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Synthesis of (1*R*,2*S*)-1-Amino-2-vinylcyclopropanecarboxylic Acid Vinyl-ACCA) Derivatives: Key Intermediates for the Preparation of Inhibitors of the Hepatitis C Virus NS3 Protease

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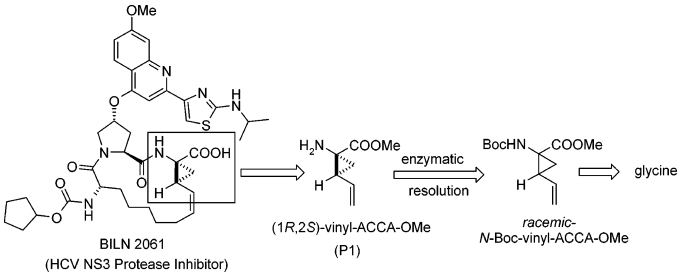

(1*R*,2*S*)-1-Amino-2-vinylcyclopropanecarboxylic acid (vinyl-ACCA) is a key building block in the synthesis of potent inhibitors of the hepatitis C virus NS3 protease such as BILN 2061, which was recently shown to dramatically reduce viral load after administration to patients infected with HCV genotype 1. We have developed a scalable process that delivers derivatives of this unusual amino acid in >99% ee. The strategy was based on the dialkylation of a glycine Schiff base using *trans*-1,4-dibromo-2-butene as an electrophile to produce racemic vinyl-ACCA, which was subsequently resolved using a readily available, inexpensive esterase enzyme (Alcalase 2.4L). Factors that affect diastereoselection in the initial dialkylation steps were examined and the conditions optimized to deliver the desired diastereomer selectively. Product inhibition, which was encountered during the enzymatic resolution step, initially resulted in prolonged cycle times. Enrichment of racemic vinyl-ACCA through a chemical resolution via diastereomeric salt formation or the use of forcing conditions in the enzymatic reaction both led to improvements in throughput and the development of a viable process. The chemistry described herein was scaled up to produce multikilogram quantities of this building block.

Introduction

The hepatitis C virus, discovered more than a decade ago,[1] has infected more than 170 million people worldwide.[2] In 70−80% of cases, the viral infection leads to a chronic liver disease that can progress to life-threatening cirrhosis of the organ or hepatocellular carcinomas. Currently available therapies are limited to the use of PEGylated interferons (IFN-α) in combination with the broad-spectrum antiviral ribavarin. Severe side effects are associated with these regimes, and a significant

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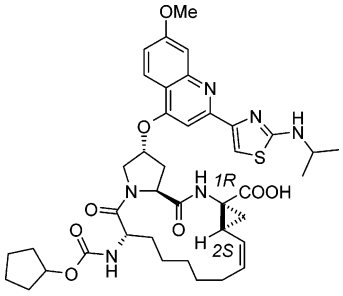
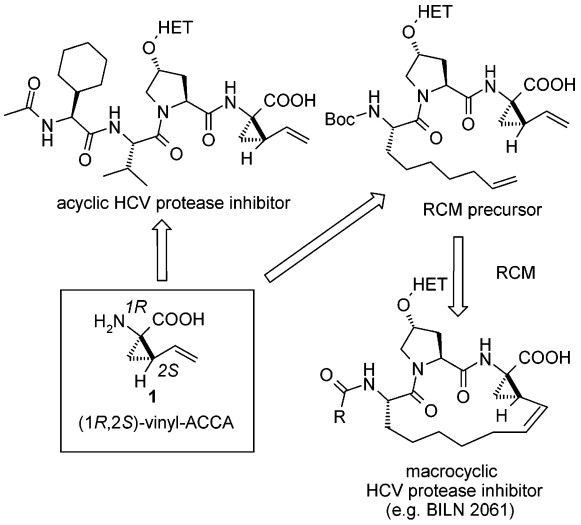


FIGURE 1. Structure of HCV protease inhibitor BILN 2061.

proportion of the patient population does not respond to treatment.[3] The virally encoded enzymatic functions that are essential for replication of the virus have been the focus of intense research aimed at the discovery of novel HCV therapeutics.[4] In particular, promising small-molecule leads have been discovered that target the serine protease activity of the NS3/NS4A enzyme−cofactor complex, which is responsible for maturation of the single polyprotein encoded by the 9.6 Kb genome of the HCV virus.[4] Recently, the design and optimization of novel and specific inhibitors of the protease were reported,[5a,b] culminating in the discovery of BILN 2061 (Figure 1), a macrocyclic peptidomimetic molecule that possesses biopharmaceutical properties suitable for development as an antiviral agent.[5c] BILN 2061, the first small-molecule inhibitor of HCV RNA replication to advance into clinical trials, demonstrated an unprecedented antiviral effect when administered to patients infected with HCV genotype 1, establishing the first proof-of-concept in man for HCV NS3 protease inhibitors.[6]

We recently reported the synthesis of BILN 2061, used during the discovery phase of the program.[7] As depicted in Scheme 1, a key feature of this class of inhibitors is a configurationally defined (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic acid (vinyl-ACCA) **1** being either

SCHEME 1. Synthesis of HCV Protease Inhibitors



present at the C-terminus (P1 position) of acyclic versions of inhibitors[8] or required as an intermediate for the formation of macrocyclic molecules by ring-closing metathesis.[5a] In support of preclinical and clinical activities associated with these new potential HCV therapeutics, we required large quantities of a suitably protected form of (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic acid (**1**), and chemistry that would allow the large-scale preparation of this compound had to be developed. We report herein the successful achievement of this objective through the development of a scalable sequence involving the initial preparation of racemic material followed by an enzymatic resolution of this highly hindered α,α-disubstituted amino acid derivative on multikilogram batches.

Results and Discussion

Analogues of 1-aminocyclopropanecarboxylic acid (ACCA) have found widespread application as inhibitors of plant biosynthesis and components of conformationally restricted peptidomimetics in drug design.[9] Several reports in the literature describe the syntheses of dehydrocoronamic acid derivatives such as **1**; however, none were felt to be suitable for producing derivatives of this compound on a large scale.[10] After some initial exploratory work, we rapidly came to the realization that the

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(7) Faucher, A.-M.; Bailey, M. D.; Beaulieu, P. L.; Brochu, C.; Duceppe, J.-S.; Ferland, J.-M.; Ghiro, E.; Gorys, V.; Halmos, T.; Kawai, S. H.; Poirier, M.; Simoneau, B.; Tsantrizos, Y. S.; Llinàs-Brunet, M. *Org. Lett.* **2004**, *6*, 2901.

(8) Rancourt, J.; Cameron, D. R.; Gorys, V.; Lamarre, D.; Poirier, M.; Thibeault, D.; Llinàs-Brunet, M. *J. Med. Chem.* **2004**, *47*, 2511. Since the initial discovery that vinyl-ACCA confers exceptional potency when incorporated in the P1 position of peptidomimetic-based HCV protease inhibitors (Llinas-Brunet, M.; Bailey, M. D.; Cameron, D. R.; Faucher, A.-M.; Ghiro, E.; Goudreau, N.; Halmos, T.; Poupart, M.-A.; Rancourt, J.; Tsantrizos, Y. S.; Wernic, D.; Simoneau, B. *PCT Int. Appl.* **2000**, WO 00/09543 A2), others have since adopted the use of this fragment and derivatives thereof for the design of HCV protease inhibitors. See for example: (a) Campbell, J. A.; Good, A. *PCT Int. Appl.* **2002**, WO 02/060926 A2. (b) Wang, X.-d. A.; Sun, L.-Q.; Sit, S.-Y.; Sin, N.; Scola, P. M.; Hewawasam, P.; Good, A. C.; Chen, Y.; Campbell, J. A. *PCT Int. Appl.* **2003**, WO 03/099274 A1. (c) Miao, Z.; Sun, Y.; Wu, F.; Nakajima, S.; Xu, G.; Or, Y. S.; Wang, Z. *PCT Int. Appl.* **2004**, WO 04/072243 A2.

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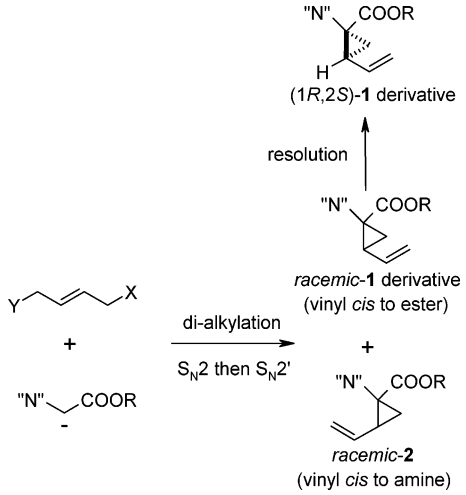
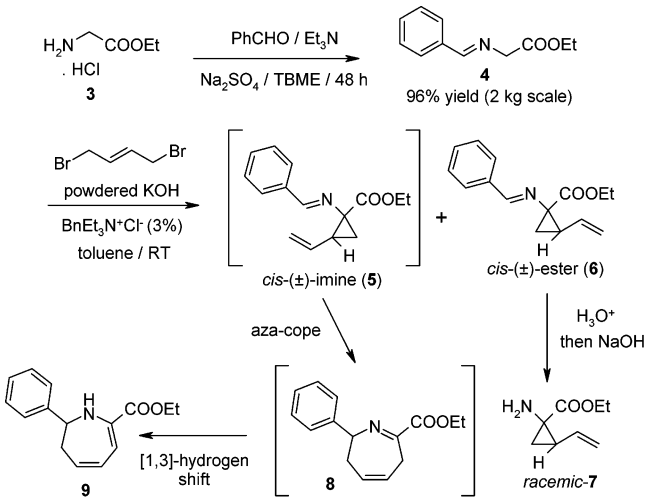
SCHEME 2. Strategy for the Synthesis of Vinyl-ACCA



SCHEME 3. Initial Synthesis of Racemic Vinyl-ACCA-OEt



development of an enantioselective route to derivatives of **1** on a large scale would be challenging and require a significant investment in time and resources. Therefore, we elected for the synthesis of easily accessible racemic versions of **1**, for which some precedent is available from the literature. We then hoped that a suitable procedure could be identified to carry out the resolution of this hindered substance and provide enantiomerically pure derivatives.

Synthesis of Racemic Vinyl-ACCA Derivatives. As shown in Scheme 2, and building on literature precedent, the sequential S_N2-S_N2' dialkylation of protected glycine anions with 2-butene-1,4-dielectrophiles should lead to the formation of two diastereomeric derivatives (**1** and **2**) in racemic form.[11] Separation of the desired isomer (racemic-**1**), which positions the vinyl substituent in a cis orientation relative to the ester group, followed by resolution, should provide access to derivatives of **1** in enantiomerically pure form. To develop an efficient process, factors governing the control of stereochemistry at C-2 to provide the desired orientation of the vinyl group with optimal efficiency would have to be investigated first. The proper choice of protecting groups for the nitrogen and carboxylic acid functionalities, which would allow convenient resolution of the material by either chemical (diastereomeric salt formation) or enzymatic means, would impose additional restrictions.

After considering several protected forms of glycine esters as potential starting materials, we found that readily available and inexpensive Schiff bases prepared from aromatic aldehydes provided convenient protection and activation of the starting substrate. The pK_a of such aromatic glycine imines (equilibrium acidities in DMSO ~19)[12] allows deprotonation and alkylation under a variety of basic conditions, including phase transfer catalysis. In the last 15 years, several groups have published elegant methodologies for the stereoselective synthesis of α-alkylamino acids using asymmetric phase-transfer-catalyzed alkylation of glycine imines,[13] and more recently, the development of more powerful catalysts has extended the scope to the synthesis of chiral, nonracemic α,α-dialkylamino acids.[14] While enantioselective processes such as those mentioned above would appear to be attractive, they generally require the use of the expensive benzophenone imine of *tert*-butyl glycinate to achieve practical levels of enantioselectivity. Initial attempts at asymmetric phase transfer catalysis did not generate promising results, and our efforts were then focused on optimizing a simple entry into the racemic series. Preliminary experiments using the benzaldehyde imine of ethyl glycinate (**4**) are shown in Scheme 3.

Imine **4** was prepared by condensation of benzaldehyde with ethyl glycinate hydrochloride (**3**) in the presence of a desiccant as shown in Scheme 3.[15] This reaction was easily carried out on a multikilogram scale, delivering quantitative yields of imine **4**, which was used without

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(15) Haddow, J.; Suckling, C. J.; Wood, H. C. S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1297.

purification following isolation from an aqueous workup. Imine **4** was then reacted with *trans*-1,4-dibromo-2-butene, excess powdered KOH, and a catalytic amount of phase transfer catalyst, providing a 45% yield of crude racemic vinyl-ACCA ethyl ester **7** after an acid/base workup (Scheme 3). ^{1}H NMR analysis of **7** revealed the presence of a single diastereomer (vinyl group cis to the ester) in the isolated product. We were intrigued by the fact that only one diastereomer was isolated from this reaction since a priori we did not expect such a level of diastereomeric control in the ring-closing step. The reaction was repeated under identical conditions, but following completion, an aliquot of the reaction mixture was analyzed by ^{1}H NMR prior to the aqueous acidic workup (see Experimental Section). Analysis indicated the presence of the desired benzaldehyde imine of vinyl-ACCA-OEt (**6**) and a second component in a 3:1 molar ratio. Following the usual aqueous acidic workup, the desired racemic vinyl-ACCA ester **7** was isolated in the usual yield and diastereomeric purity.[16] ^{1}H NMR analysis of the organic wash of the acidic aqueous phase revealed the presence of benzaldehyde from imine hydrolysis and a second component. This byproduct was isolated by flash chromatography and following spectroscopic characterization was assigned the seven-membered ring structure **9**. The formation of compound **9** can be rationalized through initial formation of diastereomeric cyclopropane derivative **5** with the vinyl group cis to the imine. Imine **5** is ideally set up for a facile and spontaneous aza-Cope rearrangement to give **8**, which then undergoes a [1,3]-hydride shift to deliver **9**. Such aza-Cope rearrangements have been reported previously on similar systems.[11b,c] This result demonstrated that, under these precise reaction conditions, ring closure was poorly diastereoselective (3:1 mixture of vinyl cis/trans to the ester), providing a partial explanation for the modest recovery[16] of the desired product **7** in this experiment. Despite the decrease in yield resulting from the poor diastereoselectivity, the unexpected aza-Cope rearrangement of the isomeric product to give a neutral molecule provided a convenient means of removing this unwanted isomer by a simple extraction, and the desired vinyl-ACCA derivative **7** was obtained in relatively pure form without need for potentially difficult separations/purifications.

Studies were then performed with the objective of increasing the overall efficiency of this process by improving on its diastereoselectivity. Changing the substrate from a benzaldehyde to a benzophenone imine[17] had no effect on the diastereomeric ratio or yield of racemic amino ester **7** (results not shown). Similarly, the presence of substituents at the 4-position of the aromatic ring of imine **4** (4-chloro or 4-bromo)[14a] had no influence on the dr or yield of **7** and only contributed to increasing the cost of raw materials. Changing the electrophile from *trans*-1,4-dibromo-2-butene to the corresponding *cis*- or *trans*-1,4-dichloro, *cis*-1,4-dimesylate, or *cis*-1,4-ditosylate electrophiles resulted in the formation of varying amounts of the isomeric 1-amino-3-cyclopentenecarboxylate as previously described in the literature (results not shown).[11a] Temperature similarly had no significant effect on the outcome of this reaction. The use of methyl glycinate instead of the ethyl ester resulted in a slight decrease in yield, presumably as a result of competing hydrolysis or self-condensation of the less hindered ester under the reaction conditions.

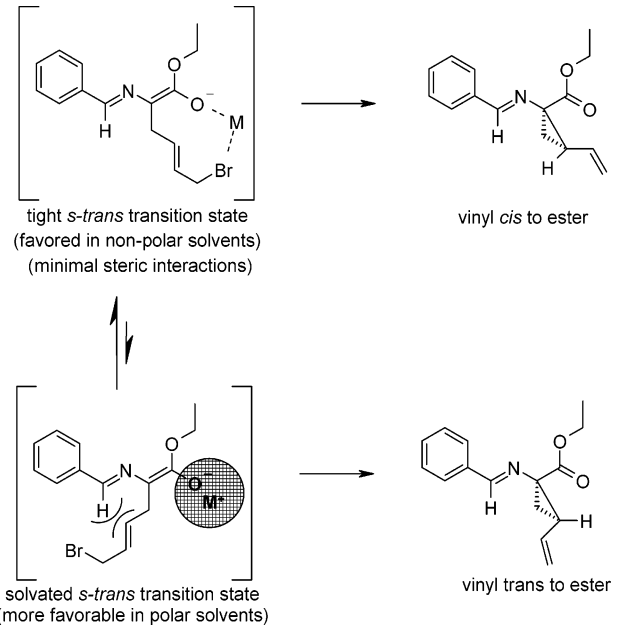
A systematic investigation of bases and solvents for carrying out the alkylation of imine **4** with *trans*-1,4-dibromo-2-butene was then undertaken, and the results are summarized in Table 1.

The use of lithium, sodium, or noncoordinating tetramethylammonium hydroxide in toluene (entries 1, 2, and 5) did not result in the formation of the desired cyclopropane derivative and eventually led to decomposition of the imine substrate. The more soluble cesium hydroxide (entry 4)[13e] did not provide any advantage in diastereomeric ratio over KOH (entry 3). When hindered *tert*-butoxide bases were investigated, remarkable countercation and solvent effects were encountered, suggesting that a strong control of diastereoselectivity could be achieved with the appropriate choice of reaction conditions. As seen in Table 1, the use of strongly coordinating lithium *tert*-butoxide in a hydrophobic nonpolar solvent such as toluene, favoring the formation of strong aggregates, led to the almost exclusive formation of the desired vinyl cyclopropane **6** (entry 6; >40:1 dr). The use of more polar THF as a solvent led to an erosion of this selectivity (entry 7; dr = 6.5:1), suggesting that species controlling diastereoselectivity were being affected.[18] Further reinforcing our suspicions for the implication of strongly aggregated transition state enolates during the cyclopropanation of imine **4** was the outcome of the

(16) Amino ester **7** is partially soluble in water and volatile under reduced pressure. Special precautions such as saturating aqueous phases with NaCl and evaporating organic solutions of **7** at room temperature under reduced pressure must be taken to ensure good recovery of the material.

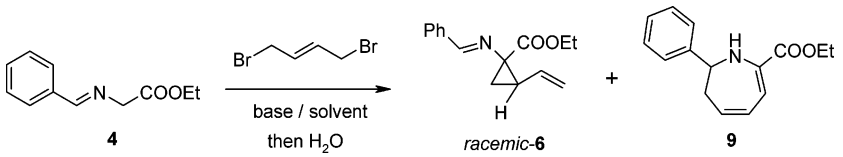
(17) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663.

(18) Similar effects of counterions on the diastereochemical outcome of similar S_N2' displacements have been observed in other systems; see for example: Boeckman, R. K., Jr.; Reeder, M. R. *J. Org. Chem.* **1997**, *62*, 6456. Wiliams, R. M.; Glinka, T.; Kwast, E. *J. Am. Chem. Soc.* **1988**, *110*, 5927. Such behaviors can be ascribed to the existence of tight aggregational states of the enolate in nonpolar solvents:



(19) Keegstra, M. A.; Verkruijsse, H. D.; Andringa, H.; Brandsma, L. *Synth. Commun.* **1991**, *21*, 721.

TABLE 1. Alkylation of Imine 4: Optimization Studies[a]



4 racemic-6 9

entry	base (equiv)	solvent	reaction time	ratio **6/9**[b]	comments
1	$LiOH{\cdot}H_2O$ $BnEt_3N^+Cl^-$ (3%)	toluene	18 h		decomposition
2	powdered NaOH $BnEt_3N^+Cl^-$ (3%)	toluene	18 h		decomposition
3	powdered KOH $BnEt_3N^+Cl^-$ (3%)	toluene	18 h	3:1	
4	$CsOH{\cdot}H_2O$ $BnEt_3N^+Cl^-$ (3%)	toluene	18 h	3:1	
5	25% w/w $Me4N^+OH^-H_2O$	toluene	18 h		decomposition
6	**LiO*t*Bu**	**toluene**	**1 h**	**>40:1**	
7		THF	1 h	6.5:1	
8	NaO*t*Bu	toluene	1 h	4.8:1	
9		THF	1 h	1.9:1	
10	KO*t*Bu	toluene	1 h	1.9:1	
11		THF	1 h	1.2:1	
12	**LiHMDS**	**hexane/toluene**	**1 h**	**>40:1**	
13	NaHMDS	toluene	1 h	14.3:1	
14	KHMDS	toluene	1 h	3.2:1	

[a] All reactions carried out at room temperature on a 500 mg scale and with 0.2 M concentration using 1.5 equiv of imine, 3 equiv of base, and *trans*-1,4-dibromo-2-butene as a limiting reagent. All reactions performed by adding dropwise a preformed mixture of imine and electrophile to the base. [b] Determined by ^1H NMR analysis after aqueous quench.

reactions using more loosely coordinated species such as those derived from sodium or potassium *tert*-butoxide. A significant decline in selectivity (from 40 to 4.8 and 1.9:1, respectively, as shown in entries 6, 8, and 10) was seen in toluene, which was further accentuated by the use of polar THF as a solvent (from 6.5 to 1.9 and 1.2:1; compare entries 7, 9, and 11). Similar results were obtained with the use of hexamethyldisilazane bases in toluene where ratios ranged from >40 to 14.3 to 3.2:1 for Li, Na, and K bases, respectively (entries 12−14). The slight increase in selectivity observed with HMDS bases compared to *tert*-butoxide could be the result of small quantities of *tert*-butyl alcohol being released during the reaction with the latter, which could contribute to a small solvent effect. In addition to the influence of the metal counterion and solvent on the degree of selectivity, we also noticed that reactions performed with less basic LiO*t*Bu generated cleaner reaction profiles (as judged by NMR analysis of crude reaction mixtures) and less polymeric side products (resulting from self-condensation of the imine enolates) than the stronger NaO*t*Bu, KO*t*Bu, and HMDS bases. These effects were reflected in the overall yield of isolated product (See Table 1, Supporting Information). Furthermore, it is known that 1,4-dibromo-2-butene will undergo E2′ elimination of HBr in the presence of bases such as KOH to produce isomeric mixtures of 1-bromo-1,3-butadienes,[19] and therefore conditions resulting in extended reaction times or the use of strong bases could also impact the yield of the reaction. Other bases (e.g., LiH, NaH, KH, LiOEt, LiOiPr, LDA) were also investigated with either disappointing results or no further improvements (results not shown).

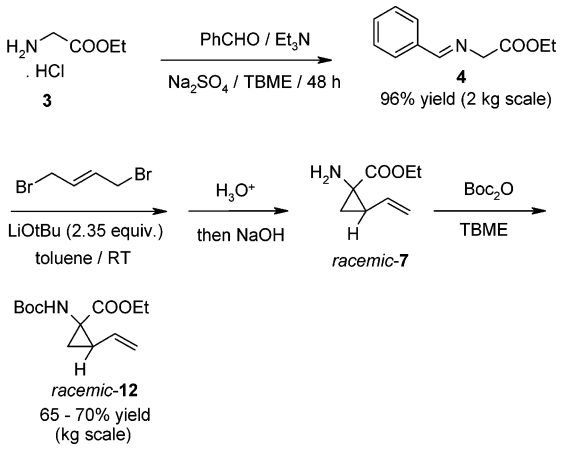
Having identified LiO*t*Bu and LiHMDS as the best choices for performing the dialkylation of glycine imine **4**, the protocol's parameters were further optimized to ensure its reproducibility and efficiency upon further scale-up. The results are shown in Table 1 in Supporting Information.

The optimal conditions called for using 1.25 equiv of imine **4** and 2.35 equiv of base, giving rise to a 69% isolated yield of Boc-protected racemic vinyl-ACCA-OEt **12** when the reaction was performed at room temperature (entry 5 in Table 1 of Supporting Information). Running the optimal reaction conditions with LiO*t*Bu at 0 °C or increasing the final concentration of reactants from 0.28 to 0.7 M had no effect on the yield (results not shown). Furthermore, the reaction was not sensitive to the rate of addition of reactants, although a slight exotherm was apparent upon addition of the imine and electrophile to the base (on scale, we found it preferable to add the imine and dibromide from separate reservoirs since mixtures of these two reactants were found to produce a white precipitate over time).[20] We were then confident that the above attributes made this process well suited for scale-up. In the event, the protocols proved to be highly reproducible. As shown in Scheme 4, the racemic Boc-protected vinyl-ACCA derivative **12** was obtained in 65−70% overall yield (kg scale) from glycine ethyl ester hydrochloride **3** and 1,4-dibromo-2-butene through a four-step process. The crude ester was obtained in sufficient purity for further processing, and no purifications were required in this sequence other than simple washes and back extractions.

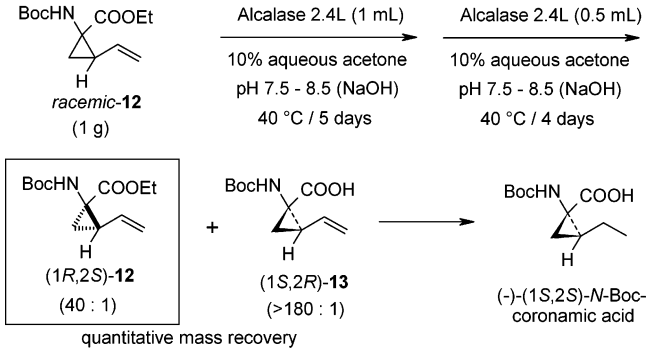
Enzymatic Resolution of Vinyl-ACCA Derivatives. The use of esterases for the enzymatic resolution of carboxylate esters derived from natural amino acid substrates is well documented.[21] However, reports of unnatural and hindered α,α-disubstituted amino esters

(20) Mixtures of imine **4** and 1,4-dibromo-2-butene generate small amounts of a white precipitate upon standing in toluene at room temperature. The solid was identified as glycine ethyl ester hydrobromide.

SCHEME 4. Optimized Synthesis of Racemic *N*-Boc-Vinyl-ACCA-OEt



SCHEME 5. Enzymatic Resolution of *N*-Boc-Vinyl-ACCA-OEt: Initial Result



acting as substrates for such processes are rare.[22] Recently, the use of inexpensive, commercially available, food-grade *Subtilisin-Carlsberg* (Alcalase 2.4L) for carrying out a very efficient, enantioselective hydrolysis of a variety of substituted succinate esters was reported.[23] This procedure was found to be readily scalable, and we demonstrated its application to the preparation of advanced homochiral intermediates on a kg scale, for the synthesis of peptidomimetic renin inhibitors.[24] Because this enzyme appeared to have rather large substrate tolerance and yet produced hydrolyzed products in very high enantiomeric purity, we decided to investigate its use for the enantiospecific hydrolysis of vinyl-ACCA esters such as **12** and the corresponding methyl ester **11** as shown in Scheme 5 for the ethyl analogue.

As one might have expected, the hydrolysis turned out to be quite difficult, requiring a total of 9 days at 40 °C (pH 7.5−8.5) on a 1 g scale with replenishing of the enzyme after 5 days. This is to be contrasted with our previous experience with succinate derivatives in which the resolution of 10 mol of substrate could be carried out in 3 days at room temperature.[24] Nevertheless, we were delighted that under forcing conditions, the enzyme did accept racemic-**12** as a substrate, which in itself was quite remarkable. Furthermore, HPLC analysis on a chiral support (see Experimental Section) of the unreacted ester **12** and of the hydrolyzed acid **13** (after re-esterification with diazomethane) revealed that the hydrolysis was highly enantioselective. The hydrolyzed isomer **13** was assigned the natural (1*S*,2*R*)-configuration (>180:1), while the unreacted ester **12** had the desired (1*R*,2*S*)-stereochemistry (40:1). The assignments are based on comparison with authentic samples from our previous studies and conversion of (1*S*,2*R*)-**13** to authentic (+)-(1*S*,2*S*)-*N*-Boc-coronamic acid by hydrogenation of the double bond.[8,25] It is noteworthy that in the case of ethyl ester **12**, despite the vigorous conditions (40 °C for 9 days at pH 7.5−8.5), no background saponification of racemic-**12** was observed as suggested by the high enantiomeric purity of the isolated carboxylic acid **13**. This is presumably a consequence of the steric bulk surrounding the ester function, which does not readily allow basic saponification at pH < 8.5 but nevertheless proceeds smoothly under the influence of the enzyme. As expected, the amino ester with the natural (*S*)-configuration at the α-center was preferentially hydrolyzed by the enzyme. Since for our studies we required the isomer of opposite (*R*)-configuration, this implied that resolution had to proceed to complete consumption of the (*S*)-isomer in order to isolate the (*R*)-antipode with good enantiomeric purity. In its present state, this enzymatic process required improvements in order to provide a practical route to enantiopure (1*R*,2*S*)-vinyl-ACCA derivatives on a large scale. While very efficient in terms of chemical and optical yields, reaction time had to be reduced significantly, and studies were conducted to optimize the resolution.

To improve on the rate of enzymatic hydrolysis of racemic vinyl-ACCA esters, a series of conditions were examined using both methyl and ethyl esters as substrates (**11** and **12**). The results are shown in Table 2.

As can be seen in the case of the ethyl derivative **12**, the % ee of remaining ester was not affected by the presence of cosolvents such as DMSO and acetone (entry 1 versus entry 2) or by modifying the ionic strength of the system using salts (entries 3−5).[26] However, when the reaction was carried out under 2-fold dilution, conversion increased, delivering material of 29% ee versus 13% ee. Furthermore, methyl ester **11** hydrolyzed faster than the corresponding ethyl ester **12** (16 vs 13%, entries 5 and 7), presumably due to increased solubility in water and/or reduced steric hindrance. Combining these two observations, we found that methyl ester **11** under the more dilute conditions (0.09 M) gave hydrolyzed material with 34% ee after 24 h (compare entries 7 and 8). These observations are indicative of product inhibition of the enzyme activity. Dilution of the reaction

(21) (a) *Enzymes in Synthetic Organic Chemistry*; Wong, C. H., Whitesides, G. M., Eds.; Elsevier Science, Inc.: New York, 1994. (b) *Enzyme Catalysis in Organic Synthesis. A Comprehensive Handbook*; Drauz, K., Waldmann, H., Eds.; VCH Publishers: New York, 1995; Vol. 1.

(22) See for example: (a) Weiguo, L.; Ray, P.; Benezra, S. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 553. (b) Spero, D. M.; Kapadia, S. R. *J. Org. Chem.* **1996**, *61*, 7398. (c) Kaptein, B.; Boesten, W. H. J.; Broxterman, Q. B.; Peters, P. J. H.; Schoemaker, H. E.; Kamphuis, J. *Tetrahedron: Asymmetry* **1993**, *4*, 1113. (d) Weiguo, L. *Application of Biocatalysis in Chemical Process Development: A Few Case Studies*; ACS Symposium Series 776; American Chemical Society: Washington, DC, 2001; p 178.

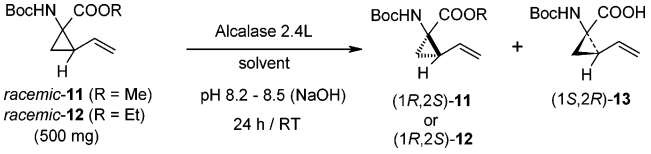
(23) Bailey, M. D.; Halmos, T.; Adamson, D.; Bordeleau, J.; Grand-Maître, C.; *Tetrahedron: Asymmetry* **1999**, *10*, 3285.

(24) Beaulieu, P. L.; Gillard, J.; Bailey, M.; Beaulieu, C.; Duceppe, J.-S.; Lavallée, P.; Wernic, D. *J. Org. Chem.* **1999**, *64*, 6622.

(25) Charette, A. B.; Côté, B. *J. Am. Chem. Soc.* **1995**, *117*, 12721.

(26) Bonneau, P. R.; Eyer, M.; Graycar, T. P.; Estell, D. A.; Jones, J. B. *Bioorg. Chem.* **1993**, *21*, 431.

TABLE 2. Enzymatic Resolution of *N*-Boc-Vinyl-ACCA Esters: Optimization[a]



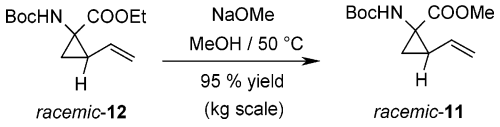
entry	R	conditions	[substrate] **11** or **12**	% ee of remaining ester[b]
1	Et (**12**)	H_2O	0.2 M	11
2	Et (**12**)	5% DMSO or 10% acetone	0.2 M	11
3	Et (**12**)	10 mM Na_2HPO_4	0.2 M	13
4	Et (**12**)	35 mM guanidinium chloride + 1 mM NaH_2PO_4	0.2 M	12
5	Et (**12**)	100 mM KCl	0.2 M	13
6	Et (**12**)	100 mM KCl/2x dilution	0.09 M	29
7	Me (**11**)	100 mM KCl	0.2 M	16
8	Me (**11**)	100 mM KCl/2x dilution	0.09 M	34

[a] All reactions carried out on a 2 mmol scale using 10 or 22 mL of solvent. Alcalase 2.4L (150 or 300 μL for 2x dilutions) was used. [b] Enantiomeric purity of remaining ester was determined by HPLC on a chiral support after stirring for 24 h at ambient temperature.

mixture results in more dilute concentrations of the inhibitory product (1*S*,2*R*)-**13** as it forms (compared to more concentrated conditions), allowing for further conversion of substrate. This study provided a simple and convenient solution to the long reaction times required under the initial conditions and led to a practical large-scale process for the resolution of vinyl-ACCA esters as described below.

Since methyl ester **11** provided greater conversion rates (Table 2), racemic ethyl ester **12** was transesterified as shown in eq 1 using methanolic NaOMe at 50 °C.

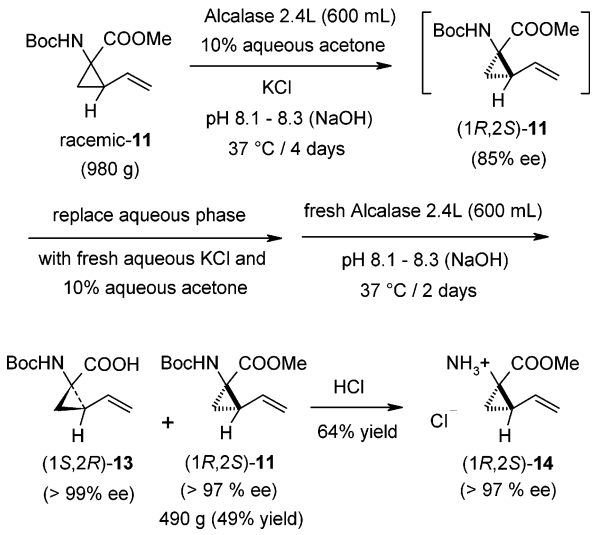
Transesterification of vinyl-ACCA esters.



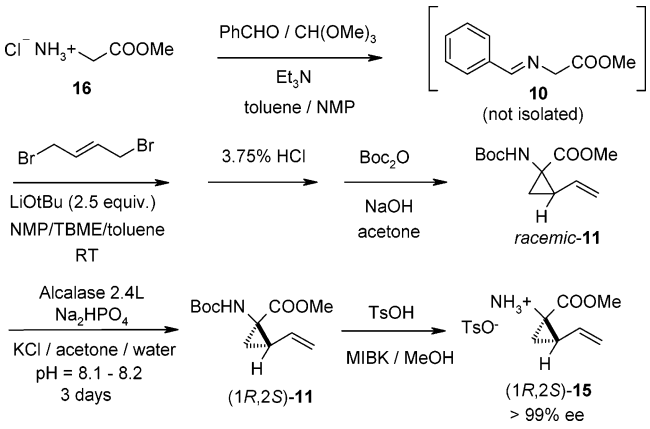
The enzymatic resolution or racemic-**11** was then carried out as shown in Scheme 6. After 91 h, the aqueous phase containing inhibitory product **13** was conveniently siphoned off and replaced with fresh 100 mM KCl and enzyme.[26] The enzyme-catalyzed hydrolysis of the organic phase containing enriched (1*R*,2*S*)-**11** (85% ee) was then resumed for an additional 48 h at which point HPLC analysis of the remaining ester indicated a dr of 154:1 (98.7% ee). The desired (1*R*,2*S*)-**11** was isolated by simple extraction (100% yield) and used without need for further purification. Deprotection using 4 N HCl in dioxane provided (1*R*,2*S*)-vinyl-ACCA methyl ester hydrochloride **14** as a crystalline solid in 64% yield (>97% ee) from crude (1*R*,2*S*)-**11** (Scheme 6).

Pilot Plant, Large-Scale Synthesis of (1*R*,2*S*)-1-Amino-2-vinylcyclopropanecarboxylic Acid Ethyl Ester, Tosylate Salt 15. Having demonstrated on a kg scale that the synthesis of racemic dehydrocoronamic acid derivatives followed by an enzymatic resolution was a viable approach to enantiomerically pure vinyl-ACCA

SCHEME 6. Enzymatic Resolution of *N*-Boc-Vinyl-ACCA-OMe: Optimized Conditions



SCHEME 7. Pilot Plant Synthesis of (1*R*,2*S*)-1-Amino-2-vinylcyclopropanecarboxylic Acid Methyl Ester, Tosylate Salt 15



derivatives, we began searching for further improvements to the overall process. In particular, we wanted to address the persistent need for extended reaction times necessitated by the formation of increasing amounts of inhibitory product (**13**) during the enzymatic resolution of the ester and the ensuing requirement for performing this step in two cycles. We envisaged that partial enrichment of **7** through a chemical resolution of the racemic amine should reduce the amount of inhibitory **13** formed during the resolution step, hence providing an effective solution to this issue. Overall, the combination of partial chemical enrichment/purification and enzymatic resolution provided a small improvement in efficiency, allowing the final enzymatic step to take place in a single cycle, thus minimizing plant time and operations (see Supporting Information). However, upon transfer from the kilogram lab to the pilot plant, the above enrichment step was not retained and the initial procedure was implemented with final modifications to streamline the overall process, minimizing the number of operations and isolation of intermediates. The final sequence is depicted in Scheme 7 (see Supporting Information for details).

Despite slightly reduced yields encountered during small-scale optimization of the cyclopropanation step,

methyl glycinate hydrochloride **16** was chosen as starting material rather than the corresponding ethyl ester **3** to avoid the subsequent trans-esterification step in the original sequence. Solid $MgSO_4$ was replaced by trimethylorthoformate as a dehydrating agent, and following hydrolysis and protection, racemic Boc-protected derivative **11** was isolated. The enzymatic resolution of racemic-**11** was performed under forcing conditions using a large excess of Alcalase 2.4L (~1:1.4 w/w ratio of racemic-**11** to enzyme solution respectively), maintaining similar dilutions and using a Na_2HPO_4 buffer system instead of NaOH to avoid tedious pH control. (1*R*,2*S*)-**11** was produced in 99% ee after a single 70 h cycle. The only purification step in the overall sequence occurred during the isolation of crystalline (1*R*,2*S*)-**15**, which was isolated in enantiomerically pure form and 28.7% overall yield from 1,4-dibromo-2-butene (12 kg scale). This strategy allowed for more efficient use of plant time, minimizing steps and organic wastes.

Conclusion

A practical synthesis of (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic acid derivatives in enantiomerically pure form has been developed and scaled up to produce multikilogram quantities of this important building block for the preparation of HCV NS3 protease inhibitors. A highly diastereoselective assembly of a protected, racemic form of this amino acid from glycine imines was first secured. Subsequent enzymatic resolution using a commercially available and inexpensive crude enzyme preparation delivered the desired building block in essentially enantiomerically pure form. The overall scheme takes advantage of multistep streamlining, minimizing isolation and purification of intermediates. Ultimately, the six-step sequence was performed in three operations, including a final purification by crystallization, affording the end product in 28.7% overall yield (>99% ee) on >10 kg scale.

Experimental Section

(*E*)-*N*-Phenylmethyleneglycine Ethyl Ester 4.[15] Glycine ethyl ester hydrochloride (500.0 g, 3.58 mol) was charged in a 5 L flask equipped with a mechanical stirrer. The material was suspended in *tert*-butylmethyl ether (TBME, 3 L), and benzaldehyde (380.1 g, 3.58 mol, 1 equiv) was added followed by anhydrous Na_2SO_4 (305.3 g, 2.15 mol, 0.6 equiv). The stirred suspension was cooled in ice to an internal temperature of 5 °C, and triethylamine (749 mL, 5.37 mol, 1.5 equiv) was added dropwise over 10 min. The mixture was then stirred for 24 h at room temperature. The mixture was filtered over Celite using *tert*-butylmethyl ether for washings, and the filtrate was evaporated under reduced pressure. The residue was dried to a constant weight under high vacuum to give the desired crude imine **4** as a yellow oil (685 g, 100% yield) that was used directly in the next step. Similar results were obtained on a 2 kg scale: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.78 (m, 2H), 7.41 (m, 3H), 4.39 (s, 2H), 4.23 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 165.3, 135.5, 131.1, 128.5, 128.4, 62.0, 61.0, 14.1; ES-MS *m/z* 192 (MH^+).

Alternatively, imine **4** can be isolated in similar yields and purity using an aqueous workup to remove triethylamine hydrochloride and inorganic salts.

(*E*)-*N*-Phenylmethyleneglycine Methyl Ester 10.[15] Crude imine **10** was prepared in 96% yield following an analogous procedure to that described above for the ethyl analogue **4**, but starting from glycine methyl ester hydrochloride: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.80−7.76 (m, 2H), 7.48−7.38 (m, 3H), 4.42 (d, J = 0.8 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 165.4, 135.4, 131.2, 128.5, 128.4, 61.9, 52.1; ES-MS *m/z* 178 (MH^+).

General Procedure for the Dialkylation of Imine 4: Optimization Studies Using Hydroxide Bases and Phase Transfer Catalysis (Table 1). The following procedure using KOH is representative. To a stirred mixture of imine **4** (0.574 g, 3.00 mmol, 1.5 equiv), *trans*-1,4-dibromo-2-butene (0.428 g, 2.0 mmol, 1 equiv) in toluene (10 mL), and triethylbenzylammonium chloride (0.068 g, 0.3 mmol, 0.15 equiv) was added powdered KOH (0.336 g, 6.00 mmol, 3 equiv). The mixture was stirred for 18 h at room temperature. An aliquot (2 mL) was then diluted with *tert*-butylmethyl ether (TBME, 5 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The organic portion was dried ($MgSO_4$), concentrated under reduced pressure, and analyzed by ^{1}H NMR in $CDCl_3$ (see below for complete assignments) to determine the ratio of the desired vinyl-ACCA imine intermediate **6** (δ 2.27, q = 1H or δ 2.00, dd = 1H or 1.70, dd = 1H) and side product **9** (δ 6.04−5.95, m = 2 olefinic Hs). In this case, a 3:1 ratio of **6** to **9** was obtained.

Similar procedures were used for other hydroxide bases, replacing KOH with NaOH, $CsOH\cdot H_2O$, $LiOH\cdot H_2O$, or tetramethylammonium hydroxide.

General Procedure for the Dialkylation of Imine 4: Optimization Studies Using Aprotic Bases (Table 1). The following procedure using Li*O*t*Bu and either toluene or anhydrous THF as a solvent is representative. Li*O*t*Bu (0.483 g, 6.00 mmol, 3 equiv) was suspended in toluene (7 mL). *trans*-1,4-Dibromo-2-butene (0.428 g, 2.00 mmol, 1 equiv) and imine **4** (0.574 g, 3.00 mmol, 1.5 equiv) were mixed together in toluene (3 mL), and this solution was added dropwise over 10−15 min to the magnetically stirred suspension of the base at room temperature. After 60 min, a 2 mL aliquot was withdrawn, worked up, and analyzed by ^{1}H NMR as above. In this case, the ratio of the desired vinyl-ACCA imine **6** to side product **9** was ~48:1. Crude imine **6** had the following spectral characteristics: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.60 (m, 2H), 7.42 (m, 3H), 5.83−5.72 (m, 1H), 5.27 (broad d, J = 17.0 Hz, 1H), 5.13 (dd, J = 10.2, 1 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 2.27 (dd, J = 8.8, 8.6 Hz, 1H), 2.00 (dd, J = 7.8, 5.5 Hz, 1H), 1.70 (dd, J = 9.4, 5.5 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H).

Racemic 1-*tert*-Butoxycarbonylamino-*syn*-2-vinylcyclopropanecarboxylic Acid Methyl Ester 11 (5 g Scale). This procedure is representative of the optimization studies carried out on a 5 g scale with either the methyl or ethyl ester of the glycine Schiff base (**4** or **10**) as described in Table 1 of Supporting Information. Li*O*t*Bu (4.703 g, 58.75 mmol, 2.35 equiv) was suspended in toluene (70 mL), and the suspension was placed in a water bath at room temperature. A freshly prepared mixture of imine **10** (5.537 g, 31.25 mmol, 1.25 equiv) and *trans*-1,4-dibromo-2-butene (5.347 g, 25.0 mmol, 1 equiv) in toluene (20 mL) was added dropwise over 30 min to the stirred suspension of the base. After stirring for 60 min at room temperature, the reaction was quenched by addition of water (50 mL), and organic solubles were extracted into TBME (50 mL). The organic phase was mixed with 1 N HCl (50 mL) and stirred for 2 h at room temperature to affect hydrolysis of the intermediate imine. The organic phase was removed and back-extracted with water (40 mL). The combined aqueous phases were mixed with NaCl (35 g) and TBME (100 mL), and 10 N NaOH was added dropwise to bring the pH to 12−13. The organic phase was separated and the aqueous phase extracted with additional TBME (50 mL). The combined extracts were mixed with di-*tert*-butyl dicarbonate (Boc_2O, 6.00 g, 27.5 mmol, 1.1 equiv) and the solution stirred overnight at room temperature. To ensure completion of this protection step (TLC R_f = 0.5 in EtOAc), the mixture was then heated to 60 °C for 2 h. The cooled solution was then dried ($MgSO_4$) and concentrated

under reduced pressure. The residue was purified by flash chromatography using 5−15% EtOAc in hexane as eluents to give ester **11** as a clear oil (3.34 g, 55% yield) identical in all respects to the material obtained by trans-esterification of **12** with methoxide as described below.

Intermediate Vinyl-ACCA-OEt (Racemic-7): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (ddd, J = 19.4, 10.2, 9.2 Hz, 1H), 5.21 (ddd, J = 17.2, 1.9, 0.6 Hz, 1H), 5.03 (dd, J = 10.5, 1.9 Hz, 1H), 4.21−4.14 (m, 2H), 2.5 (broad s, 2H), 2.05−1.98 (m, 1H), 1.55 (dd, J = 7.6, 4.8 Hz, 1H), 1.32 (dd, J = 9.2, 4.8 Hz, 1H), 1.28 (t, J = 7.2 Hz, 3H).

Intermediate Vinyl-ACCA-OMe: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (ddd, J = 19.4, 10.2, 9.2 Hz, 1H), 5.22 (ddd, J = 17.2, 1.9, 0.6 Hz, 1H), 5.04 (dd, J = 10.8, 1.9 Hz, 1H), 3.73 (s, 3H), 2.60 (broad s, 2H), 2.07−1.99 (m, 1H), 1.56 (dd, J = 7.3, 4.8 Hz, 1H), 1.34 (dd, J = 9.5, 4.8 Hz, 1H).

Isolation and Characterization of 7-Phenyl-6,7-dihydro-1*H*-azepine-2-carboxylic Acid Ethyl Ester 9. Imine **4** (5.737 g, 30.0 mmol, 1.5 equiv) was alkylated with *trans*-1,4-dibromo-2-butene (4.278 g, 20.0 mmol, 1 equiv) and KO*t*Bu (6.172 g, 55 mmol, 2.75 equiv) in THF (100 mL) using the general procedure described above. Following acidic cleavage of the imine, the organic phase containing benzaldehyde and **9** was separated from the aqueous phase containing vinyl-ACCA-OEt **7**. The solution was washed with 1 N HCl (50 mL) and brine (50 mL) and dried over Na_2SO_4. After removal of volatiles under vacuum at 60 °C to remove benzaldehyde, the residual oil was purified by flash chromatography using 0−5% EtOAc in hexane as an eluent. Dihydroazepine **9** was obtained as a colorless oil (0.300 g), which slowly turned orange on prolonged exposure to air: TLC R_f = 0.55 (10% EtOAc−hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.33 (m, 2H), 7.32−7.24 (m, 3H), 6.04−5.96 (m, 2H), 5.93−5.84 (m, 1H), 5.22 (broad s, 1H), 4.23 (q, J = 7.0 Hz, 2H), 4.15 (broad d, J = 7.4 Hz, 1H), 2.88−2.78 (m, 1H, part of AB), 2.68 (broad dd, J = 17.4, 7.4 Hz, 1H, part of AB), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 144.0, 135.4, 131.4, 128.8, 127.5, 126.6, 124.7, 103.2, 61.6, 58.2, 42.7, 14.1; HRMS (FAB) *m/z* $C_{15}H_{18}NO_2$ (MH^+) calcd 244.1338, found 244.1338.

Racemic 1-*tert*-Butoxycarbonylamino-*syn*-2-vinylcyclopropanecarboxylic Acid Ethyl Ester 12 (Kilogram Scale). A 22 L round-bottomed flask equipped with a mechanical stirrer and two addition funnels was flushed with argon and charged with lithium *tert*-butoxide (1059.7 g, 13.237 mol, 2.35 equiv). Toluene (4.3 L) was added and the mixture cooled to an internal temperature of 15 °C by immersing in an ice−water bath. One addition funnel was charged with a solution of the glycine imine **4** from above (1346.6 g, 7.042 mol, 1.25 equiv) in toluene (1.9 L) and the other with *trans*-1,4-dibromo-2-butene (1200.0 g, 5.633 mol, 1 equiv), also in toluene (2.4 L). The two solutions were added dropwise and simultaneously at similar rates to the butoxide suspension, over a period of 1.5 h. During the addition, the internal temperature was maintained between 15 and 20 °C using the cooling bath. After addition of the two reagents, the brown reaction mixture was stirred at room temperature for an additional 30 min. The reaction was then quenched by addition of 10% aqueous $NaHCO_3$ (3.4 L) followed by ice−water (1 L). The now yellow suspension was stirred for 30 min and filtered over a sintered glass funnel to remove solids. The solid was washed with TBME (2 × 500 mL) and the aqueous phase back-extracted with TBME (2 × 750 mL). The organic phases were combined in a 22 L flask equipped with a mechanical stirrer. Water (2.2 L) and concentrated HCl (1023 mL) were added, and the mixture was vigorously stirred for 20 h at room temperature. The organic phase was separated and washed with water (2 × 600 mL). The combined aqueous phases were cooled to 5 °C in an ice−water bath, and solid NaCl (525 g) was added, followed by TBME (3.5 L). The mixture was then basified to pH 13 by portionwise addition of 10 N NaOH (1.2 L) over 20 min and stirred vigorously for 15 min. The organic phase containing the free base of the amino ester was separated and the aqueous phase extracted again with TBME (3.4 L). The combined organic extracts containing racemic **7** were charged into a 22 L flask, and a solution of di-*tert*-butyl dicarbonate (1229.4 g, 5.63 mol, 1 equiv) in TBME (500 mL) was added dropwise over 30 min. The internal temperature was raised from 23 to 32 °C over 1 h, and CO_2 gas evolved. The reaction mixture was allowed to stir at ambient temperature for 17.5 h after which the reaction was judged to be complete by TLC analysis. Anhydrous $MgSO_4$ (300 g) was added to the reaction mixture, and after the amber solution was stirred for 15 min, the mixture was filtered and evaporated under reduced pressure. The residual amber-colored oil was dried to a constant weight under high vacuum (1511 g, >100% yield; ~70% homogeneity). The crude product **12** (contaminated with *tert*-BuOH and di-*tert*-butyl dicarbonate) was used directly in the next step.

An analytical sample was obtained as a waxy solid by flash chromatographic purification using 5−15% EtOAc in hexane as eluents: TLC R_f = 0.59 (2:1 EtOAc−hexane); mp 49−50 °C; ^{1}H NMR (400 MHz, DMSO-d_6, 3:1 mixture of rotamers[25]) δ 7.64 (broad s, 0.75H), 7.30 (broad s, 0.25H), 5.62 (dt, J = 17.0, 9.6 Hz, 1H), 5.23 (d, J = 17.2 Hz, 1H), 5.06 (dd, J = 10.4, 1.6 Hz, 1H), 4.15−3.96 (m, 2H), 2.10 (q, J = 8.6 Hz, 1H), 1.58−1.52 (m, 1H), 1.38 (s, 6.8H), 1.35 (s, 2.2H), 1.27 (dd, J = 9.0, 4.9 Hz, 1H), 1.15 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 3:1 mixture of rotamers[25]) δ (major) 170.5, 155.5, 134.2, 117.3, 78.1, 60.5, 40.1, 32.4, 28.1, 22.6, 14.1; δ (minor) 170.8, 155.2, 134.4, 117.1, 40.7, 34.0, 23.0, 14.2; ES-MS *m/z* 156 (MH^+ − Boc), 278 (M + Na). Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.45; H, 8.55; N, 5.48.

Following an analogous procedure but starting from imine **10**, racemic *N*-Boc-vinyl-ACCA-OMe **11** was prepared in 55% yields. The material was identical in all respect to batches prepared by trans-esterification of **12** as described below.

Racemic 1-*tert*-Butoxycarbonylamino-*syn*-2-vinylcyclopropanecarboxylic Acid Methyl Ester 11 from Trans-esterification of the Corresponding Ethyl Ester 12. The crude racemic ethyl ester **12** (1511 g) was dissolved in MeOH (2 L) in a 12 L flask equipped with a mechanical stirrer and a reflux condenser. NaOMe (25% w/w solution in MeOH; 902 mL, 3.94 mol, 1 equiv) was added dropwise over 30 min (internal temperature raised to 40 °C). The reaction mixture was brought to reflux over 30 min and stirred at that temperature for 1.5 h. After cooling to room temperature, a mixture of AcOH (237 mL, 4.137 mol, 1.05 equiv) and MeOH (237 mL) was added dropwise over 15 min, bringing the pH of the reaction mixture to ~6. Volatiles were removed under reduced pressure, resulting in a brown paste that was partitioned between 0.1 N NaOH (2 L) and TBME (2 L). The organic phase was separated and the aqueous phase extracted with TBME (3 × 500 mL). The combined organic phases were washed with brine, dried over a mixture of $MgSO_4$ (200 g) and Darco G60 charcoal (100 g), and filtered over Celite. Removal of solvents under reduced pressure gave a brown oily residue. The material was dissolved in CH_2Cl_2 (1 L) and purified by passage through a pad of silica gel (15 × 20 cm) using CH_2Cl_2 (5 L) as an eluent. Pure fractions were collected and evaporated to yield the desired methyl ester **11** as an orange oil after drying overnight under high vacuum (985.5 g, 72% overall yield based on 1,4-dibromo-2-butene): TLC R_f = 0.58 (2:1 EtOAc−hexane); ^{1}H NMR (400 MHz, DMSO-d_6, 3:1 ratio of rotamers[25]) δ 7.65 (broad s, 0.7H), 7.31 (broad s, 0.3 H), 5.62 (dt, J = 16.8, 8.8 Hz, 1H), 5.24 (dd, J = 16.8, 1.0 Hz, 1H), 5.06 (dd, J = 19.4, 1.6 Hz, 1H), 3.62 (s, 0.9H), 3.60 (s, 2.1H), 2.12 (dt, J = 8.8, 8.6 Hz, 1H), 1.60−1.51 (m, 1H), 1.38 (s, 6.3H), 1.35 (s, 2.7H), 1.30 (dd, J = 9.4, 5.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, 3:1 ratio of rotamers[25]) δ (major) 171.1, 155.5, 134.2, 117.4, 78.2, 51.940.1, 32.7, 28.1, 22.7; δ (major) 171.3, 155.2, 117.2, 40.8, 33.9, 23.1; IR (neat) 3359, 3084, 2978, 1728 cm^{-1}; ES-MS *m/z* 142 (MH^+ − Boc), 264 (M + Na); HPLC analysis (ChiralCel OD-H, 1% EtOH in hexane isocratic, flow

rate = 0.75 mL/min) t = 14.75 min (1*R*,2*S*)-**11**, t = 17.66 min (1*S*,2*R*)-**11** in a 1: 1 ratio.

An analytical sample was obtained by flash chromatographic purification using 5−15% EtOAc in hexane as the eluent: TLC, ^{1}H and ^{13}C NMR, MS, and HPLC data were identical to those of the above material. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.80. Found: C, 59.92; H, 8.26; N, 5.72.

Enzymatic Resolution of Racemic-11; (1*R*,2*S*)-1-*tert*-Butoxycarbonylamino-2-vinylcyclopropanecarboxylic Acid Methyl Ester (1*R*,2*S*)-11. A 50 L three-necked flask was equipped with a mechanical stirrer, thermometer, pH electrode, and heating mantle. The flask was charged with water (32 L) and KCl (238.6 g, 3.2 mol) and the solution heated to 35−37 °C. Alcalase 2.4L (600 mL) was added and the solution adjusted to pH of 8.1−8.2 with 10 N NaOH (∼15 mL). The racemic methyl ester **11** (979.5 g, 4.065 mol) was dissolved in acetone (800 mL) and added with vigorous stirring to the 100 mM KCl solution (used 200 mL of acetone for rinses). Using a peristaltic pump and pH meter, a 1 N NaOH solution was fed into the flask to maintain the pH between 8.1 and 8.3. After 91 h, 1790 mL of 1 N NaOH solution was consumed (consumption of NaOH progressively decreases with time as the concentration of inhibitory hydrolyzed product increases). HPLC analysis of an aliquot on a ChiralCel OD-H column as described above indicated that the remaining esters consisted of a 12.45:1 ratio of isomers (85% ee).

The reaction mixture was allowed to cool to room temperature, and the aqueous phase containing (1*S*,2*R*)-**13** was separated from the organic phase. The aqueous phase was extracted with 20% TBME in hexane (2 × 4 L) and the extract evaporated to dryness under reduced pressure to give ∼100 g of an oily yellow residue (the aqueous phase can be saved for recovery of (1*S*,2*R*)-**13** as described below). The residue was dissolved in acetone (600 mL) and added to the organic phase left in the 50 L flask using additional acetone (200 mL) for rinses. Fresh water (26 L) was added followed by KCl (194 g) and Alcalase 2.4L (600 mL). The pH was again adjusted to 8.1−8.2 with 10 N NaOH (∼5 mL), and the mixture was heated to 37−38 °C. Addition of 1 N NaOH was then resumed, again maintaining the pH in the 8.1−8.3 range. After 48 h, 220 mL of 1 N NaOH were consumed for a total of 2010 mL (theoretical amount for complete hydrolysis of (1*S*, 2*R*)-**11** is 2032 mL). HPLC analysis of an aliquot as described previously indicated an 85.9:1 ratio of isomers (97.2% ee).

Heating was discontinued, and NaCl (1 kg) was added. After stirring for 15 min, the mixture was extracted with 2:1 TBME−hexane (total of 8 L). The aqueous phase can be combined with the previous one for recovery of (2*R*,1*S*)-**13** (see below). The organic extract was washed with brine and dried over $MgSO_4$. Removal of volatiles under reduced pressure gave an orange oil that was purified by passage through a pad of silica gel (12 × 15 cm) using CH_2Cl_2 as an eluent. Resolved ester (1*R*,2*S*)-**11** was obtained as an orange oil after evaporation and drying to constant weight under vacuum (489.8 g, 49% yield): TLC, ^{1}H and ^{13}C NMR, and MS data were identical to those of racemic-**11**; HPLC analysis (ChiralCel OD-H, 0.8% EtOH in hexane isocratic, flow rate = 0.75 mL/min) t = 20.5 min (1*R*,2*S*)-**11**, t = 23.9 min (1*S*,2*R*)-**11** in a 154.4:1 ratio (98.7% ee).

An analytical sample was obtained after purification by flash chromatography on silica gel using 5−15% EtOAc in hexane as an eluent: TLC R_f = 0.14 (10% EtOAc−hexane); $[\alpha]^{25}_D$ +42.8° (c = 1.00, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6, 3:1 ratio of rotamers[25]) δ 7.65 (broad s, 0.75H), 7.31 (broad s, 0.25H), 5.64 (t, J = 17.0, 8.8 Hz, 1H), 5.24 (d, J = 17.0 Hz, 1H), 5.07 (dd, J = 10.2, 1.6 Hz, 1H), 3.62 (s, 0.75H), 3.60 (s, 2.25H), 2.11 (q, J = 8.6 Hz, 1H), 1.57 (m, 1H), 1.37 (s, 6.75H), 1.34 (s, 2.25H), 1.30 (dd, J = 9.4, 5.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, 3:1 ratio of rotamers[25]) δ (major) 171.1, 155.5, 134.2, 117.4, 78.2, 51.9, 40.2, 32.7, 28.1, 22.7; δ (minor) 171.3, 155.2, 117.2, 40.8, 33.9, 23.1; ES-MS m/z 142 (MH^+ − Boc), 264 (M + Na); HPLC analysis (ChiralCel OD-H, 1% EtOH in hexane isocratic, flow rate = 0.75 mL/min) t = 16.57 min (1*R*,2*S*)-**11**, t = 19.73 min (1*S*,2*R*)-**11** in a 92.1:1 ratio (97.8% ee). Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.80. Found: C, 59.79; H, 7.93; N, 5.82.

Recovery of (1*S*,2*R*)-1-*tert*-Butoxycarbonylamino-2-vinylcyclopropanecarboxylic Acid (1*S*,2*R*)-13. On a similar resolution run carried out on 943 g (3.91 mol) of racemic-**11**, all aqueous phases containing the hydrolyzed salt of acid **13** were combined and concentrated under reduced pressure at 45 °C to a total volume of 3 L. The resulting solution was washed with TBME (2 × 1 L) and saturated with solid NaCl (500 g). EtOAc (1 L) was then added, followed by concentrated HCl (∼170 mL) dropwise with vigorous stirring over a 75 min period, until a pH of 2−3 was reached. Celite (200 g) was added, and after stirring for 1 h, the suspension was filtered. The solid was washed with EtOAc (5 × 200 mL), and the combined organic phases were washed with brine (500 mL) and dried (Na_2SO_4). Removal of volatiles under reduced pressure gave crude (1*S*,2*R*)-**13** as a brownish foam (386.7 g, 87% yield). An aliquot was treated with ethereal CH_2N_2, and the resulting methyl ester was analyzed in the usual way by HPLC on a chiral support: 94.7% ee.

An analytical sample of (1*S*,2*R*)-**13** was obtained by crystallization of the crude foam from above as follows: 1.80 g of the crude material was dissolved in warm TBME (10 mL), and hexane (20 mL) was added. The cloudy suspension was filtered through a 45 μM filter, and the solvent was slowly evaporated to 2/3 of the original volume, at which point a white solid began to precipitate. The solution was cooled and the solid collected by filtration. The solid was washed with hexane and dried under vacuum (550 mg): mp 99−100.5 °C; $[\alpha]^{25}_D$ −21.7° (c = 1.00, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6, 3:1 mixture of rotamers[25]) δ 12.41 (broad s, 1H), 7.53 (broad s, 0.75 H), 7.18 (broad s, 0.25 H), 5.68 (dt, J = 17.0, 9.6 Hz, 1H), 5.22 (d, J = 17.2 Hz, 1H), 5.04 (dd, J = 10.4, 1.8 Hz, 1H), 2.05 (dt, J = 8.8, 8.6 Hz, 1H), 1.54−1.48 (m, 1H), 1.36 (s, 9H), 1.24 (dd, J = 9.0, 4.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, 3:1 mixture of rotamers[25]) δ (major) 172.4, 155.5, 134.9, 116.8, 77.9, 40.5, 32.4, 28.2, 22.5; δ (minor) 172.7, 116.6, 33.7, 22.8; ES-MS m/z 128 (MH^+ − Boc), 226 (M − H). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.30; H, 7.55; N, 6.18.

(1*S*,2*R*)-1-*tert*-Butoxycarbonylamino-2-vinylcyclopropanecarboxylic Acid, Methyl Ester (1*S*,2*R*)-11. The purified acid (1*S*,2*R*)-**13** from the above analytical sample (250 mg) was dissolved in TBME (10 mL), and excess ethereal diazomethane was added until the yellow color persisted. Volatiles were removed under reduced pressure, and the residue was purified by flash chromatography on silica gel using 0−10% EtOAc in hexane as an eluent (200 mg): TLC, ^{1}H and ^{13}C NMR, and MS data were identical to those of its previously described antipode; $[\alpha]^{25}_D$ −41.2° (c = 1.00, MeOH); HPLC analysis (ChiralCel OD-H, 1% EtOH in hexane isocratic, flow rate = 0.75 mL/min) t = 16.10 min (1*R*,2*S*)-**11**, t = 19.73 min (1*S*,2*R*)-**11** in a 1: 31.43 ratio (93.8% ee). Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.80. Found: C, 59.37; H, 7.82; N, 5.81.

Conversion of (1*S*,2*R*)-13 to Authentic (+)-(1*S*,2*S*)-*N*-Boc-Coronamic Acid.[25] Crude (1*S*,2*R*)-**13** from above (estimate ∼94% ee, 1.000 g, 4.40 mmol) was dissolved in TBME (25 mL) and hydrogenated (1 atm H_2 gas) over 20% $Pd(OH)_2$/C (100 mg) for 3 h. The suspension was then filtered and volatiles removed under reduced pressure. The residue was dissolved in TBME (3 mL), and hexane (30 mL) was added to induce crystallization. After 1 h, the crystallized solid was collected by filtration, washed with hexane, and dried under vacuum (0.500 g, 50% yield): TLC R_f = 0.36 (EtOAc); mp 122−123.5 °C, lit.[25] 125−126 °C; $[\alpha]^{25}_D$ +29.1° (c = 1.1, MeOH), lit.[25] $[\alpha]^{25}_D$ +33.1° (c = 0.7, MeOH); ^{1}H NMR (400 MHz, benzene-d_6 + 5% DMSO-d_6, 52 °C, mixture of rotamers[25]) δ 5.87 (broad s, 1H), 1.82−1.62 (m, 2H), 1.53 (dd, J = 7.7, 4.6 Hz, 1H), 1.45 (s, 9H), 1.42−1.29 (m, 1H), 1.16 (dd, J = 8.1, 4.0 Hz, 1H), 0.98 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, benzene-d_6 + 5% DMSO-d_6,

27 °C, mixture of rotamers[25]) δ (major) 174.8, 156.7, 78.8, 39.3, 33.2, 29.0, 23.4, 21.3, 14.2; ES-MS *m/z* 228 (M−H). Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.27; H, 8.24; N, 6.17.

(1*R*,2*S*)-1-Amino-2-vinylcyclopropanecarboxylic Acid Methyl Ester Hydrochloride (1*R*,2*S*)-14. A 5 L three-necked flask was equipped with a mechanical stirrer and charged with anhydrous HCl (4 N in dioxane, 2 L). The resolved methyl ester (1*R*,2*S*)-**11** (490.6 g, 2.034 mol) was dissolved in dioxane (400 mL + 100 mL rinse) and added dropwise over 50 min with vigorous stirring. After completion, the mixture was stirred for an additional 1 h. Volatiles were removed under reduced pressure and the residue coevaporated with MeOH (2 × 500 mL). The product was dissolved in MeOH (150 mL); TBME (800 mL) was added slowly and the mixture allowed to stand for 18 h at room temperature. The precipitated off-white solid was collected by filtration and washed with 5% MeOH−TBME (2 × 200 mL) and TBME (2 × 200 mL). After drying overnight under vacuum, the desired hydrochloride salt (1*R*,2*S*)-**14** was obtained as a light-beige solid (208.9 g). The mother liquors described above contained a contaminant and were processed as follows: solvents were evaporated under reduced pressure, and the residue was dissolved in $CHCl_3$. Aqueous $NaHCO_3$ was added until a pH of 9 was obtained, and the organic phase was separated. The extract was passed through a pad of silica gel using $CHCl_3$ as an eluent and the filtrate acidified with anhydrous 1 N HCl in ether. Volatiles were removed under reduced pressure to give a residue that was dissolved in MeOH (50 mL) and saturated with TBME (250−300 mL). A second crop of the hydrochloride was obtained and recovered as previously described (21.4 g, 97.7% ee). The two crops were found to be identical in all respects and amounted to a total of 230.3 g (64% yield). Analytical data is provided for the first crop: mp 115−118 °C; $[\alpha]^{25}_D$ +52.4° (*c* = 1.05, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (broad s, 3H), 5.66−5.55 (m, 1H), 5.34 (dd, *J* = 17.2, 0.8 Hz, 1H), 5.17 (dd, *J* = 10.2, 1.0 Hz, 1H), 3.72 (s, 3H), 2.53 (dt, *J* = 9.4, 8.6 Hz, 1H), 1.88 (dd, *J* = 9.8, 5.9 Hz, 1H), 1.61 (dd, *J* = 8.0, 5.9 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.8, 132.2, 119.3, 52.8, 29.4, 18.5; ES-MS *m/z* 142 (MH^+); HPLC analysis (ChiralCel OD-H, 0.8% EtOH in hexane isocratic, flow rate = 0.75 mL/min) *t* = 20.59 min (1*R*,2*S*)-**14**, *t* = 23.97 min (1*S*,2*R*)-**14** in a 376:1 ratio (99.5% ee). Anal. Calcd for $C_7H_{12}ClNO_2$: C, 47.33; H, 6.81; N, 7.89. Found: C, 47.34; H, 6.89; N, 7.69.

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Supporting Information Available: Optimization studies for the preparation of racemic *N*-Boc-vinyl-ACCA esters and experimental procedures for the kilogram lab-scale preparation of enriched (1*R*,2*S*)-**12** and (1*R*,2*S*)-**11**, resolution of enriched (1*R*,2*S*)-**11**, conversion to the crystalline tosylate salt (1*R*,2*S*)-**15**, and pilot plant synthesis of (1*R*,2*S*)-**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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