and (*S*)-homoproline, two cyclic β-amino acid derivatives in which a nitrogen-containing ring is chirally substituted in the C1-position with an acetic acid moiety [41].

An elegant example of catalytic asymmetric β-amino acid synthesis has recently been reported by Tang and co-workers [42]. This is an attractive method of synthesis since chirality can be induced *via* a chiral catalyst instead of by expensive, and sometimes difficult to make, starting materials. In Tang's approach, a ruthenium and chiral biaryl ligand system was used for the asymmetric hydrogenation of easily synthesized tetra-substituted olefins of cyclic β-(acylamino)acrylates (Scheme **5**). Quantitative conversions and enantiomeric excesses up to >99 % were reported when the chiral ligand C^3-TunaPhos was used in the system to hydrogenate the five- and six-member cyclic olefins (**23**). Further base-induced epimerization of the *cis*-(1*S*,2*R*)-products (**24**) at the C^1 position of the ring affords the *trans*-(1*R*,2*R*)-β-amino acids (**25**) with stereoretention at the C^2 position. This approach allows for the asymmetric synthesis of both *cis* and *trans* isomers of the cyclic β-amino acids. The scope of this system has also been expanded for the synthesis of the heteroatom-containing *trans*-(1*R*,2*R*)-4-aminopyrrolidine-3-carboxylic acid ((1*R*,2*R*)-APC, **26**), another important cyclic β-amino acid. Gellman's laboratory has also developed several enantioselective methods for the production of both **26** and the six-member ring analog *trans*-4-aminopiperidine-3-carboxylic acid (APiC, **27**) for use in the generation of short water-soluble β-peptides [43, 44].

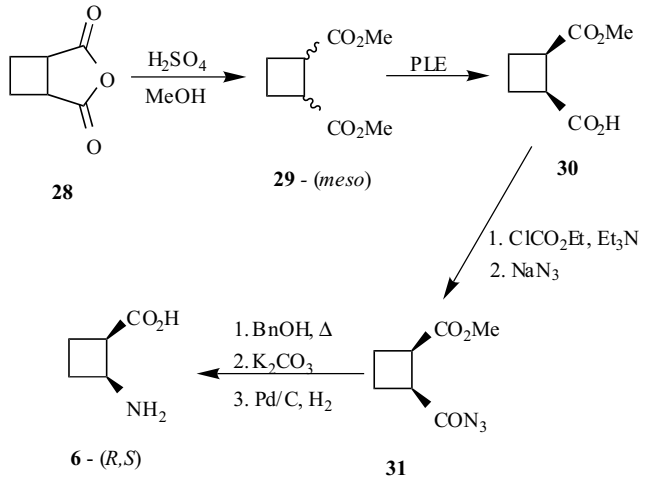
Romo and co-workers recently employed an asymmetric nucleophile-catalyzed aldol-lactonization reaction to synthesize carbocycle-fused β-lactones. One such bicyclic lactone can be induced to undergo ring cleavage under mild conditions to afford the precursor to enantiomerically pure (*S,S*)-*trans*-2-ACPC, **5** [45].

III. CHIRAL CYCLOBUTYL AND CYCLOPROPYL β-AMINO ACIDS

Fewer approaches have been developed for the asymmetric synthesis of 2-aminocyclobutanecarboxylic acid (2-ACBC, **6**) and 2-aminocyclopropanecarboxylic acid (2-ACC, **7**). Much like the five- and six-member analogs, the most common synthetic routes to these molecules are based on resolution and desymmetrization; however, more recent procedures have been reported in which other methodologies were utilized.

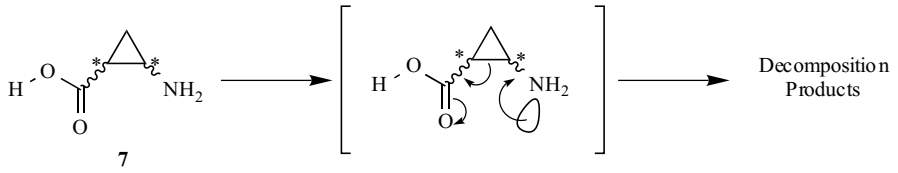
Resolution Methods

An enantioselective synthesis of (*R,S*)-2-ACBC (**6**) starting from the maleic anhydride derivative **28** was reported by Martin-Vilà *et al.* (Scheme **6**) [46]. The anhydride was successfully converted to the meso-diester **29** through Fisher esterification. Chemoenzymatic desymmetrization of the diester using PLE proved to be an efficient route to the *cis*-hemiester analog **30** with greater than 97% ee. Degradative conversion of the carboxylic acid moiety of **30** to an amino group was accomplished *via* an intermediate acyl azide (**31**). Following a Curtius rearrangement in the presence of benzyl alcohol and after deprotection of the amino group through catalytic hydrogenation, **6**-(*R,S*) was produced with 91% ee.



Scheme 6. PLE-mediated desymmetrization of cyclobutyl β-amino acid.

Unprotected 2-aminocyclopropanecarboxylic acids such as **7** are not known to date. These compounds have not been isolated due to the well-known tendency of donor-acceptor substituted cyclopropanes to rapidly undergo ring-opening and subsequent hydrolysis or condensation reactions



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Scheme 7. The rapid decomposition of unprotected 2-aminocyclopropanecarboxylic acid.

(Scheme **7**) [47-49]. Optically pure 2-ACC's, however, represent a very important class of β-amino acids in that they are the most conformationally rigid β-alanine or γ-aminobutyric acid (GABA) derivatives [50]. Although free-base 2-ACC's cannot be isolated (*vide supra*), they can be formed and used in further synthesis if the amino group is protected with an electron-withdrawing group such as a carbamate.

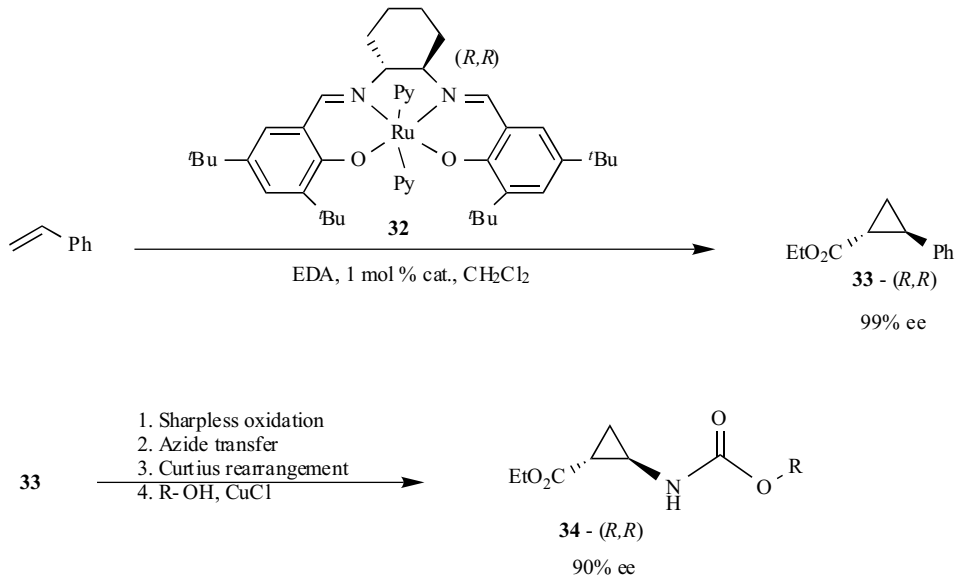
Similar to 2-ACBC, cyclopropyl β-amino acids have also been synthesized asymmetrically through chemoenzymatic desymmetrization as demonstrated by Csuk and Scholz [51]. They prepared *N*-Boc-protected 2-ACC starting from *meso*-dimethyl-1,2-cyclopropanedicarboxylate, obtained from the reaction of methyl acrylate and methyl chloroacetate. PLE-mediated selective hydrolysis desymmetrized the ring and afforded the mono ester in >99% ee. Curtius degradation of the carboxylic acid functionality by reaction with diphenylphosphoryl azide while heating in *tert*-butanol gave the final *N*-Boc-protected 2-ACC product. While this synthetic scheme proved successful as a route to cyclopropyl β-amino acids, the enantiopurity of the final product was not reported. Other groups have taken a similar approach to 2-ACC formation but have noted a dramatic decrease in the enantiomeric excess of the final cyclopropyl product. This racemization is presumably caused by heating required during the rearrangement and carbamate protecting group formation steps [46].

An analogous method for the formation of cyclopropyl β-amino acid derivatives has been developed by Hibbs and coworkers [52]. Desymmetrization of cyclopropane 1,2-dicarboxylic anhydride using (*S*)-proline *tert*-butyl ester afforded a large diastereomeric excess of one of the cyclopropyl amino acid products. Separation of the major product and subsequent conversion to an acyl azide followed by a Curtius rearrangement and amine protection furnished the (1*S,*2*R*)-*cis*-ACC analogs. As previously noted with other approaches, final ee's of the synthetic products were not reported.

More recently, catalytic methods have been developed to aid in the selective formation of the cyclopropane unit. The use of copper(II) triflate and phenylhydrazine as a catalyst system for the cyclopropanation of *N*-protected pyrroles has been reported by the Reiser laboratory [53]. Chirality was not induced *via* the catalyst but through kinetic enzymatic resolution by PLE on the cyclopropane-containing bicyclic product of the catalytic reaction. Ring-cleavage by reductive ozonolysis and subsequent oxidation yielded an *N*-Boc-protected derivative of **7** in high optical purity.

Asymmetric Synthesis and Catalysis

Chiral catalyst induction of optical purity into cyclopropyl β-amino acids has recently been developed by the Nguyen laboratory (Scheme **8**) [54]. This approach utilized the high enantioselectivity of a chiral (salen)ruthenium(II) catalyst (**32**) for the cyclopropanation of styrene with ethyl diazoacetate (EDA) to form (*R,R*)-*trans*-2-phenyl cylcopropanecarboxylic acid ethyl ester, **33**. Oxidation of the phenyl moiety of **33** using the Sharpless oxidation protocol (*in-situ* generated RuO_4 oxidation)



Scheme 8. Synthesis of 2-ACC using a chiral (salen)Ru(II) catalyst.

followed by azide transfer (with ethyl chloroformate/sodium azide) and subsequent Curtius rearrangement in toluene gave rise to a chiral cyclopropyl isocyanate. Further protecting group formation yielded the β-amino acid derivative (**34**) in high ee. The overall yield for this method was amongst the highest reported in the literature. Further, the chirality of the final cyclopropyl amino acid is introduced through the chiral catalyst and not through yield-lowering resolution.

IV. CONCLUSION

In recent years, there have been numerous advances in the development of efficient asymmetric syntheses to produce conformationally constrained cyclic β-amino acids. Compounds such as **4-7** are currently in high demand due to their importance in the fields of medicinal and biological chemistry. Further, they are versatile starting materials and chiral auxiliaries for a plethora of important reactions. As the number of exciting applications of these molecules continue to grow, high-yielding and non-resolution approaches for their synthesis are certain to gain even more attention.

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