DISSERTATION

THE ASYMMETRIC SYNTHESIS OF ARYLGLYCINES

Submitted by

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY JAMES A. HENDRIX ENTITLED THE ASYMMETRIC SYNTHESIS OF ARYLGLYCINES BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

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ABSTRACT OF DISSERTATION

THE ASYMMETRIC SYNTHESIS OF ARYLGLYCINES

The asymmetric synthesis of several arylglycines is discussed. Several methods for the coupling of an aromatic group to the chiral bromoglycinates (**171**, **172**) were developed. It was found that the cuprate and Friedel-Crafts couplings provided the desired aryl-coupled glycinates in the greatest yield with excellent selectivity. An oxidative protocol was employed to unmask the oxazinone chiral auxiliary which provided the desired free α-amino acids. A reductive deprotection method was also employed in two unique cases which efficiently gave the arylglycine products. The % ee's ranged from 82 to 94 %. This methodology was further utilized in an approach to the asymmetric synthesis of the bis-arylglycine, actinoidic acid. This study explored the scope of the Stille biphenyl cross-coupling reaction and produced methodology for the synthesis of biphenyl amino acid precursors.

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DEDICATION

This dissertation is dedicated to my parents, my sister, Janet, her husband Birch and my dear friends Mark and Beverly Propp, and Matt Brothers. Without their love, friendship, encouragement and support this work could not have been possible.

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CHAPTER I

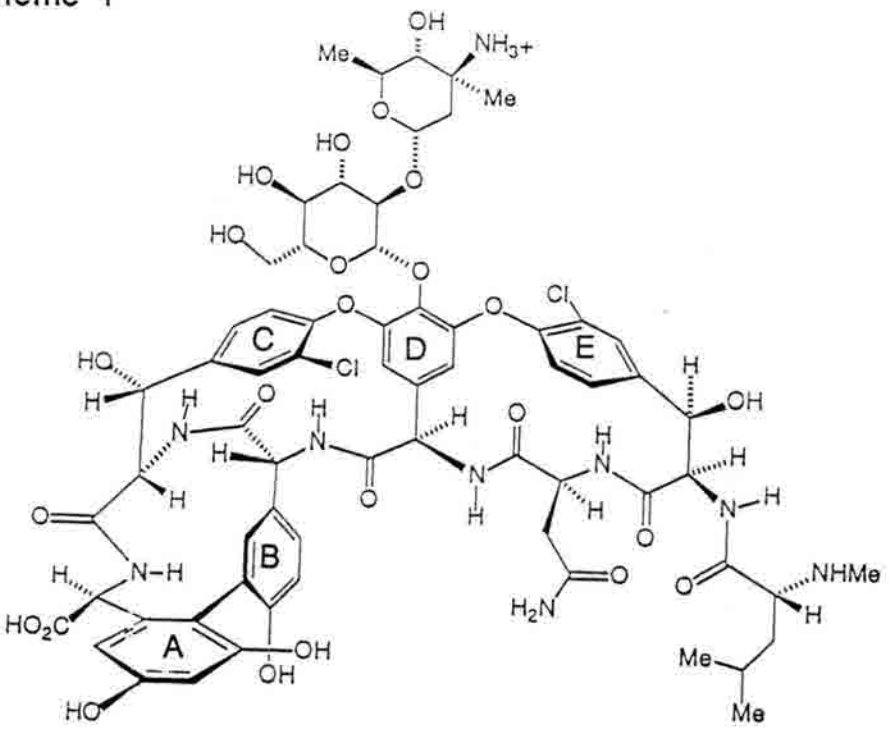
INTRODUCTION

A. Background

α-Amino acids have been the focus of great interest in all areas of both the physical and life sciences for over 150 years. It is well known that α-amino acids are vital to life itself as the "building blocks" of peptides, proteins and many other natural products. Beyond this fundamental role, amino acids are used extensively as food additives, agrochemicals and pharmaceuticals. Amino acids have also been used in organic synthesis as targets, a source of chirality and as reagents and/or catalysts in asymmetric synthesis. The importance of amino acids has prompted the development of a multitude of methods for their racemic and asymmetric synthesis.[1]

An interesting and important non-proteinogenic class of amino acids are the arylglycines. The isolation of arylglycines from natural sources is rare but has increased in frequency over the past 25 years. For example, *m*-hydroxy and 3',5'-dihydroxy phenylglycine were isolated from latex.[2] One of the best studied and most interesting sources of arylglycines are the glycopeptide antibiotics. In 1956, the first glycopeptide antibiotic, vancomycin (**1**), was discovered.[3] Vancomycin's structure (Scheme 1), not completely known until the early 1980's, consists of a heptapeptide in which three of the amino acid residues are arylglycines. Vancomycin (**1**) is isolated from *Amycolatopsis orientalis* (previously designated as *Streptomyces orientalis*) and is active against Gram-positive bacteria. It is used clinically in the treatment of severe staphylococcal

Scheme 1



1, VANCOMYCIN

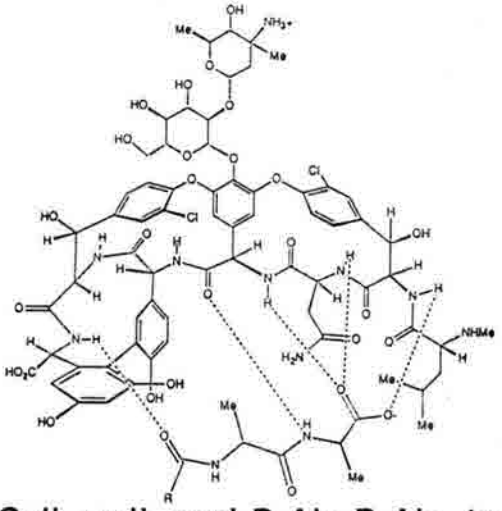
infections such as endocarditis and wound septicaemia.[4] Vancomycin (**1**) is also used to treat pseudomembranous colitis, a potentially lethal infection usually associated with antibiotic treatment after major gastrointestinal surgery.[5] Teicoplanin, another glycopeptide antibiotic, was recently approved for use in Italy and France and is under clinical trials in other European countries and the United States.[4d]

Since the discovery of vancomycin, many other glycopeptide antibiotics have been isolated and characterized. Members of the vancomycin group include ristocetin,[6] teicoplanin,[7] avoparcin,[8] ristomycin[9] and actaplanin.[10] The isolation and characterization of new glycopeptide antibiotics continues to be a very active area of research as a review of the current literature will attest.[11]

Glycopeptide antibiotics are inhibitors of bacterial cell-wall biosynthesis.[12] It is now known that vancomycin blocks cell-wall biosynthesis by complexing strongly to the cell-wall peptidoglycan precursor at a specific D-Ala-D-Ala site

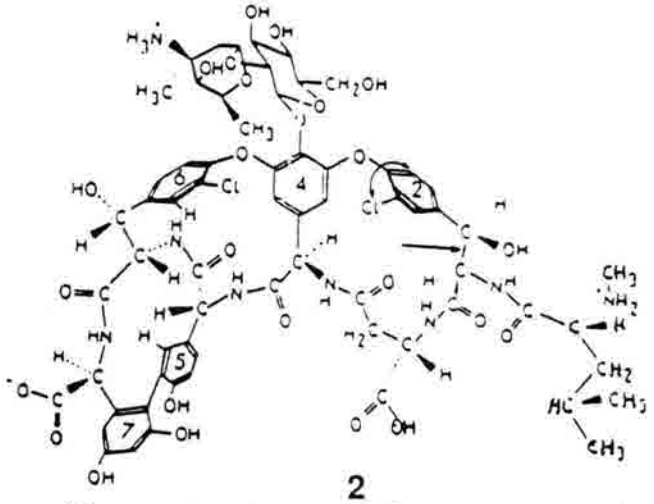
near the C-terminus.[13] Furthermore, the binding site on vancomycin has been determined by the use of NMR experiments indicating that the amino acid residues B, C, and D form the binding pocket for the D-Ala-D-Ala cell-wall subunit. Computer and molecular modeling support the idea that hydrogen bonding from these amino acid residues holds the D-Ala-D-Ala cell-wall subunit in place, (Scheme 2).[14] This proposal is also supported by the X-ray structure for the vancomycin analog, CDP-1 (**2**) (Scheme 3).[14] Further work with

Scheme 2



Cell wall acyl-D-Ala-D-Ala terminus binding to vancomycin

Scheme 3



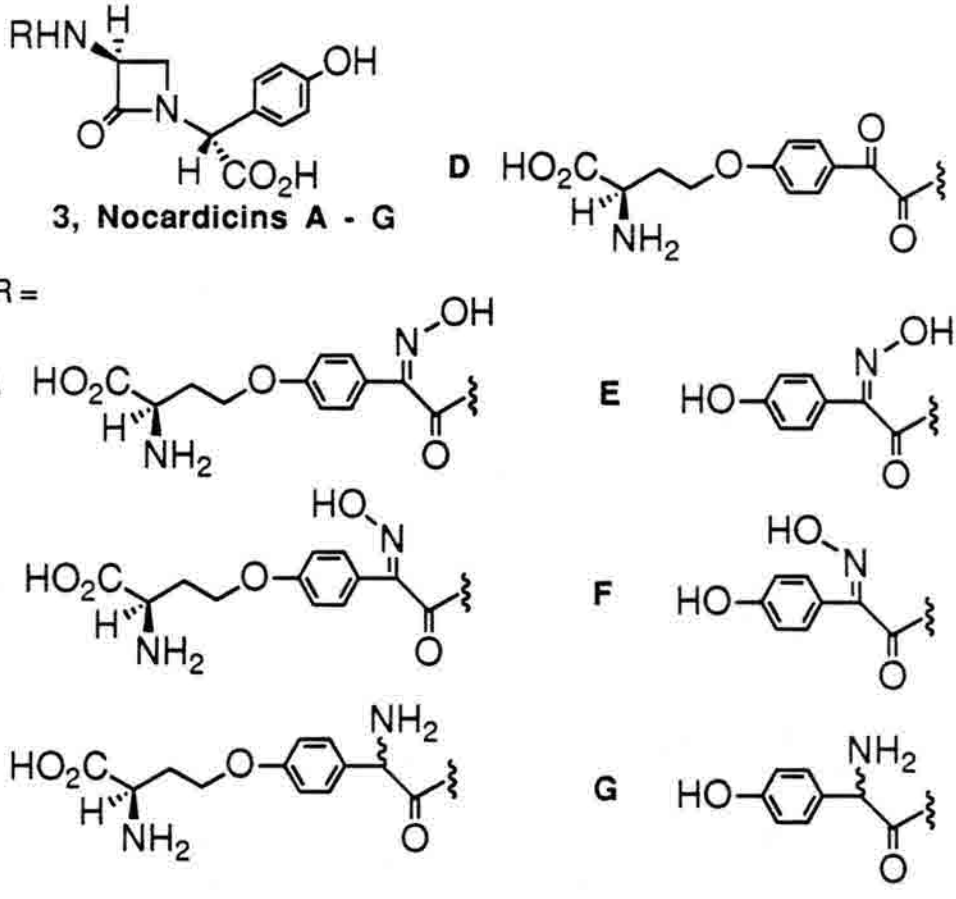
2

X-ray structure of the vancomycin degradation product, CDP-1 (2).

ristocetin A also indicates that a conformational change is associated with binding.[15] It is believed that all members of the vancomycin group inhibit cell-wall biosynthesis in an analogous manner.[4]

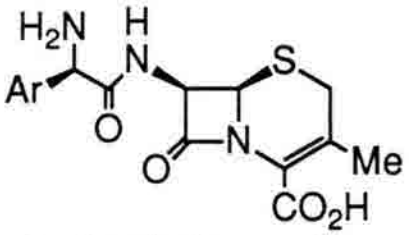
Another natural source of arylglycines is the family of monocyclic ß-lactam antibiotics known as the nocardicins (**3**).[16] Nocardicin A, the best-known and most active member of this group of ß-lactam antibiotics, was isolated from *Nocardia uniformis* subsp. *tsuyamanensis*. The nocardicins (**3**) contain two *p*-hydroxyphenylglycine derivatives in their unusual structure (Scheme 4). It is hypothesized that two molecules of *p*-hydroxyphenylglycine act as the starting material for nocardicin (**3**) biosynthesis.

Scheme 4



Aside from the interesting naturally occurring arylglycines, there are also a number of unique synthetic arylglycines. Synthetic D-arylglycines are used as a side-chain moiety of semisynthetic penicillins and cephalosporins (**4**). The arylglycine side-chain aids in the oral absorption of these ß-lactam antibiotics. For example, the synthetic antibiotic cephalexin contains phenylglycine as a side-chain constituent[17] and *p*-hydroxyphenylglycine is used as a side-chain moiety in the antibiotic amoxicillin,[18] (Scheme 5).

Scheme 5



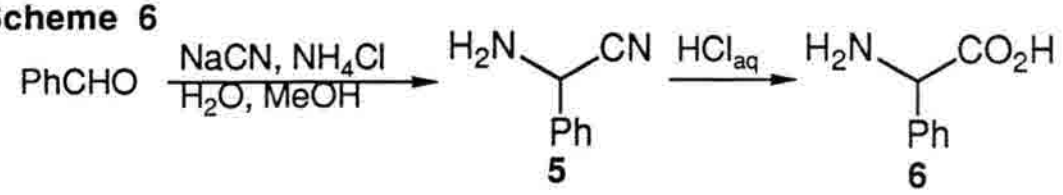
4, Cephalosporins
Cephalexin; Ar = Ph
Cefadroxil; Ar = *p*-HO-C_6H_4

B. Racemic Synthesis of Arylglycines

The arylglycines are an example of a class of α-amino acids that have rarely been synthesized asymmetrically due to the ease with which the α-methine proton can undergo base-catalyzed racemization. As a result, many arylglycines are synthesized in racemic form and the enantiomers are then separated by resolution. The racemic synthesis of arylglycines dates back over 100 years. To gain some historical perspective it may be instructive to look at the synthesis of the simplest arylglycine, phenylglycine. In 1878 Stockenius[19] reported a synthesis of phenylglycine by heating α-bromo phenylacetic acid with excess ammonium hydroxide to 100-110° C. In 1885, Elbers[20] prepared phenylglycine by the reduction of benzoylformic acid phenylhydrazone with

sodium amalgam in dilute sodium hydroxide. Starting in 1880, several groups utilized the Strecker synthesis to produce α-aminophenyl acetonitrile (**5**) which was hydrolyzed to phenylglycine in hydrochloric acid (**6**)[21] (Scheme 6).

Scheme 6

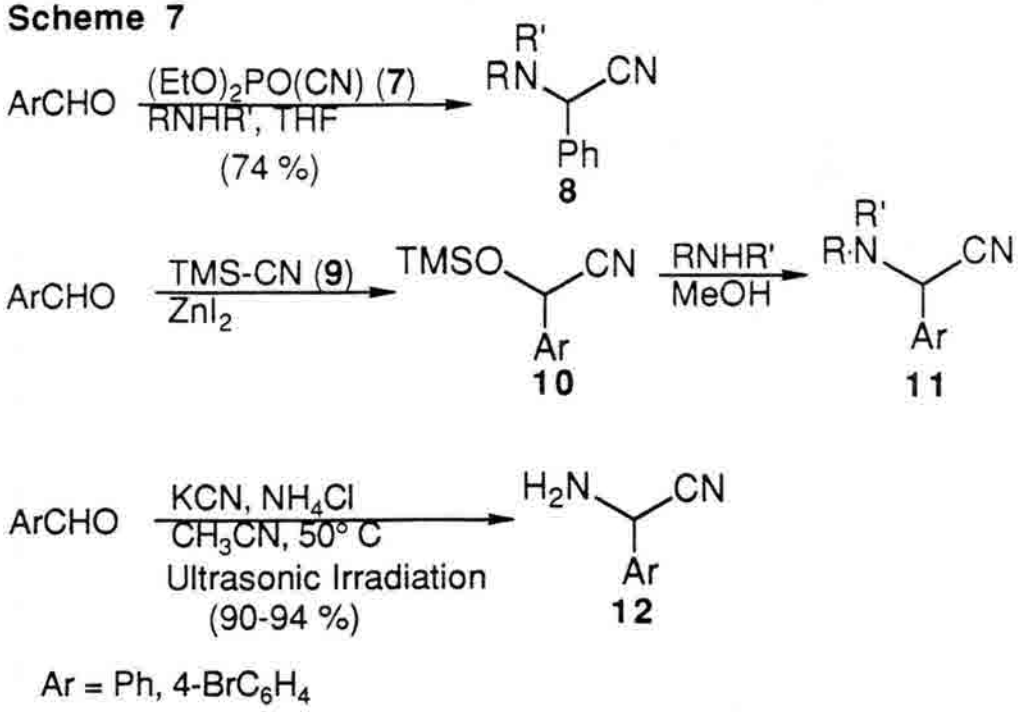


The Strecker Synthesis

Over the years, the Strecker synthesis has been the most widely used method for the synthesis of arylglycines. In recent years there have been many modifications of the classical Strecker synthesis. The advent of organic-soluble cyanide sources has provided new-found versatility to the Strecker reaction. Diethyl phosphorocyanidate (**7**)[22] and trimethylsilyl cyanide (**9**)[23] have both been used in the synthesis of a variety of α-amino arylnitriles. Another interesting modification has been the application of ultrasound to the Strecker synthesis[24] (Scheme 7). The Strecker synthesis has also been utilized in the asymmetric synthesis of arylglycines, the details of which will be discussed later.

Aside from the Strecker synthesis, there are numerous modern examples of racemic arylglycine syntheses. It is not the goal of this introductory chapter to act as a comprehensive review of racemic arylglycine syntheses, but only to give the flavor of some of this chemistry. Nitriles (**13**) and isonitriles (**17**) have been converted to arylglycines under quite harsh conditions[25] (Scheme 8). Electrophilic aromatic substitution of a variety of glycinate equivalents is a popular method in the synthesis of arylglycines. α-Hydroxyglycine equivalents (**20, 23**) have been used in amidoalkylation reactions to produce arylglycine

Scheme 7



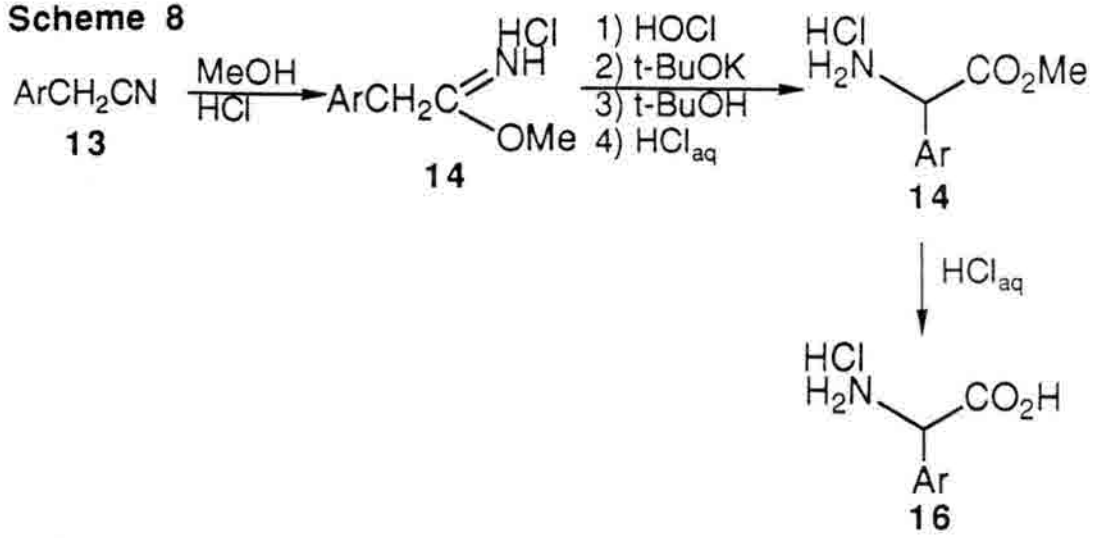
Ar = Ph, 4-BrC_6H_4

Modern Modifications of the Strecker Synthesis

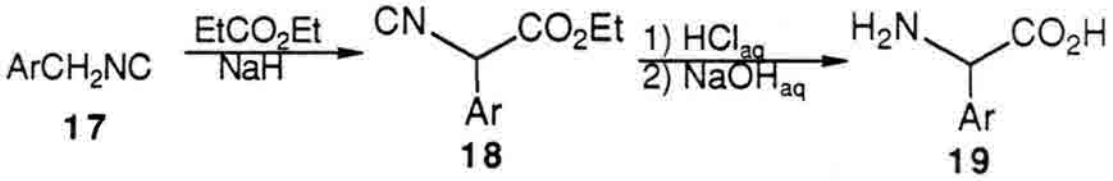
derivatives[26] (Scheme 9). The standard amidoalkylation conditions were modified for acid-sensitive aromatic groups such as furyl groups.[26b] Regiochemical control is sometimes difficult to attain with substituted aromatics in these reactions. In an analogous reaction, O'Donnell and Bennett[27] have utilized an electrophilic Schiff base ester (**26**) in reactions with active aromatics under Friedel-Crafts conditions. The resulting arylated amino ester (**27**) can easily be hydrolyzed to the desired free amino acid, (Scheme 10). In yet another electrophilic substitution reaction, furan and thiophene was reacted with an active iminoacetate (**28**) yielding the desired arylglycine derivative (**29**)[28], (Scheme 11).

The use of organometallic reagents as a source of aromatic nucleophiles in reactions with electrophilic glycine equivalents is also a popular method in the synthesis of arylglycines. O'Donnell's[29] electrophilic Schiff base (**26**) has also

Scheme 8



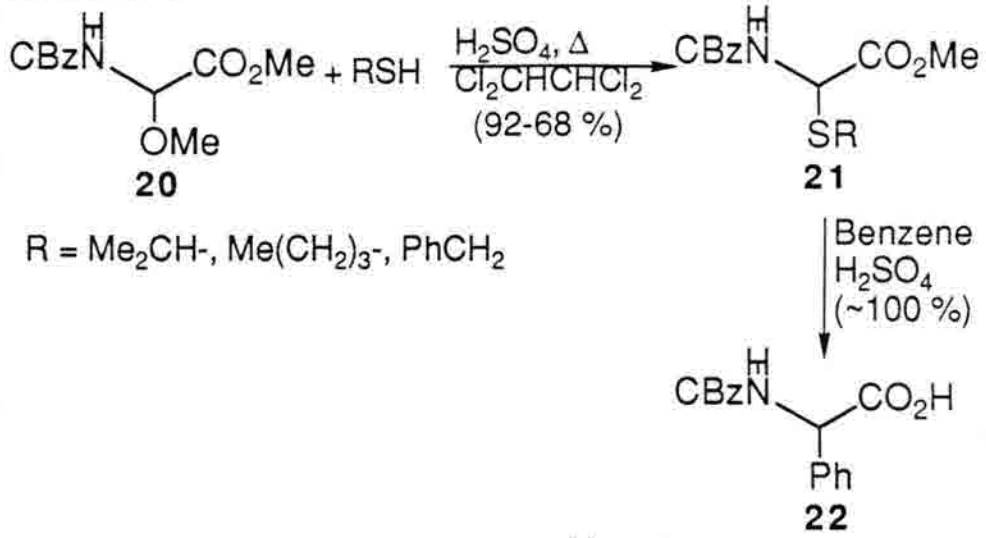
Ar	% Yield (14)	% Yield (15)	% Yield (16)
Ph	71-100	69-75	54-74
1-naphthyl	79-89	44-54	43-53
4-$MeOC_6H_4$	64-77	32	31
4-MeC_6H_4	74		67
4-ClC_6H_4	80		55
4-$NO_2C_6H_4$	25		0

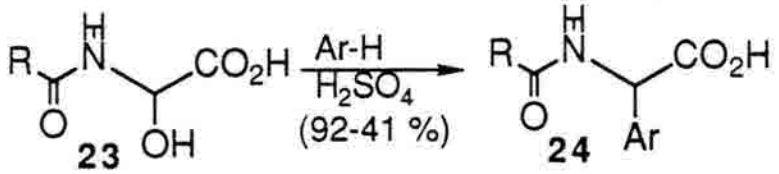


Ar	% Yield (18)	% Yield (19)
Ph	63	57
2-furyl	61	55
4-$MeOC_6H_4$	60	54
4-MeC_6H_4	59	51
4-ClC_6H_4	62	56

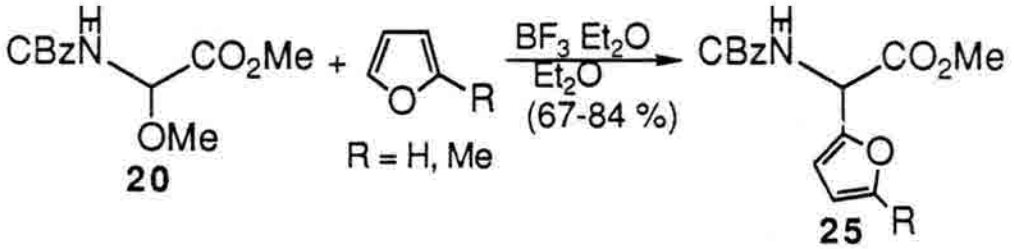
been used with organoboranes (**29**) and cuprates (**30**) to make arylglycines (Scheme 12). Cuprates as well as Grignard reagents were reacted with imino acetates (**33**) yielding arylglycines,[30] (Scheme 13). Many of the same basic bond-forming reactions used in the racemic synthesis of arylglycines have also been modified for use in asymmetric synthesis.

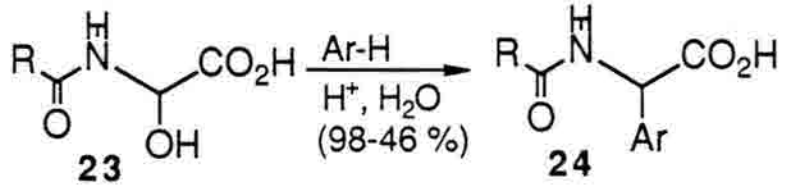
Scheme 9





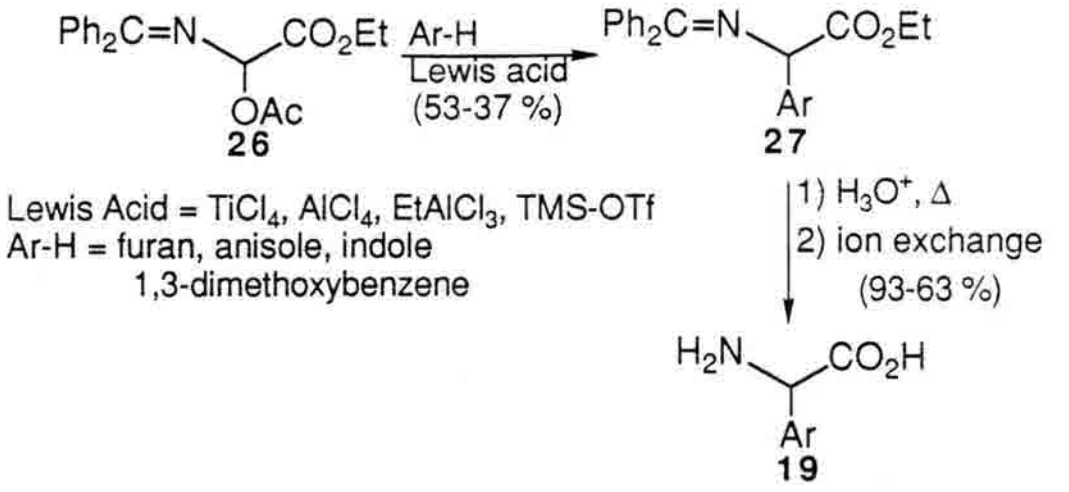
R = Ph, $PhCH_2$, MeO, $PhCH_2O$
Ar = Ph, *p*-MeC_6H_4-, *p*-ClC_6H_4-, *p*-$AcNHC_6H_4$-, *p*-$MeOC_6H_4$-, *p*-HOC_6H_4-, 1-naphthyl, $C_{14}H_9$-, thienyl



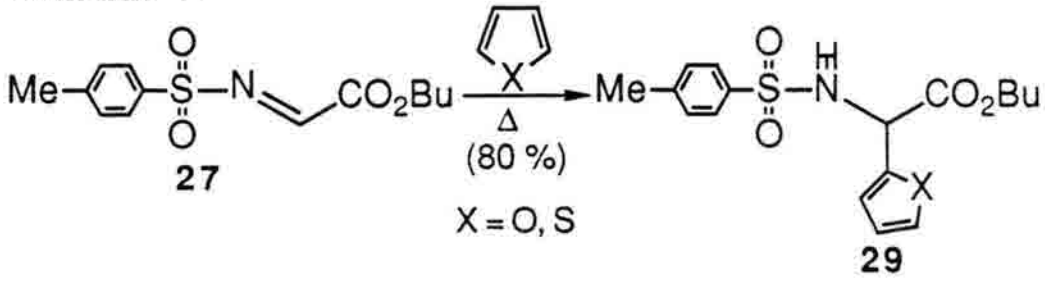


Ar-H = *o*-nitropenol, *p*-nitrophenol, benzene, flurobenzene, guaiacol thiophene, phenol, toluene, 2-naphthol

Scheme 10



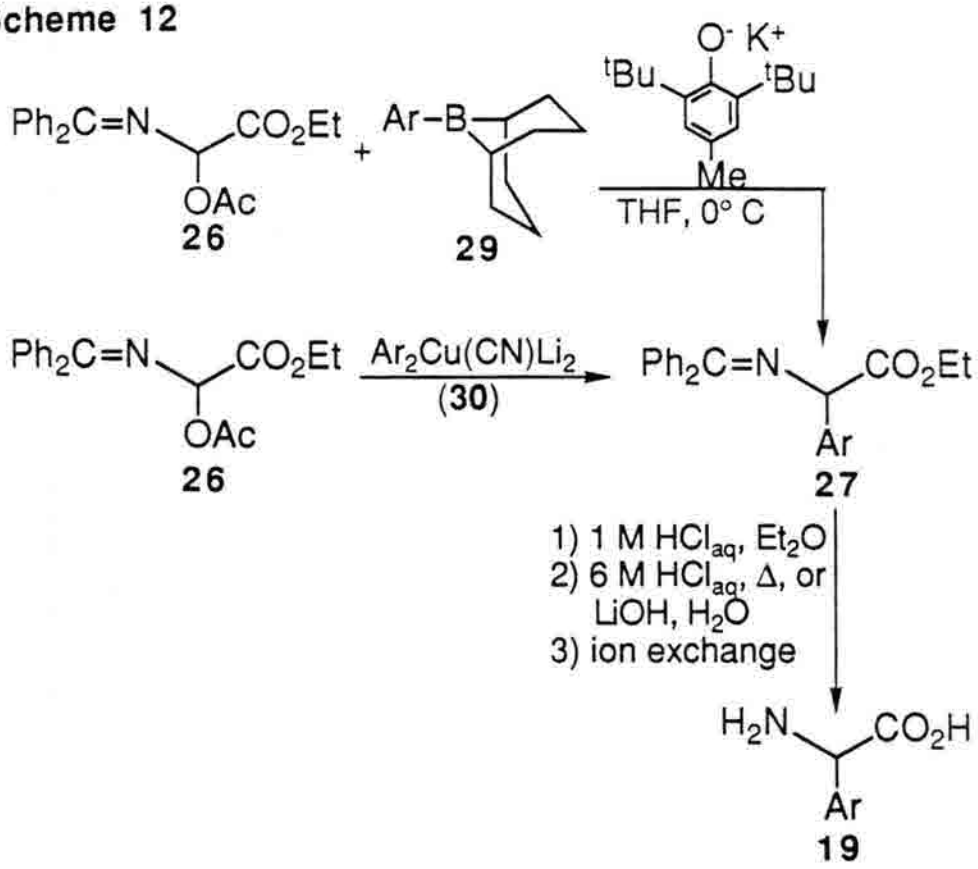
Scheme 11



C. Separation of Optically Active Arylglycines from Racemic Mixtures

The most common method of obtaining optically active arylglycines is the separation of synthetically prepared racemic mixtures. Four general methods can be employed: 1) fractional crystallization of diastereomeric salts; 2) chromatographic resolution on columns with chiral carriers; 3) the enzymatic resolution of racemic arylglycine derivatives; and 4) the relatively new technique of retroracemization. Chemical resolution represents a classical technique that has long been applied to a variety of amino acids including arylglycines. For example, the fractional crystallization with camphorsulphonic acid of D-phenylglycine has long been known.[1b] The optical resolution of a variety of amino acids and amino acid derivatives has also been achieved

Scheme 12



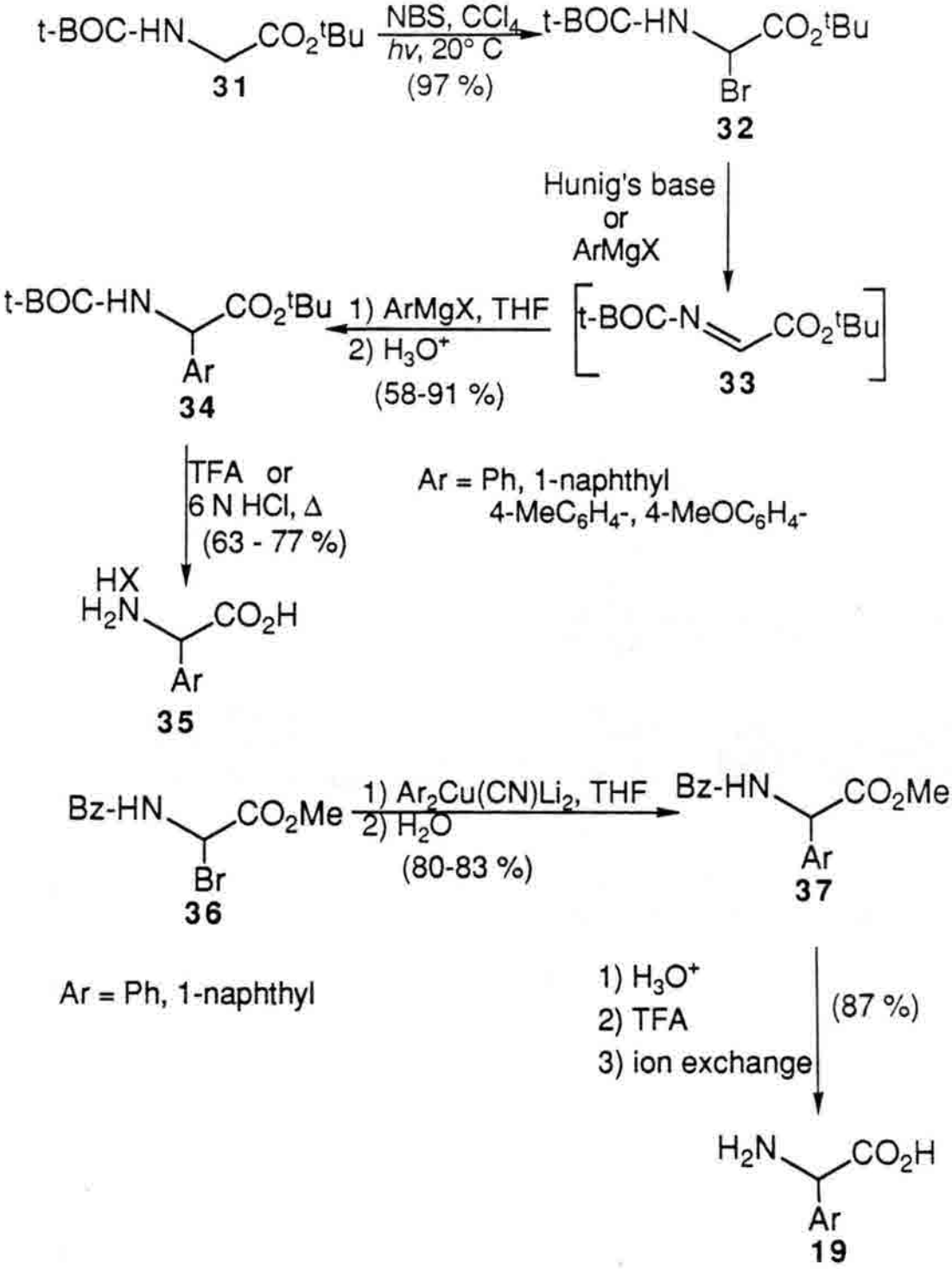
Ar	% Yield (27) via **29**	% Yield (27) via **30**	% Yield (19)
Ph	57	70	55
1-naphthyl	64	63	37
2-thienyl	47	71	40

using chiral column chromatography.[31] While this technique can be quite effective in the separation of arylglycine racemates, it is often difficult to use this method on a preparative scale.

1. Enzymatic Methods

A more recent and promising development for the resolution of amino acids is the use of enzymes. The enzymes used for this purpose are purified, immobilized enzymes, cell-free enzymes or whole cell systems. The use of this technology has become quite popular in industry since the desired amino acids

Scheme 13

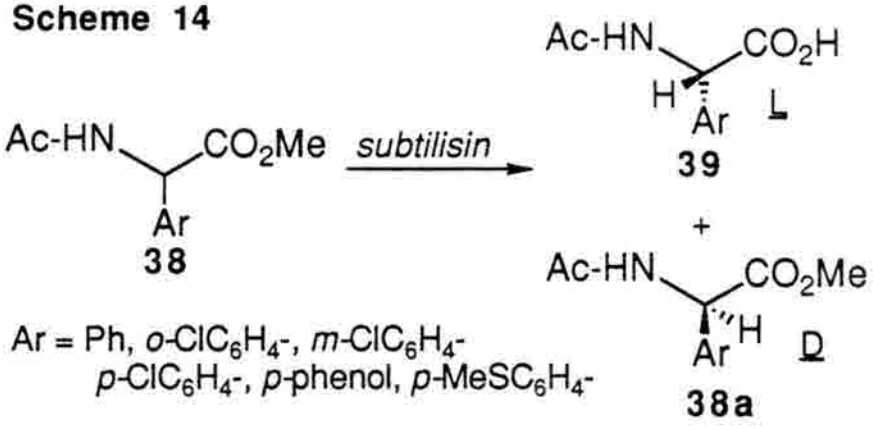


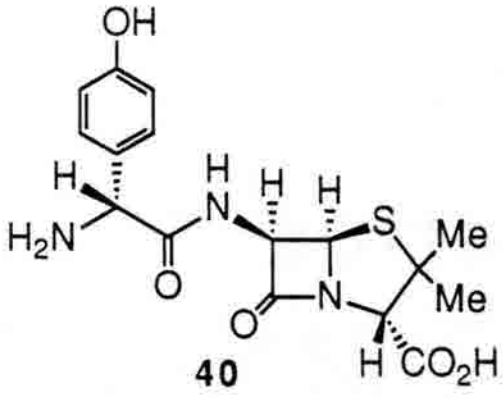
can be prepared on both large and intermediate scales.[32] Esterases, amidases, and hydantoinases are three types of enzymes that have proven effective in the production of optically active arylglycines.

a. Esterases

Esterases have been used in the industrial preparation of D-arylglycines which are important side-chain constituents of semi-synthetic penicillins and cephalosporins. Specifically, the immobilized proteolytic enzyme *subtilisin* has been used in the resolution of arylglycines such as D-*p*-hydroxyphenylglycine. D-*p*-Hydroxyphenylglycine is a very important arylglycine as it is used as a side chain constituent of the ß-lactam antibiotic, amoxicillin (**40**)[33] (Scheme 14).

Scheme 14

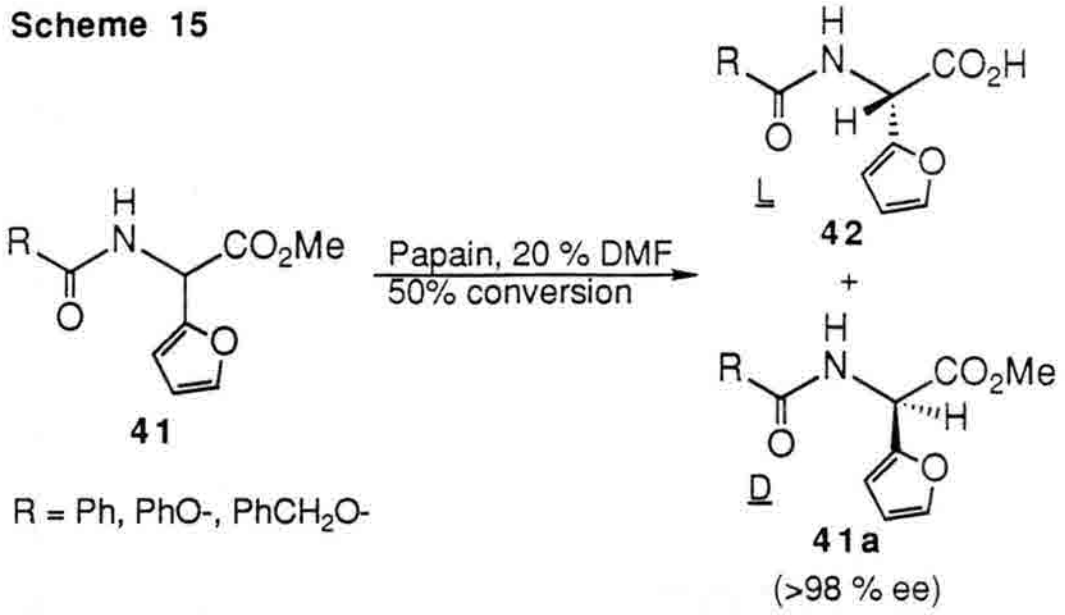




Amoxicillin

Papain has been reported to act as an effective esterase in the resolution of D,L-furyl glycine. The D-methyl esters (**41a**) were obtained in greater than 98 % ee but in only 31-44 % yield,[34] (Scheme 15). A creative use of enzymatic resolution involved the use of α-chymotrypsin to resolve α-nitro-α-methyl

Scheme 15



R = Ph, PhO-, $PhCH_2O$-

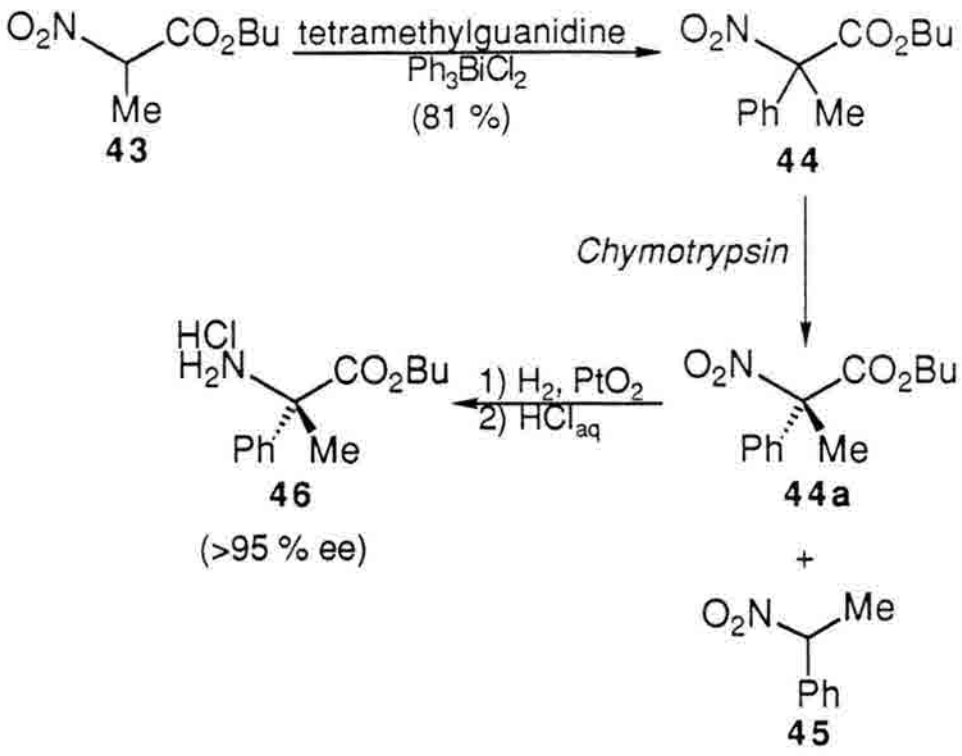
(>98 % ee)

carboxylic acid ester (**44**). α-Chymotrypsin hydrolyzed the D-ester to the free acid which spontaneously decarboxylated under the reaction conditions. The products formed could then be readily separated by radial chromatography. α-Methyl-α-phenylglycine butylester (**46**) was produced using this method in better than 95 % ee[35] (Scheme 16).

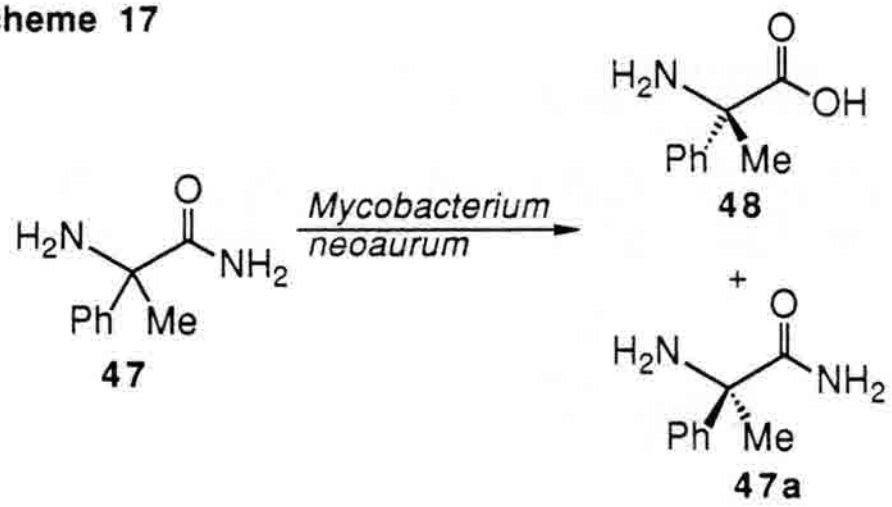
b. Amidases

Aromatic amino acid amides (**47**) can also be hydrolyzed stereoselectively to produce the L-arylglycine (**48**) and the D-arylamide (**47a**) using an amino peptidase from *Mycobacterium neoaurum*. The D,L-amino acid amides are mixed with whole cell *Mycobacterium neoaurum* in water at 37° C. L-α-methyl-α-phenylglycine (**48**) has been produced in this way,[36] (Scheme 17). An L-specific aminopeptidase from *Pseudomonas putida* has been utilized in the synthesis of D-phenylglycine (**6b**). D-Phenylglycine (**6b**) is used as a side chain precursor of ampicillin and is therefore in great demand industrially. The Strecker synthesis is utilized to prepare the racemic α-phenylamino amide (**49**) that can then be hydrolyzed stereoselectively yielding L-phenylglycine (**6a**) and D-phenylglycine amide (**49a**). The unwanted L-phenylglycine (**6a**) can be

Scheme 16



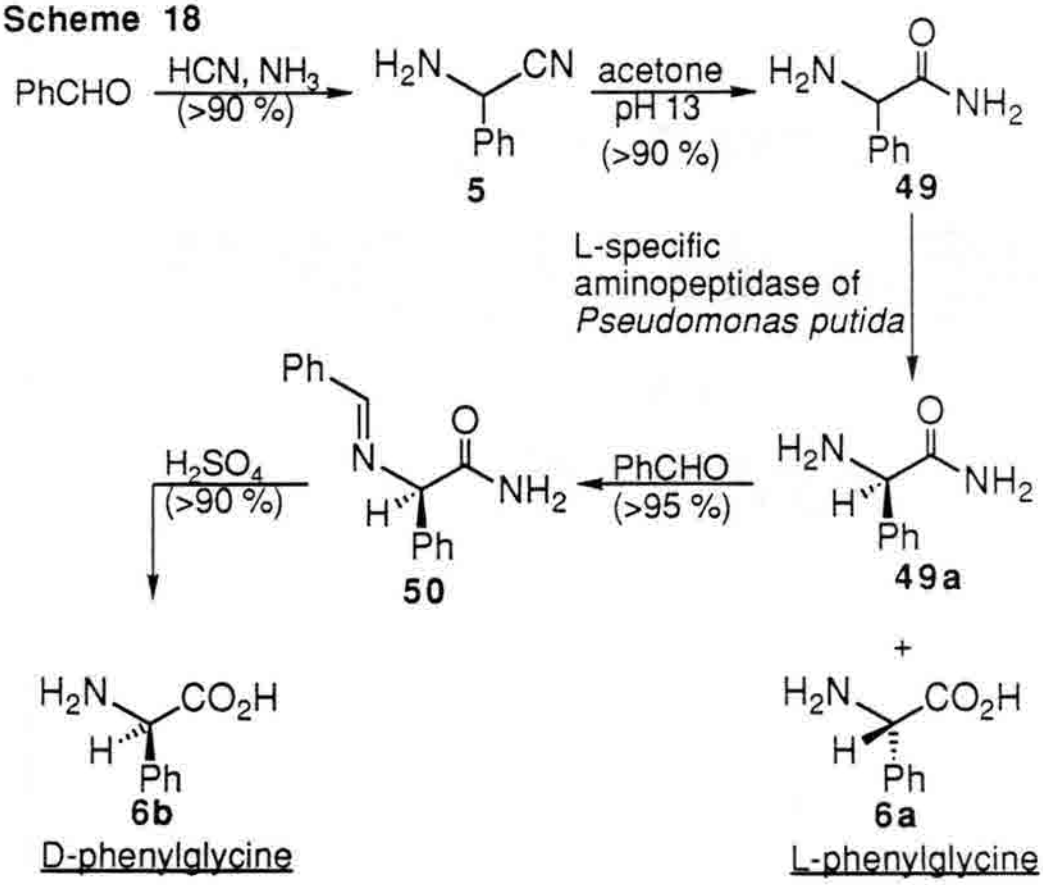
Scheme 17



collected and racemized, esterified and subjected to aminolysis forming the racemic α-phenylamino amide (**49**) which can be recycled in the resolution. The D-phenylglycine amide (**49a**) precipitated from the aqueous resolution

mixture by the addition of benzaldehyde forming the insoluble Schiff base (**50**). The Schiff base (**50**) is then hydrolyzed to D-phenylglycine (**6b**),[18] (Scheme 18).

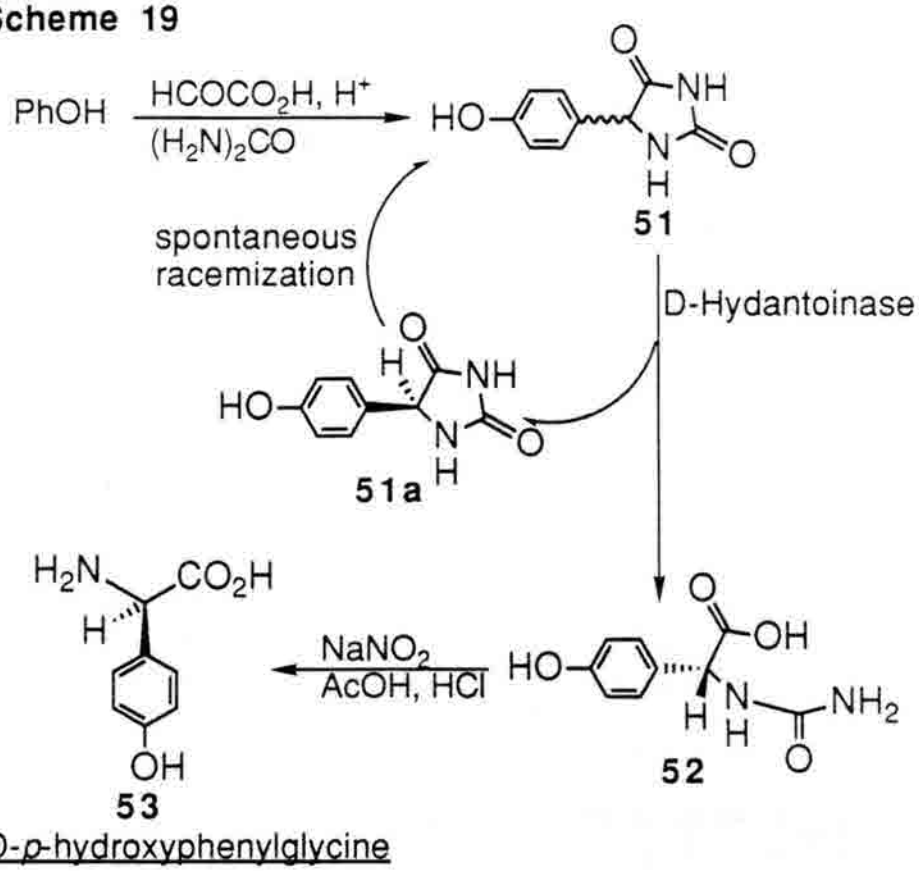
Scheme 18



c. Hydantoinases

D-*p*-Hydroxyphenylglycine (**53**) has been prepared from racemic (*p*-hydroxy phenyl) hydantoin (**51**) using a D-specific hydantoinase from *Bacillus brevis*. The racemic hydantoin (**51**) is selectively hydrolyzed to D-N-carbamoyl-*p*-hydroxyphenylglycine (**52**) and the unreacted L-isomer (**51a**) spontaneously racemizes under the reaction conditions giving this reaction a 100 % turnover, theoretically. The carbamoyl product is then chemically converted to the desired D-*p*-hydroxyphenylglycine (**53**) with sodium nitrite in hydrochloric and acetic acids,[18] (Scheme 19).

Scheme 19

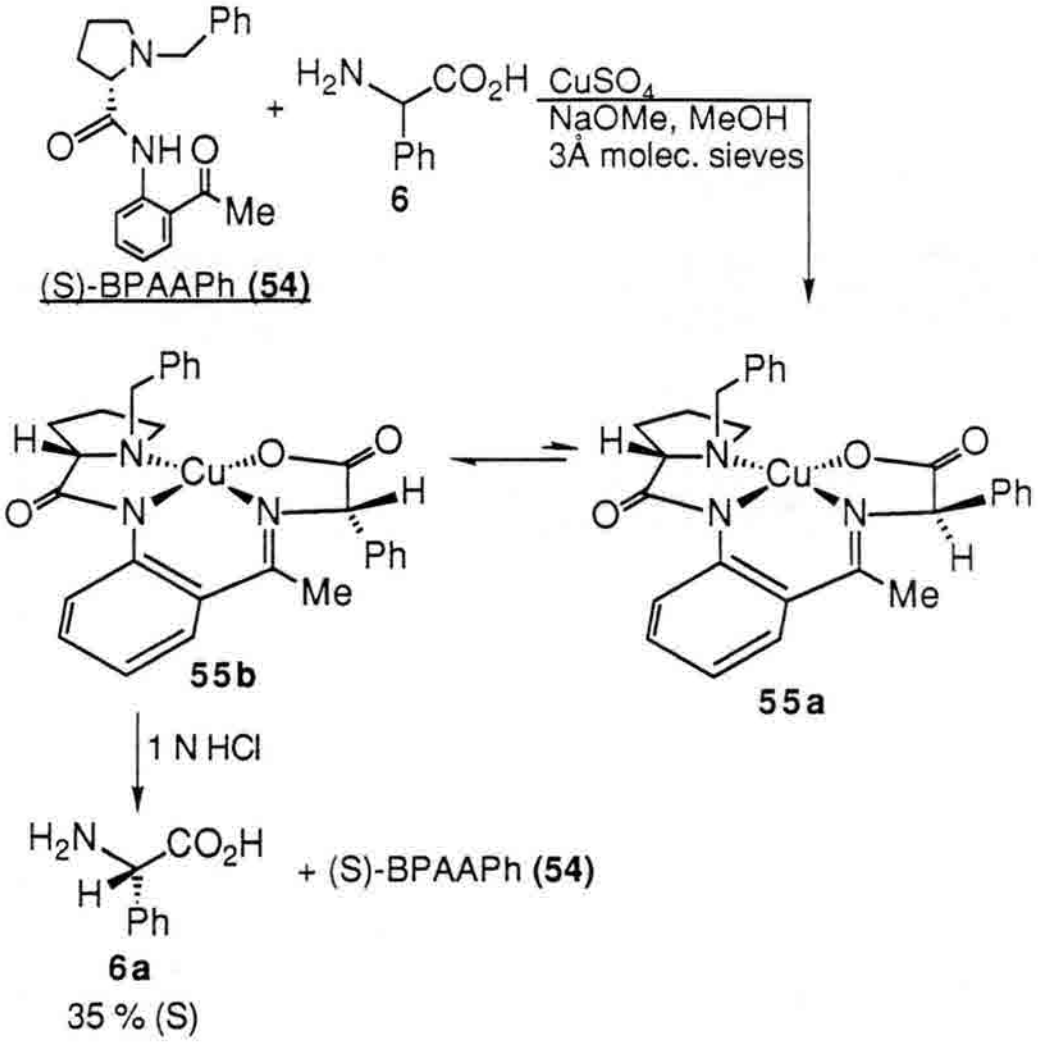


D-*p*-hydroxyphenylglycine

2. Retroracemization

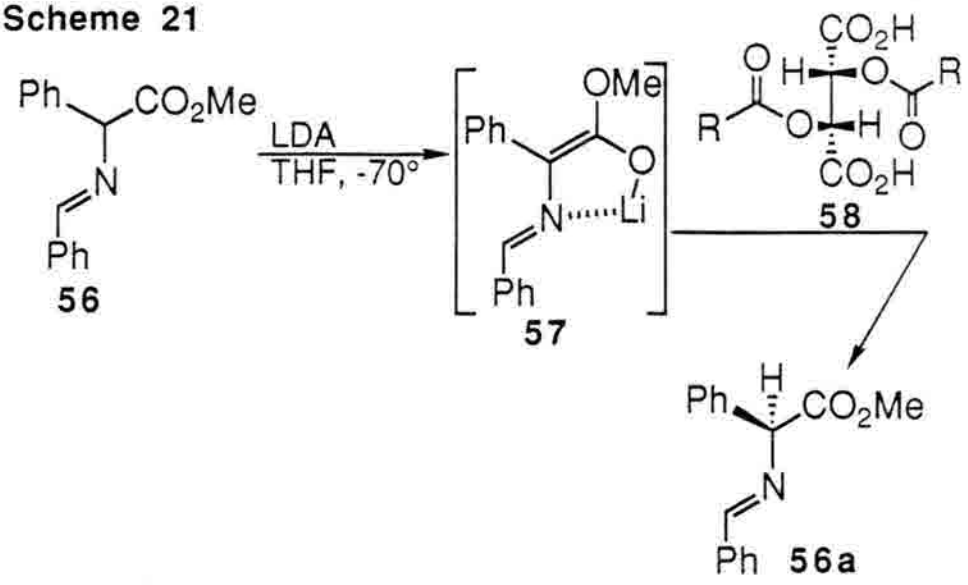
Apart from enzymatic methods for the resolution of arylglycines, the chemical method of deracemization or retroracemization has also been employed. Belokon and associates[37] used a chiral copper Schiff base complex (**55**) to perform a retroracemization and resolution on phenylglycine (**6**). The complex is formed by the condensation of racemic phenylglycine (**6**) with (S)-2-N-(N'-benzylprolyl)-aminoacetophenone (BPAAPh, **54**) in the presence of Cu^{II}. The chiral Schiff base complex (**55**) undergoes thermodynamic equilibration under basic conditions to the more stable *anti*- complex (**55b**). Acidic hydrolysis separates the chiral auxiliary from the optically enriched phenylglycine, (Scheme 20).

Scheme 20



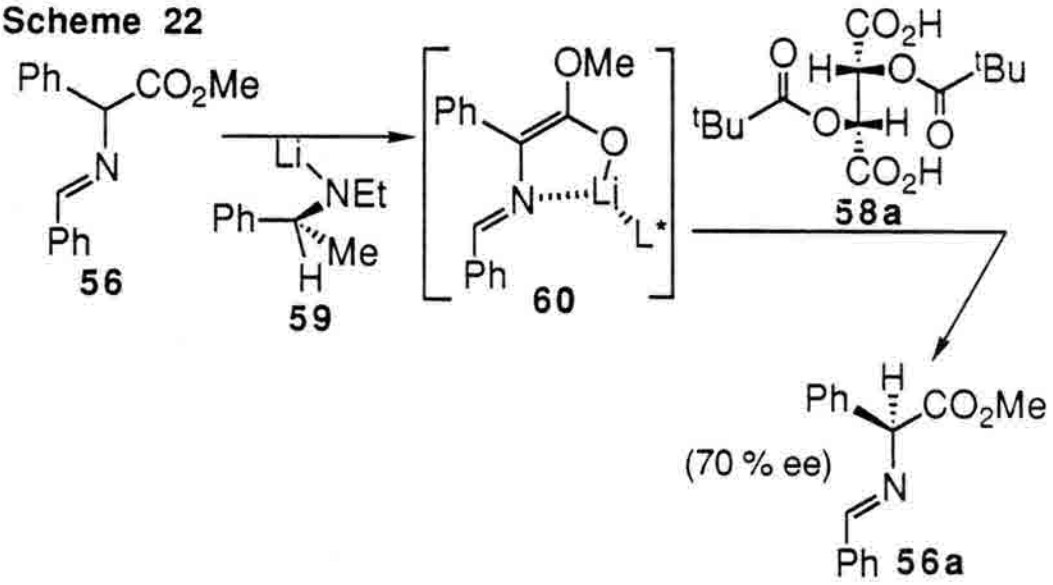
Duhamel and co-workers[38] have developed a strategy for the enantioselective protonation of the lithium enolate of a phenylglycine Schiff base (**57**). The benzylidene phenylglycine derivative (**56**) was treated with LDA yielding the desired enolate (**57**). This enolate (**57**) was then protonated with a series of tartrates (**58**) furnishing the phenylglycine derivative (**56a**) in moderate enantiomeric excess, (Scheme 21). In a related study,[39,38b] the same group substituted a chiral amide base (**60**) for LDA. The additional chirality donated from the chiral base improved the maximum % ee to 70 % for the phenylglycine derivative (**56a**), (Scheme 22).

Scheme 21



R	S:R Ratio (56a)	% Yield (56a)
t-Bu	79:21	85
t-$BuCH_2$	59:41	84
t-$BuCH_2CH_2$	70:30	82
Ph	57:43	80
$PhCH_2$	55:45	81
$PhCH_2CH_2$	54:46	83
$(Me)_2CBr$	70:30	85
cyclohexyl	71:29	85
ß-styryl	65:35	86
1-adamantyl	81:19	79

Scheme 22



D. The Asymmetric Synthesis of Arylglycines

As previously stated, arylglycines have been difficult to synthesize in optically active form due to the ease with which the α-methine proton can undergo base-catalyzed racemization. However, there have recently been several groups that have addressed the asymmetric synthesis of arylglycines in a variety of ways. One approach has been the modification of the Strecker synthesis in an asymmetric fashion. Other strategies include the asymmetric alkylation of nucleophilic glycinates, the asymmetric alkylation of electrophilic glycinates, enantioselective carboxylation, the asymmetric electrophilic amination of enolates, and the asymmetric nucleophilic amination of α-substituted acids, as well as other unique methods that defy categorization.

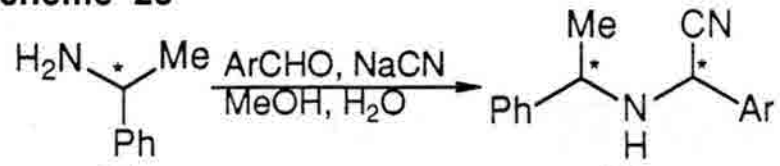
1. The Asymmetric Strecker Synthesis

The first asymmetric Strecker synthesis was reported in 1963 by Harada.[40] Since that time, the general strategy for the induction of asymmetry in the Strecker synthesis has been to generate a chiral Schiff base from the condensation of an aldehyde and an optically active amine. The subsequent addition of a nitrile source forms an optically active α-aminonitrile that is then hydrolyzed to the amino acid. This methodology has been quite successful in the synthesis of many amino acids but has rarely been used in the synthesis of arylglycines.

One reason that the asymmetric Strecker synthesis has not been applied often to arylglycines is the difficulty in removing the chiral auxiliary. For example, Stout and co-workers[41] examined the asymmetric synthesis of α-amino nitriles (**62**) using (R)- and (S)-α-methylbenzylamine (**61**) and a collection of benzaldehydes. The authors found that the α-aminonitriles (**62**) were formed with poor diastereoselection and concluded that the reaction proceeded under thermodynamic rather than kinetic control. Another problem

with this method was that the α-aminonitriles (**62**) could not be converted into the desired arylglycines. The reductive procedure usually employed to remove the N-α-methylbenzyl moiety could not be used since this method would also result in the cleavage of the second benzylic residue present, (Scheme 23).

Scheme 23



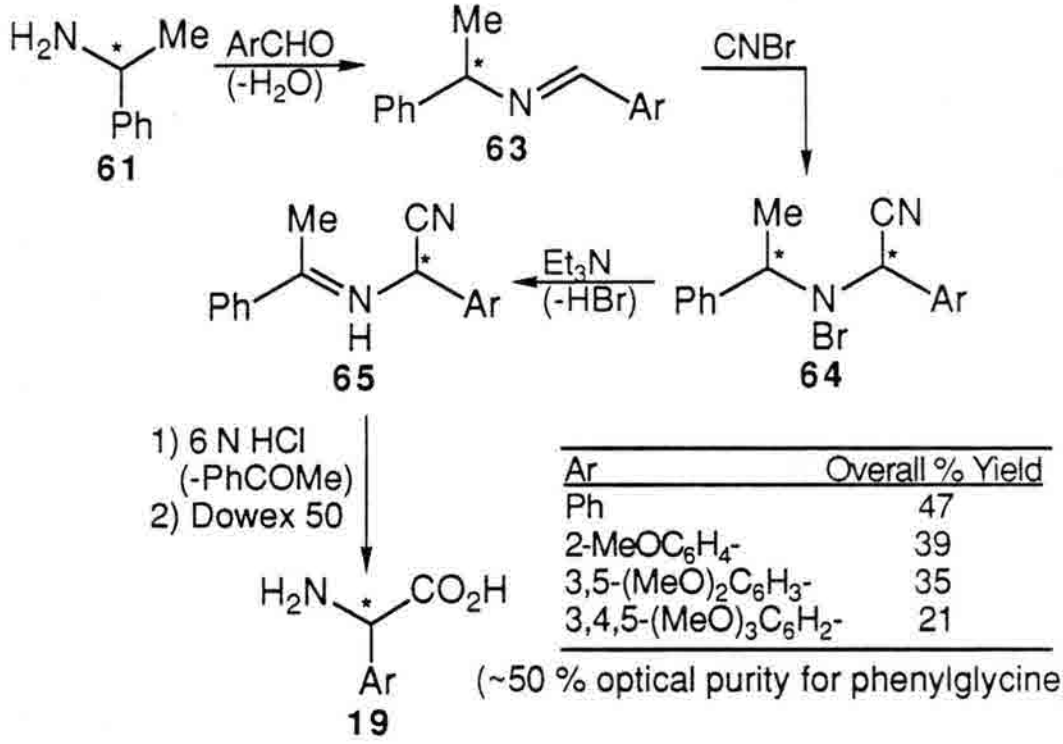
61 **62**

Ar	Config. (61)	Config. (62)	Diastereomeric Ratio	% Yield (62)	% Yield of Pure Diastereomer
Ph	R	R	3.2 : 1	93	33
	S	S	3.2 : 1	97	26
2-ClC_6H_4	R	R	6.0 : 1	96	78
	S	S	4.5 : 1	96	19
3-ClC_6H_4	R	R	2.1 : 1	96	14
	S	R	2.7 : 1	89	29
4-ClC_6H_4	R	R	3.3 : 1	93	39
	S	S	3.2 : 1	85	21
2-$MeOC_6H_4$	R	R	2.5 : 1	97	8
	S	S	2.3 : 1	97	5
3-$MeOC_6H_4$	R	R	2.4 : 1	90	8
	S	S	2.5 : 1	94	3
4-$MeOC_6H_4$	R	R	3.0 : 1	97	48
	S	S	3.0 : 1	97	46
4-MeC_6H_4	R	R	3.0 : 1	87	45
	S	S	3.0 : 1	80	54

More recently, however, Panse and associates[42] were able to selectively remove the N-α-methylbenzyl moiety which gave rise to optically active arylglycines (**19**). The protocol called for the addition of cyanogen bromide to

the chiral Schiff base (**63**) yielding the N-bromo-α-aminonitrile. Dehydrobromination occurred with the addition of triethylamine followed by acid hydrolysis that furnished the desired arylglycine (**19**), (Scheme 24).

Scheme 24



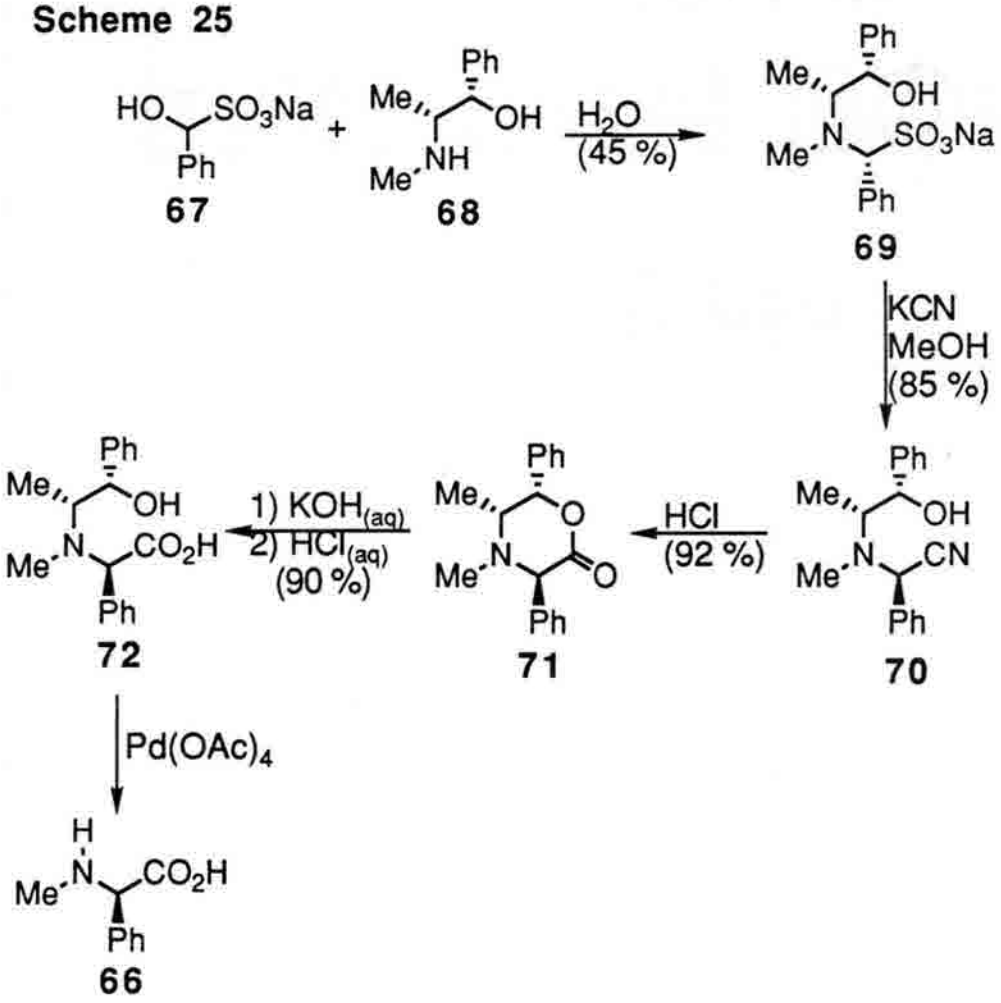
Ar	Overall % Yield
Ph	47
2-$MeOC_6H_4$-	39
3,5-$(MeO)_2C_6H_3$-	35
3,4,5-$(MeO)_3C_6H_2$-	21

(~50 % optical purity for phenylglycine)

The utility of the asymmetric Strecker synthesis was greatly enhanced with the discovery that chiral auxiliaries can be cleaved in an oxidative manner. In an early demonstration of this methodology, Neelakantan[43] synthesized D-(-)-α-phenylsarcosine (**66**). In this example, benzaldehyde bisulfite (**67**) was treated with (-)-ephedrine (**68**) under aqueous conditions to form sodium (-)-α-ephedrinophenylmethanesulfonate (**69**). Potassium cyanide in methanol reacted with **69** in an Sn2 displacement to provide the desired nitrile (**70**) with inversion. The nitrile (**70**) was then treated with concentrated HCl which gave the lactone material (**71**) which was further hydrolyzed in base yielding (+)-α-

ephedrinophenylacetic acid (**72**). The ephedrin auxiliary was then cleaved with lead tetraacetate yielding D-(-)-α-phenylsarcosine (**66**), (Scheme 25). While this example is not strictly a Strecker synthesis, the oxidative cleavage strategy does provide an important tool in the synthesis of arylglycines.

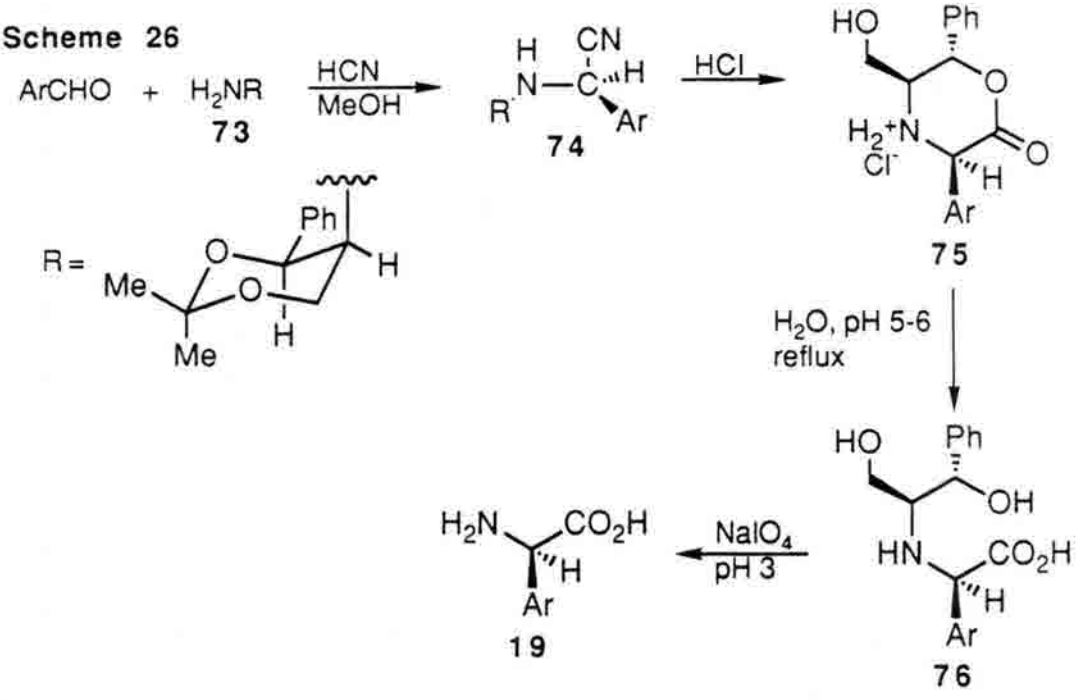
Scheme 25



The first use of an asymmetric Strecker synthesis to produce arylglycines was reported by Weinges *et. al.*[44] These workers also used an oxidative method for the cleavage of the chiral auxiliary to gain access to arylglycines. The authors condensed benzaldehyde derivatives in the presence of sodium cyanide with a sterically hindered 1,3-dioxolane (**73**) which produced a

crystalline, diastereomerically pure aminonitrile (**74**). The aminonitrile (**74**) then underwent mild hydrolysis which furnished the oxazinone (**75**) which was further hydrolyzed to the desired hydroxy acid (**76**). Oxidative cleavage of the amino alcohol residue with sodium periodate in water at pH 3 gave the desired arylglycines (**19**), (Scheme 26).

Scheme 26



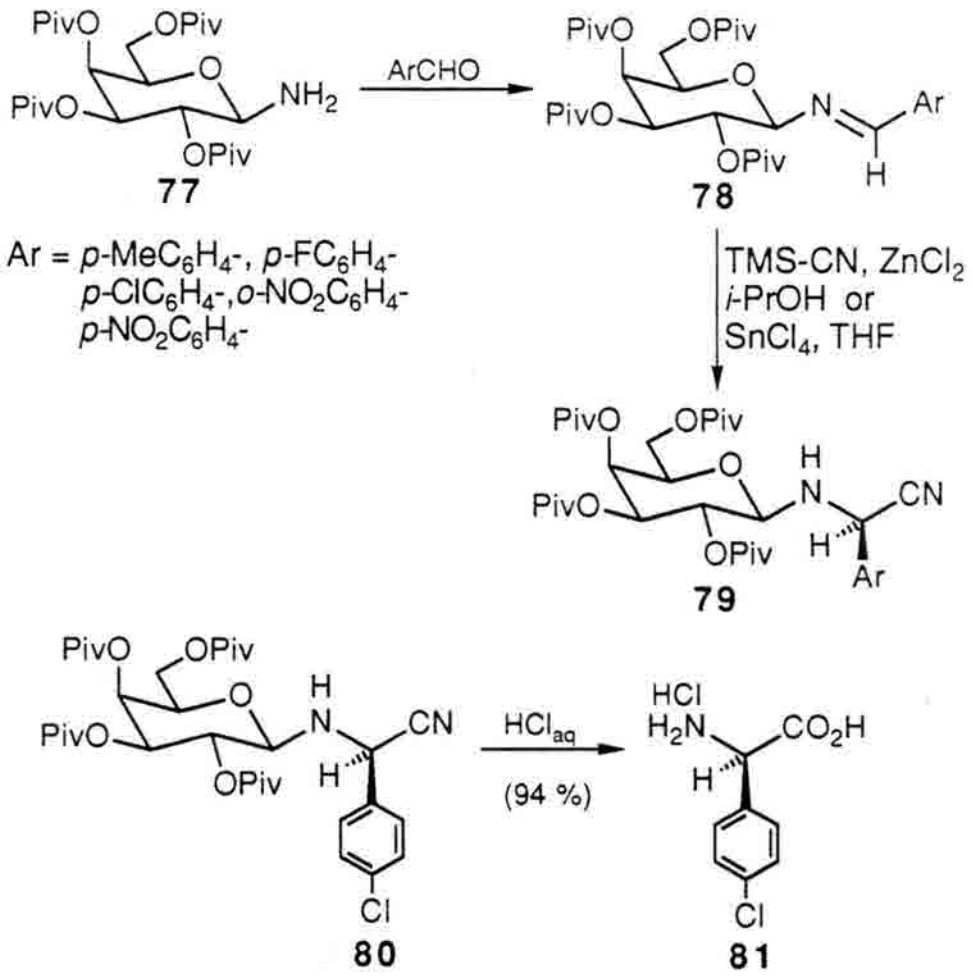
Ar	% Yield (74)	% Yield (76)	% Yield (19)
Ph	65	82	68
4-$MeOC_6H_4$	60	73	49
2-thienyl	24	65	64
3-thienyl	35	76	60

Using a similar strategy to those previously discussed, Kunz and co-workers[45] developed an amino-galactose derivative (**77**) as a chiral amine source for the asymmetric Strecker synthesis. As seen before, a chiral imine

(**78**) is pre-formed from the condensation of a benzaldehyde derivative. The diastereoselective addition of TMSCN followed yielding the aminonitrile (**79**). The use of trimethylsilylcyanide and zinc chloride as a Lewis acid gave high yields and minimized the amount of anomerization of the carbohydrate from ß- to α-. Hydrolysis under acidic conditions of the carbohydrate and the nitrile gave the desired amino acid (**81**) in at least one case, (Scheme 27). The diastereofacial selectivity of the cyanide addition to the imine (**78**) can be altered due to solvent effects.[46] When the addition of trimethylsilylcyanide is performed in chloroform with zinc chloride, the S-isomer (**82**) is the major product. As shown above, the R-isomer (**79**) predominated when the same reaction is carried out in THF or isopropanol. The reason for this reversal of stereochemistry is not very clear since the authors clearly showed that the conformation of the imine (**78**) remains the same regardless of whether THF or chloroform was used. The stereochemical result of this reaction may be due to aggregation and salt complexation differences in different solvents. Despite the reasons for the stereochemistry, these results show that with a simple change of solvents, either (R)- or (S)- isomers can be accessed, (Scheme 28).

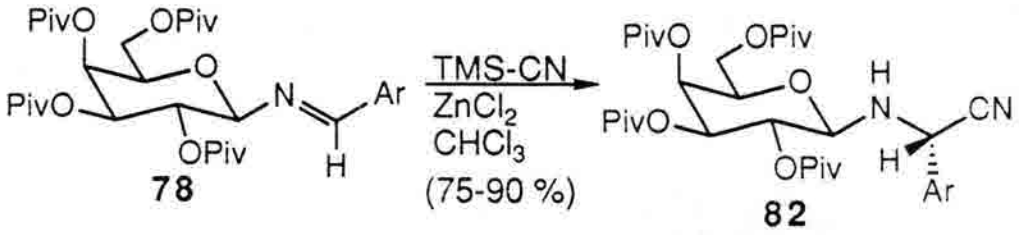
In related work, the Kunz group[47] used their galactose derivative (**77**) in an asymmetric Ugi synthesis. The galactose derivative (**77**) was condensed with a benzaldehyde, an isonitrile, and formic acid in the presence of zinc chloride. The desired Ugi products (**83**) were formed with high diastereoselection, furthermore, the diastereomers were separable via recrystallization. The chiral auxiliary (**84**) was then cleaved and recovered after hydrolysis with methanolic HCl which also gave the amide (**85**). The amide (**85**) was hydrolyzed further in hot 6 N HCl yielding the desired arylglycine (**19**), (Scheme 29).

Scheme 27



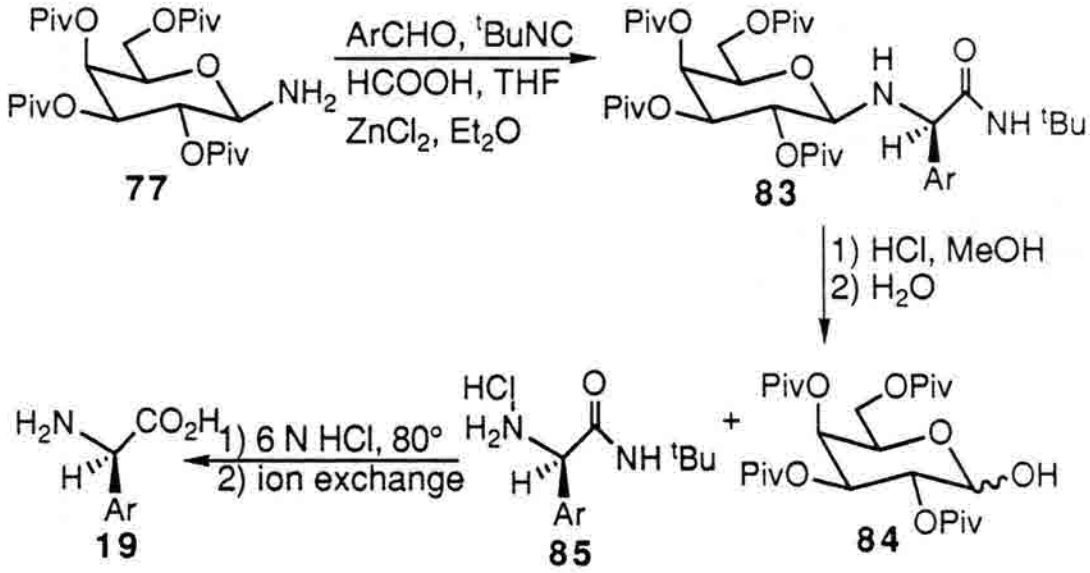
Ar	Solvent	Cat. (mol%)	Diastereomeric Ratio (R : S)	% Yield (79)
4-MeC_6H_4	*i*-PrOH	$ZnCl_2$ (100)	6.5 : 1	78
	THF	$SnCl_4$ (130)	12 : 1	87
4-FC_6H_4	*i*-PrOH	$ZnCl_2$ (5)	6.5 : 1	75
	THF	$SnCl_4$ (130)	10 : 1	84
4-ClC_6H_4	THF	$SnCl_4$ (130)	11 : 1	84
4-$NO_2C_6H_4$	*i*-PrOH	$ZnCl_2$ (5)	7 : 1	80
2-$NO_2C_6H_4$	THF	$SnCl_4$ (130)	1 : 0	91

Scheme 28



Ar	$ZnCl_2$ (mol%)	Diastereomeric Ratio (R : S) (82)
4-MeC_6H_4	100	1 : 4.5
4-FC_6H_4	100	1 : 3
4-ClC_6H_4	5	1 : 4
	300	1 : 5
3-ClC_6H_4	5	1 : 6
	100	1 : 5

Scheme 29



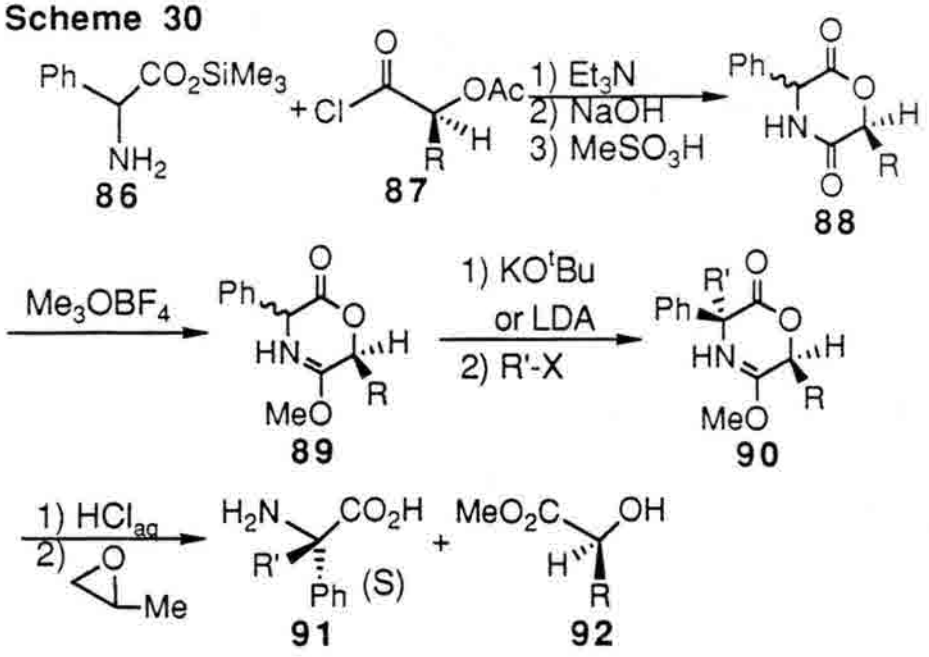
Ar	Diastereomeric Ratio (R : S) (83)	% Yield (83)	% Yield (19)
Ph	91 : 9	81	85
4-ClC_6H_4	97 : 3	92	90
4-$NO_2C_6H_4$	94 : 6	91	
2-furyl	95 : 5	90	
2-thienyl	96 : 4	93	

2. The Alkylation of Nucleophilic Glycinates

The alkylation of nucleophilic glycinates is a method that has been widely used to prepare α-alkylated phenylglycine products. These di-alkylated amino acids are not prone to racemization, as are standard arylglycines, and are thus stable to the basic conditions used for alkylation. An example of this approach reported by Schollkopf[48] utilized optically active dihydro-oxazinones (**88**) which are prepared from phenylglycine and several optically active α-hydroxy acids (**87**). This product was then converted to a mono-lactim ether (**89**) that was then subjected to an enolate alkylation with activated electrophiles. The resulting oxazinone (**90**) was cleaved with mild aqueous acid yielding the desired α-alkylated phenylglycine derivatives (**91**), (Scheme 30). In a related approach,[49] 2-furylglycine was used as the amino acid template. Following the same alkylation procedure as above, α-alkylated-2-furyl glycine derivatives were produced, (Scheme 31).

In another nucleophilic alkylation approach, Seebach and associates[50] prepared an α-ethylphenylglycine (**102**) derivative using an optically active imidazolidinone (**101**). The imidazolidinone (**101**) was synthesized from phenylglycine ethyl or methyl ester (**98**) which, when treated with concentrated methyl amine, formed the corresponding N-methyl amide. Treatment of the amide with pivaldehyde coupled with the azeotropic removal of water produced the pivaloyl imine (**99**). The pivaloyl imine (**99**) was then reacted with methanolic HCl followed by acylation with benzoyl chloride which resulted in a stereoselective ring closure to the anti-imidazolidinone (**100**) as the major product. The syn-imidazolidinone (**101**) can be formed from the same pivaloyl imine (**99**) when treated with benzoic anhydride at 130° C. Enolate alkylation with ethyliodide of the syn-imidazolidinone (**101**) proceeded in 80 % yield at >95 % ds, (Scheme 32). The deprotection of this substrate to the amino acid

Scheme 30

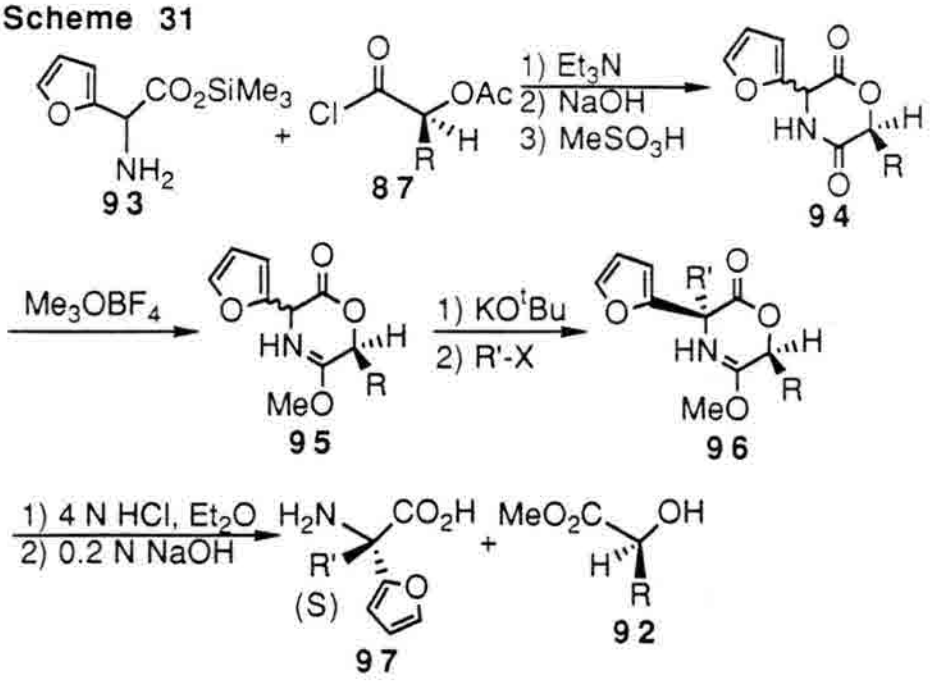


R	R'	% Yield (90)	% de(90)
i-Pr	$PhCH_2$	90	>95
i-Pr	$CH_2CH{=}CH$	95	83
i-Pr	Me	95	60
t-Bu	$PhCH_2$	90	>95
t-Bu	Me	95	90
Ph	Me	85	77
Ph	$PhCH_2$	91	>95
$PhCH_2$	Me	86	49

was not reported. Other alkylated imidazolidinones were deprotected to amino acids under quite harsh acidic conditions and the ethylphenylglycine derivative (**102**) may not have survived deprotection.

In related work, Seebach and co-workers[51] phenylated proline at the α-center via the enolate of a bicyclic aminal (**106**) with retention of configuration, (Scheme 33). To describe this observed stereochemical outcome, the authors have used the phrase "self reproduction of chirality." "Self reproduction of chirality" describes how the proline stereogenic center controlled the relative

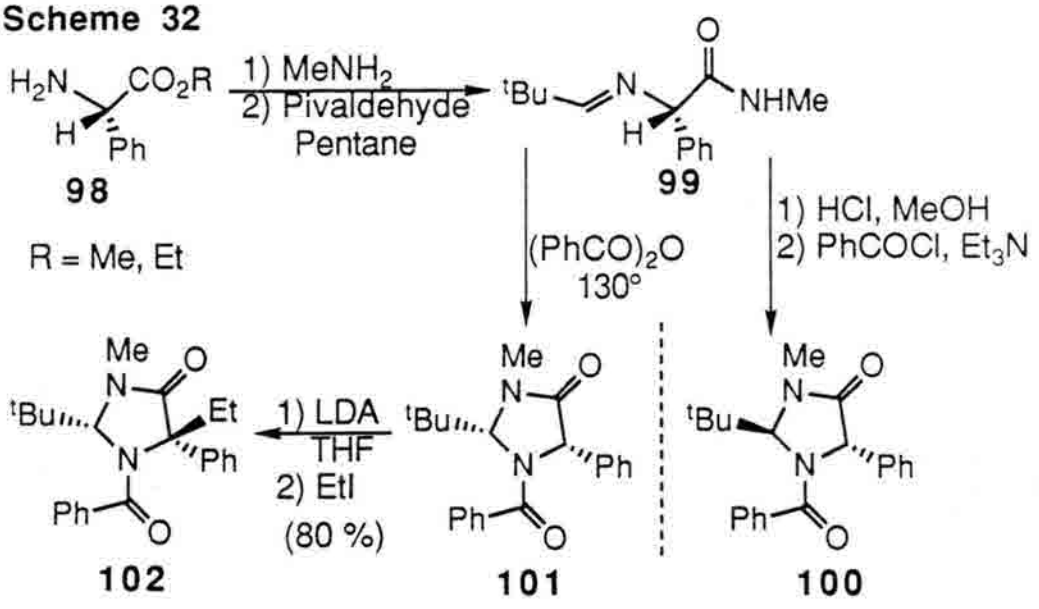
Scheme 31



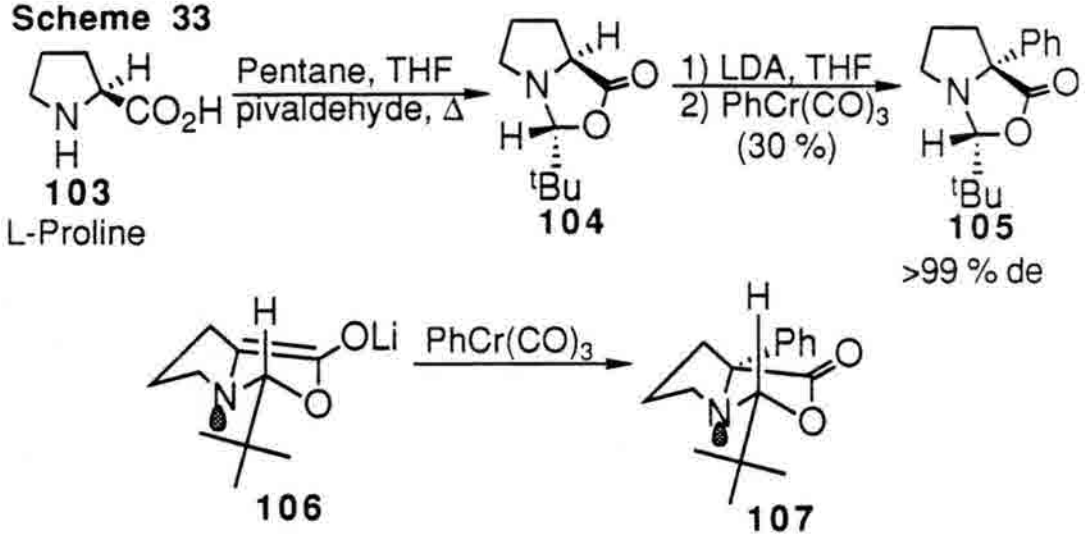
R	R'	% Yield (96)	%de (96)
i-Pr	$PhCH_2$	91	>95
i-Pr	Me	92	58
i-Pr	Et	83	61
i-Pr	$CH(Me)_2$	81	62
i-Pr	$CH_2CH_2CH{=}CH_2$	93	70
i-Pr	CH_2-cyclohexyl	75	62
i-Pr	CH_2-2-thienyl	92	>95
i-Pr	CH_2-2-naphthyl	91	>95
t-Bu	$PhCH_2$	92	>95
t-Bu	$CH_2CH_2CH{=}CH_2$	85	>95
t-Bu	Me	92	>95

stereochemistry in the formation of the aminal stereogenic center and was subsequently rendered planar upon the formation of the enolate (**106**). The researchers believe that the enolate's conformation (**106**) placed the aminal methine in a pseudo-axial geometry which hindered the approach of the electrophile *anti*- to the *t*-butyl group.

Scheme 32



Scheme 33

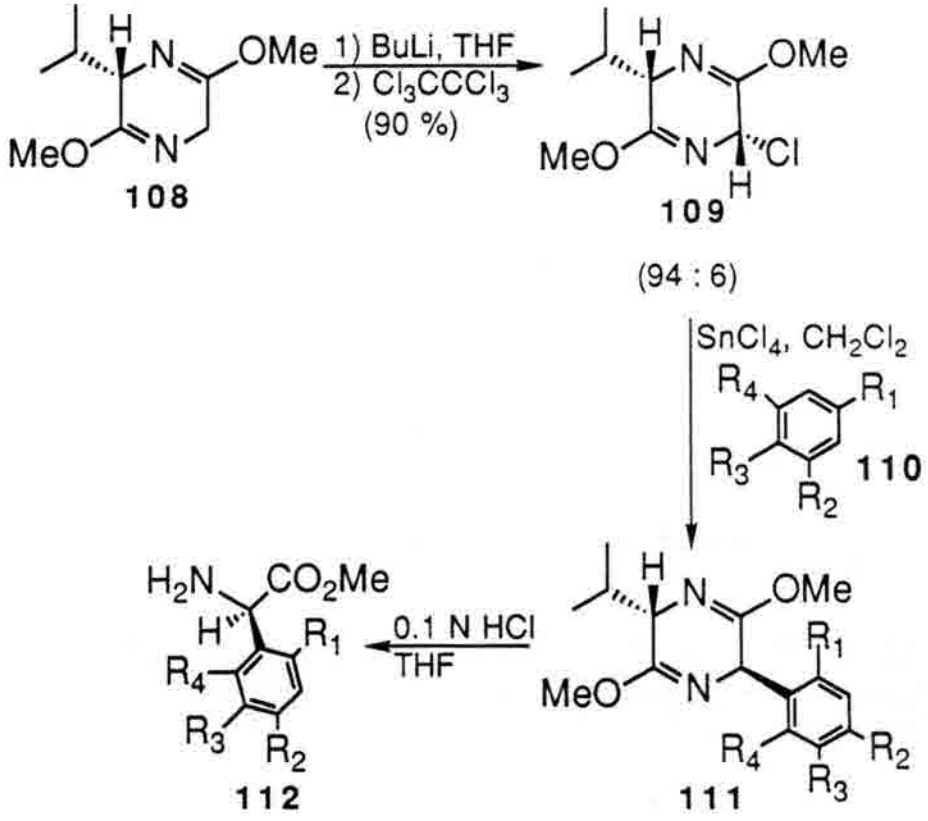


3. The Alkylation of Electrophilic Glycinates

The alkylation of electrophilic glycinates is a strategy pioneered by Ben-Ishai[26a,b] in the racemic synthesis of many classes of α-amino acids. In modifying this concept for use in the asymmetric synthesis of arylglycines, Schollkopf and associates[52] chlorinated the enolate of their bis-lactim ether (**108**) with hexachloroethane in a 94:6, cis:trans mixture. The resulting chloride (**109**) was condensed with electron-rich aromatic compounds (**110**) in Friedel-

Crafts couplings with tin tetrachloride as a Lewis acid. The resulting *anti*-products (**111**) were hydrolyzed to the desired arylglycine methylesters (**112**) in good yields and in 84 to 95 % ee, (Scheme 34). The use of an acidic deprotection avoids the possibility of arylglycine racemization.

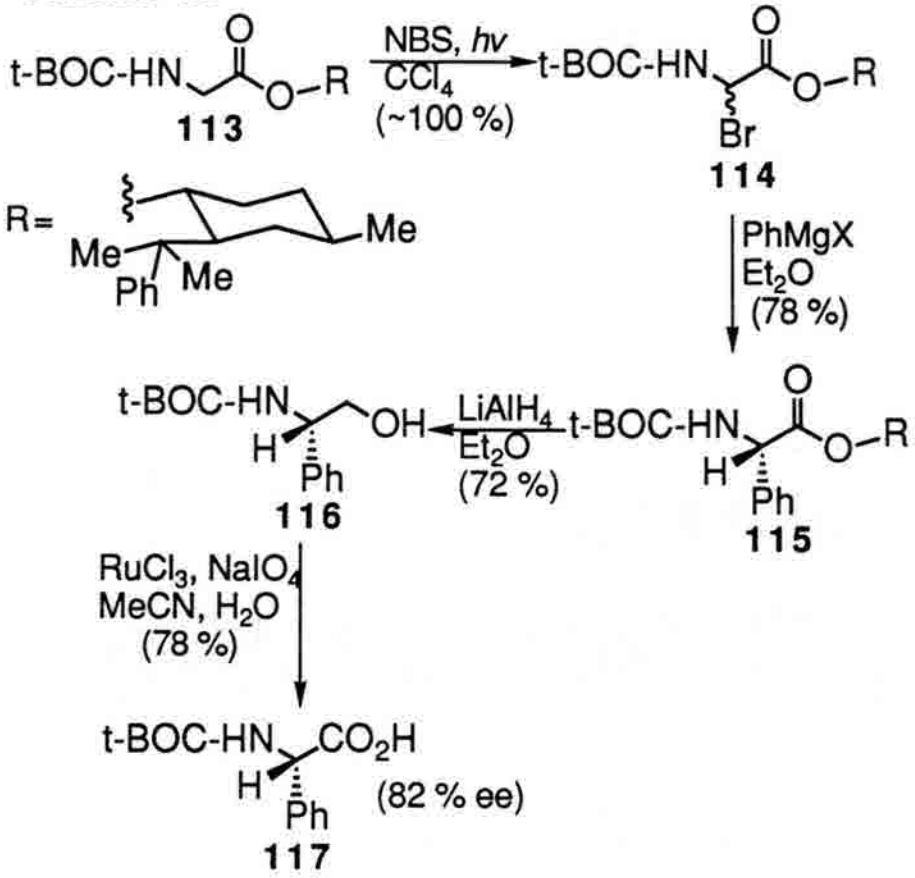
Scheme 34



R_1	R_2	R_3	R_4	% Yield (111)	% Yield (112)	% ee(112)
OEt	H	OEt	H	65	89	>95
OMe	OMe	H	OMe	67	60	>95
H	OMe	H	H	62 (11.5 : 1; *p:o*)	69	~84
OMe	H	H	H	62 (11.5 : 1; *p:o*)	69	~84

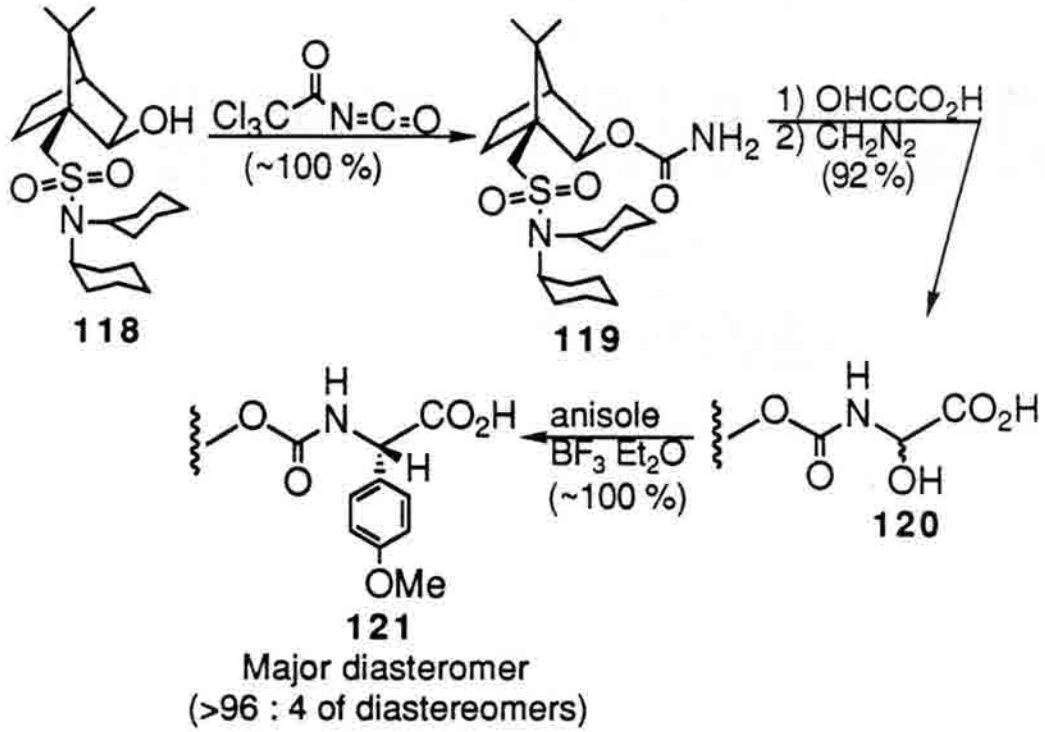
In another example, Obrecht, *et. al.*,[53] employed a 8-phenylmenthyl ester (**113**) to synthesize N-t-BOC phenylglycine (**117**). The 8-phenylmenthyl ester (**113**) was brominated with NBS giving a 1:1 mixture of the bromide (**114**) that was used immediately without purification. The addition of the phenyl Grignard reagent promoted the elimination of HBr from the phenylmenthyl ester yielding an imine which, in turn, was attacked by the Grignard reagent at the less hindered face to give **115**. The authors indicated that their attempts to remove the chiral auxiliary via hydrolysis or transesterification without racemization failed. Therefore, the authors developed a reductive method using LAH which did indeed cleave the chiral auxiliary but gave the amino alcohol (**116**). Finally, the amino alcohol (**116**) was successfully oxidized to the N-t-BOC phenylglycine (**117**) with ruthenium, (Scheme 35).

Scheme 35



Harding and Davis[54] developed another optically active electrophilic glycinate by using a camphor sultam chiral auxiliary (**118**) originally developed by Oppolzer. The camphor sultam (**118**) was functionalized in three steps, in excellent yield, to the electrophilic glycinate (**120**) as a mixture of diastereomers. The electrophilic glycinate (**120**) was then reacted with anisole and boron trifluoride etherate in quantitative yield in a >96:4 mixture of diastereomers (**121**), (Scheme 36). As seen previously with other hindered esters, the authors found that hydrolytic cleavage of the chiral auxiliary without racemization was a problem.

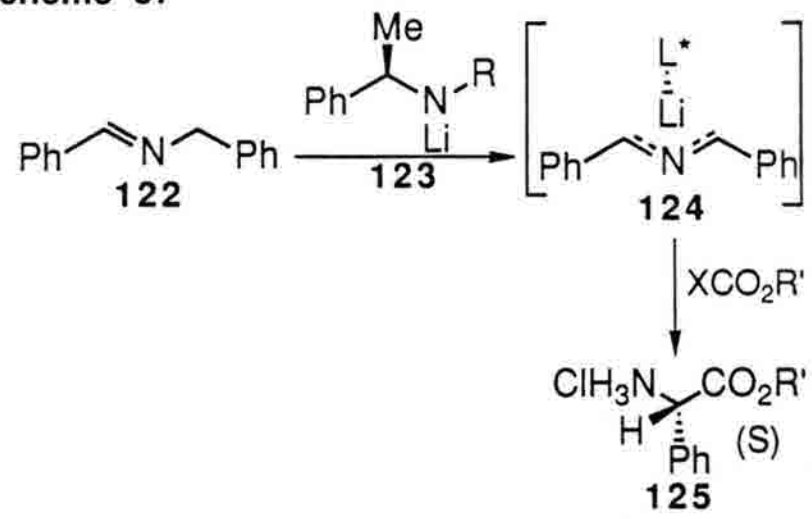
Scheme 36



4. Enantioselective Carboxylation

One of the few examples of an enantioselective carboxylation was reported by Duhamel and co-workers.[55] This study examined the use of a chiral amide (**123**) base to generate an α-lithioamide (**124**) which was then carboxylated. The carboxylation was carried out with dimethyl carbonate or a variety of chloroformates. The acidic work-up removed the benzylidene yielding the phenylglycine ester (**125**) but in low enantiomeric excess, (Scheme 37).

Scheme 37

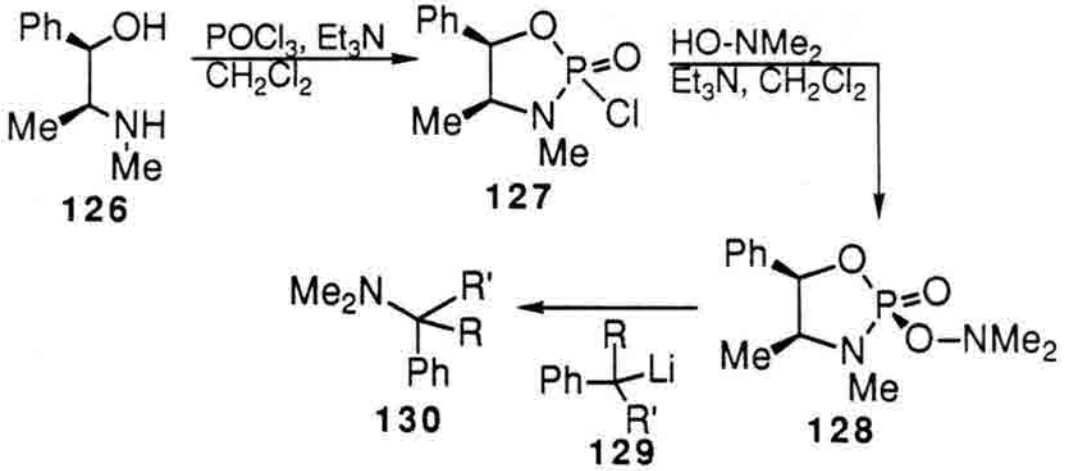


R	R'	X	% Yield (125)	% ee(125)
Et	Me	MeO	40	0
Et	Me	Cl	58	35
Pr	Me	Cl	60	32
Et	Et	Cl	56	41
Pr	Et	Cl	55	34
Et	Bu	Cl	40	40

5. The Asymmetric Electrophilic Amination of Enolates

The asymmetric electrophilic amination of enolates is a relatively recent advance in amino acid synthesis due to the general lack of electrophilic nitrogen sources. Boche and Schrott[56] developed a chiral electrophilic aminating reagent (**128**) which they used to synthesize phenylglycine derivatives. Their reagent was prepared from (-)-ephedrine (**126**), phosphorous oxychloride and N,N-dimethylhydroxylamine. The enantiospecific amination with several lithio-carbanions (**129**) was achieved yielding the dimethylamino phenylglycine derivative (**130**), (Scheme 38). The yields of the aminations were moderate and the % ee's were low indicating that the nitrogen atom was too far away from the stereogenic center which would likely make the $\Delta\Delta G^{\ddagger}$'s of the diastereomeric transition states similar in value.

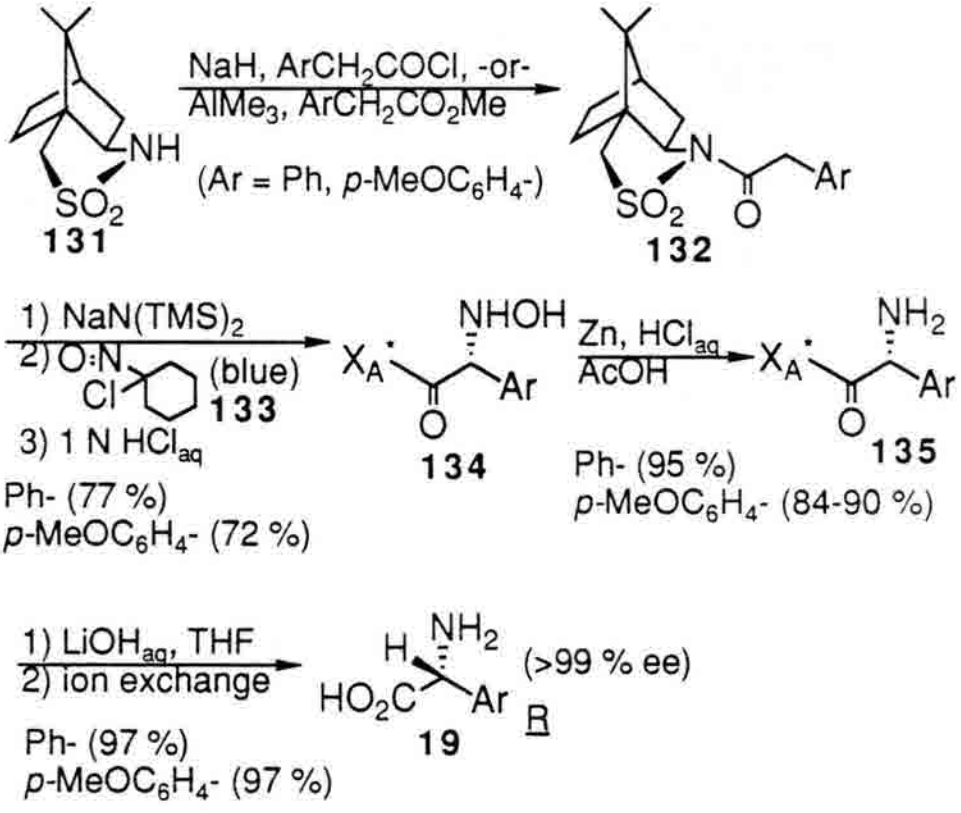
Scheme 38



R	R'	% Yield (130)	% ee(130)
H	CO_2Et	50	23
Me	CO_2Et	56	21
H	CN	62	8

In a recent communication, Oppolzer and Tamura[57] reported the use of their sultam chiral auxiliary (**131**) in an electrophilic amination. The sultam was smoothly N-acylated and subsequently deprotonated with sodium hexamethyldisilazide. The chiral enolate was then aminated with 1-chloro-1-nitrosocyclohexane (**133**) yielding the desired hydroxylamine (**134**) after an aqueous acidic quench. The hydroxylamine (**134**) was reduced to the amino sultam (**135**) with zinc dust. The sultam auxiliary was then cleaved and recovered after hydrolysis with aqueous LiOH which also afforded the desired arylglycine (**19**) in >99 % ee, (Scheme 39). Both R and S enantiomers of *p*-methoxyphenylglycine were selectively synthesized depending on which sultam antipode was chosen as the starting material.

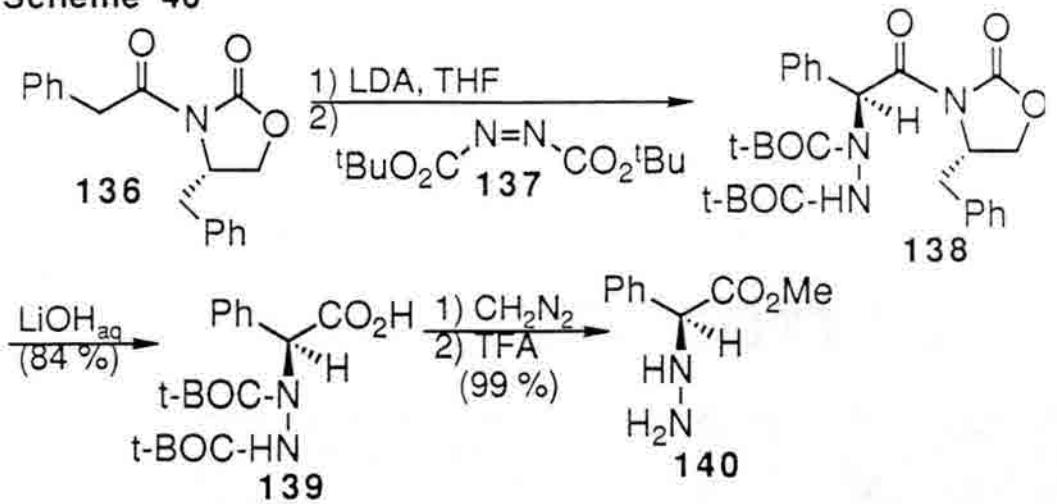
Scheme 39



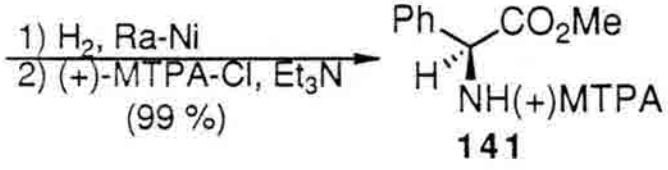
Evans and associates[58] have extended the use of their chiral carboximide enolates to electrophilic aminations in the synthesis of amino acids. The chiral carboximide enolate was generated with LDA and aminated with di-tert-butylazodicarboxylate (**137**) providing a 97:3 ratio of diastereomers. Hydrolysis of the hydrazide (**138**) with LiOH produced the hydrazido acid (**139**) with no perceptible racemization. However, attempts to transesterify the hydrazido acid (**139**) produced significant racemization. Therefore, an alternate deprotection was developed in which the hydrazido acid (**139**) was esterified with diazomethane followed by trifluoroacetic acid cleavage of the t-BOC group. The resulting solution was carried on directly and subjected to Raney nickel hydrogenation yielding an impure product that was acylated with (+)-MTPA chloride, (Scheme 40). Diastereomeric analysis of the resulting Mosher's amide (**141**) by gas chromatography showed a 99:1 mixture of isomers. In an attempt to explain the stereochemical outcome of the amination reaction, the authors considered three possible chelated transition states, T1, T2, and T3. In T1, an 8-centered transition state is formed by chelation of lithium to the oxygen of the azodicarboxylate; in T3, lithium chelates to one of the azodicarboxylate's nitrogen atoms forming a Zimmerman-Traxler-type 6-centered pericyclic transition state; however, the authors favor T2 for stereoelectronic reasons.

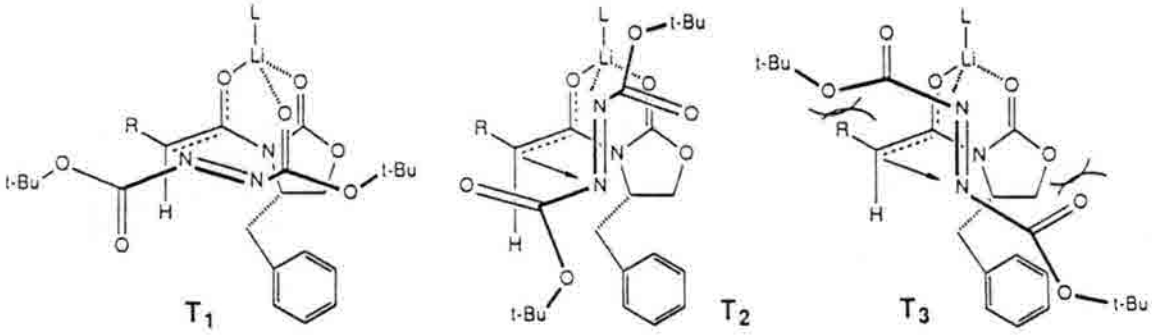
In related work, Evans and Britton[59] generated the enolate of their optically active carboximide with potassium hexamethyldisilazide. A diastereoselective azidation was achieved with the use of 2,4,6-triisopropylsulfonylazide ('trisyl azide', **142**) yielding the α-azidocarboximide (**143**) after a glacial acetic acid quench. The chiral auxiliary was removed via LiOH hydrolysis which afforded the desired α-azido acid (**144**) without racemization, (Scheme 41). A more complete study of this transformation was recently published with full experimental details.[60]

Scheme 40

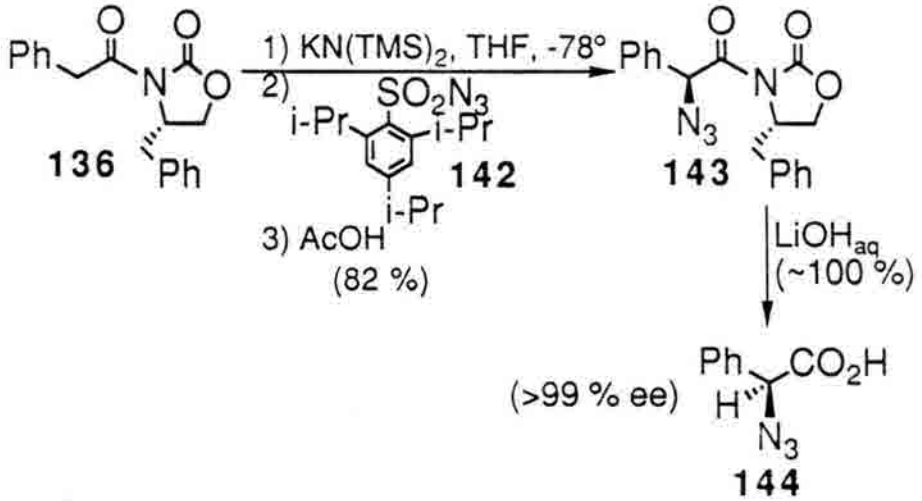


(98 % ee)





Scheme 41

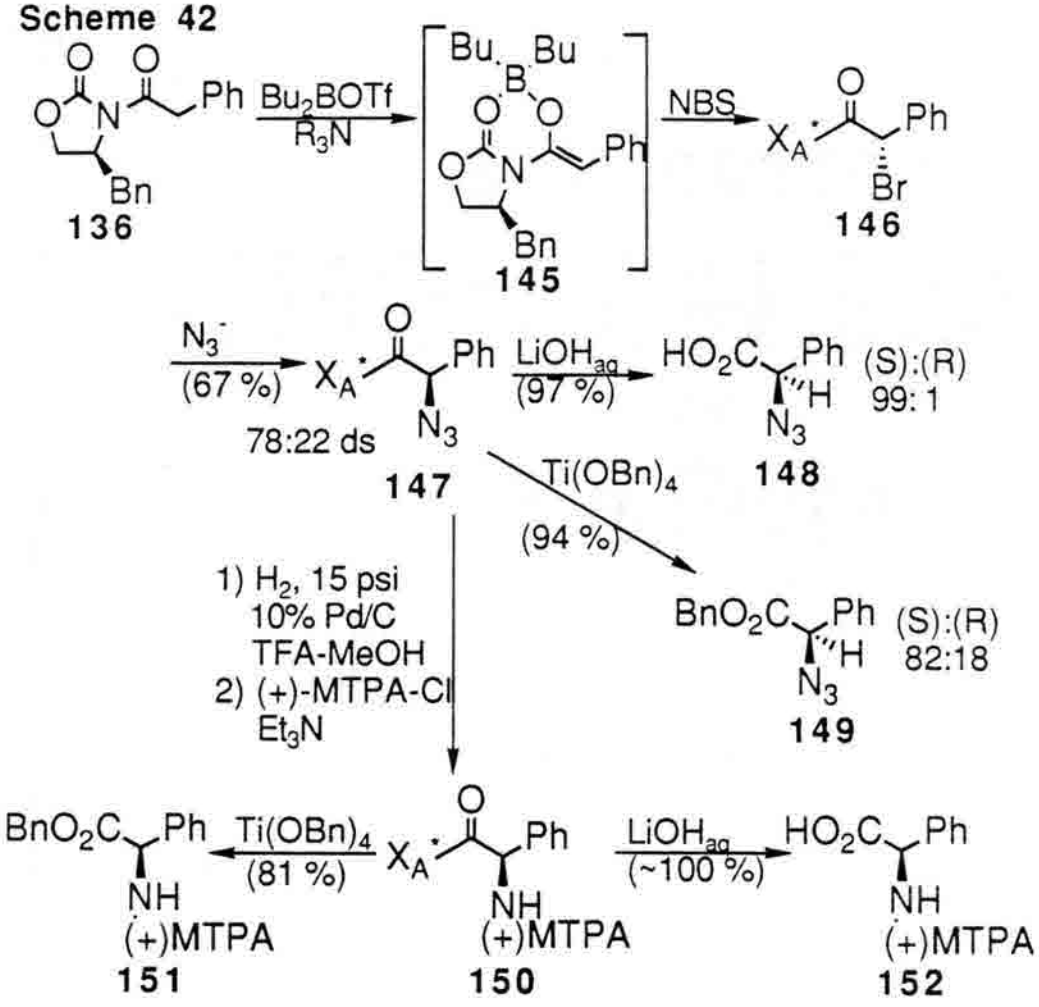


6. The Asymmetric Nucleophilic Amination of α-Substituted Acids

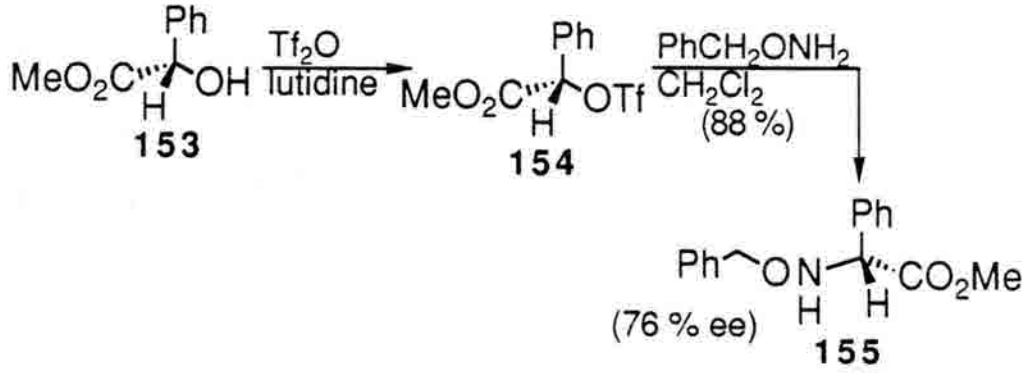
Another approach to amino acids has been the displacement of a leaving group α- to a carboxylic acid by a nucleophilic amine equivalent. The Evans group[60,61] has utilized this strategy in an extension of the use of their optically active carboximide (**136**). The chiral carboximide (**136**) is converted to the di-*n*-butylboron enolate (**145**) in a reaction with the corresponding triflate and an amine base. The boron enolate (**145**) is oxidized with NBS yielding the α-bromocarboximide (**146**) with moderate stereocontrol. Tetramethylguanidinium azide displaces the bromide cleanly giving the desired azide (**147**) in 67 % yield and a 78:22 ratio of diastereoisomers. The azido carboximide (**147**) was then deprotected in a variety of ways. Basic hydrolysis with lithium hydroxide gave the azido acid (**148**) without racemization. In contrast, transesterification to the benzylester with titanium (IV) benzyloxide showed evidence of epimerization. The azido carboximide (**147**) was also reduced to the amine via hydrogenation and was subsequently acylated with (+)-MTPA-chloride. The acylated phenylglycine derivative (**150**) was also saponified without racemization under the same conditions as above yielding the acylated phenylglycine (**152**). The transesterification of **150** using the same conditions as above, yielded the desired benzyl ester (**151**) also without loss of stereochemistry, (Scheme 42).

In another nucleophilic amination, Ottenheijm and associates[62] produced N-hydroxyl phenylglycine methyl ester (**155**) via *o*-benzylhydroxylamine displacement of a triflate (**154**). The optically active α-hydroxy acid (**153**) was converted to the triflate (**154**) with triflic anhydride and lutidine. Substitution of the triflate (**154**) with *o*-benzylhydroxlamine yields the phenylglycine derivative (**155**) with inversion in 88 % yield and 76 % ee, (Scheme 43).

Scheme 42



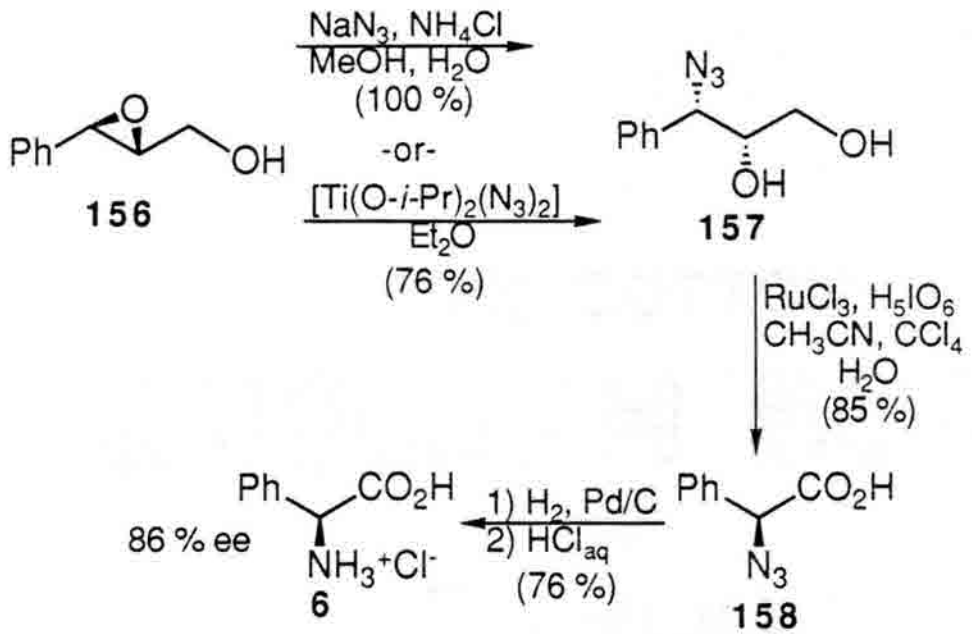
Scheme 43



In an extension of the Sharpless asymmetric epoxidation, Sharpless *et. al.*[63] found that their 3-phenyl epoxy alcohol (**156**) could be regiospecifically opened by azide attack at the 3-position. The resulting azido diol (**157**) was converted

to phenylglycine (**6**) by a ruthenium-catalyzed oxidative cleavage of the diol substituent yielding the azido acid (**158**). The azide (**158**) was reduced to the amine via hydrogenation with palladium on carbon which gave phenylglycine (**6**) in 86 % ee. The slight racemization observed was attributed to the lability of the α-azido aldehyde, an intermediate in the ruthenium-catalyzed oxidation, (Scheme 44).

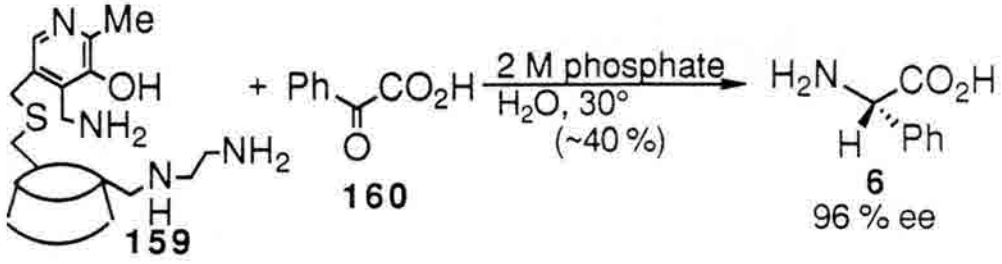
Scheme 44



In a unique approach, Breslow and co-workers[64] used an artificial enzyme system (**159**) to perform a chiral aminotransfer reaction to phenyl ketoacids (**160**) to produce phenylglycine (**6**). In this procedure, pyridoxylamine is bound to a modified ß-cyclodextrin which contained both a binding domain and an amine group. The researchers observed that the aromatic ketoacid (**160**) would bind inside the cyclodextrin pocket and then the stereoselective transamination occurred yielding L-phenylglycine (**6**) in modest chemical yield

but in 96 % ee, (Scheme 45). The high % ee's of phenylglycine (**6**) clearly indicates that the conditions of the reaction are very mild and do not promote racemization.

Scheme 45

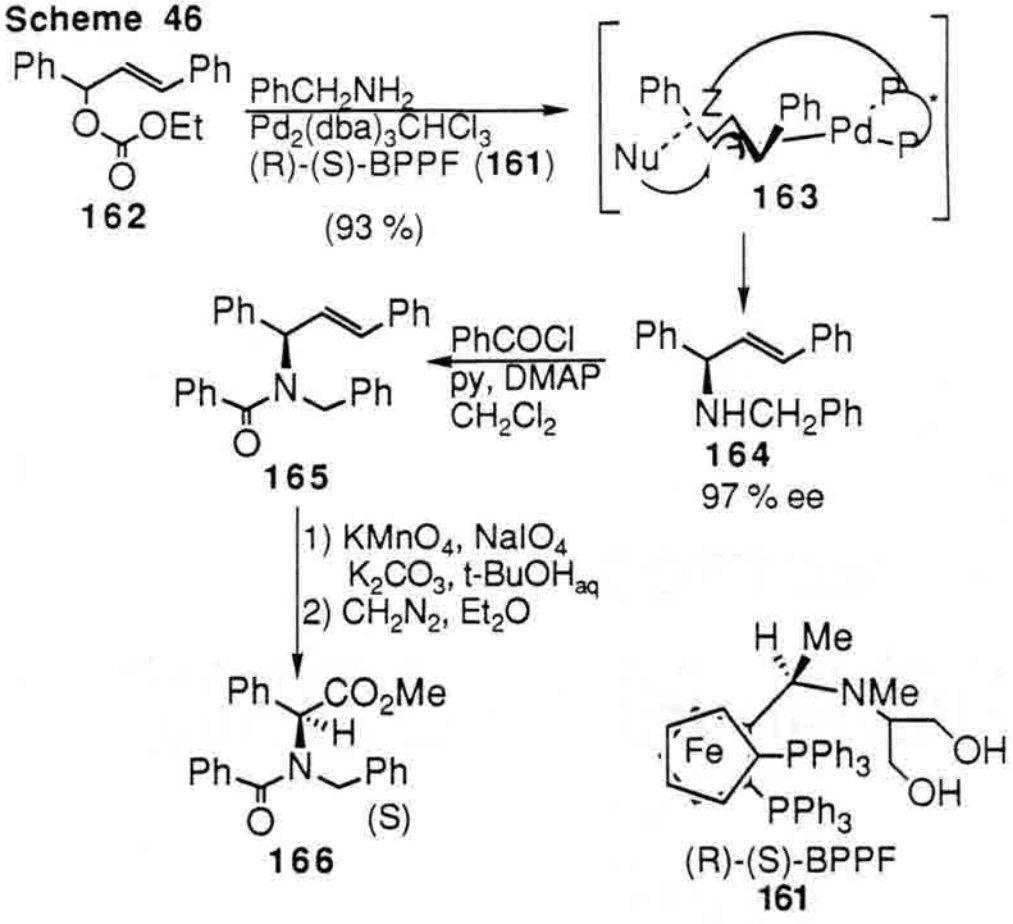


7. Miscellaneous Enantioselective Arylglycine Syntheses

In a recent publication, Hayashi, *et. al.*,[65] reported a unique method for the synthesis of a phenylglycine derivative using an asymmetric palladium-catalyzed allylic amination as the key step. The authors reported the use of a chiral ferrocenylphosphine catalyst (**161**) which forms a palladium complex *in situ* when reacted with $Pd(dba)_3CHCl_3$. This chiral complex forms a π-allylpalladium complex (**163**) with the diphenylpropenyl substrate (**162**). Directed nucleophilic attack by an attractive interaction with the functional group of the pendant side chain yields the desired diphenyl benzylamine (**164**) in 97% ee. The diphenyl benzyl amine (**164**) can be converted to a phenylglycine derivative (**166**) via an oxidative route. The diphenyl benzylamine (**164**) was first N-acylated with benzoyl chloride followed by the oxidation of the olefin with $KMnO_4/NaIO_4$, yielding the acid which was immediately esterified with diazomethane yielding the desired protected phenylglycine derivative (**166**), (Scheme 46).

In another unique arylglycine synthesis, Zhang and Li[66] reported the use of a chiral surfactant to obtain asymmetric induction. In this one-step synthesis,

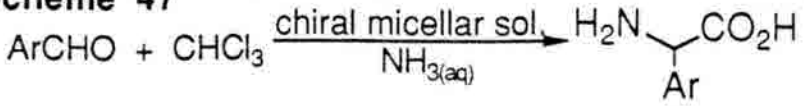
Scheme 46



aqueous micelles were formed from the chiral surfactant, N-hexadecyl-N-methylephedrine bromide. The benzaldehyde derivatives were captured in a rigid enzyme-like layer where CCl_3^- attacked the aldehyde in the presence of NH_4OH. Very few details on this interesting reaction are available but the authors do report that they obtained the arylglycine products (**19**) in moderate yields and in approximately 28 % ee, (Scheme 47).

There clearly are a wide variety of strategies available for the asymmetric synthesis of arylglycines but relatively few examples are present in the literature. Presumably the problem of arylglycine racemization still limits the asymmetric synthesis of these targets. With the value of arylglycines to pharmaceuticals on the rise, the question of how to synthesize arylglycines in a

Scheme 47



19

Ar	% Yield (19)
Ph	93
4-ClC_6H_4	48
3-ClC_6H_4	19
4-BrC_6H_4	72
4-$MeOC_6H_4$	33
4-MeC_6H_4	15
3-MeC_6H_4	18

general, versatile and asymmetric way still needs to be addressed. The research presented in the succeeding chapters of this dissertation will attempt to address this important question.

Chapter II

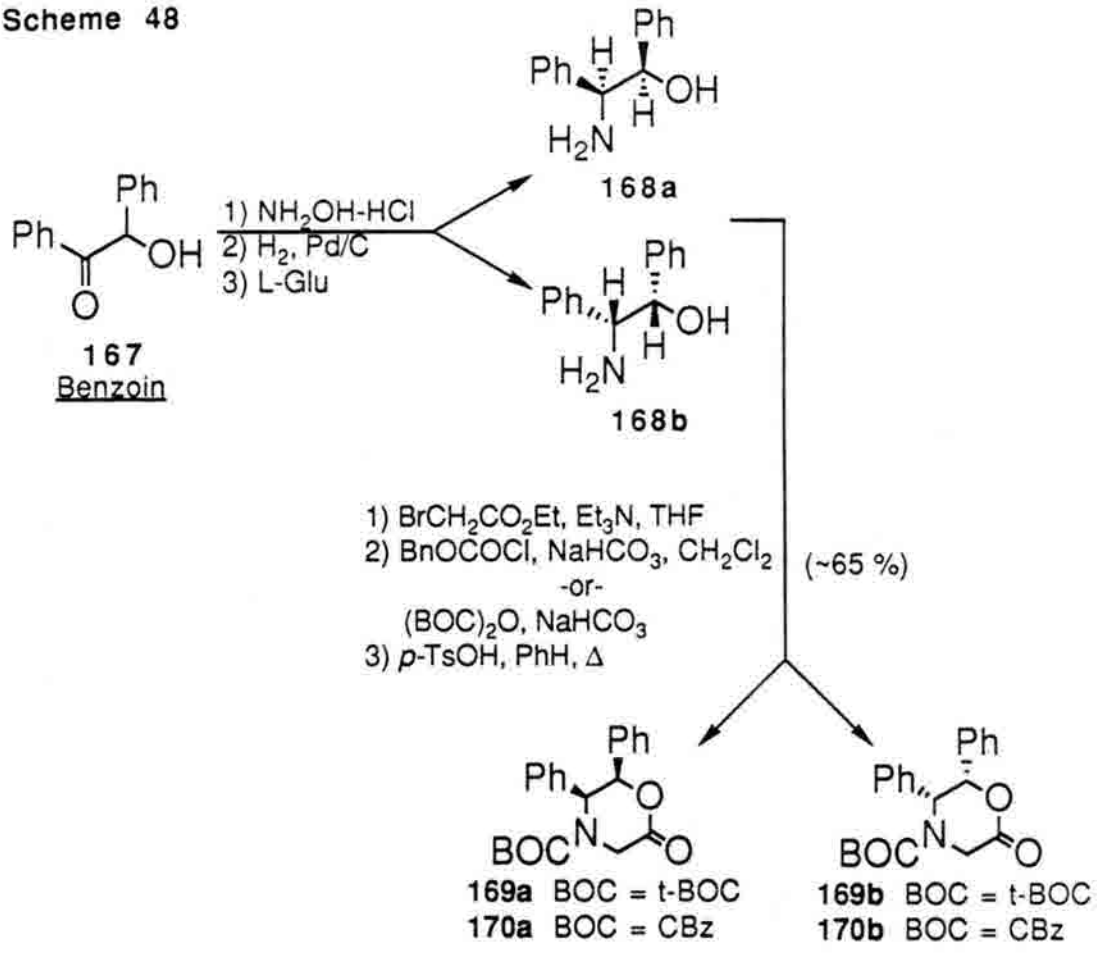
The Asymmetric Synthesis of Arylglycines via an Electrophilic Glycinate Template

A. Background

In an on-going effort to synthesize a wide variety of α-amino acids in optically pure form, Williams[67] and co-workers have developed an optically active glycinate template. The glycinate templates were prepared from benzoin (**167**) which was converted to the oxime and subsequently hydrogenated to the racemic *erythro*-amino alcohols (**168**). The amino alcohols (**168**) were resolved via the method of Tishler[68] using L-glutamic acid salts. The individual isomers were then alkylated with ethyl bromoacetate and acylated with either benzylchloroformate or di-*t*-butyldicarbonate. Lactonization was then achieved with catalytic *p*-TsOH in hot benzene or toluene which yielded the lactone templates (**169, 170**) as white crystalline solids in ~65 % overall yield from the amino alcohols, (Scheme 48). This methodology gives the chemist a choice of four lactone templates, two N-t-BOC-protected isomers (**169**) and two N-CBz-protected isomers (**170**). The advantage of this system is clear, either D- or L-configured amino acids are accessible and predictable depending on the lactone template chosen.

The oxazinone templates (**169, 170**) have been homologated in a variety of ways.[67] Bromination of the lactones with NBS in refluxing carbon tetrachloride proceeded in essentially quantitative yield. After the succinimide was removed by filtration and the solvent was evaporated, the N-t-BOC bromo-oxazinone

Scheme 48



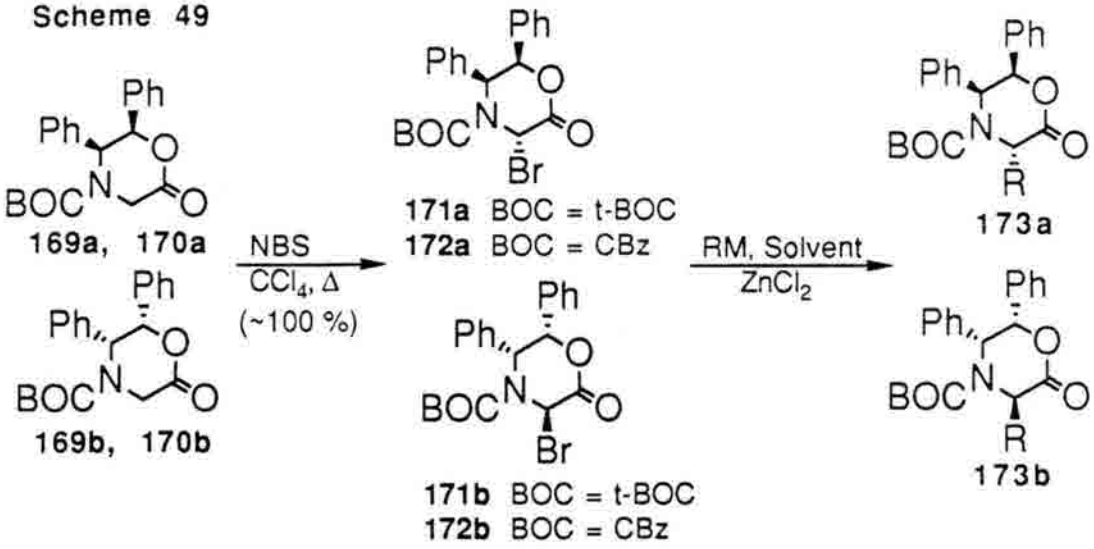
(**171**) appeared as a white foam while the N-CBz bromo-oxazinone (**172**) was a white solid. Both brominated products (**171, 172**) were relatively unstable and, therefore, utilized directly without further purification. Purification of the bromolactones (**171, 172**) was unnecessary when the NBS and lactone reagents were pure and the CCl_4 was freshly distilled. The relative stereochemistry of the bromides (**171, 172**) was *anti-* with just one diastereomer formed. The bromolactones (**171, 172**) were then reacted with various organometallic reagents in the presence of a Lewis acid, usually zinc chloride. The relative stereochemistry of the homologated products (**173**) were seen to be *anti-* in most cases meaning that the coupling reactions proceeded with net retention. To explain the stereochemical outcome of the homologation

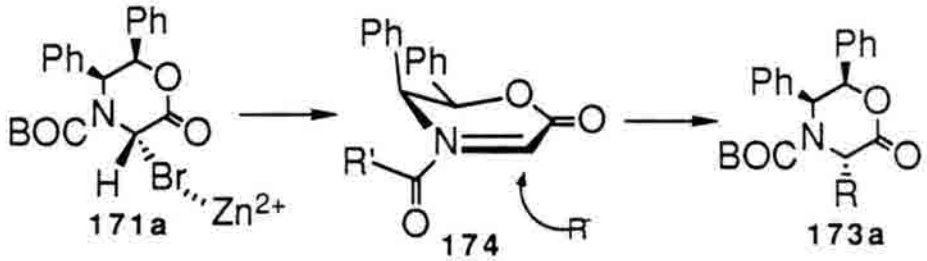
reactions, the authors hypothesized that a reactive iminium intermediate (**174**) is formed by coordination of the bromide to the Lewis acid, (Scheme 49). It was proposed that the *cis*- phenyl rings of the iminium species (**174**) block the approach to one face, therefore, the addition occurred at the less sterically hindered face yielding the observed *anti*- product (**173**).

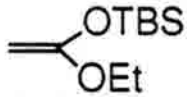
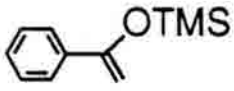
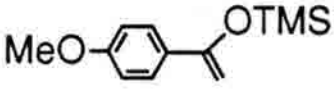
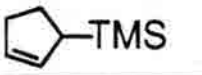
The oxazinone template (**169a**) has also been homologated by enolate alkylation[69] which demonstrates the ability of the glycinate template to behave as either an electrophile or as a nucleophile. The enolate (**175**) was generated using lithium, sodium, or potassium bis(trimethylsilyl)amide that was quenched with an activated electrophile, (Scheme 50). The resulting coupled products (**173**) show great selectivity for kinetic alkylation *anti*- to the two phenyl rings. The authors speculate that the enolate (**175**) adopts a conformation where the C-5 phenyl moiety is pseudo-axial which would leave the bottom face sterically unencumbered facilitating electrophilic addition. The alkylation proceeded in quite good yield and with high diastereoselectivity.

Once the oxazinone template has been alkylated, two methods were developed for the deprotection to the free zwitterionic amino acids.[67] When the side chains ('R' groups) are stable to catalytic hydrogenation, as is the case with a saturated side chain, a reductive cleavage was employed. The hydrogenation was usually performed with $PdCl_2$ at ~40 psi for 1-2 days at room temperature. The work-up of this reaction was relatively straightforward and provided the desired amino acid quite cleanly. When the 'R' group was unsaturated and labile to hydrogenation, a dissolving metal reduction was used for the cleavage. The reduction was carried out in liquid ammonia with either lithium or sodium metal followed by a quench with solid ammonium chloride. After work-up and ion exchange chromatography, either the free amino acids or, if the t-BOC lactone substrate was used, the t-BOC amino acids are obtained.

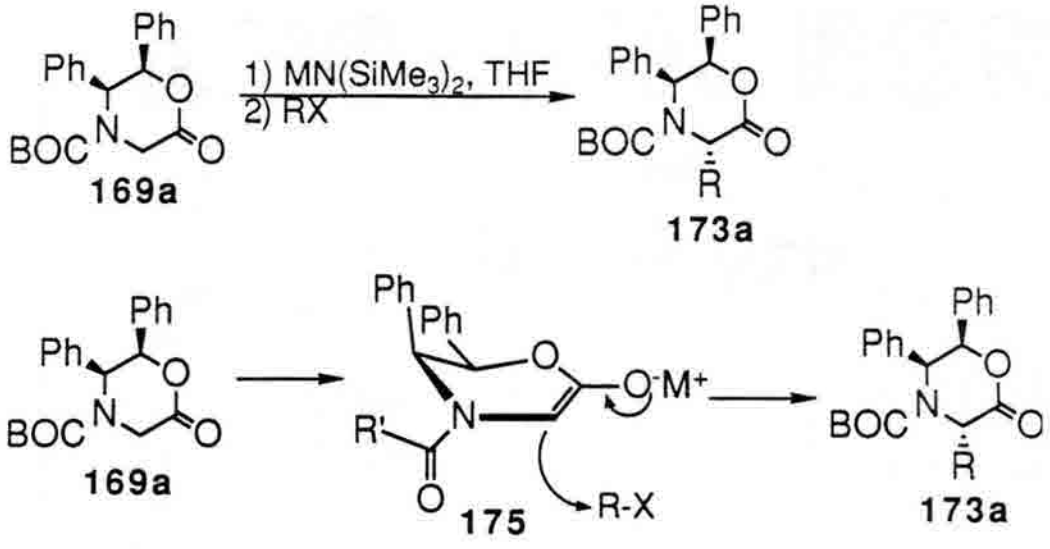
Scheme 49

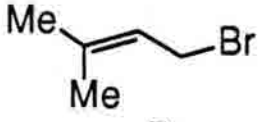
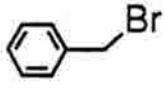




RM	BOC Group	Cond.	% Yield (173)
ClZnMe	CBz	THF, -78°C	46
$Bu_2Cu(CN)Li$		THF, Et_2O, -78°C	48
		THF, 25°C	74
		THF, 25°C	66
		MeCN, 25°C	72
		THF, MeCN, 25°C	72
		THF, 25°C	82
	t-BOC	THF, 25°C	63
		THF, 25°C	59

Scheme 50

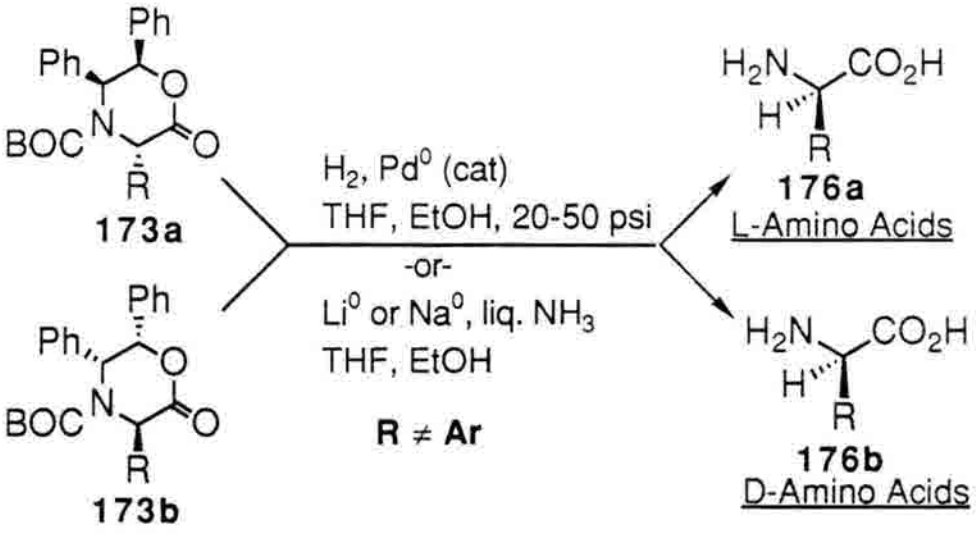


RX	% Yield (173a)
MeI	91
	48
	68
	70
	56
	48
	42
	68

These two deprotection procedures have been used with great success in the synthesis of many amino acids, (Scheme 51).

In attempting to apply the optically active oxazinone template to the synthesis of arylglycines, it was immediately clear that an alternate deprotection

Scheme 51



R	BOC Group	Cond.	% Yield (176)	% ee	Amino Acid
Me	CBz	H_2, $PdCl_2$ EtOH, 20 psi	100	>96	Alanine
Bu	CBz	H_2, $PdCl_2$ EtOH, 20 psi	52	>99	Norleucine
CH_2=$CHCH_2$-	CBz	H_2, $PdCl_2$ EtOH, 20 psi	93	>96	Norvaline
CH_2=$CHCH_2$-	CBz	Li^0, NH_3, EtOH	90	>91	Allylglycine
$C_6H_5C(=CH_2)$-	CBz	H_2, $PdCl_2$ EtOH, 40 psi	91	>96	Homophenyl-alanine
4-$MeOC_6H_4C(=CH_2)$-	CBz	H_2, $PdCl_2$ EtOH, 40 psi	94	>98	*p*-(MeO)-Homo-phenylalanine
2-Cyclopentenyl-	CBz	H_2, $PdCl_2$ EtOH, 40 psi	91	>96	Cyclopentyl-glycine
2-Cyclopentenyl-	CBz	Li^0, NH_3, EtOH	94	>96	Cyclopentenyl-glycine
CH_2=$CHCH_2$-	t-BOC	Li^0, NH_3, EtOH	70	>98	N-t-BOC-Allyl-glycine
2-Cyclopentenyl-	t-BOC	Li^0, NH_3, EtOH	70	>95	N-t-BOC-Cyclopentenyl-glycine

procedure would be needed. For example, if a hydrogenation were attempted on a lactone substrate with an aromatic 'R' group, the aromatic group would expected to be cleaved just as the other benzylic groups on the lactone are cleaved. Likewise, in the case of the dissolving metal reduction on an arylglycine precursor, the aromatic ring would be labile to Birch reduction, (Scheme 51). Since the reductive deprotections seemed doomed to failure, the oxidative methodology developed by Weineges[44] on a similar oxazinone system was considered as a logical alternative. However, before this oxidative deprotection could be tested on the optically active lactone system, methodology was needed for the coupling of aromatic groups to the template.

B. Aromatic Couplings

In the development of aromatic coupling methodology, a variety of bond forming reactions were explored. Two types of coupling reactions, aryl cuprate couplings and Friedel-Crafts alkylations, have proven to be the most successful methods for coupling an aromatic ring to the lactone. Other organometallic coupling reactions were attempted with very limited success. An attempt was also made to react the lactone enolate with aromatic electrophiles. The syntheses of di-alkylated arylglycine precursors were explored as well.

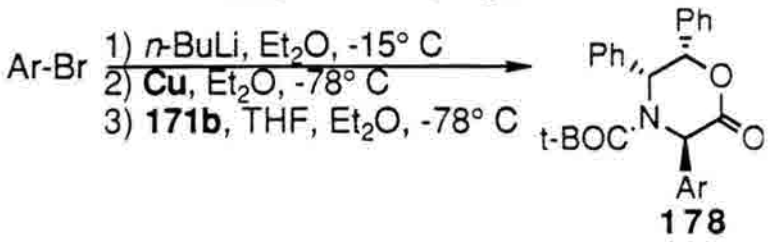
1. Cuprate Couplings

The success of cuprates in the coupling of aromatic rings to the oxazinone template has proven to be directly related to the nature of the aromatic substrate and the type of copper salt used in the generation of the aryl cuprate. The general procedure used for this coupling was to first generate the aryl-lithium reagent by reacting *n*-butyllithium with an arylbromide in dry diethylether at -15° C. To the aryl-lithium solution, the copper salt was added and the mixture was cooled to -78° C where the aryl cuprate reagent formed over 3-4 hours. Once the aryl cuprate formed, a solution of the freshly produced N-*t*-BOC-

bromolactone (**171**) in a 1:1 mixture of dry THF and Et_2O was added and allowed to react at -78° C for 1-2 hours (Scheme 52). The reaction was quenched with a saturated solution of ammonium chloride at -78° C and allowed to warm to room temperature. The reaction mixture was worked-up and the coupled product was separated by silica gel chromatography and recrystallized yielding the desired product, usually as a white solid. These reactions were generally messy and purification required a great deal of patience.

Scheme 52

Cuprate Couplings



178

Ar	Cu	% Yield (178)
Ph	CuI	50
Ph	CuI / TMEDA	0
Ph	CuCN	S.M.
Ph	CuCN / TMEDA	12
Ph	$BrCuSMe_2$	56
p-Anisole	CuI	0
m-Anisole	CuI	0
o-Anisole	CuI	0
o-Anisole	$BrCuSMe_2$	0
1-Naphthalene	CuI	43
1-Naphthalene	$BrCuSMe_2$ / SMe_2	42
6-Methoxy-2-naphthalene	$BrCuSMe_2$ / SMe_2	22
4-Phenol	$BrCuSMe_2$	0

The first cuprate coupling was an attempt to couple the simplest aromatic group to the lactone: the phenyl group. The use of copper(I)iodide as the copper salt gave the desired phenyl-coupled product in moderate yield but all attempts to scale-up the reaction resulted in widely unpredictable results. Attempts at adding a co-solvent or using the higher order cuprate generated from CuCN also failed to produce satisfactory results. However, it was found that the use of the copper bromide-dimethylsulfide complex gave moderate and consistent results on both small and large scales. Similar results were observed for the 1-naphthyl case. It was found that the use of methylsulfide as a co-solvent aided the solubility of the cuprate reagent in some cases. Disappointing results were seen in the anisole series, however, and no coupled products were ever fully characterized. It may be the case that the anisole cuprate complex is too stable and would not undergo coupling to the lactone. In the case of 6-methoxy-2-naphthyl, where the methoxy group is far from the reactive center, coupling was observed but only in low yield. The attempted coupling of a phenol failed, indicating that a free alcohol group was not compatible with the reaction conditions. These experiments established methodology for the coupling of aromatics to the glycinate template. While the yields of these couplings were moderate to poor, the reaction did provide regiochemical control about the aromatic ring.

2. Friedel-Crafts Alkylations

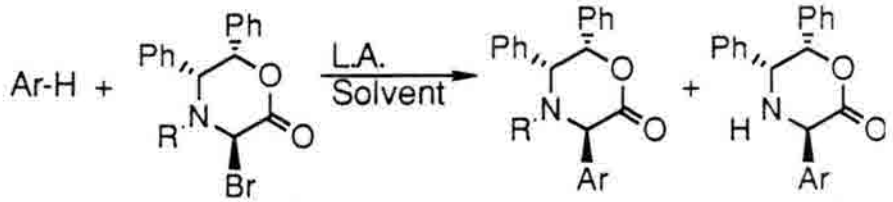
The success of Friedel-Crafts alkylations in the coupling of aromatic rings to the chiral glycinate template also proved to be substrate-specific. The general procedure called for the use of 10-15 equivalents of the aromatic substrate to 1 equivalent of the bromolactone (**171, 172**). The freshly produced bromolactone (**171, 172**) and the aromatic substrate were stirred together in a dry, relatively polar organic solvent with a Lewis acid usually at room

temperature for several hours (Scheme 53). After work-up, the purification was sometimes difficult, if only for the removal of the excess unreacted aromatic substrate.

In the search for an appropriate Lewis acid it was found that $AlCl_3$ was too harsh and resulted in only the decomposition of the lactone template. Tin tetrachloride gave coupled products but also resulted in significant decomposition of the lactone. The best results were observed with $ZnCl_2$ which was a strong enough Lewis acid to promote coupling but mild enough to limit lactone decomposition. The use of $ZnCl_2$ didn't represent a panacea, however, since only the most electron-rich aromatic substrates would react under these mild conditions. It was also observed that in many cases the coupled lactone products were mixtures of the N-*t*-BOC protected (**178**) and unprotected amine (**179**). This did not represent a major problem unless the unprotected amine (**179**) was unstable to the reaction conditions as was the case with furan (**179f**) and, to a lesser extent, methylfuran (**179g**). In these cases, 4 Å powdered molecular sieves were used to moderate the acidity of the reaction conditions and thus limit the amount of t-BOC deprotection. While this addition eliminated the t-BOC deprotection problem it did, in most cases, reduce the yield. This result showed that the reactivity of the aromatic substrates was very sensitive to the acidity of the reaction conditions. It was also observed that the N-CBz protected bromolactones (**172**) were stable to the standard $ZnCl_2$ reaction conditions in most cases.

The selection of appropriate aromatic substrates for this Friedel-Crafts alkylation also represented a challenge. It was observed that only electron-rich aromatics would couple to the lactone. For example, benzene, halogenated benzene derivatives, an aryl triflate, and even a silyl-protected phenol did not couple to the lactone. In contrast, electron rich aromatics such as anisole, the

Scheme 53 Friedel-Crafts Alkylations

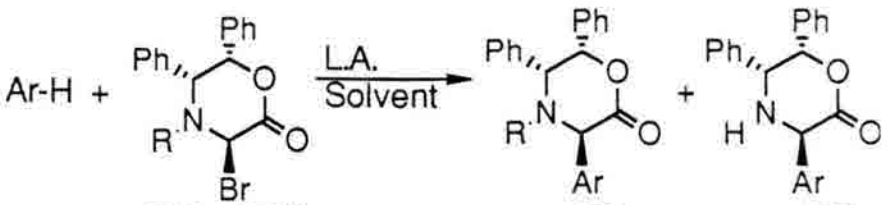


171b, 171b **178** **179**

Ar-H	Entry	R	Lewis Acid	Solvent	% Yield 178	179
Anisole	**a**	t-BOC	$AlCl_3$	-	Decomp.	
		t-BOC	$SnCl_4$	CH_2Cl_2	35*	0
		t-BOC	$ZnCl_2$	THF	33*	0
1,3,5-Trimethoxy-benzene	**b**	t-BOC	$SnCl_4$	CH_2Cl_2	11	0
		t-BOC	$ZnCl_2$	THF	[2) TMSI]	83
		t-BOC	$ZnCl_2$	THF (4 Å sieves)	43	0
		CBz	$ZnCl_2$	THF	25	0
Veratrole	**c**	t-BOC	$ZnCl_2$	THF	21*	0
1,3-Dimethoxy-benzene	**d**	t-BOC	$ZnCl_2$	THF	20*	33*
Benzene	**e**	t-BOC	$ZnCl_2$	THF	0	0
Furan	**f**	CBz	$ZnCl_2$	THF	66	0
		t-BOC	$ZnCl_2$	THF	15	40
		t-BOC	ZnCl2	THF (4 Å sieves)	50	0
		t-BOC	$ZnCl_2$	CH_3CN (4 Å sieves)	33	0
		t-BOC	$ZnCl_2$	(4 Å sieves)	33	0
2-Methylfuran	**g**	CBz	$ZnCl_2$	THF	65	0
		t-BOC	$ZnCl_2$	THF	25	43
		t-BOC	$ZnCl_2$	CH_3CN (4 Å sieves)	39	0

* (A mixture or regeoisomers)

Scheme 53 Friedel-Crafts Alkylations (cont.)



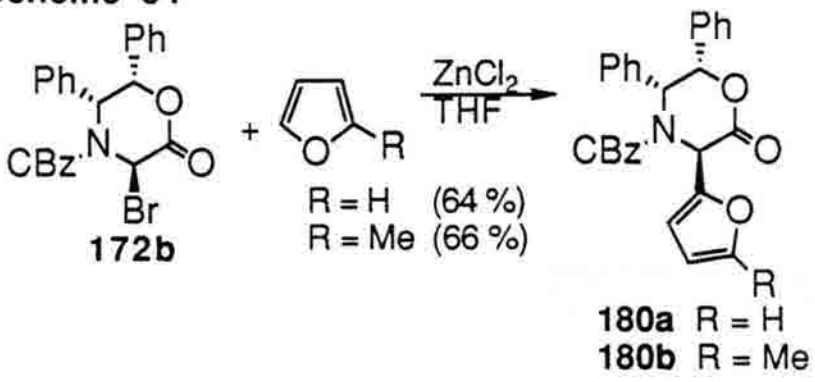
171b, 171b **178** **179**

Ar-H	Entry	R	Lewis Acid	Solvent	% Yield 178	179
Thiophene	**h**	CBz	$ZnCl_2$	THF	0	0
		t-BOC	$ZnCl_2$	THF	0	0
2-Chlorophenol	**i**	t-BOC	$ZnCl_2$	THF	0	0
4-Bromophenol	**j**	CBz	$ZnCl_2$	THF	0	0
		t-BOC	$ZnCl_2$	THF	0	0
2-Iodo-1,3,5-trimethoxy-benzene	**l**	t-BOC	$ZnCl_2$	THF	0	0
PhO-TBDMS	**m**	t-BOC	$ZnCl_2$	THF	0	0
1-*tert*-butyldimethyl-siloxy-3,5-dimethoxy-benzene	**n**	t-BOC	$ZnCl_2$	THF	0	*p* 25 *o* 33
		CBz	$ZnCl_2$	THF	0	32 37
1-*tert*-butylphenyl-siloxy-3,5-dimethoxy-benzene	**o**	CBz	$ZnCl_2$	THF, 0° C	0	31 34
		CBz	$ZnCl_2$	THF	0	27 0
3,5-Dimethoxyphenyl-trifluoromethane-sulfonate	**p**	t-BOC	$ZnCl_2$	THF (4 Å sieves)	0	0

di- and tri-methoxybenzenes, the dimethoxy silyl-protected phenols, and the furans all coupled to the lactone with excellent results in some cases. Unfortunately, in the cases of anisole and the dimethoxybenzenes, regiochemical control could not be achieved. With the use of 1,3,5-trimethoxybenzene the problem of regiochemical control was avoided and coupling was achieved despite the potential problem of steric hinderance. In this coupling reaction, mixtures of the N-*t*-BOC protected (**178b**) and unprotected amine (**179b**) were formed, so trimethylsilyl iodide was added to the crude mixture of products which resulted in the isolation of only the unprotected coupled lactone amine (**179b**) in excellent yield. This procedure could be followed since this unprotected amine product (**179b**) was relatively stable to the acidic conditions of these reactions. The pure amine product (**179b**), however, was observed to begin to decompose after a week or two at room temperature. In the cases of the 3,5-dimethoxy silyl-protected phenols, it was hoped that alkylation at the position *ortho*- to the large silyl group would be blocked giving regiochemical control. Unfortunately, both the *ortho*- and *para*-positions were alkylated in most cases. Furthermore, only the unprotected coupled amines (**179n, 179o**) were isolated even when the less labile N-CBz lactone (**172**) was employed. This unexpected result indicated that the presence of a silyl group on the aromatic must increase the acidity of the reaction mixture resulting in the N-BOC deprotections. The furan and methylfuran rings coupled in good yield with regiochemical control, as expected. The N-CBz-coupled furan (**180a**) and methylfuran (**180b**) were prepared previously, (Scheme 54).[67] With the success of the furan couplings, thiophene was naturally expected to couple as well but, inexplicably, did not. These Friedel-Crafts alkylation experiments showed that electron-rich aromatics were necessary to react under the mild Lewis acid conditions that were required

to limit the decomposition of the lactone template. The experiments also indicated that regiochemical control was sometimes difficult to achieve and partial acid catalyzed N-BOC deprotection was also observed.

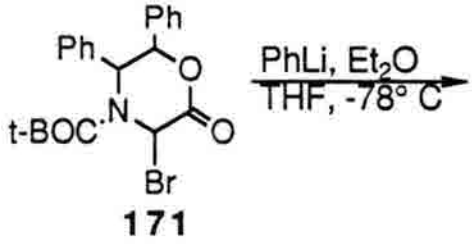
Scheme 54



3. Miscellaneous Coupling Attempts

In the further exploration of aromatic couplings to the optically active oxazinone template, several other types or organometallic reagents were tested. The simple use of phenyllithium in a reaction with the bromolactone (**171**) at low temperature failed. The attempted reaction of a phenylcadmium reagent with the bromolactone (**171**) also failed, (Scheme 55). Aryl-trimethyltin

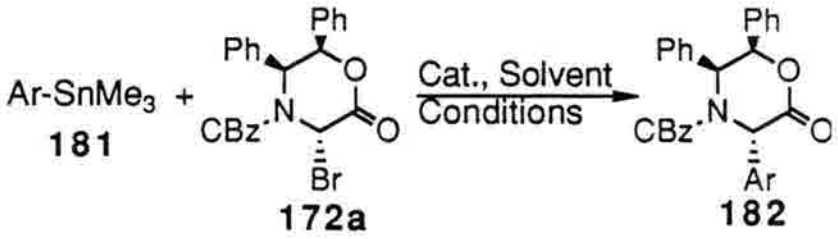
Scheme 55



PhBr $\xrightarrow[\text{2) } CdCl_2\text{, Ph-H, reflux}]{\text{1) } n\text{-BuLi, } Et_2O\text{, -15° C}}$ 3) **171**, THF, Et_2O

reagents (**181**), however, did achieve coupling with modest success. The best results for these low yielding couplings were achieved with $ZnCl_2$ as the catalyst in the mildest conditions attempted. Interestingly, the use of a palladium catalyst failed to effect coupling, (Scheme 56). This type of behavior of organostannanes, while certainly unusual, is not unprecedented.[70]

Scheme 56 Aryl-Tin Couplings

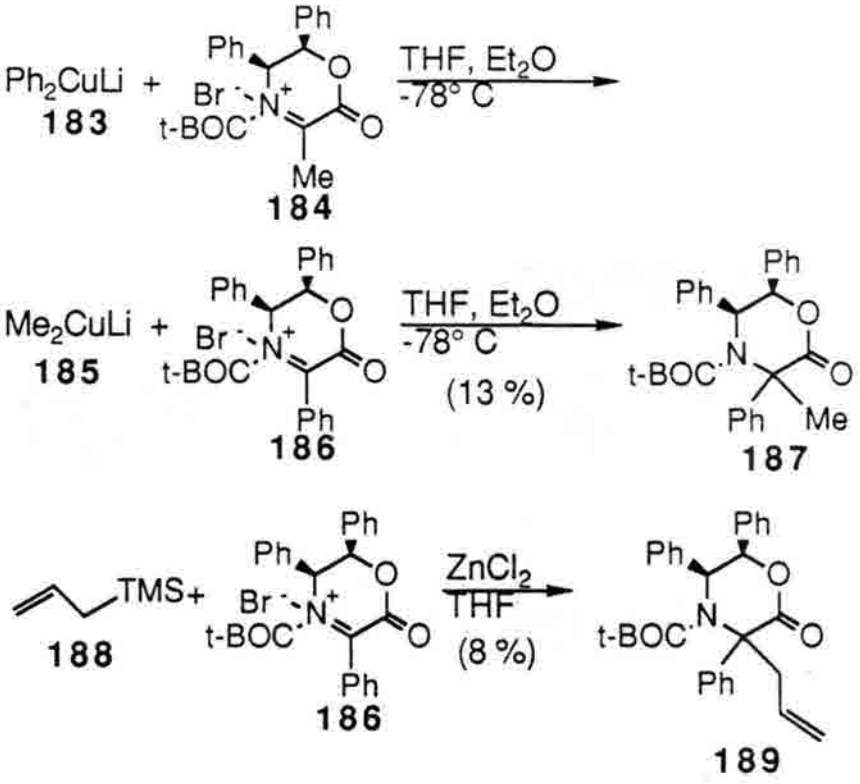


Ar	Cond.	Cat.	Solvent	% Yield
4-Methoxyphenyl-	reflux	$ZnCl_2$	CCl_4	15
3,4-Dimethoxyphenyl-	reflux	$ZnCl_2$	1,4-dioxane	8
	room temp.	$ZnCl_2$	CCl_4	16
	room temp.	$ZnCl_2$	THF	26
	reflux	$Pd(PPh_3)_4$	THF	0

The synthesis of dialkylated arylglycine precursors were attempted in the hope of avoiding the potential problem of arylglycine racemization, (see Chapter I). To this end, it was found that the methyl- or phenyl-coupled lactones could be brominated and reacted with organometallic reagents. These extremely messy reactions yielded little or none of the desired products, (Scheme 57). In another approach, the enolate of the phenyl-coupled lactone (**178a**) was generated via the method of Williams and Im.[69] The enolate was quenched with several active electrophiles but no alkylation was observed. The enolate was also quenched with D_2O to discover whether the enolate had

Scheme 57

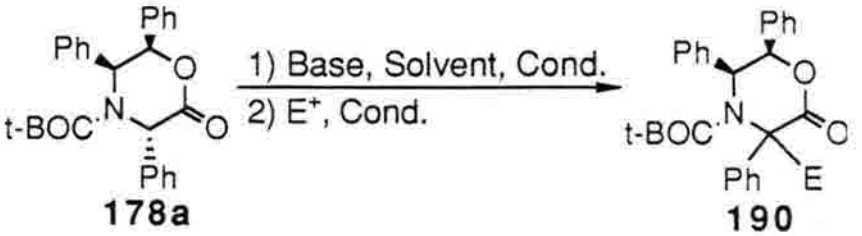
Dialkylation Attempts



indeed been formed. Proton NMR experiments indicated approximately 67 % deuterium incorporation at the α-center, (Scheme 58). This result seemed to show that the enolate does form but the electrophiles may not be able to add due to steric hinderance. In another enolate alkylation attempt, the enolate of the simple lactone template (**169a**) was generated with sodium bis(trimethylsilyl)amide and quenched with an aromatic triflate (**191**) yielding the desired product in only 4 % yield, (Scheme 59).

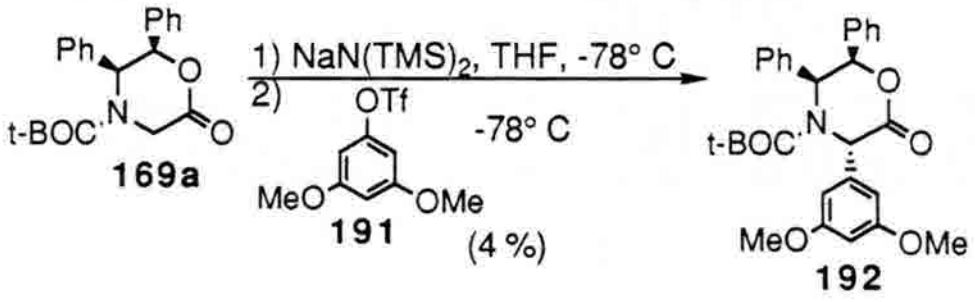
The aryl-coupled lactone products (**178**) were all diastereomerically pure as determined by high-temperature proton NMR. At room temperature two conformations of the lactone six-membered ring can be seen on the NMR time scale. At >110° C the conformations rapidly interconvert and can not be seen by the NMR, and only one diastereomer is observed.

Scheme 58



Base	Solvent	Cond. (1)	E±	Cond. (2)	% Yield
$LiN(TMS)_2$	THF	-78° C	MeI	-78° C - r.t.	0
$KN(TMS)_2$	THF / HMPA	-78° C	MeI	-78° C	0
$LiN(TMS)_2$	THF / HMPA	-15° C	allyliodide	-15° C - r.t.	0
$KN(TMS)_2$	THF / HMPA	-15° C	EtI	0° C	0
$KN(TMS)_2$	THF / HMPA	-15° C	D_2O	room temp.	~67

Scheme 59



The methodology developed for the synthesis of the aryl-coupled lactones was limited to two preparatively useful methods, the aryl cuprate couplings and the Friedel-Crafts alkylations. The limitations of these two procedures dictated a strategy for the synthesis of these arylglycine precursors. The Friedel-Crafts alkylation was the method of choice if the aromatic was readily available, electron-rich and if regiochemical chemical control was not a problem. On the other hand, a cuprate coupling was chosen if the aromatic was not electron-rich and/or if regiochemical control was needed. With two methods available for the

aromatic alkylation of the glycinate template, it was clearly time to focus on the deprotection of the auxiliary to produce arylglycines.

C. Lactone Template Deprotections

The cleavage of the chiral auxiliary to obtain the desired arylglycines required new methodology previously untried on this glycinate system. The synthetic plan involved three steps, first the removal of the N-BOC group, second the hydrolytic ring opening on the lactone, and third the oxidative cleavage of two equivalents of benzaldehyde. To avoid racemization all reactions and work-ups were carried out under acidic or neutral conditions.

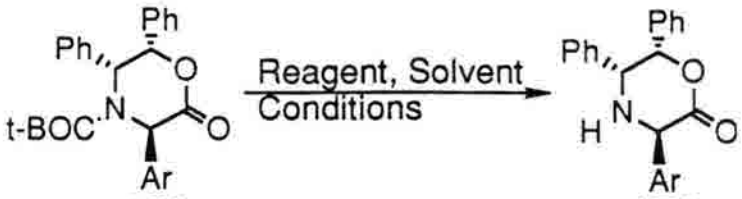
1. N-t-BOC Deprotections

The methodology for the t-BOC deprotection was developed using the phenyl coupled lactone (**178a**). Early experiments attempted this transformation under various aqueous acidic conditions. One experiment involved the use of aqueous acetic acid and CrO_3 in the hope of performing the entire deprotection in one step. However, this experiment and all others performed with aqueous acid failed. An attempt was also made to pyrolyze the t-BOC group with refluxing xylenes but this also failed, (Scheme 60).

Success was finally achieved when purely organic acids were applied to this deprotection. The use of neat trifluoroacetic acid at room temperature gave the desired amine (**179a**) in a moderate yield but also with a great deal of decomposition. The use of dichloromethane as a solvent improved the yield of this reaction presumably by reducing the amount of decomposition. Thiophenol was also used as a t-butyl cation scavenger and the reaction temperature was also reduced but these changes failed to improve the yield, (Scheme 60). It should also be noted that the standard work-up for these types of TFA reactions called for the use of triethylamine. The use of Et_3N in the work-up of this reaction caused the phenylglycine precursor (**179a**) to racemize giving

Scheme 60

t-BOC Deprotections



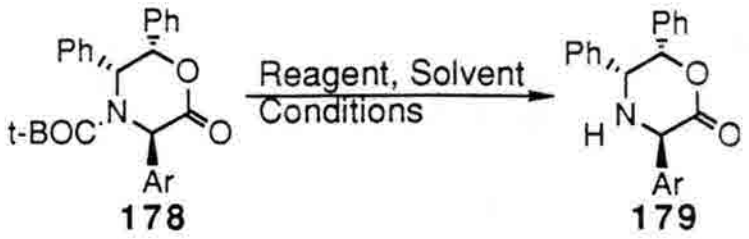
178 **179**

Ar	Entry	Reagent	Solvent	Cond.	% Yield
Ph	**a**	conc. HCl	THF	r.t., 1 h	0
		10 % HCl	THF	reflux, 5 h	0
		AcOH	THF / H_2O	reflux, 12 h	0
		CrO_3	AcOH / H_2O	r.t., 5 d	0
			Xylenes	reflux, 36 h	0
		TFA		r.t., 30 m	44
		TFA	CH_2Cl_2	r.t., 30 m	65
		TFA	PhSH / CH_2Cl_2	r.t., 1 h	31
		TFA	THF	-78° - 0° C	S.M.
		p-TsOH	Benzene	reflux, 23 h	45 + S.M.
		p-TsOH	Toluene	reflux, 3 h	64 + S.M.
		p-TsOH	Xylenes	reflux, 1.5 h	44
		H_2, $PdCl_2$	EtOH, THF	r.t., 40 psi, 36 h	0
		TMSI	CH_2Cl_2	r.t., 10 m	73
2,4,6-Trimethoxy-phenyl-	**b**	*p*-TsOH	Xylenes	reflux, 1.5 h	26
		TMSI	CH_2Cl_2	r.t., 10 m	78
1-Naphthyl-	**c**	*p*-TsOH	Toluene	reflux, 1.5 h	0
		TMSI	CH_2Cl_2	r.t., 10 m	85
2-Furyl-	**d**	TMSI	CH_2Cl_2	r.t., 10 m	92*
		BBr_3	CH_2Cl_2	-15° C, 1 h	31*

* (Product decomposes rapidly)

Scheme 60

t-BOC Deprotections (cont.)



178 **179**

Ar	Entry	Reagent	Solvent	Cond.	% Yield
5'-Methyl-2-furyl	**e**	*p*-TsOH	Xylenes	reflux, 2.5 h	0
		TMSI	CH_2Cl_2	r.t., 10 m	86
(4'-Methoxy-3'-trifluoromethane-sulfonato) phenyl-	**f**	TMSI	CH_2Cl_2	r.t., 10 m.	91

diastereomeric mixtures of about 2.4 : 1 *anti*- to *syn*-, and thus Et_3N was subsequently avoided.

Pyrolysis was attempted again but with the addition of a catalytic amount of *p*-toluene sulfonic acid. Benzene, toluene, and xylenes were all used as solvents. The reaction times were varied, the lowest boiling solvent, benzene, took 23 hours and still produced starting material (**178a**) and xylenes. The highest boiling solvent took only 1.5 hours but produced significant decomposition. The use of toluene produced the highest yielding pyrolysis reaction with a small amount of starting material (**178a**) but it limited the amount of decomposition, (Scheme 60).

Finally, trimethylsilyl iodide was employed to remove the t-BOC group. The use of TMSI proved to be very effective in that it gave the desired product (**179a**) in good yield under very mild conditions, (room temperature in 10 minutes). The TMSI deprotection also worked quite well for the 1-naphthyl (**178c**), trimethoxyphenyl (**178b**), methylfuran (**178e**), and aryl triflate (**178f**)

substrates. Under the mild conditions of this reaction, no racemization was observed and decomposition was limited. In the case of the furyl substrate (**178d**), however, it was found that the t-BOC was readily removed in good yield but the product was unstable to acid and would decompose in a matter of hours even after purification. All the t-BOC deprotected substrates (**179**) exhibited some measure of instability, decomposing over a matter of days or weeks. The rapid decomposition of the deprotected furyl substrate (**179d**) made it necessary to find another method for the t-BOC deprotection. The use of another Lewis acid, boron tribromide, to effect the deprotection not only gave a poorer yield as compared to the TMSI reaction but also showed the same kind of decomposition, (Scheme 60). It was then clear that an alternate deprotection method was needed.

2. N-CBz Deprotections

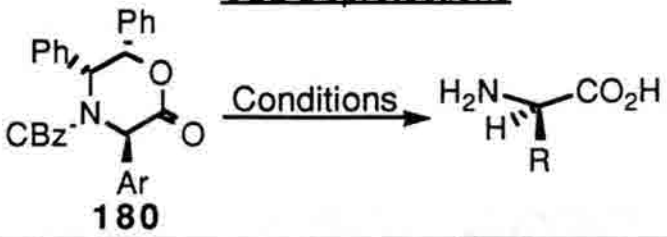
The instability of the furyl amine lactone substrate (**179d**) prompted an investigation into the feasibility of deprotecting the CBz-protected furyl lactone (**180a**) instead of the t-BOC furyl substrate (**178d**). The acidic TMSI deprotection of the CBz substrate (**180a**) was a slower reaction than that for the t-BOC deprotection and the same type of decomposition was observed. From this result and the results obtained with the t-BOC substrate (**178d**), it became clear that a neutral BOC deprotection method was needed to obtain the desired furyl amine lactone (**179d**). To that end, mild catayltic hydrogenations were attempted on the CBz furyl lactone (**180a**) in the hope that the CBz group would be cleaved without reducing the furyl double bonds. It was observed that under atmospheric hydrogen with palladium on carbon, the furyl amine lactone (**179d**) could be obtained in moderate yield without the decomposition associated with the acidic deprotection methods. In a serendipitous discovery, it was found that if the reaction was allowed to continue for ~2 hours, the

desired amino acid, furylglycine (**194d**), was isolated in 57 % yield and 90 % ee. The mild conditions of this reaction are in contrast to the conditions used previously[67] for the synthesis of the trihydrofurylglycine (**193**) where the furan double bonds were reduced. The mild hydrogenation CBz methylfuryl lactone substrate (**180b**) also gave the desired amino acid cleanly in 82 % yield and 93% ee. The 1-naphthyl (**179c**) and trimethoxyphenyl (**179b**) substrates were also subjected to the mild hydrogenation but failed to yield the desired amino acids, (Scheme 61). It appears that the furan C-N benzylic residue was relatively unreactive to the hydrogenation conditions as compared to the C-N benzylic residue of other aryl species.

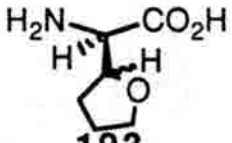
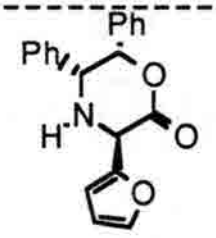
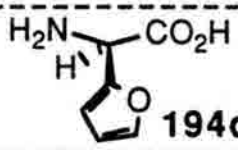
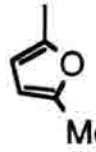
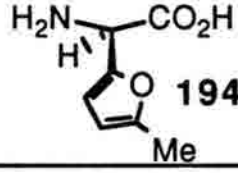
3. Oxidative Deprotections

Despite the success of the hydrogenation method with the furyl substrates (**180**), the oxidative route was still necessary to access most arylglycine targets. The standard procedure usually required the hydrolytic ring opening of the lactone amine (**179**) with 10 % hydrochloric acid and THF as a co-solvent. The mixture was usually heated to reflux for 15-60 minutes and then allowed to cool to room temperature. At this point the ring-opened product was sometimes isolated to confirm that the reaction was proceeding as planned. However, it was found that it was more efficient to simply adjust the pH of the hydrolysis reaction to ~3 with the dropwise addition of dilute sodium hydroxide and then add the sodium periodate. The oxidative cleavage occurred over 36 hours yielding two equivalents of benzaldehyde and the desired arylglycine (**194**) without destroying the Ar-C-N linkage, (Scheme 62). In the case of the furylglycine synthesis, the unstable furyl-coupled amine lactone (**179d**), obtained from a TMSI / t-BOC deprotection reaction, was carried on to the hydrolysis directly without purification in an attempt to limit decomposition. The hydrolysis and oxidation reactions were very messy in all cases which made

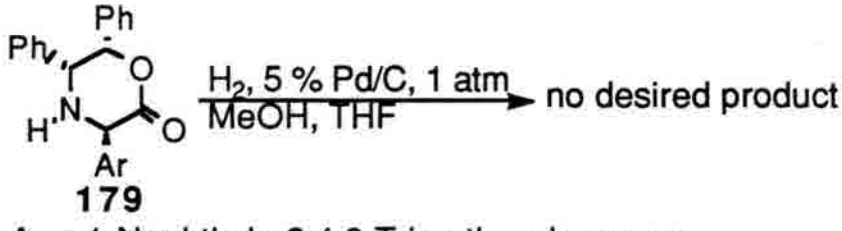
Scheme 61 CBz Deprotections



180

Ar	Cond.	Product	% Yield
	H_2, $PdCl_2$, 40 psi EtOH, THF, 36 h	 **193**	93
	TMSI, CH_2Cl_2, 2 h, r.t.	 **179d**	49 *
	H_2, 10 % Pd/C, 1 atm MeOH, THF, 30 m		51 + S.M.
	1.5 h		30
	3.5 h		18
	H_2, 5 % Pd/C, 1 atm MeOH, THF, 30 m		62
	1 h		54
	H_2, 5 % Pd/C, 1 atm MeOH, THF, 2 h	 **194d**	57 (90 % ee)
	H_2, 5 % Pd/C, 1 atm MeOH, THF, 2 h	 **194e**	82 (93 % ee)

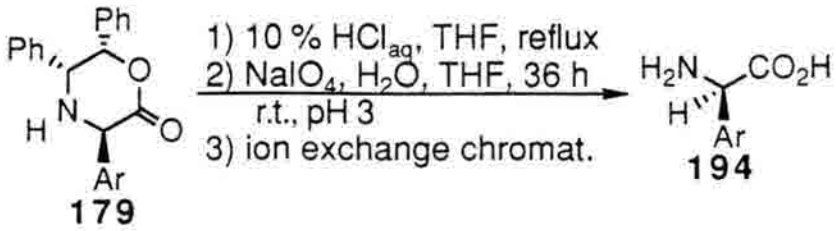
* (Product decomposes rapidly)



179

Ar = 1-Naphthyl; 2,4,6-Trimethoxybenzene

Scheme 62 Oxidative Deprotections



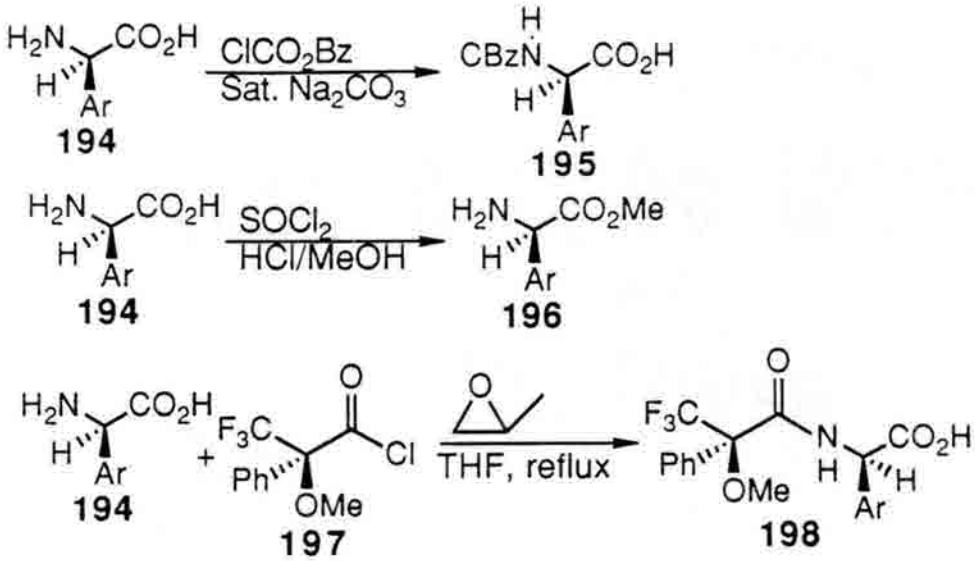
Ar	Entry	% Yield	% ee	Overall Yield
Phenyl-	**a**	71	82	29
1-Naphthyl-	**b**	32	94	11
2,4,6-Trimethoxyphenyl-	**c**	62	91	51
2-Furyl-	**d**	50*	90	13
5'-Methyl-2-furyl-	**e**	85	93	28
	Reductive Deprotections			
2-Furyl-	**d**			38
5'-Methyl-2-furyl-	**e**			63

* (From **178f**)

purification of the arylglycine products (**194**) quite a challenge. Further complicating purification was the unique and unusual solubility properties of the arylglycine products (**194**). Many purification techniques were applied including ion exchange chromatography, recrystallization, and reverse phase chromatography (see Chapter IV) but, in most cases only impure arylglycine samples could be obtained.

To fully characterize the impure arylglycine products, it became necessary to derivatize the amino acids. The crude amino acids were acylated and/or esterified to known compounds and the spectral data were compared to literature values; see Chapter IV. To determine enantiomeric excesses, the Mosher's amides were synthesized from the acylation of the arylglycines with (+)-MTPA-Cl, (Scheme 63). The % ee's were then determined by the ^{19}F NMR spectra of the Mosher's amides. In several cases, chiral HPLC separation was used to confirm the % ee values. The free amino acids were separated on a

Scheme 63



Ar = Ph, 1-Naphthyl, 2,4,6-Trimethoxyphenyl, Furyl, 5-Methylfuryl

Crownpak CR(+) chiral column with an aqueous perchloric acid buffer, pH 2, used as the mobile phase. Phenylglycine (**194a**), 1-naphthylglycine (**194b**), furylglycine (**194d**), and 5-methylfurylglcine (**194e**) were all separated in this way. The % ee's determined by chiral HPLC agreed with the values determined by the Mosher's amide within experimental error. The yield and ee data for the arylglycine syntheses are summarized in Scheme 62.

This study showed the utility of the optically active oxazinone in synthesizing arylglycines. Several aryl-coupling reactions were attempted but cuprate couplings and the Friedel-Crafts alkylations proved to be the most synthetically useful. A new acidic-oxidative deprotection method was developed which produced the desired arylglycines while limiting racemization. In the furyl examples, the furyl- and methylfuryl- glycines could be efficiently synthesized using a mild hydrogenation reaction. With the development of this methodology it was felt that the synthesis of more challenging arylglycine targets should be attempted.

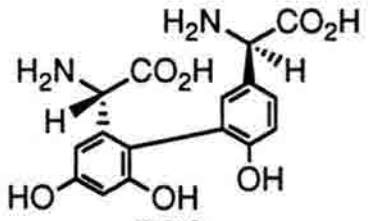
Chapter III

Approaches to the Synthesis of Actinoidic Acid

A. Background

Actinoidic acid (**199**) is a degradation product of most glycopeptide antibiotics.[4] In the degradation of ristocetin, a protected actinoidic acid derivative was isolated as a mixture of four diastereomers.[6a] Actinoidic acid (**199**) is a bis-aryl glycine which contains a biphenyl bond that links the two arylglycine residues, (Scheme 64). Another interesting feature is that the two

Scheme 64



199
Actinoidic Acid

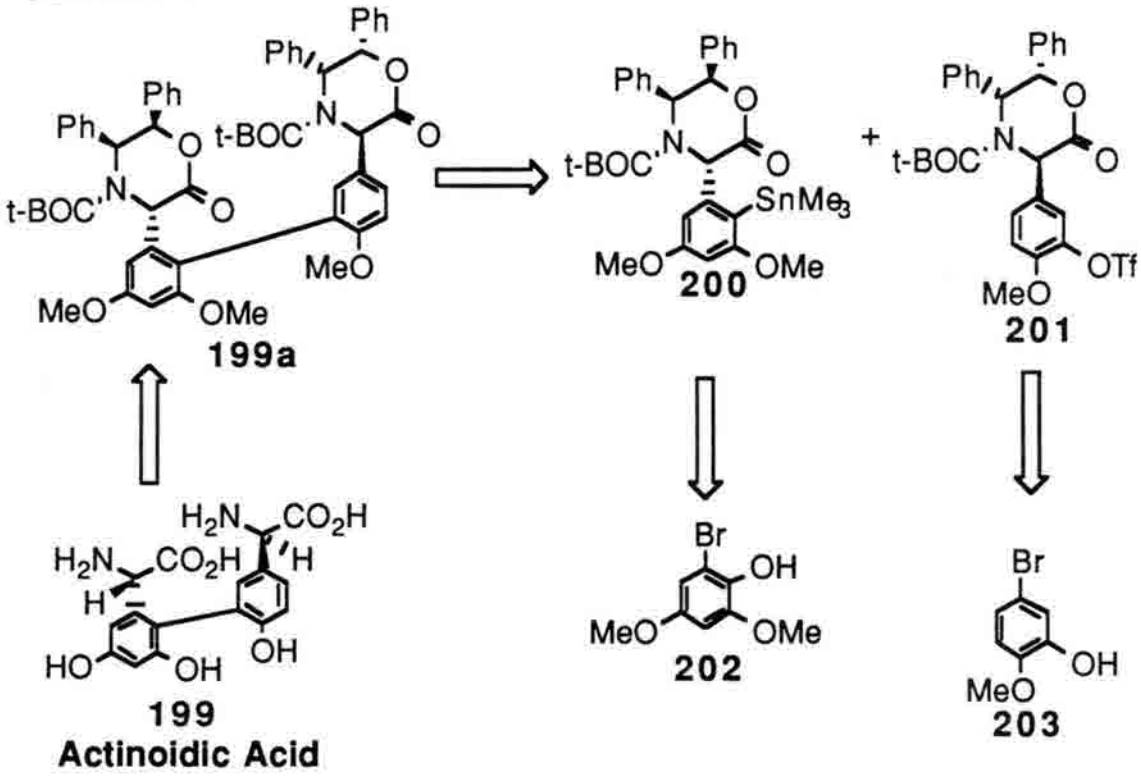
amino acid residues have different stereochemical configurations about their α-centers. The 3,5-dihydroxy residue has an (S)- configuration while the 4-hydroxy residue is an (R)- amino acid. An asymmetric synthesis of actinoidic acid (**199**) must consider, not only the stereochemistry about the two α-centers, but also the formation of the biaryl nucleus with the proper phenolic substitution with control of atropisomerism about the biaryl bond. The synthesis of this challenging target has so far eluded synthetic organic chemists despite the efforts of the Williams and Evans research groups.[71]

The initial synthetic strategy proposed involved the cuprate coupling of each properly substituted aromatic group (**202, 203**) to the optically active oxazinone template. The need for regiochemical control in the aromatic couplings dictated the use of cuprate coupling reactions. The biphenyl bond was then to be formed under neutral conditions by utilizing the palladium catalyzed aryl-tin coupling reaction developed by Stille and co-workers.[72] The classical biphenyl coupling alternatives,[73] such as the Ullmann reaction, are usually performed under quite harsh reaction conditions at pH extremes. It was felt that the lactone template could not survive classical biphenyl couplings and the arylglycine products, if formed, would certainly racemize under the harsh reaction conditions. To carry out the mild Stille biphenyl coupling, the phenolic groups of the aryl coupled lactones would need to be converted to triflates and one of the triflates would then be converted to the active aryl trimethyltin (**200**). It was felt that the aryl trimethyltin would be more reactive to the biphenyl bond forming reaction than the alternative and less toxic tributyltin reagent. The decision to put the trimethyltin on the more electron rich aromatic was a reflection of literature precedent.[72] With the biphenyl bond in place, the oxidative deprotection discussed in Chapter II would be applied yielding the actinoidic acid target, (Scheme 65). Before embarking on this synthetic route, a model study was performed to determine if the α-center of an arylglycine precursor would racemize under the reaction conditions of the triflate, trimethyl tin, and biphenyl bond-forming reactions.

B. Lactone Model Study

In the model study a silyl-protected *p*-bromophenol (**204**) was used in a cuprate coupling reaction, (Scheme 66). It was shown previously that free phenols would not couple under these reaction conditions but there was some concern about the compatibility of a silyl group in the cuprate coupling. This

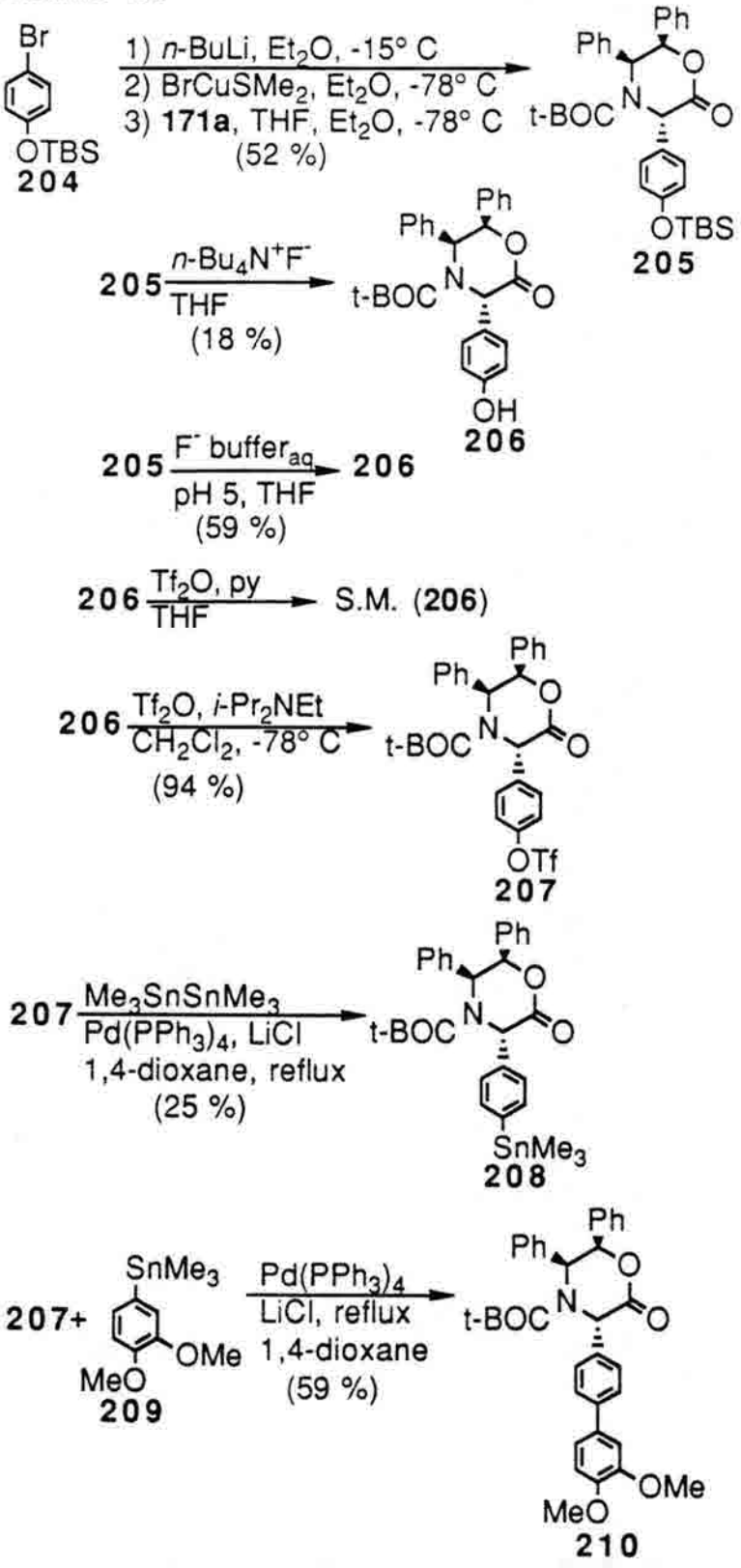
Scheme 65



fear was unfounded as the silyl group seemed to aid the reaction by enhancing the solubility of the aryl-cuprate complex. The coupled silyl-protected *p*-phenol (**205**) was obtained in good yield as one diastereomer, as determined by high temperature proton NMR.

With the coupled product (**205**) in hand, it became necessary to cleave the silyl group. The use of the standard method of tetra-butylammonium fluoride proved to be inadequate. A mild fluoride buffer solution that was originally developed for the silyl deprotection of phenol was applied.[74] The silyl group was cleaved in the aqueous fluoride buffer solution with a pH of 5 at room temperature with THF which yielded the free *p*-phenol derivative (**206**). The standard conditions for the synthesis of an aryl triflate from a phenol involve the use of an amine base.[75] There was great concern that the α-center would racemize in the presence of such a base. Use of the standard conditions of

Scheme 66


Br
OTBS
204
1) n-BuLi, Et2O, -15° C
2) BrCuSMe2, Et2O, -78° C
3) 171a, THF, Et2O, -78° C
(52 %)
Ph
Ph
O
N
t-BOC
O
O
OTBS
205
205
n-Bu4N+F-
THF
(18 %)
t-BOC
OH
206
205
F- buffer aq
pH 5, THF
(59 %)
206
206
Tf2O, py
THF
S.M. (206)
206
Tf2O, i-Pr2NEt
CH2Cl2, -78° C
(94 %)
OTf
207
207
Me3SnSnMe3
Pd(PPh3)4, LiCl
1,4-dioxane, reflux
(25 %)
SnMe3
208
207+
SnMe3
OMe
MeO
209
Pd(PPh3)4
LiCl, reflux
1,4-dioxane
(59 %)
OMe
MeO
210

excess pyridine and triflic anhydride at room temperature failed to yield the desired product (**207**). Alternatively, the triflate (**207**) was generated in excellent yield using Hunig's base and triflic anhydride in dry dichloromethane at -78° C. The triflate product (**207**) showed no evidence of racemization with high temperature proton NMR. Presumably, the use of a hindered base and low temperature in the reaction prevented racemization from occurring. The triflate (**207**) was then converted to the trimethyltin reagent (**208**) with hexamethylditin, $Pd(PPh_3)_4$, and lithium chloride in dry dioxane at reflux. The yield of this reaction was low but not unexpected since, this type of transformation usually occurs in low to moderate yield.[76] The triflate (**207**) was also reacted with an electron-rich trimethyltin (**209**) in a Stille palladium-catalyzed cross coupling, (Scheme 66). The yield of the resulting biphenyl (**210**) was quite good for an intermolecular biphenyl coupling. At this point the model study was complete. The study had shown that the conditions of the Stille biphenyl coupling reaction were compatible with the lactone template. Furthermore, it was seen that aryl-trimethyltin reagents could be produced and that the lactone triflates could be synthesized without base-catalyzed racemization. The methodology developed from this study was then applied to the target system but first the aromatic starting materials needed to be synthesized with the proper substitution.

C. Aromatic Syntheses

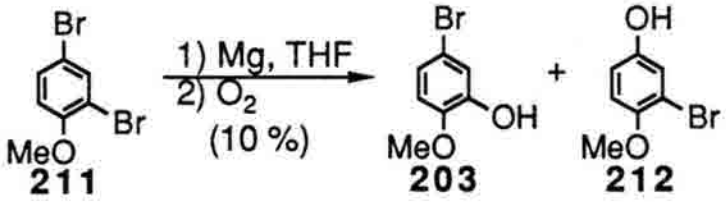
From the retrosynthetic analysis of actinoidic acid, the two aromatic systems needed were determined to be 5-bromoguaiacol (**203**) and 6-bromo-2,4-dimethoxyphenol (**202**). The phenolic groups of the target were protected as methyl ethers due to the stability of the methoxy groups under most reaction conditions. It was hoped that the phenolic groups could be deblocked late in

the synthesis under acidic conditions. The synthesis of these two aromatic compounds was not trivial, unfortunately.

1. The Synthesis of 5-Bromoguaiacol

In a search of the literature, only one synthesis of 5-bromoguaiacol (**203**) was uncovered. In 1944, in occupied France, Paty and Quelet[77] reported the synthesis of 5-bromoguaiacol (**203**) from 2,4-dibromoanisole (**211**), (Scheme 67). This method proved to be inadequate since in repeating this work only a

Scheme 67

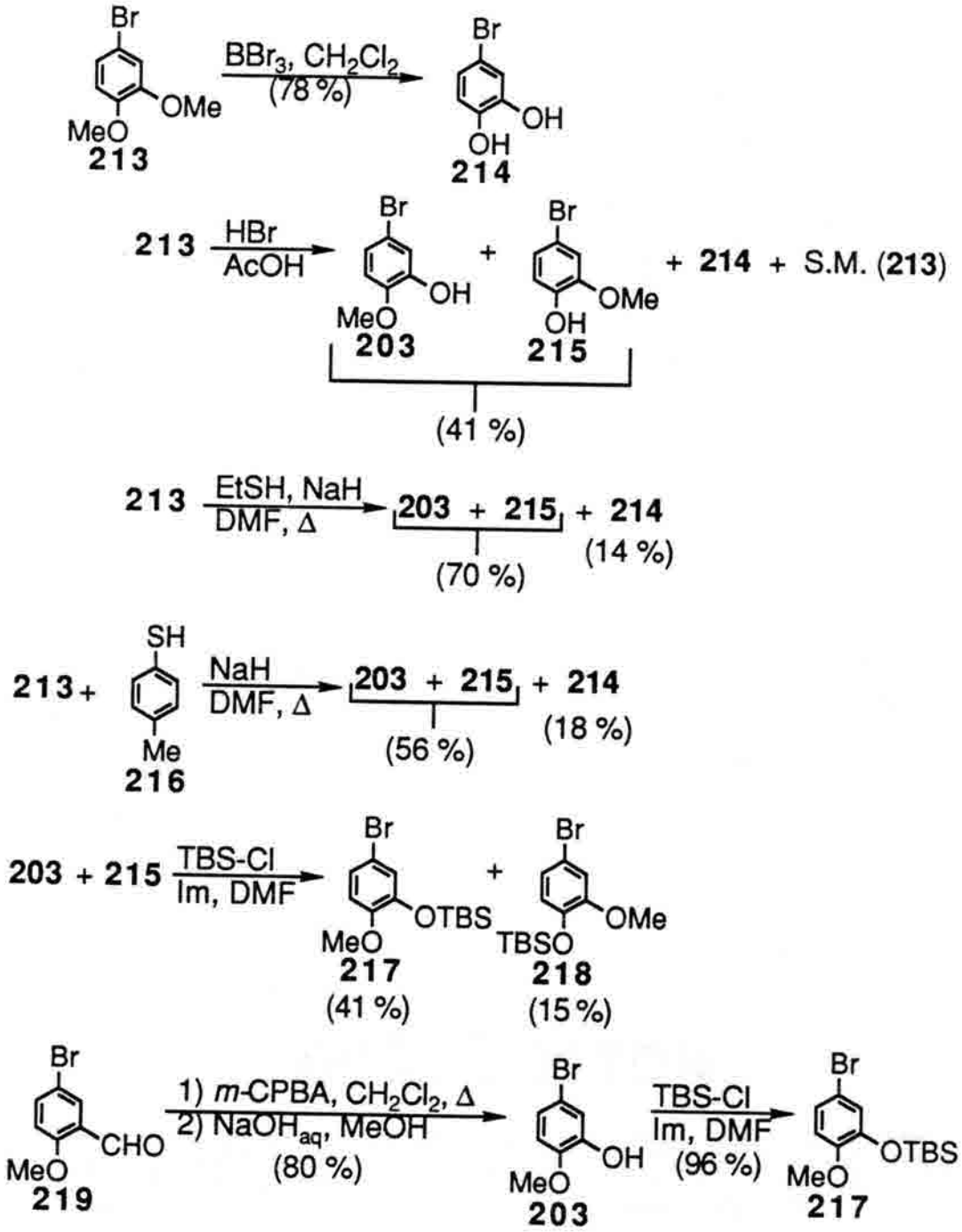


211 **203** **212**

small amount of a mixture of 5-bromoguaiacol (**203**) and 3-bromo-4-methoxyphenol (**212**) was isolated. In another approach, the mono-demethylation of 4-bromoveratrol (**213**) was attempted. Both acidic and nucleophilic methods were tried but most resulted in mixtures of 4-bromocatechol (**214**) and the two bromoguaiacol products (**203, 215**). The two bromoguaiacols (**203, 215**) were inseparable, but upon silylation the two silyl-protected guaiacol products (**217, 218**) were separable by chromatography with a great deal of difficulty. It was also difficult to determine, unequivocally, the identity of the two guaiacol derivatives (**217, 218**). The solution to this problem finally came in the form of a modern modification of the classical Dakin oxidation.[78] In this reaction, 5-bromo-*o*-anisaldehyde (**219**) was oxidized with *meta*-chloro-peroxybenzoic acid to give, unambiguously, 5-bromoguaiacol (**203**) in good yield after basic hydrolysis. 5-Bromoguaiacol (**203**) was then easily protected with t-butyldimethylsilyl chloride yielding the

the silylated 5-bromoguaiacol (**217**) that was ready for cuprate coupling to the lactone template, (Scheme 68).

Scheme 68

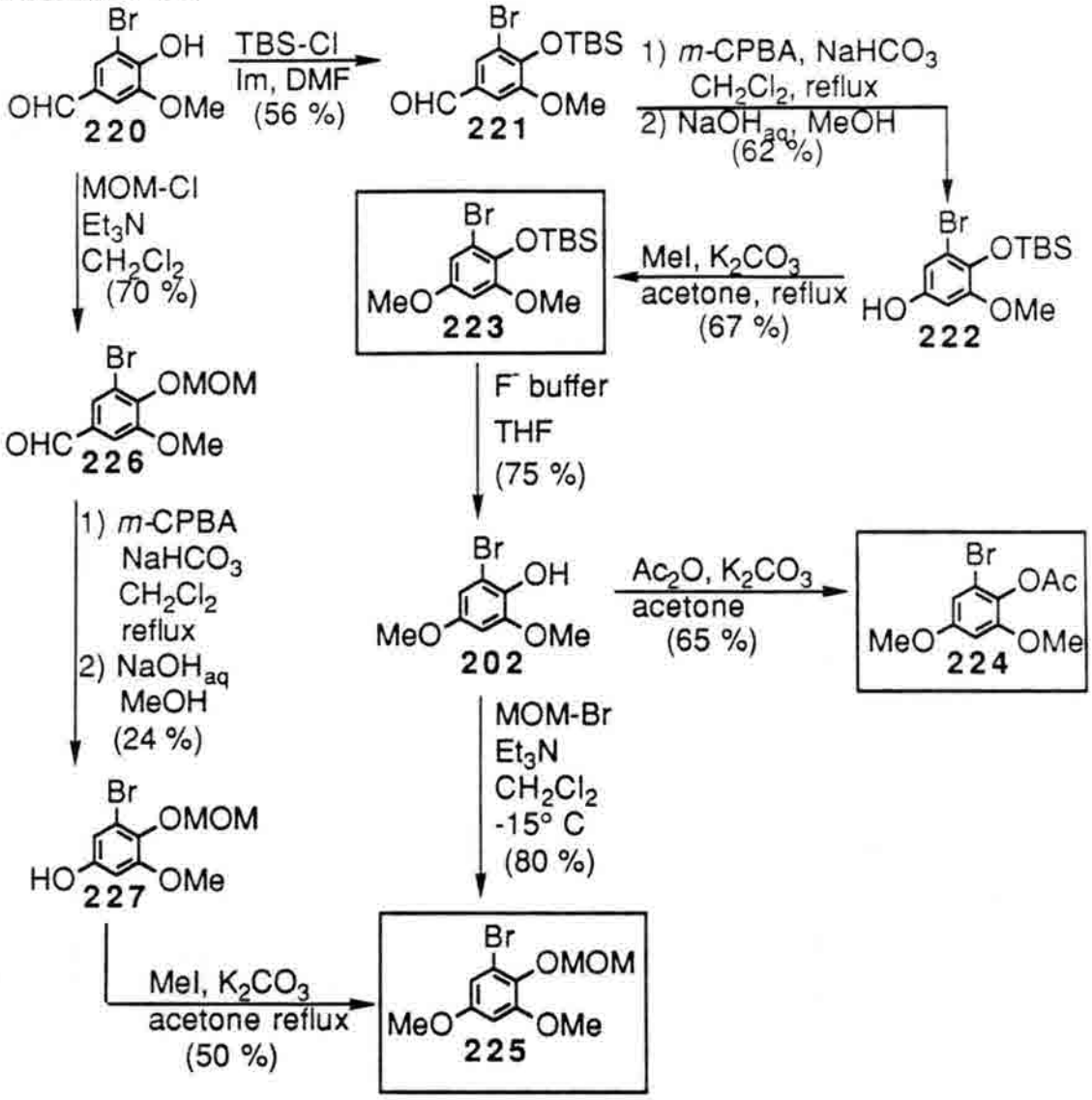


2. The Synthesis of 6-Bromo-2,4-dimethoxyphenol

With the success of the 5-bromoguaiacol synthesis, a similar strategy was employed in the synthesis of 6-bromo-2,4-dimethoxyphenol (**202**). Starting with 5-bromovanillin (**220**), the phenolic group was protected with a t-butyldimethylsilyl group. The modified Dakin oxidation conditions were then applied to the silyl-protected bromovanillin (**221**) yielding only a small amount of the desired phenol (**222**). It was found, however, that the reaction was significantly improved with the use of sodium bicarbonate as a buffer for the acid. The resulting phenol (**222**) was then methylated with methyl iodide in a suspension of solid potassium carbonate and dry acetone yielding the silyl-protected 6-bromo-2,4-dimethoxyphenol (**223**). The methylation reaction resulted in a good yield of the desired product (**223**) but a significant amount of a starting material mixture was also isolated, (Scheme 69). The mixture contained the starting material (**222**) and the product of silyl group migration to the 4-phenolic position. These two phenolic compounds were inseparable and as a result the unreacted starting material (**222**) could not be recycled.

The silyl-protected 6-bromo-2,4-dimethoxyphenol (**223**) could be used directly in cuprate coupling reactions to the lactone or the silyl group could be replaced by alternative phenolic protecting groups. The silyl group was easily cleaved with the fluoride buffer solution previously discussed yielding 6-bromo-2,4-dimethoxyphenol (**202**). The phenol (**202**) was then reacted with acetic anhydride and solid potassium carbonate in dry acetone yielding the desired acetate (**224**) which was also to be used in a cuprate coupling attempt. The phenol was also reacted with bromomethylmethyl ether (MOM-Br) and triethylamine in dry dichloromethane which produced the desired MOM-protected phenol (**225**). The use of MOM-Cl under a variety of conditions failed to produce the desired product in significant yield. The MOM-protected

Scheme 69



substrate was also synthesized via the Dakin oxidation route. 5-Bromovanillin (**220**) was reacted with MOM-Cl and triethylamine in dry dichloromethane and smoothly gave the MOM-protected bromovanillin (**226**). The modified Dakin oxidation gave the desired MOM-protected phenol (**227**) in a disappointing yield. Methylation of the phenol (**227**) with methyl iodide gave the desired bromo-dimethoxy MOM-protected substrate (**225**) in a low overall yield,

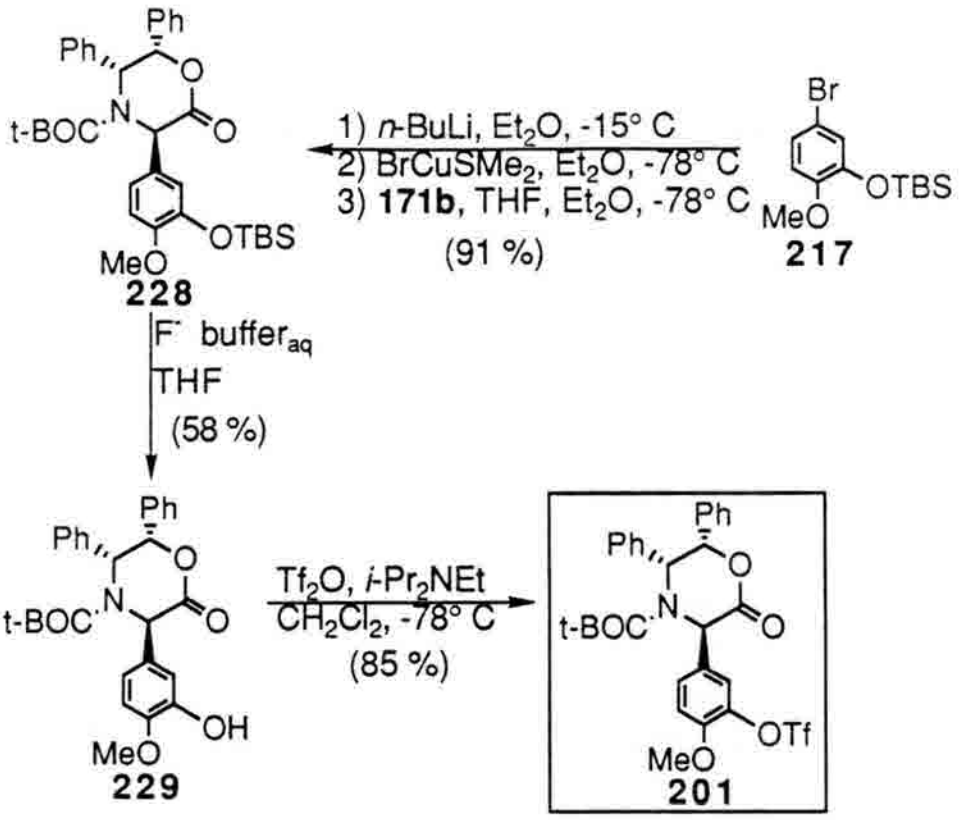
(Scheme 69). With the synthesis of the MOM-protected substrate (**225**), three aromatic substrates were available for cuprate coupling to the lactone.

D. Approaches to the Biphenyl-Coupling Precursors

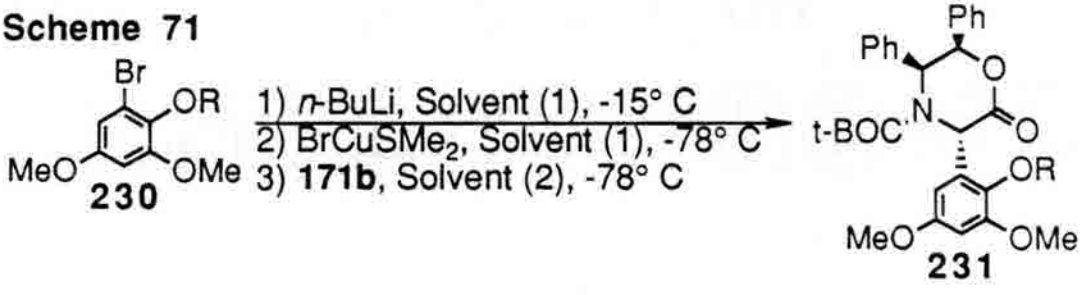
The synthesis of the lactone triflate (**201**) derived from 5-bromoguaiacol (**203**) utilized the methodology developed in the model study. The TBS-protected 5-bromoguaiacol (**217**) was coupled to the bromolactone (**171b**) using standard cuprate coupling conditions (Chapter II) which yielded the desired coupled guaiacol derivative (**228**) as a single diastereomer in excellent yield. The reason for the exceptional yield was unclear but the presence of the silyl group certainly contributed by aiding the solubility of the cuprate reagent in ether. The silyl group was then cleaved with the fluoride buffer in THF yielding the free guaiacol derivative (**229**) in moderate yield. The desired triflate (**201**) was produced in good yield with triflic anhydride and Hunig's base from the coupled guaiacol substrate (**229**). The overall yield for the synthesis of the triflate (**201**) was 45 % from the bromolactone (**171b**), (Scheme 70). High temperature proton NMR experiments showed no evidence of racemization in the formation of the triflate (**201**).

In contrast, the attempted cuprate couplings of the 6-bromo-2,4-dimethoxyphenol derivatives (**230**) all failed to yield any desired products (**231**). In the cuprate coupling attempts, standard conditions were used as well as a modification which utilized dimethylsulfide as the sole solvent, (Scheme 71). It is known that dimethylsulfide as a solvent or co-solvent can aid many cuprate reactions.[79] All three aromatic substrates were subjected to the standard and modified conditions with no success. It was, therefore, concluded that the sterics of a large group *ortho*- to the reactive center of the aromatic (**230**) prevented the desired coupling. With this disappointing result, a new approach to actinoidic acid was devised.

Scheme 70



Scheme 71

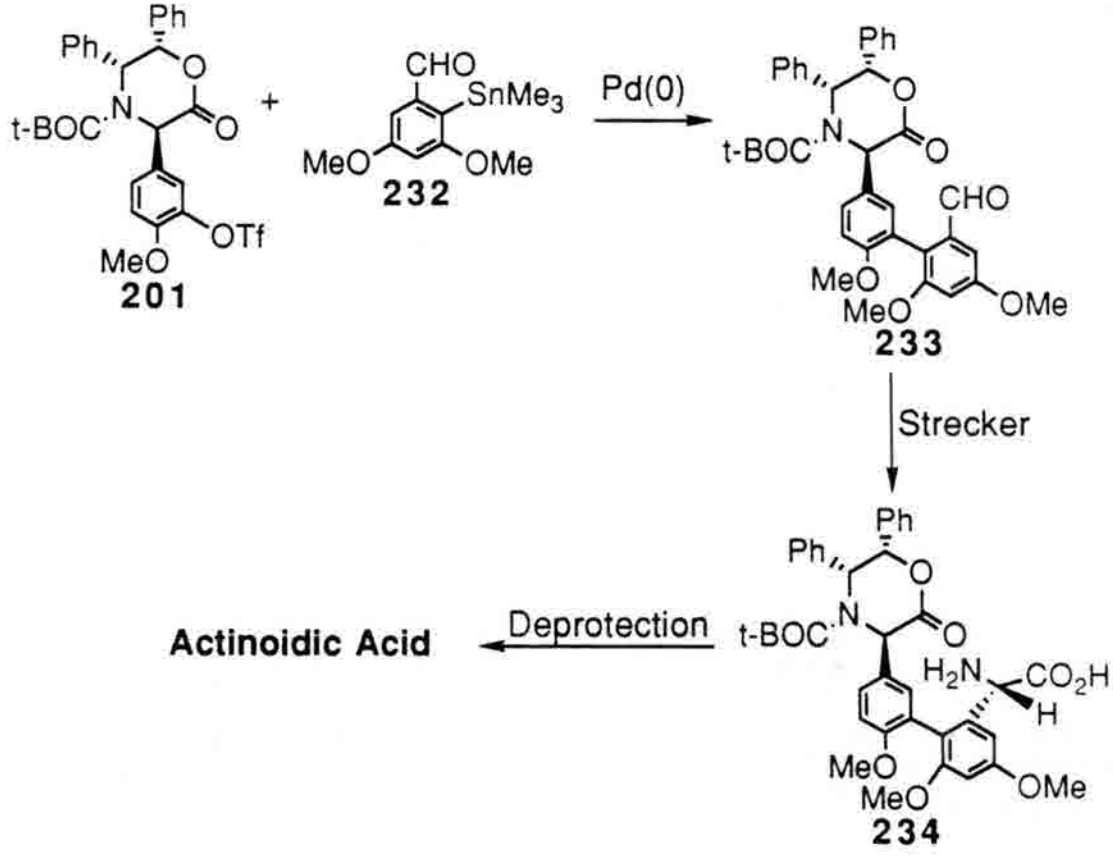


R	Solvent (1)	Solvent (2)	% Yield (231)
TBS	Et_2O	Et_2O, THF	0
TBS	SMe_2	SMe_2	0
MOM	Et_2O	Et_2O, THF	0
MOM	SMe_2	SMe_2	0
Ac	Et_2O	Et_2O, THF	0
Ac	SMe_2	SMe_2	0

E. Alternate Strategy

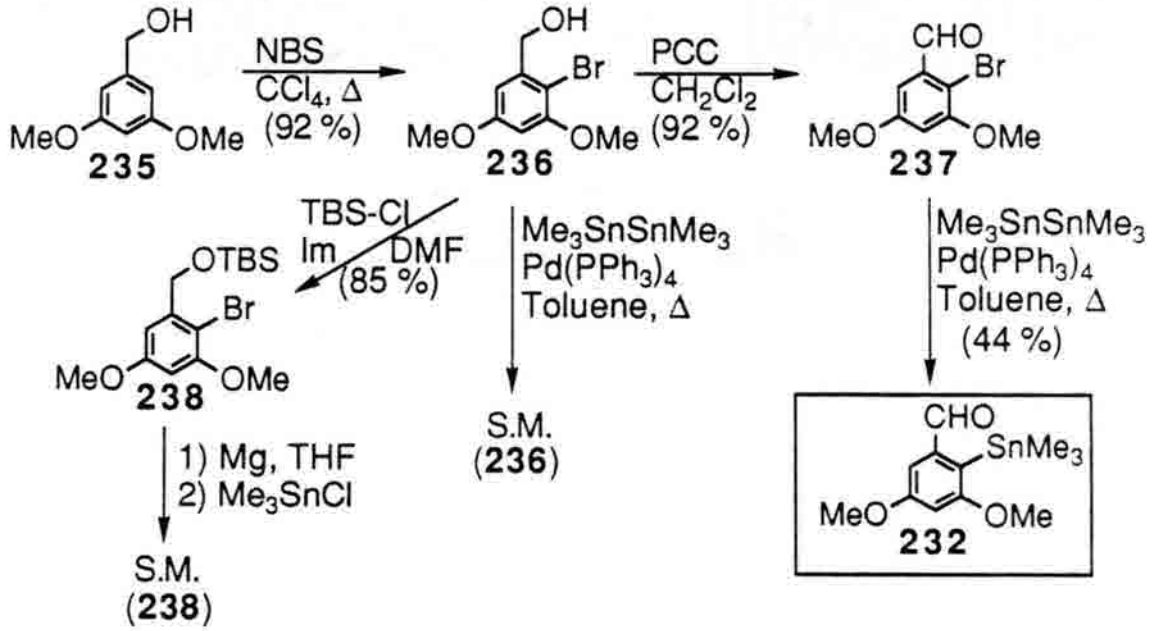
The failure of the 6-bromo-2,4-dimethoxyphenol derivatives to couple to the oxazinone template made it necessary to come up with an alternate route to actinoidic acid. Since the guaiacol triflate (**201**) was readily available, it was proposed that the triflate (**201**) could be coupled to a benzaldehyde derivative (**232**) in a Stille biphenyl-coupling reaction. The resulting benzaldehyde (**233**) could then be converted to the desired amino acid (**234**) via an asymmetric Strecker reaction; see Chapter I. Acidic demethylation of the methoxy-goups followed by oxidative deprotection of the lactone template would then yield the actinoidic acid target, (Scheme 72).

Scheme 72



The trimethyltin benzaldehyde derivative (**232**) needed for the biphenyl coupling was smoothly synthesized in three steps from 3,5-dimethoxybenzyl alcohol (**235**). The benzyl alcohol (**235**) was brominated[80] and oxidized[81] in excellent yield using literature procedures. The 2-bromo-3,5-dimethoxybenzaldehyde (**237**) was converted to the trimethyltin reagent (**232**) using hexamethylditin and tetrakis(triphenylphosphine)palladium(0) in toluene at reflux in 44 % yield after column chromatography. The synthesis of two synthetic equivalents was also attempted. The generation of the trimethyltin benzyl alcohol derivative from a hexamethylditin reaction with 2-bromo-3,5-dimethoxybenzyl alcohol (**236**) failed to produce the desired stannane. The generation of the Grignard reagent of the TBS-protected benzyl alcohol (**238**), followed by the addition of trimethyltin chloride, also failed to yield the desired aryltin reagent, (Scheme 73).

Scheme 73

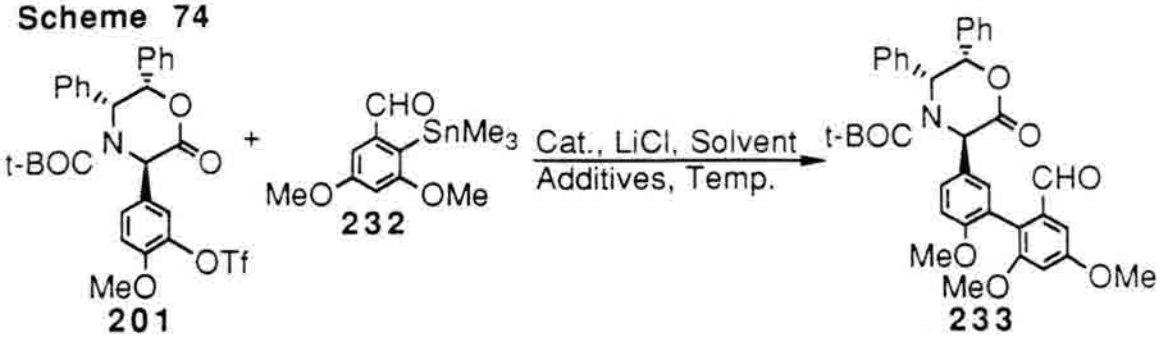


The biphenyl coupling reaction between the lactone triflate (**201**) and the trimethyltin benzaldehyde reagent (**232**) was finally attempted under Stille reaction conditions. The standard conditions of the reaction called for the use of tetrakis (triphenylphosphine) palladium(0) and dry solid lithium chloride in refluxing 1,4-dioxane for 36-48 hours. Unfortunately, this reaction failed to produce any of the desired biphenyl product (**233**). Recently there has been a great interest in modifications of the Stille reaction,[82] mainly as it pertains to aryl-vinyl coupling. Some of these modifications were applied to this biphenyl coupling attempt. In addition to the standard Pd(0) catalyst, several Pd(II) catalysts were tried. The high boiling and very polar solvents N,N-dimethylformamide (DMF) and N-methylpyrollidinone (NMP) were also used with different reaction temperatures. In some attempts triphenylphosphine was also added to help preserve the catalyst. Despite the use of these various conditions, the desired biphenyl product (**233**) was never isolated, (Scheme 74). These disappointing results prompted the start of another model study in the hope of attaining a better understanding of this type of biphenyl coupling reaction.

F. Biphenyl Coupling Model Study

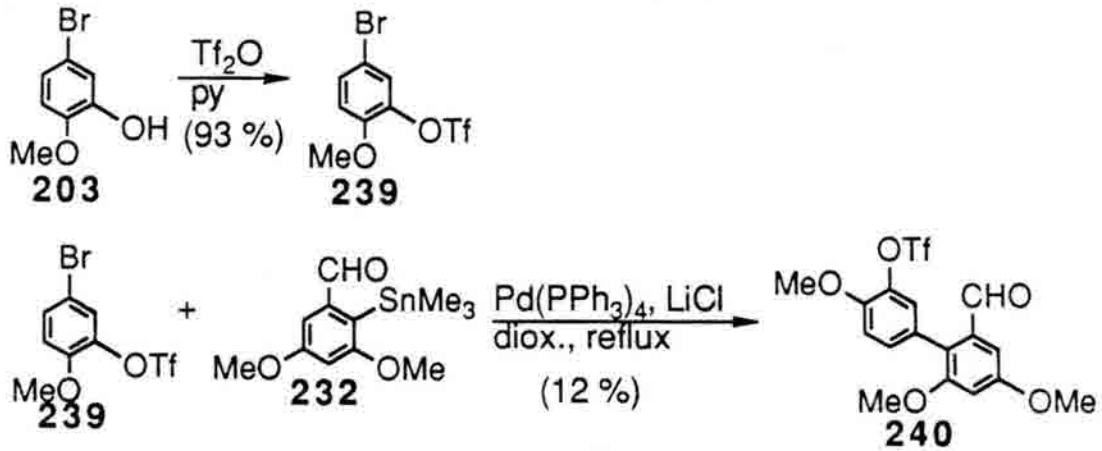
The biphenyl coupling model study was prompted, not only by the failed coupling reactions discussed above, but also by a simple experiment performed with the triflate of the 5-bromoguaiacol (**239**). The 5-bromoguaiacol triflate (**239**) was reacted with the trimethyltin benzaldehyde (**232**) used previously in the hope that the triflate and not the bromide would react to form the desired biphenyl bond. It has been observed in the literature that the aryl triflate is more reactive to organotin reagents than aryl bromides.[82b] This reaction, however, produced the undesired biphenyl triflate (**240**) in low yield and with no evidence of the desired bromo-biphenyl product, (Scheme 75). This result

Scheme 74



Cat.	Solvent	Additives	Temp.	% Yield (233)
$Pd(PPh_3)_4$	dioxane	-	reflux	0
$Pd(PPh_3)_4$	DMF	-	reflux	0
$Pd(PPh_3)_4$	dioxane	PPh_3	reflux	0
$Pd(PPh_3)_4$	NMP	-	135° C	0
$Pd(OAc)_2$	NMP	-	r.t.	0
$Pd(OAc)_2$	NMP	-	100° C	0
$Cl(Ph)Pd(PPh_3)_2$	dioxane	-	reflux	0
$Cl(Ph)Pd(PPh_3)_2$	DMF	PPh_3	reflux	0
$Cl(Ph)Pd(PPh_3)_2$	NMP	-	140° C	0
$Cl_2Pd(PPh_3)_2$	DMF	PPh_3	reflux	0

Scheme 75



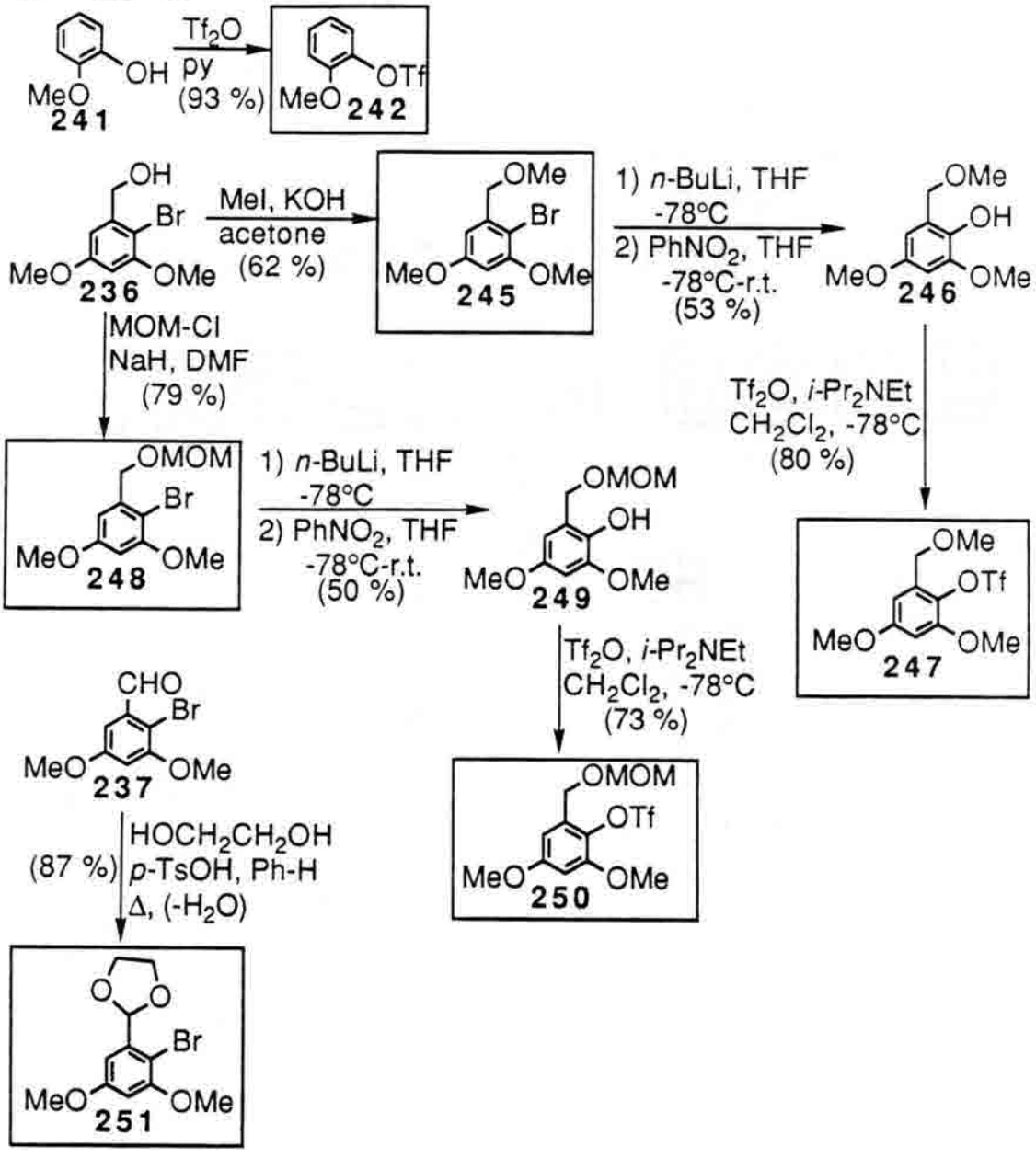
indicated that sterics must play an important role in this type of biphenyl coupling where three out of four *ortho*- positions in the desired biphenyl product (**233**) are occupied. With this information, a variety of aromatic compounds

were tested under differing reaction conditions. Some of the aromatic compounds tested were either commercially available or were known compounds and easily synthesized. However, many of the aromatic compounds used in this model study were previously unknown and synthesized by methods summarized in Scheme 76.

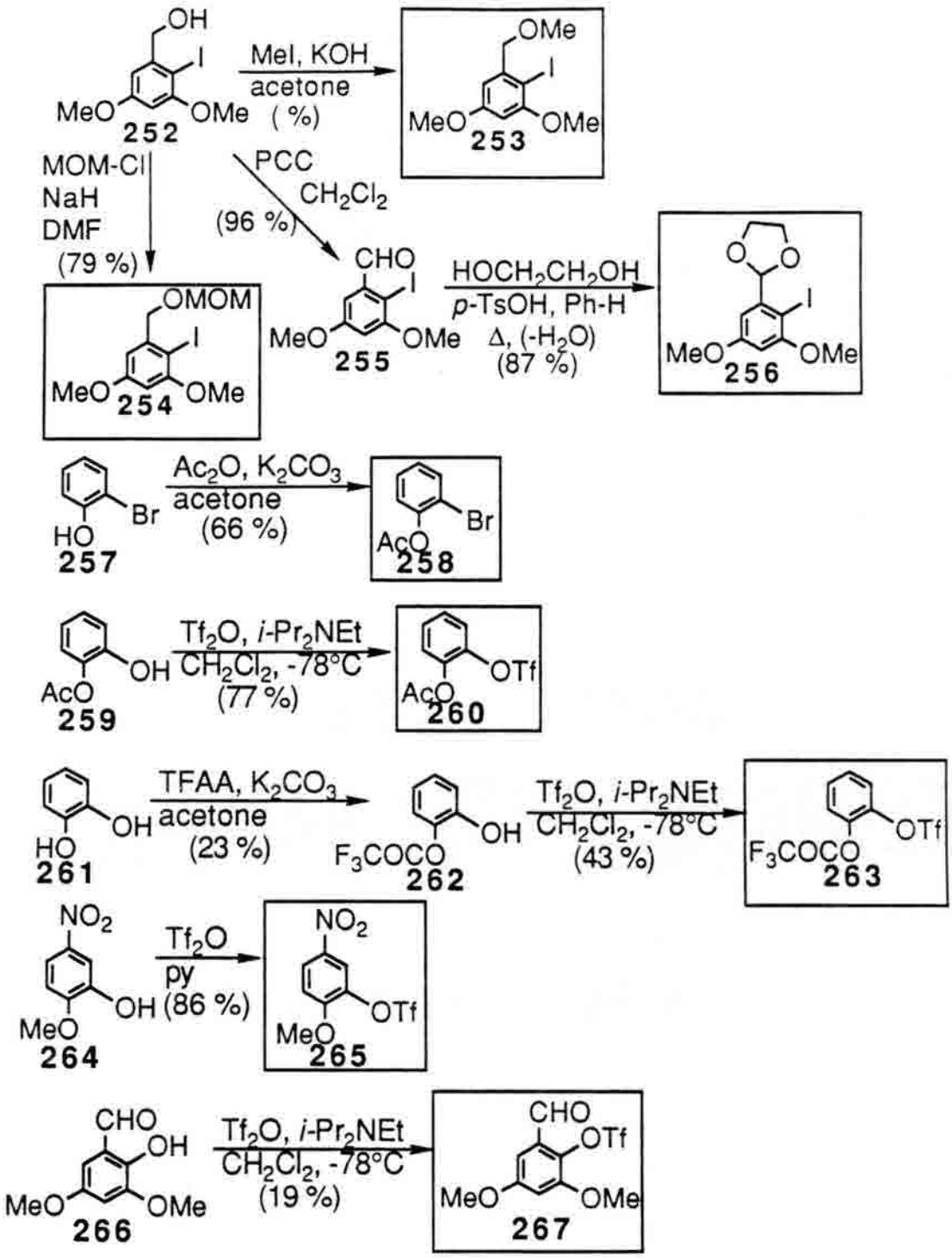
A wide variety of aromatic bromides, iodides and triflates were reacted with the trimethyltin benzaldehyde (**232**) under various conditions.[82] The *o*-substituted anisole derivatives were reacted with Pd(0) and Pd(II) catalysts and gave the desired biphenyl product in very low yield in most cases. The addition of the electron-withdrawing nitro-group to the 2-substituted anisole ring resulted in quite good coupling yields. This result indicated that, while sterics certainly play a role in the biphenyl coupling reaction, the electronic characteristics of the aromatic substrates are of greater influence. As further proof of the small role that sterics play in the success of this reaction, bromobenzene and the unsubstituted phenyltriflate were reacted with the trimethyltin reagent (**232**) yielding only small amounts of the desired biphenyl (**269**). In an attempt to find a coupling reaction that could be synthetically useful in the 'real' system, electron-withdrawing phenolic protecting groups were employed. The use of the acetate and trifluroacetate groups only produced the biphenyl (**269**) in low yield indicating that the acetate groups did not possess strong enough electron-withdrawing power to promote the reaction, (Scheme 77).

In another approach, the reactivity of the aromatic substrates was reversed. The 2-methoxy trimethyltin benzene reagent (**244**) was reacted with a variety of 3,5-dimethoxy benzaldehyde equivalents (**270**) under many reaction conditions. This approach utilized aryl bromides, iodides, and triflates with Pd(0) and Pd(II) catalysts but never produced any biphenyl product (**271**) in significant yield, (Scheme 78). This approach was further discredited by the low

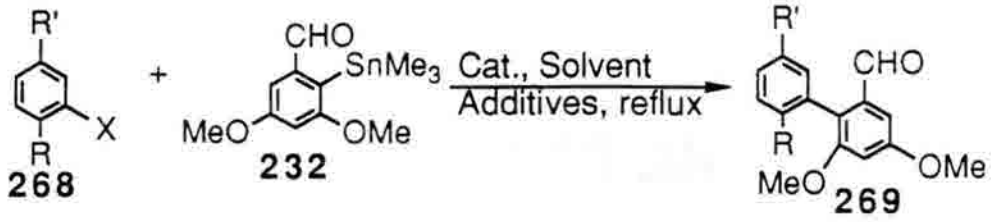
Scheme 76


Tf2O
py
(93 %)
241
242
MeI, KOH
acetone
(62 %)
236
245
1) n-BuLi, THF
-78°C
2) PhNO2, THF
-78°C-r.t.
(53 %)
246
MOM-Cl
NaH, DMF
(79 %)
Tf2O, i-Pr2NEt
CH2Cl2, -78°C
(80 %)
248
1) n-BuLi, THF
-78°C
2) PhNO2, THF
-78°C-r.t.
(50 %)
249
247
Tf2O, i-Pr2NEt
CH2Cl2, -78°C
(73 %)
237
(87 %)
HOCH2CH2OH
p-TsOH, Ph-H
Δ, (-H2O)
250
251

Scheme 76 (cont.)



Scheme 77

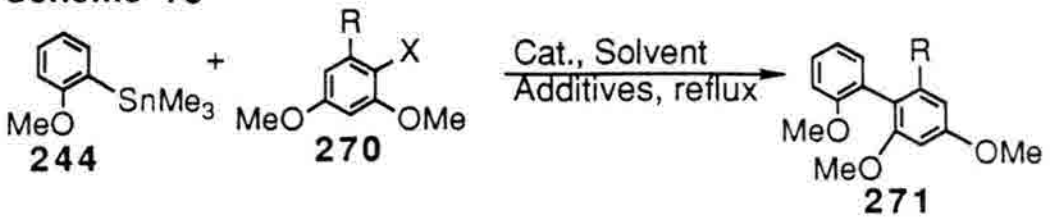


X	R	R'	Cat.	Solvent	Additives	% Yield (269)
Br	OMe	H	$Pd(PPh_3)_4$	dioxane	-	17
I	OMe	H	$Pd(PPh_3)_4$	dioxane	-	12
OTf	OMe	H	$Pd(PPh_3)_4$	dioxane	LiCl	0
Br	OMe	H	$Cl_2Pd(PPh_3)_2$	DMF	PPh_3	6
I	OMe	H	$Cl_2Pd(PPh_3)_2$	DMF	PPh_3	3
OTf	OMe	H	$Cl_2Pd(PPh_3)_2$	DMF	PPh_3, LiCl	7
Br	OMe	NO_2	$Pd(PPh_3)_4$	dioxane	-	54
OTf	OMe	NO_2	$Pd(PPh_3)_4$	dioxane	LiCl	42
Br	H	H	$Pd(PPh_3)_4$	dioxane	-	7
OTf	H	H	$Pd(PPh_3)_4$	dioxane	LiCl	4
Br	OAc	H	$Pd(PPh_3)_4$	dioxane	-	4
OTf	OAc	H	$Pd(PPh_3)_4$	dioxane	LiCl	11
OTf	F_3CCO_2	H	$Pd(PPh_3)_4$	dioxane	LiCl	6

yielding transformation the the guaiacol derived lactone triflate (**201**) to the stannane (**272**). The resulting trimethyltin reagent (**272**) was reacted with an aryl triflate (**201**) using conditions similar to those recently published[82e] but resulted in only a 6 % yield of the desired biphenyl (**273**), (Scheme 79).

In a different mild palladium-catalyzed biphenyl coupling reaction,[83] arylboronic acids have been known to couple to arylbromides. The synthesis of the desired arylboronic acids (**275**) proceeded in low yield. The three boronic acids (**275**) were reacted with *o*-bromoanisole (**243**) and tetrakis

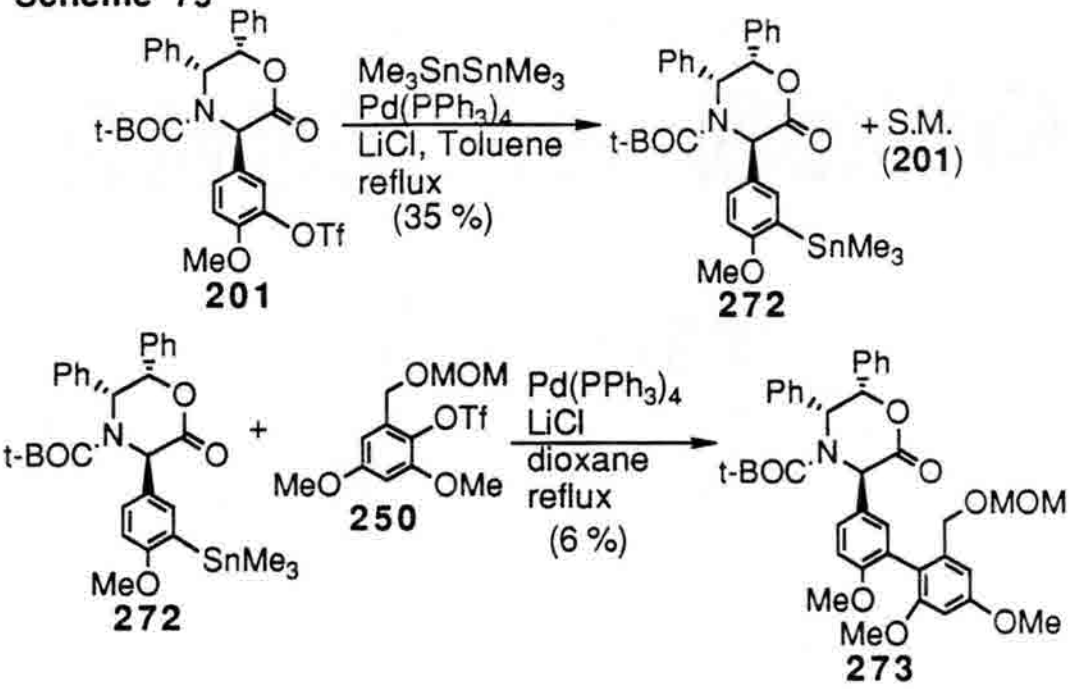
Scheme 78



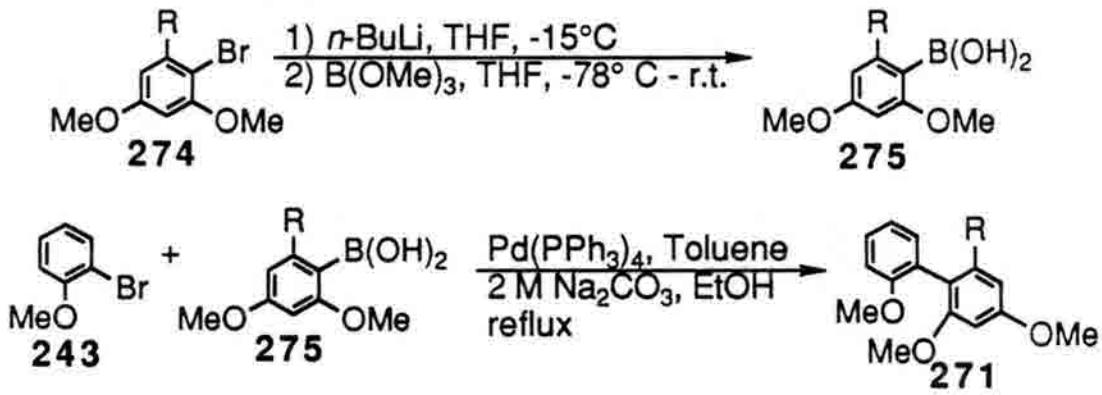
R	X	Cat.	Solvent	Additives	% Yield (271)
CHO	Br	$Pd(PPh_3)_4$	DMF	PPh_3	0
1,3-Dioxolane	Br	$Pd(PPh_3)_4$	dioxane	-	0
1,3-Dioxolane	Br	$Cl_2Pd(PPh_3)_2$	DMF	PPh_3	7
1,3-Dioxolane	I	$Pd(PPh_3)_4$	dioxane	-	0
1,3-Dioxolane	I	$Cl_2Pd(PPh_3)_2$	DMF	PPh_3	3
CH_2OMe	Br	$Cl_2Pd(PPh_3)_2$	DMF	PPh_3	6
CH_2OMe	I	$Cl_2Pd(PPh_3)_2$	DMF	PPh_3	0
CH_2OMe	OTf	$Cl_2Pd(PPh_3)_2$	DMF	LiCl, PPh_3	0
CH_2OMOM	Br	$Pd(PPh_3)_4$	dioxane	-	0
CH_2OMOM	I	$Pd(PPh_3)_4$	dioxane	-	0
CH_2OMOM	OTf	$Pd(PPh_3)_4$	dioxane	LiCl	12
CH_2OMOM	Br	$Cl_2Pd(PPh_3)_4$	DMF	PPh_3	4
CH_2OMOM	I	$Cl_2Pd(PPh_3)_4$	DMF	PPh_3	2
CH_2OMOM	OTf	$Cl_2Pd(PPh_3)_4$	DMF	LiCl, PPh_3	3

(triphenylphosphine) palladium(0) in toluene, ethanol, and aqueous 2 M sodium carbonate under reflux. These couplings yielded only small amounts of the desired biphenyl products (**271**), (Scheme 80). At this point the model studies with the biphenyl reactions were brought to a close. The Stille biphenyl coupling reaction remained the method of choice despite the disappointing results in the model study. Two strategies for the 'real' system emerged from this study. First was to synthesize a lactone triflate (**276**) with an acetate protecting group on the phenol *ortho*- to the triflate in the hope that the electron-

Scheme 79



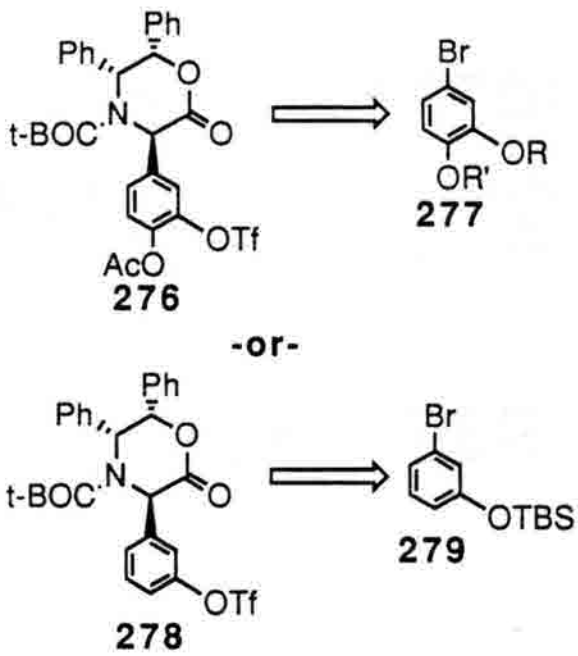
Scheme 80



R	% Yield (275)	% Yield (271)
CHO	18	4
CH_2OMe	21	11
CH_2OMOM	10	0

withdrawing nature of the acetate would promote the biphenyl coupling reaction. The second strategy was to synthesize the sterically unencumbered *meta*- triflate lactone (**278**) with no other substituents on the aromatic ring with the hope that this triflate (**278**) would be more reactive to the aryl trimethyltin reagent (**232**), (Scheme 81).

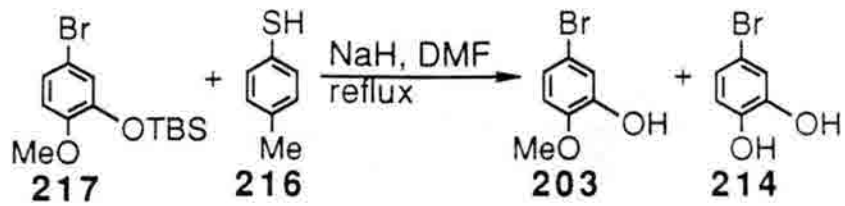
Scheme 81



G. Approaches to the Lactone Catechol Derivative

The synthesis of the desired lactone catechol derivative (**276**) with two different and unique protecting groups on each phenol proved to be quite a challenge. The selective cleavage of the methyl ether of the silyl-protected 5-bromoguaiacol (**217**) was attempted but resulted in only guaiacol (**203**) and catechol formation (**214**), (Scheme 82). The use of 5-bromosalicylaldehyde (**280**) as a starting material for this synthesis was then explored. The modified Dakin oxidation was performed on the TBS-protected 4-bromosalicylaldehyde

Scheme 82

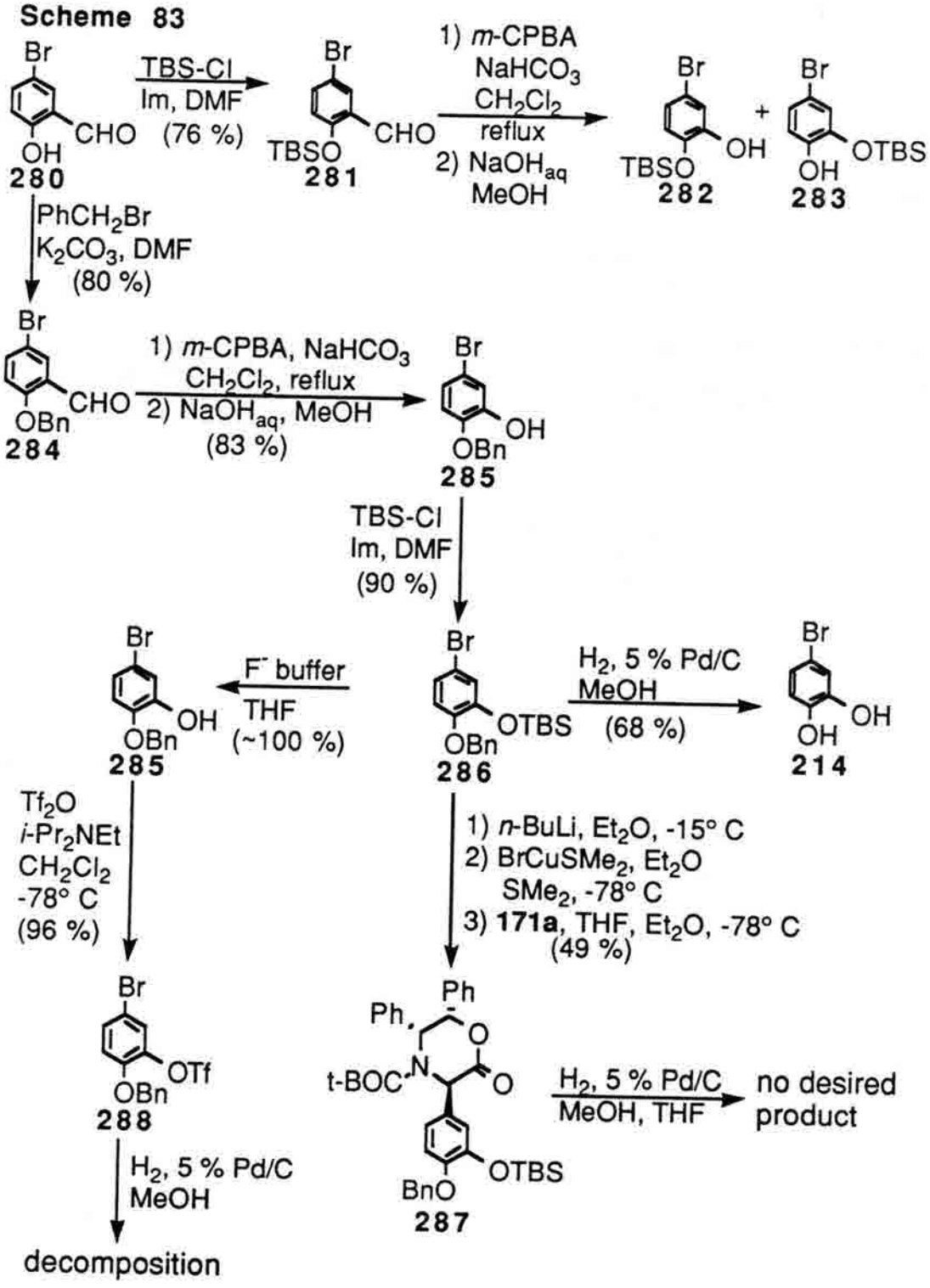


(**281**) resulted the desired oxidation but the silyl group also migrated yielding an inseparable mixture of two mono-silyl protected bromocatecol derivatives (**282, 283**).

A more promising approach was the benzyl protection of 5-bromosalicylaldehyde (**280**) followed by the modified Dakin oxidation. The desired mono-benzylated catechol (**285**) was obtained in good yield and was easily silylated to the di-protected bromocatechol (**286**). The di-protected catechol (**286**) was then coupled to the lactone template in good yield but the selective cleavage of the benzyl group by mild catalytic hydrogenation failed, yielding a variety of undesired products. With this disappointing result, the simple aromatic (**286**) was further studied. The selective benzyl deprotection of the di-protected bromocatechol (**286**) by mild catalytic hydrogenation was attempted but yielded only 4-bromocatechol (**214**). The silyl group of the di-protected bromocatechol (**286**) also was cleaved and the triflate (**288**) was subsequently formed. The mild hydrogenation of the benzyl-triflate substrate (**288**) was performed to test whether the triflate group could survive the hydrolytic cleavage of the benzyl group. Unfortunately, none of the desired product was isolated and only decomposition was observed, (Scheme 83).

The failure of the benzyl protecting group to be easily cleaved prompted the search for alternate protecting groups. Therefore, 5-bromosalicylaldehyde (**280**) was protected with a methoxymethyl group but the subsequent Dakin

Scheme 83

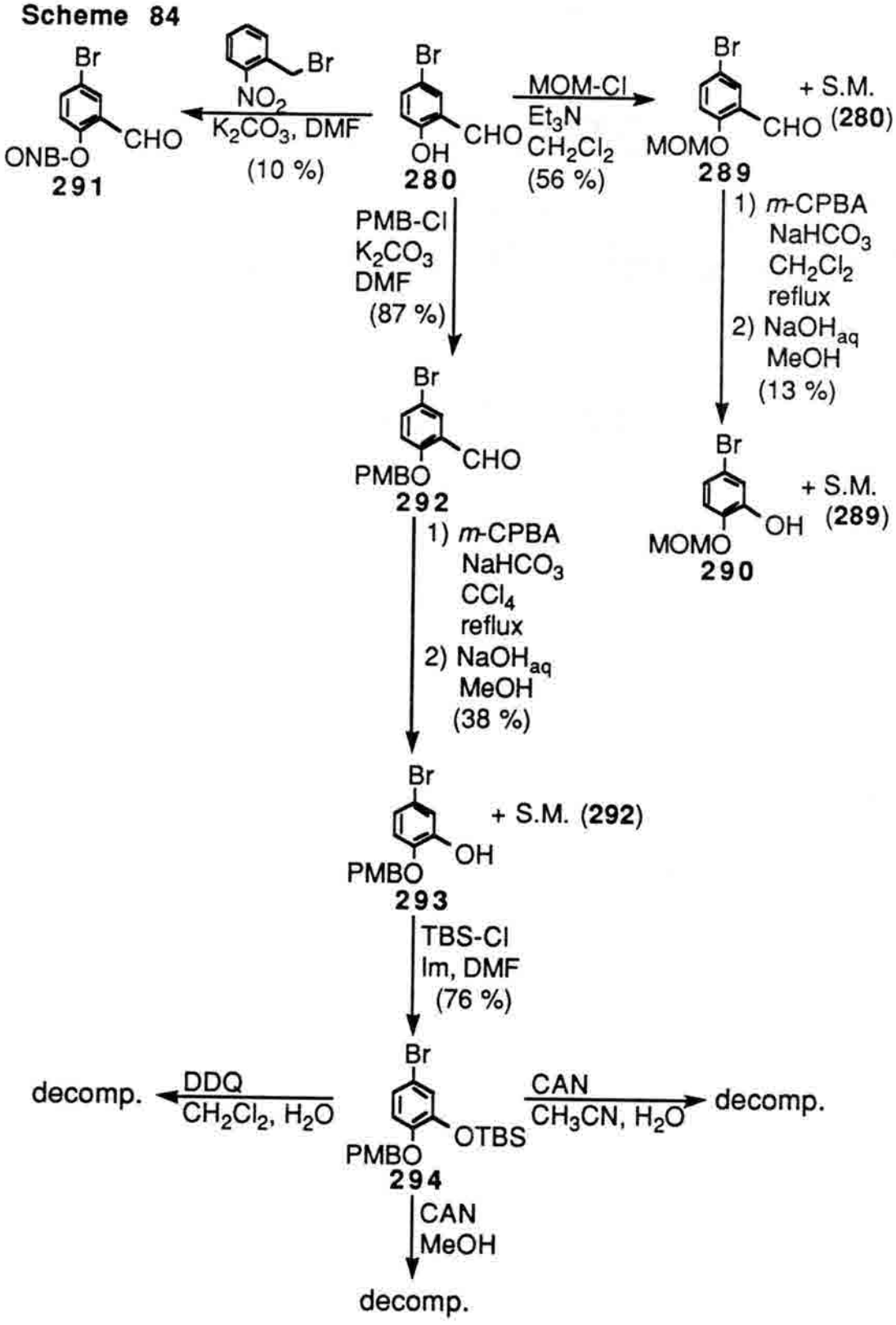

TBS-Cl
Im, DMF
(76 %)
1) m-CPBA
NaHCO3
CH2Cl2
reflux
2) NaOHaq
MeOH
280
281
282
283
PhCH2Br
K2CO3, DMF
(80 %)
284
1) m-CPBA, NaHCO3
CH2Cl2, reflux
2) NaOHaq, MeOH
(83 %)
285
TBS-Cl
Im, DMF
(90 %)
F- buffer
THF
(~100 %)
H2, 5 % Pd/C
MeOH
(68 %)
286
214
Tf2O
i-Pr2NEt
CH2Cl2
-78° C
(96 %)
288
H2, 5 % Pd/C
MeOH
decomposition
1) n-BuLi, Et2O, -15° C
2) BrCuSMe2, Et2O
SMe2, -78° C
3) 171a, THF, Et2O, -78° C
(49 %)
287
H2, 5 % Pd/C
MeOH, THF
no desired
product

oxidation gave only a low yield of the desired MOM-protected catechol derivative (**290**). The protection of 5-bromosalicylaldehyde (**280**) with an *ortho*-nitrobenzyl (ONB) group was only achieved in 10 % yield. This was very disappointing as ONB groups are known to be readily cleaved by photolysis. The use of a *para*-methoxybenzyl (PMB) group in the protection of 5-bromosalicylaldehyde (**280**) was then explored. The Dakin oxidation of the PMB-protected aldehyde (**292**) resulted in moderate yield of the desired catechol derivative (**293**). The silylation of the PMB-protected catechol (**293**) was achieved yielding the desired di-protected product (**294**). The selective cleavage of the PMB group by known oxidative methods[84] only resulted in the decomposition of the starting PMB-TBS derivative, (Scheme 84). The multiple failures in the juggling of phenolic protecting groups prompted the decision to drop the synthesis of the acetate/triflate lactone derivative (**276**) and focus instead on the synthesis of a deoxy-actinoidic acid derivative (**295**), (Scheme 85).

H. Approaches to the Dihydroxy-Actinoidic Acid Derivative

The synthesis of the less sterically hindered actinoidic acid derivative began with the cuprate coupling of the silyl-protected *m*-bromophenol (**279**) to the chiral template in good yield. The cleavage of the silyl group was then achieved with the fluoride buffer solution yielding the desired *m*-phenol (**297**). The lactone phenol derivative (**297**) was then converted to the triflate (**278**) without racemization in excellent yield with triflic anhydride and Hunig's base. The triflate (**278**) was then converted to the trimethyltin reagent (**298**) with hexamethylditin and a catalytic amount of tetrakis (triphenylphosphine) palladium(0) in very low yield. The small amount of the trimethyltin reagent (**298**) recovered was then reacted with the acetate-protected bromobenzyl

Scheme 84


Br
NO2
Br
K2CO3, DMF
(10 %)
ONB-O
CHO
291
Br
CHO
OH
280
MOM-Cl
Et3N
CH2Cl2
(56 %)
Br
+ S.M.
CHO (280)
MOMO
289
1) m-CPBA
NaHCO3
CH2Cl2
reflux
2) NaOHaq
MeOH
(13 %)
PMB-Cl
K2CO3
DMF
(87 %)
Br
CHO
PMBO
292
Br
+ S.M.
OH (289)
MOMO
290
1) m-CPBA
NaHCO3
CCl4
reflux
2) NaOHaq
MeOH
(38 %)
Br
+ S.M. (292)
OH
PMBO
293
TBS-Cl
Im, DMF
(76 %)
Br
decomp.
DDQ
CH2Cl2, H2O
CAN
CH3CN, H2O
decomp.
OTBS
PMBO
294
CAN
MeOH
decomp.

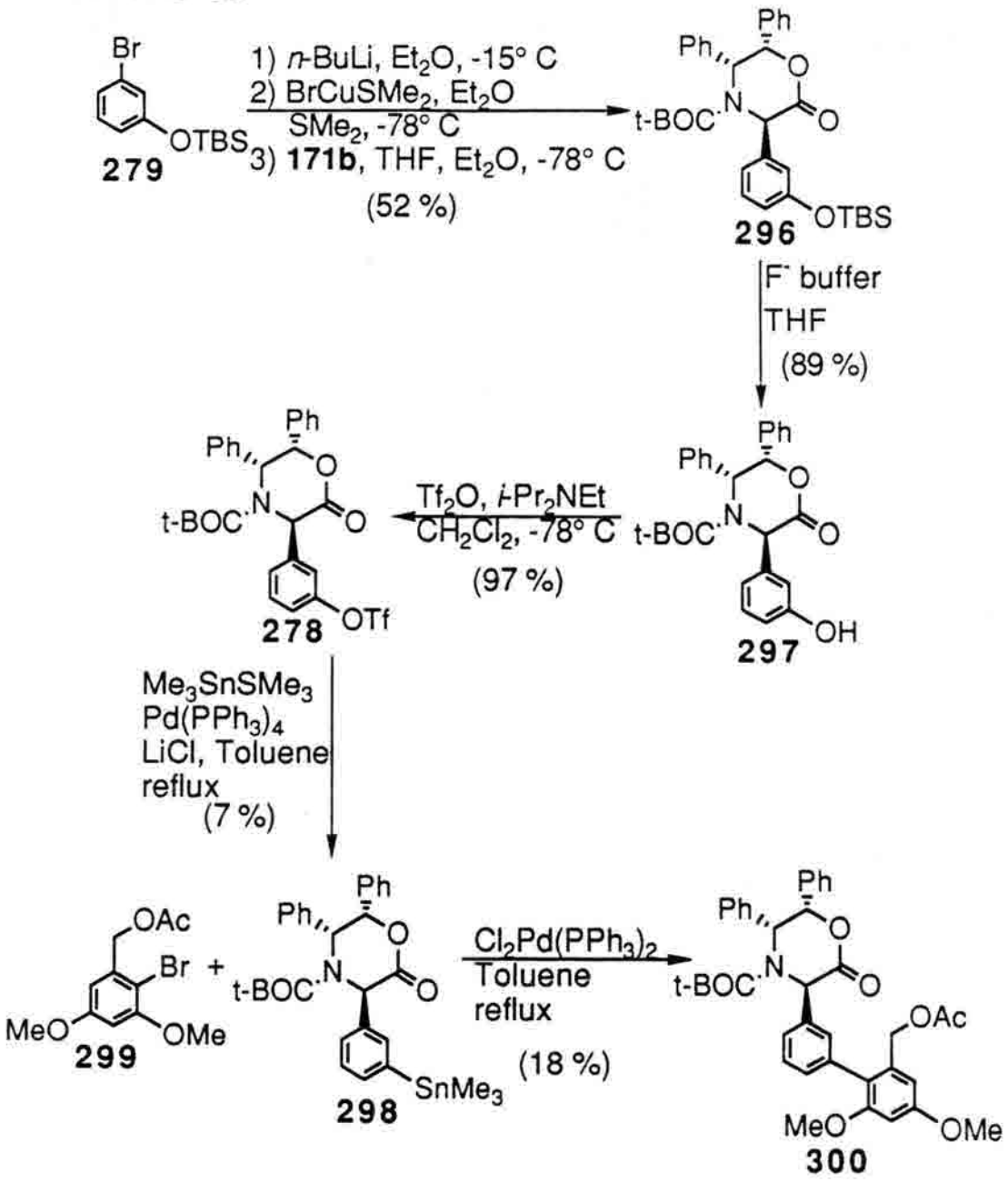
Scheme 85

295

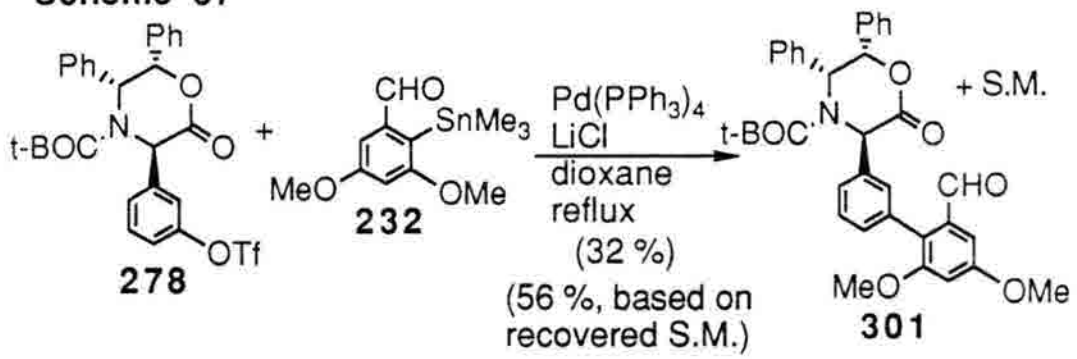
alcohol (**299**) in hot toluene with a Pd(II) catalyst.[82c] The desired biphenyl product (**300**) was formed in only 18 % yield, (Scheme 86).

Finally, the *m*-triflate lactone (**278**) was reacted with the trimethyltin benzaldehyde derivative (**232**) under standard Stille conditions and resulted in the desired biphenyl product (**301**) in 32 % yield or 56 % yield based on recovered starting material, (Scheme 87). This biphenyl coupling worked well and with reproducible results on a small scale (see Chapter IV) but all attempts at scaling the reaction up resulted in vastly reduced yields. Therefore, to obtain preparatively useful amounts of the biphenyl (**301**), multiple small scale couplings were performed simultaneously. Upon completion of the individual reactions, all the reaction mixtures were combined for the work-up and purification. Purification was achieved by column chromatography where the product (**301**) and the two starting materials (**232, 279**) were isolated along with a small but significant amount of 3,5-dimethoxybenzaldehyde (**304**). Variable temperature proton NMR experiments on the biphenyl product (**301**) indicated that the atropisomers arising from the biaryl bond equilibrated at approximately 50° C. At room temperature the atropisomers were not fully resolved which made an accurate calculation of the activation barrier to biaryl bond rotation difficult to determine. With the moderate success of this biphenyl coupling, it became possible to carry this synthesis forward to the formation of the second amino acid residue via a Strecker synthesis.

Scheme 86


Br
OTBS
279
1) n-BuLi, Et2O, -15° C
2) BrCuSMe2, Et2O
SMe2, -78° C
3) 171b, THF, Et2O, -78° C
(52 %)
Ph
Ph
N
O
O
t-BOC
OTBS
296
F- buffer
THF
(89 %)
Tf2O, i-Pr2NEt
CH2Cl2, -78° C
(97 %)
OTf
278
OH
297
Me3SnSMe3
Pd(PPh3)4
LiCl, Toluene
reflux
(7 %)
OAc
Br
MeO
OMe
299
SnMe3
298
Cl2Pd(PPh3)2
Toluene
reflux
(18 %)
OAc
MeO
OMe
300

Scheme 87

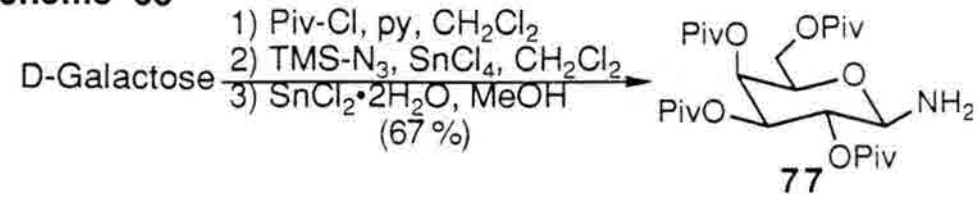


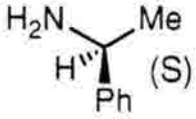
I. The Strecker Syntheses

The utilization of the Strecker synthesis in forming the desired L-amino acid residue of the dihydroxy actinoidic acid derivative (**295**) gave very disappointing results. As discussed in Chapter I, there are very few asymmetric Strecker syntheses available and most of those are designed for the synthesis of D-arylglycines. Only two methods are known for the asymmetric Strecker synthesis of D-arylglycines, the Kunz method[46] and the Panse method,[42] (see Chapter I). As an alternative to these known methods, the *erythro*-diphenyl amino alcohol (**168**), the starting material for the oxazinone template (**169, 170**), was tested for use as a chiral amine in a new asymmetric Strecker reaction. All of these methods were used in a model study with electron-rich benzaldehydes (**302**).

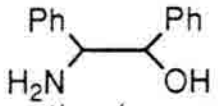
As stated in Chapter I, key to the success of the asymmetric Strecker reaction is the formation of the Schiff base from the condensation of the chiral amine and the benzaldehyde. The cyanide source is then added to the chiral Schiff base in a stereoselective manner giving the asymmetric amino nitrile. In the model system, electron-rich benzaldehydes (**302**) were reacted with the chiral amines (**303**) but there was no evidence that the Schiff base had been formed under any of the conditions used, (Scheme 88). This indicated that the electron-rich

Scheme 88



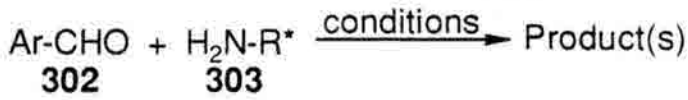


61



erythro (racemic)

168



302 **303**

Ar	H_2N-R*	Conditions	Product(s)
p-Methoxyphenyl-	**77**	1) *p*-TsOH, $CHCl_3$ 2) $ZnCl_2$, TMS-CN, $CHCl_3$	S.M.
p-Methoxyphenyl-	**77**	1) Pentane, 4 Å molec. sieves silica gel 2) TMS-CN, $ZnCl_2$, $CHCl_3$	decomp.
2-Bromo-3,5-dimethoxyphenyl-	**77**	1) Pentane, 4 Å molec. sieves silica gel 2) TMS-CN, $ZnCl_2$, $CHCl_3$	N.R.
3,5-Dimethoxyphenyl-	**77**	1) *p*-TsOH, Ph-H, Δ, (-H_2O) 2) TMS-CN, $ZnCl_2$, $CHCl_3$	S.M.
3,5-Dimethoxyphenyl-	**77**	1) TMS-CN 2) $ZnCl_2$, $CHCl_3$	S.M.
3,5-Dimethoxyphenyl-	**61**	1) Ph-H, Δ, (-H_2O) 2) CNBr, Et_2O 3) Et_3N 4) 6 N HCl_{aq}, Δ	decomp.
3,5-Dimethoxyphenyl-	**61**	Ph-H, Δ, (-H_2O)	decomp.
3,5-Dimethoxyphenyl-	**61**	*p*-TsOH, Ph-H, Δ, (-H_2O)	decomp.

Scheme 88 (cont.)

Ar-CHO + H_2N-R* $\xrightarrow{\text{conditions}}$ Products

302 **303**

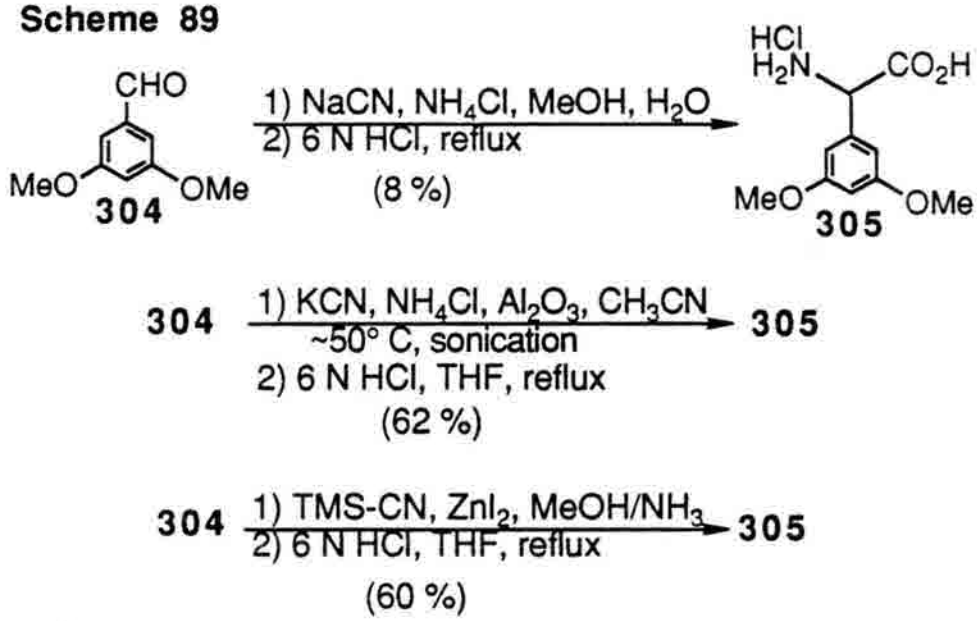
Ar	H_2N-R*	Conditions	Product(s)
3,5-Dimethoxyphenyl-	**168**	TMS-CN, $ZnCl_2$, $CHCl_3$	S.M.
3,5-Dimethoxyphenyl-	**168**	1) Ph-H, Δ, (-H_2O) 2) TMS-CN, $ZnCl_2$, $CHCl_3$ 3) 6 N HCl_{aq}, THF, Δ 4) $NaIO_4$, H_2O, pH~3	decomp.
3,5-Dimethoxyphenyl-	**168**	1) *p*-TsOH, Ph-H, Δ, (-H_2O) 2) TMS-CN, $ZnCl_2$, $CHCl_3$	S.M.
3,5-Dimethoxyphenyl-	**168**	1) Ph-H, Δ, (-H_2O) 2) TMS-CN, $ZnCl_2$, $CHCl_3$	decomp.
3,5-Dimethoxyphenyl-	**168**	TMS-CN, $ZnCl_2$, $CDCl_3$	decomp.
3,5-Dimethoxyphenyl-	**168**	NaCN, MeOH, HCl_{aq}	S.M. + cyanohydrin
3,5-Dimethoxyphenyl-	**168**	KCN, Al_2O_3, CH_3CN sonication	S.M.

benzaldehydes (**302**) are not electrophilic enough to react with the available chiral amines (**303**). These results lead to the exploration of racemic Strecker syntheses.

The use of the electron-rich 3,5-dimethoxybenzaldehyde (**304**) in a classical Strecker synthesis with ammonium chloride and sodium cyanide resulted in the desired amino acid (**305**) in low yield after acidic hydrolysis. Two modern modifications of the Strecker synthesis that were known to have success with electron-rich benzaldehydes were then attempted. 3,5-Dimethoxybenzaldehyde (**304**) was reacted with potassium cyanide and ammonium chloride in acetonitrile with alumina as a solid catalytic support at ~50° C with ultrasonic irradiation for 36 hours.[24] The desired racemic

arylglycine product (**305**) was isolated in a 62 % yield. In an alternate method, 3,5-dimethoxybenzaldehyde (**304**) was stirred with trimethylsilylcyanide and zinc iodide for 15 minutes when a solution of saturated methanolic ammonia was added.[23] The desired racemic amino acid (**305**) was isolated after acidic hydrolysis in a 60 % yield, (Scheme 89). These two results showed that it is possible to perform a racemic Strecker reaction on electron-rich benzaldehydes.

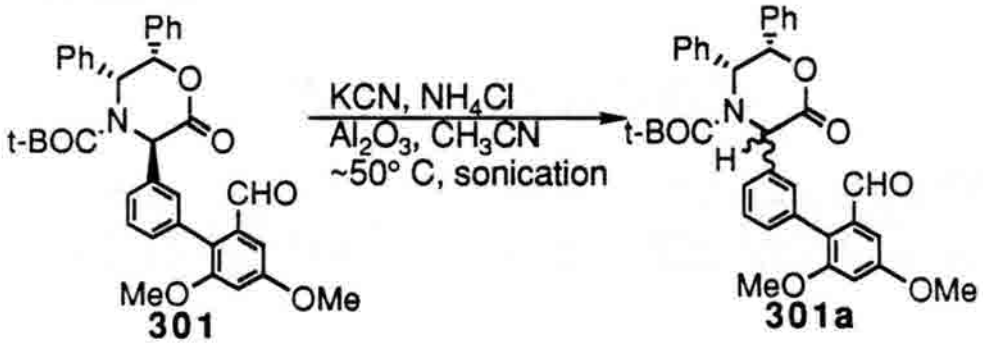
Scheme 89



The two successful racemic Strecker reaction conditions were then applied to the biphenyl aldehyde (**301**). The sonication reaction yielded no evidence of the desired product and upon close examination of the recovered starting material (**301a**), it was found that the α-center of the lactone had racemized. This disturbing resulted ended the use of sonication to promote the Strecker reaction. Two different methods of the TMS-CN reaction were attempted. In the first attempt, the lactone (**301**) was solubilized in THF and then the TMS-CN and ZnI_2 were added followed by the addition of methanolic ammonia. None of

the desired product was isolated from this reaction giving only several decomposition products and a small amount of unreacted starting material (**301**). In the final attempt, the biphenyl (**301**) was partially solubilized in an excess of TMS-CN in the presence of ZnI_2 before the methanolic ammonia was added. Only decomposition was observed under these conditions, (Scheme 90). The decomposition observed in these reactions may be due the ZnI_2 and TMS-CN which may act as Lewis acids cause the cleavage of the t-BOC group. The resulting amine biphenyl product may not be stable to the reaction conditions resulting in the observed decomposition. With these failed Strecker attempts, the synthesis of actinoidic acid and actinoidic acid derivatives was suspended until such time as an appropriate Strecker synthesis is developed.

Scheme 90



301 1) TMS-CN, ZnI_2, MeOH, THF; 2) $MeOH/NH_3$, 60° C

301 1) TMS-CN, ZnI_2; 2) $MeOH/NH_3$, 60° C → Decomposition

J. Conclusion

The preceding chapter focused on the initial aspects of the synthesis of actinoidic acid and actinoidic acid derivatives. While this work failed to achieve the ultimate goal of the research, many important aspects of the synthesis were

developed. The synthesis of lactone triflates were achieved without racemization at the α-center of the arylglycine derivatives. Several biphenyl couplings were also achieved on very interesting substrates and the scope of the Stille biphenyl coupling reaction was more fully explored. The pressing need for an asymmetric Strecker synthesis that will produce both D- and L-arylglycines from electron-rich benzaldehydes was also uncovered. The application of the new methodology developed herein will hopefully be combined with future developments and result in the asymmetric synthesis of actinoidic acid derivatives or even the elusive target, actinoidic acid.

Chapter IV

Experimental Section

A. General Information

^{1}H NMR spectra were obtained on the following instruments: Brucker WP-200SY 200 MHz Spectrometer or Brucker WP-270SY 270 MHz Spectrometer. Chemical shifts are reported in parts per million downfield from the internal standard.

Infared spectra were recorded on Perkin-Elmer 1600 Series FTIR and reported as ν_{max} in cm^{-1}.

Low resolution mass spectra were obtained on a V. G. Micromass Ltd., Model 16F spectrometer.

Uncorrected melting points were determined in an open-ended capillary tube on a "Mel-Temp" apparatus.

Optical rotations were obtained on a Rudolph Research Autopol® III Automatic Polarimeter at wavelength 589 nm (sodium D line) using a 1.0 decimeter cell with a total volume of 1 mL. Specific rotations, $[\alpha]_D$, are reported in degrees per decimeter at the specific temperature and concentration (c) given in grams per 100 mL of solvent.

Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona.

B. Chromatography

Thin layer chromatography (TLC) was performed on 0.25 mm E. Merck precoated silica gel glass plates. Visualization on TLC was achieved with ultraviolet light and/or heating of TLC plates submerged in a 5 % solution of

phosphomolybdic acid in 95 % ethanol. Ninhydrin and 2,4-DNP sprays were also used to visualize TLC plates when appropriate. Preparative thin layer chromatography (PTLC) was performed using the same TLC plates as described above. Column chromatography was performed using Merck silica gel grade 60, 230-400 mesh, 60 Å.

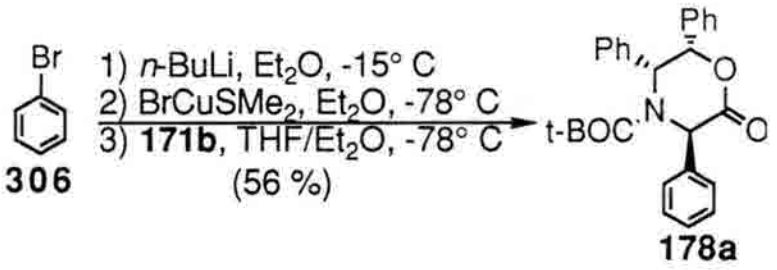
C. Reagents and Solvents

Reagents and solvents were of commercial grade and used as supplied with the following exceptions. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone. Dry carbon tetrachloride and methylene chloride were distilled over CaH_2. Dry diethyl ether, dimethyl sulfide and 1,4-dioxane were distilled over sodium and stored over 4 Å molecular sieves. Dry chloroform, toluene, benzene, and acetone were distilled over P_2O_5 and stored over 4 Å molecular sieves. N,N'-Dimethylformamide (DMF), N-methylpyrrolidinone (NMP) and acetonitrile were dried over 4 Å molecular sieves. Triethylamine and pyridine were stored over KOH pellets. N,N'-Diisopropylethylamine was distilled from solid NaOH and stored over KOH pellets. N-Bromosuccinimide (NBS) was recrystallized from water, air dried on a Buchner funnel and further dried *in vacuo* and stored under N_2 in the refrigerator. 1.0 M Zinc chloride solutions in THF were prepared by heating solid $ZnCl_2$ under vacuum to a glass and, upon cooling to room temperature, the $ZnCl_2$ was taken up in dry THF. $Pd(PPh_3)_4$ was prepared from $PdCl_2$ and PPh_3 via the method of Coulson[85] and stored under N_2, in the dark, in the refrigerator.

D. General Experimental Considerations

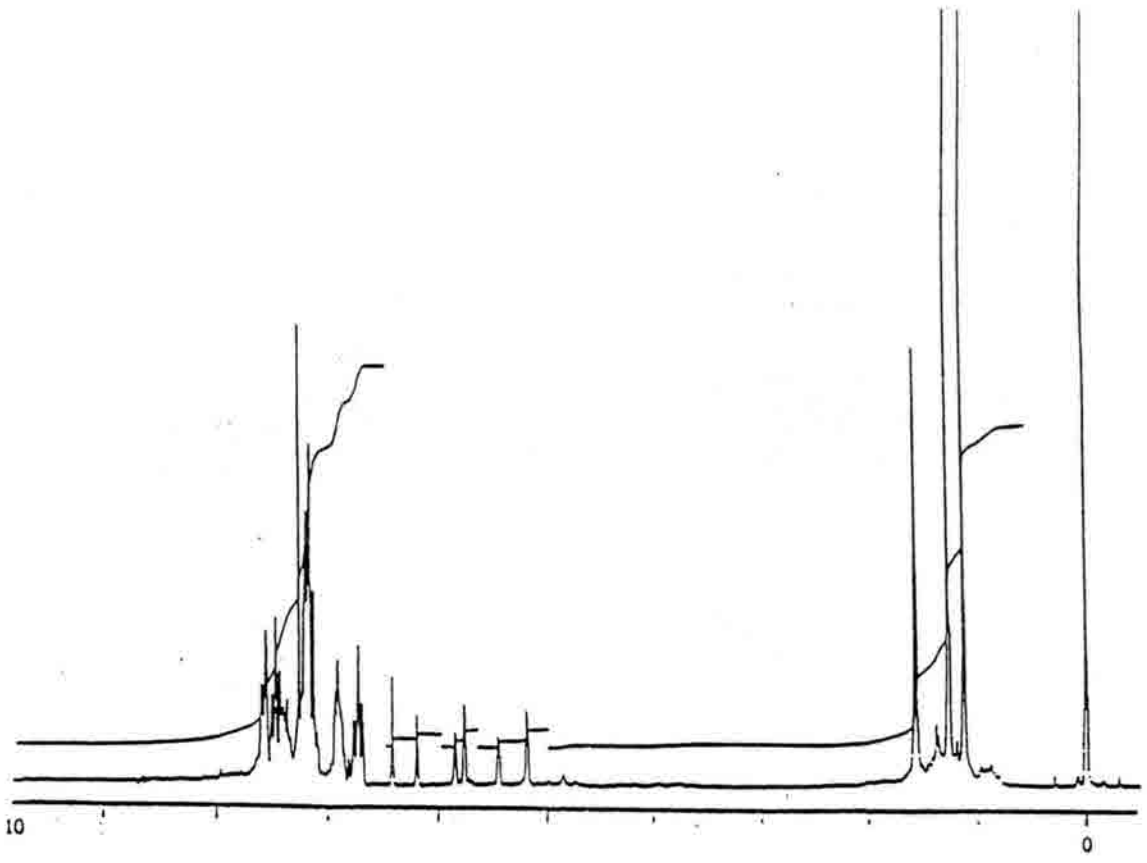
All moisture-sensitive reactions were carried out in glassware that was flame-dried under high-vacuum (0.5-2.0 mmHg) and then purged with N_2. All reactions were magnetically stirred with a Teflon coated stirring bar unless stated otherwise. The following low-temperature baths were used: 0° C (ice-

water), -15° C (ice-methanol), -78° C (acetone-dry ice). The term "evaporation" refers to solvent removal using a Buchi Rotavapor.

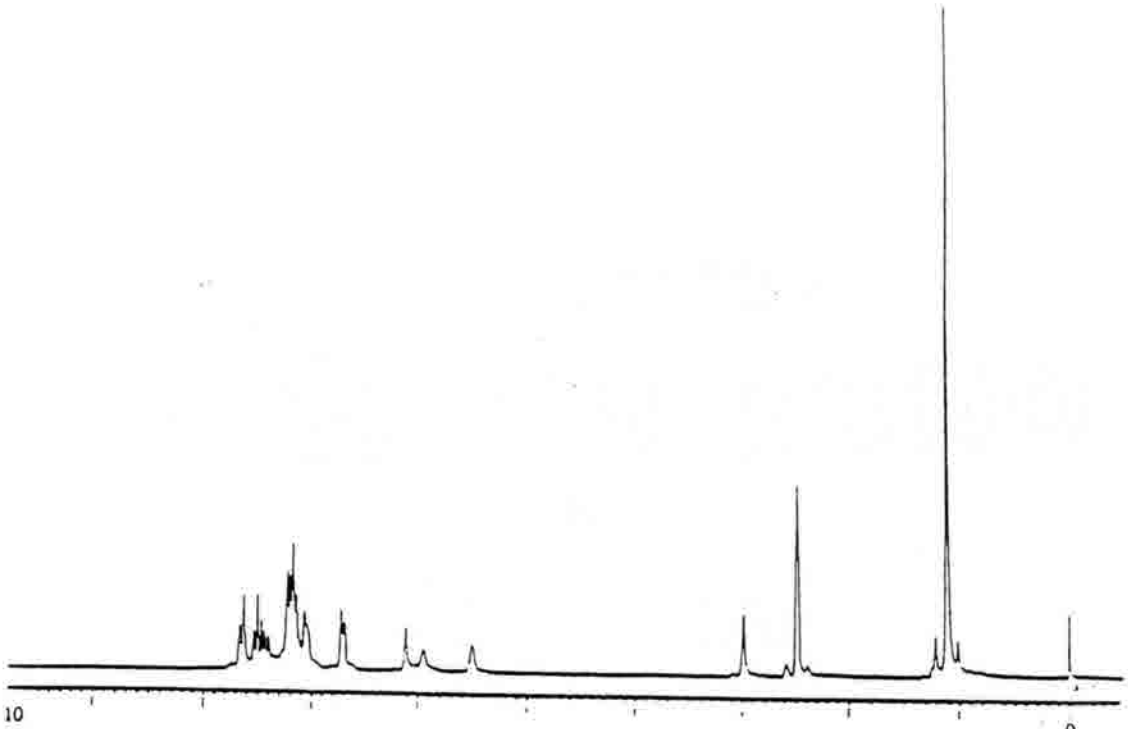


(3R,5R,6S)-4-*tert*-butoxycarbonyl-2,3,5,6-tetrahydro-3,5,6-triphenyl-1,4-oxazin-2-one (178a, Ar = Ph). To a stirred solution of bromobenzene (0.84 mL, 8.00 mmoles, 4.00 equiv.) in dry Et_2O (4.00 mL) cooled to -15° C was added *n*-BuLi (4.20 mL, 8.40 mmoles, 4.20 equiv., 2.0 M in hexanes) dropwise. The resulting solution was stirred at -15° C for 30 min when additional dry Et_2O (5.00 mL) was added with copper bromide dimethylsulfide (0.822 g, 4.00 mmoles, 2.00 equiv.). The resulting mixture was stirred at -78° C for 3 h when a solution of the (3R,5R,6S)-3-bromo-4-*tert*-butoxycarbonyl-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (**171b**) (0.864 g, 2.00 mmoles, 1.00 equiv.) in a 1:1 solution of dry Et_2O and dry THF (62.00 mL) was added via cannula. Compound **171b** was synthesized from compound **169b** by standard and previously reported methodology.[67] The resulting mixture was stirred at -78° C for 1 h when a saturated solution of NH_4Cl (40 mL) was added at -78° C. The resulting mixture was allowed to warm to room temp., separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 40 mL). The combined organic layers were washed with 10% HCl (2 x 40 mL), dried (Na_2SO_4), filtered, and evaporated. The residue was separated via column chromatography (7:2:1, Hex/$CHCl_3$/EtOAc) and recrystallized from EtOAc/hexanes yielding 484 mg (56 %) of the desired

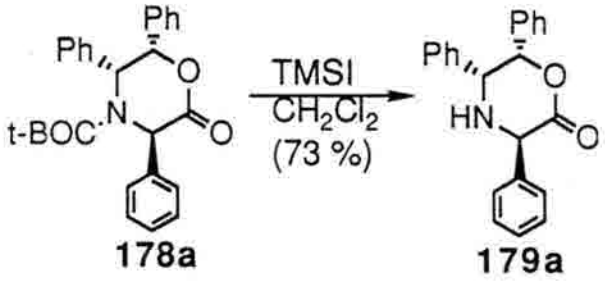
product (**178a**) as a white solid. ^{1}H NMR: (270 MHz) ($CDCl_3$) δ TMS: 1.33-1.13 (m, 9 H), 5.18 (d, J=3.1 Hz) and 5.45 (d, J=3.0 Hz) (1 H), 5.76 (d, J=3.1 Hz) and 5.85 (d, J=3.0 Hz) (1 H), 6.19 (s) and 6.42 (s) (1 H), 6.68-7.59 (m, 15 H). ^{1}H NMR: (200 MHz) (DMSO-d_6 at 380 K) δ DMSO: 1.11 (s, 9 H), 5.50 (br. s, 1 H), 5.95 (br. s, 1 H), 6.11 (s, 1 H), 6.68-6.72 (m, 2H) 7.02-7.66 (m, 13 H). IR: (NaCl, $CHCl_3$) 3020, 1755, 1695, 1375, 1210, 1150, 1110, 735, 687, 650 cm^{-1}. MS: *m/e* (relative intensity) CI (NH_3): 428 (0.2), 390 (29.4), 329 (42.6), 284 (76.5), 196 (57.7), 106 (100.0). Mp: 227-228° C (recryst. EtOAc/hexanes). Anal. Calcd. for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.34; N, 3.26. Found: C, 75.52; H, 6.61; N, 2.99. $[\alpha]^{25}_D$: + 78.2° (*c* 1.00, CH_2Cl_2).



270 MHz ^{1}H NMR of **178a** in $CDCl_3$ at room temperature.



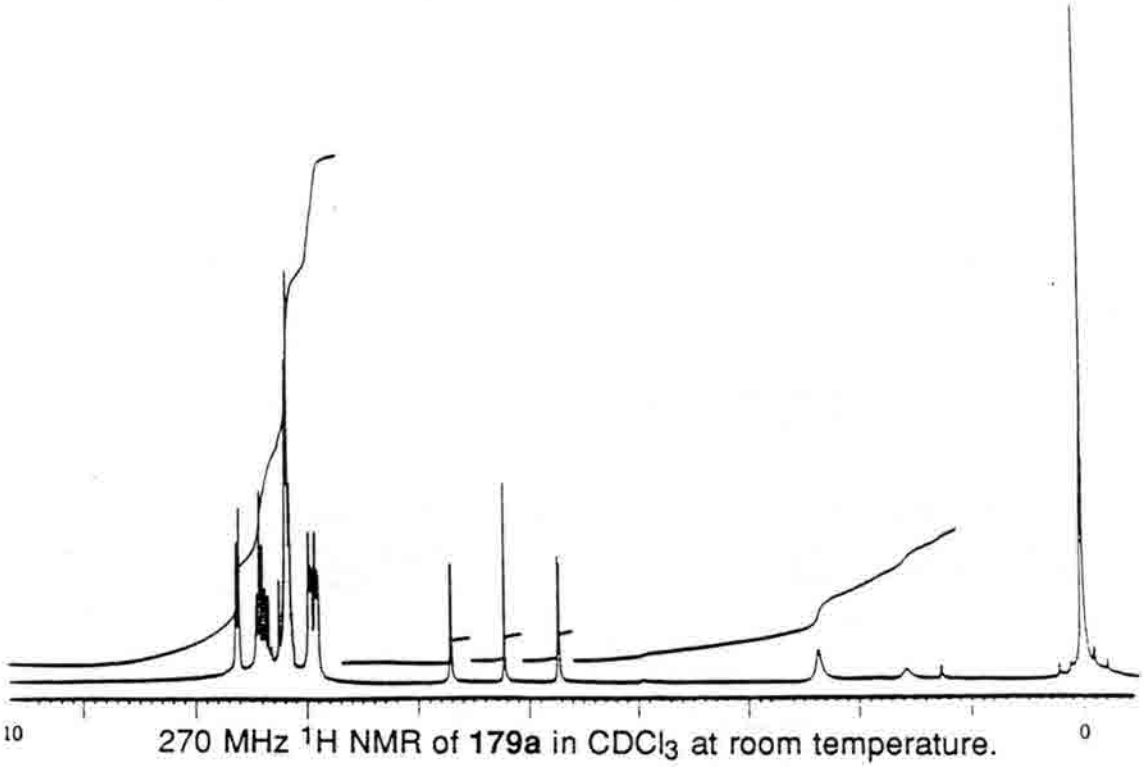
200 MHz ^{1}H NMR of **178a** in d_6-DMSO at 380 K.



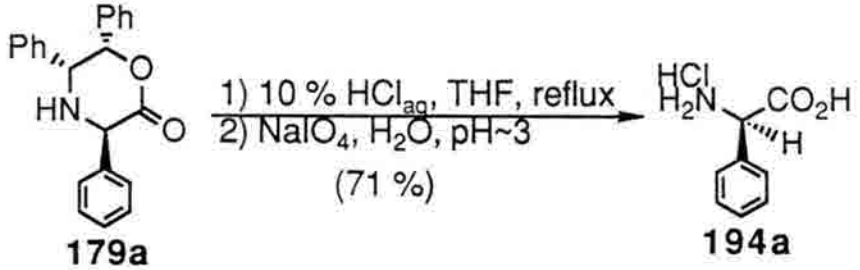
178a **179a**

(3R,5R,6S)-2,3,5,6-tetrahydro-3,5,6-triphenyl-1,4-oxazin-2-one (179a, Ar = Ph).[86] To a stirred solution of **178a** (250 mg, 0.58 mmoles, 1.00 equiv.) in dry CH_2Cl_2 (5.80 mL) was added trimethylsilyl iodide (0.20 mL, 1.40 mmoles, 2.40 equiv.). The resulting orange solution was stirred at room temperature for 10 min when water (10 mL) was added. The resulting mixture was separated and the aqueous layer extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were washed with 1 M $Na_2S_2O_3$ (2 x 20 mL), dried (Na_2SO_4), filtered and evaporated. The residue was separated via silica gel

column chromatography (5:3:2, Hex/$CHCl_3$/EtOAc) yielding 139 mg (73 %) of the desired product (**179a**) as a white foam. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 2.35 (br. s, 1 H), 4.72 (d, J=4.2 Hz, 1 H), 5.21 (s, 1 H), 5.70 (d, J=3.9 Hz, 1 H), 6.89-7.63 (m, 15 H). IR: (NaCl, $CHCl_3$) 3364, 3029, 2924, 2851, 2359, 1740, 1494, 1453, 1259, 1181, 1065, 757, 694, 689 cm^{-1}. MS: *m/e* (relative intensity) CI (NH_3): 330 (23.4), 329 (100.0), 327 (71.9), 283 (71.9), 251 (43.7), 196 (51.6), 106 (60.9), 71 (28), 35 (100.0), 31.9 (64.1). $[\alpha]^{25}_D$: +116.3° (*c* 0.32, CH_2Cl_2).



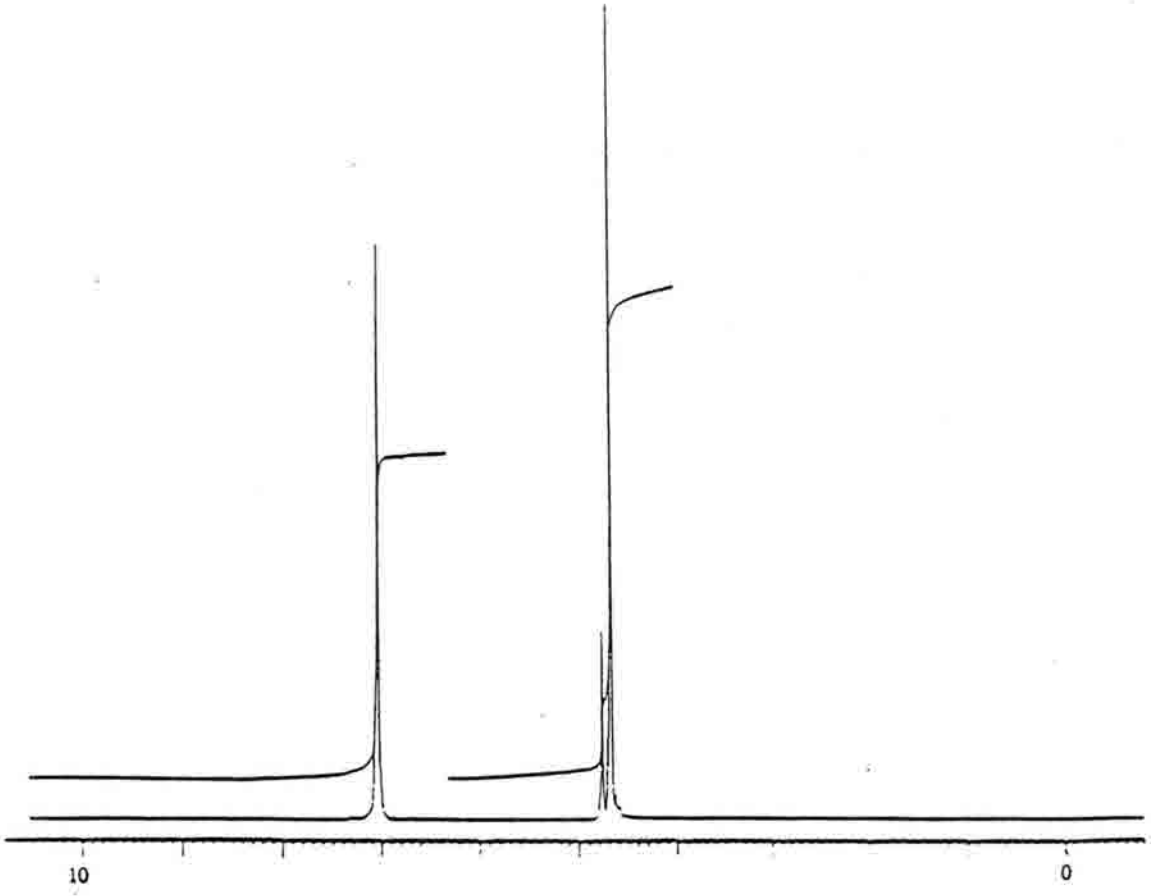
270 MHz ^1H NMR of **179a** in $CDCl_3$ at room temperature.



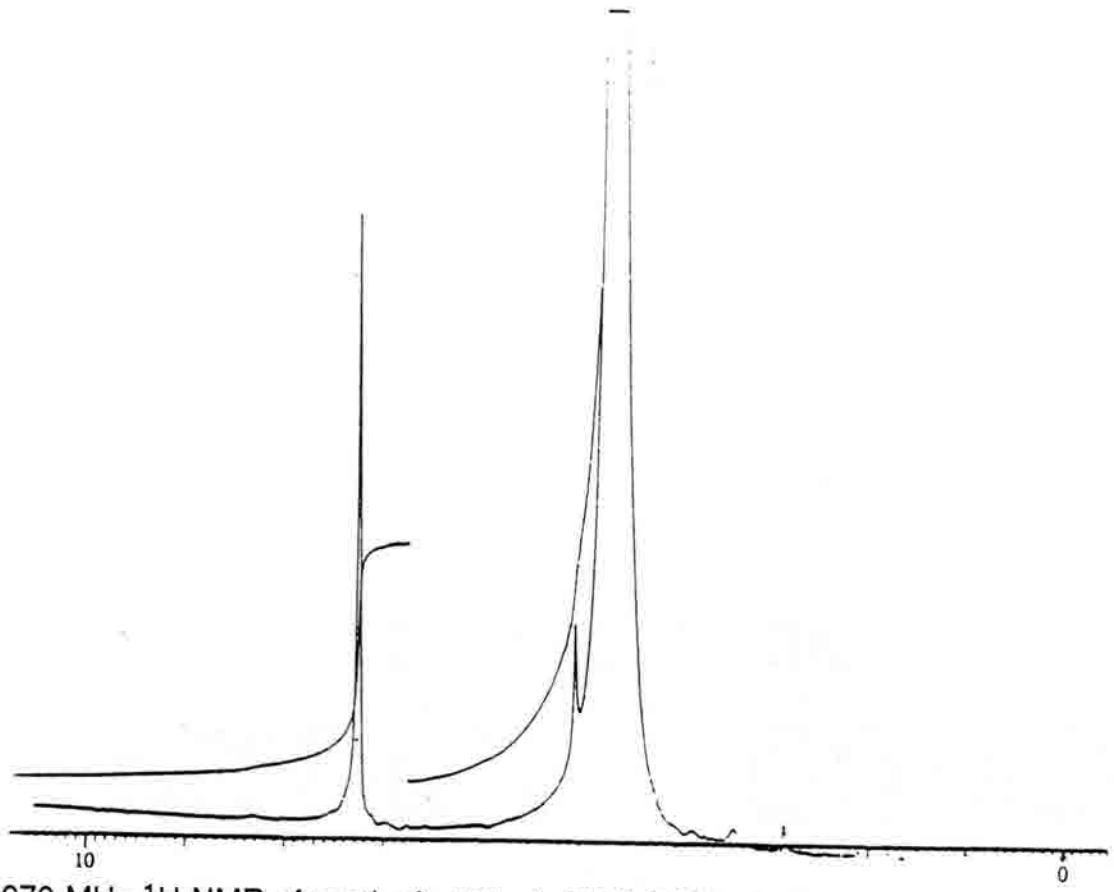
179a **194a**

D-Phenylglycine hydrochloride (194a, Ar = Ph).[44] A stirred solution of **179a** (93.8 mg, 0.285 mmoles, 1.00 equiv.) in THF (5.00 mL) and 10% HCl

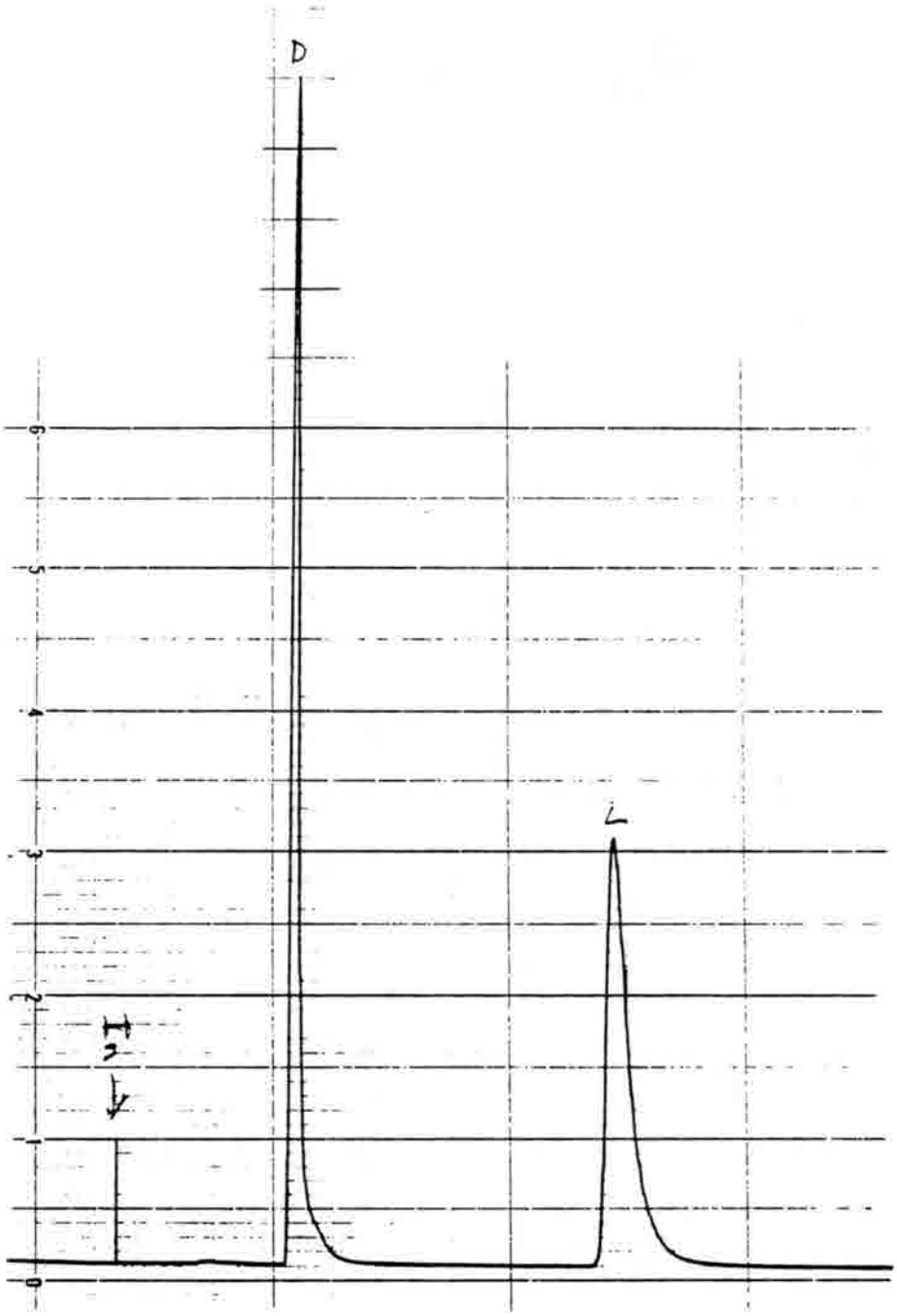
(20.00 mL) was heated at reflux for 15 min. Upon cooling, the solution was evaporated, taken up in distilled water (7.50 mL) and sodium periodate (134 mg, 0.627 mmoles, 2.2 equiv.). The pH was adjusted to 3.0 and the resulting solution was stirred at room temp. for 36 h. The pH of the resulting suspension was adjusted to approximately 5.5 with the dropwise addition of 0.1 N NaOH, 10 drops of ethylene glycol were added to destroy excess $NaIO_4$, and was stirred for 15 min. The resulting mixture was washed with EtOAc (3 x 25 mL) and evaporated. The resulting white solid was separated via anion exchange chromatography (Amberlite IRA-45) yielding 38 mg (71%) of D-phenylglycine hydrochloride (**194a**) as a white amorphous solid. Spectral data matches that of authentic material (Sigma).



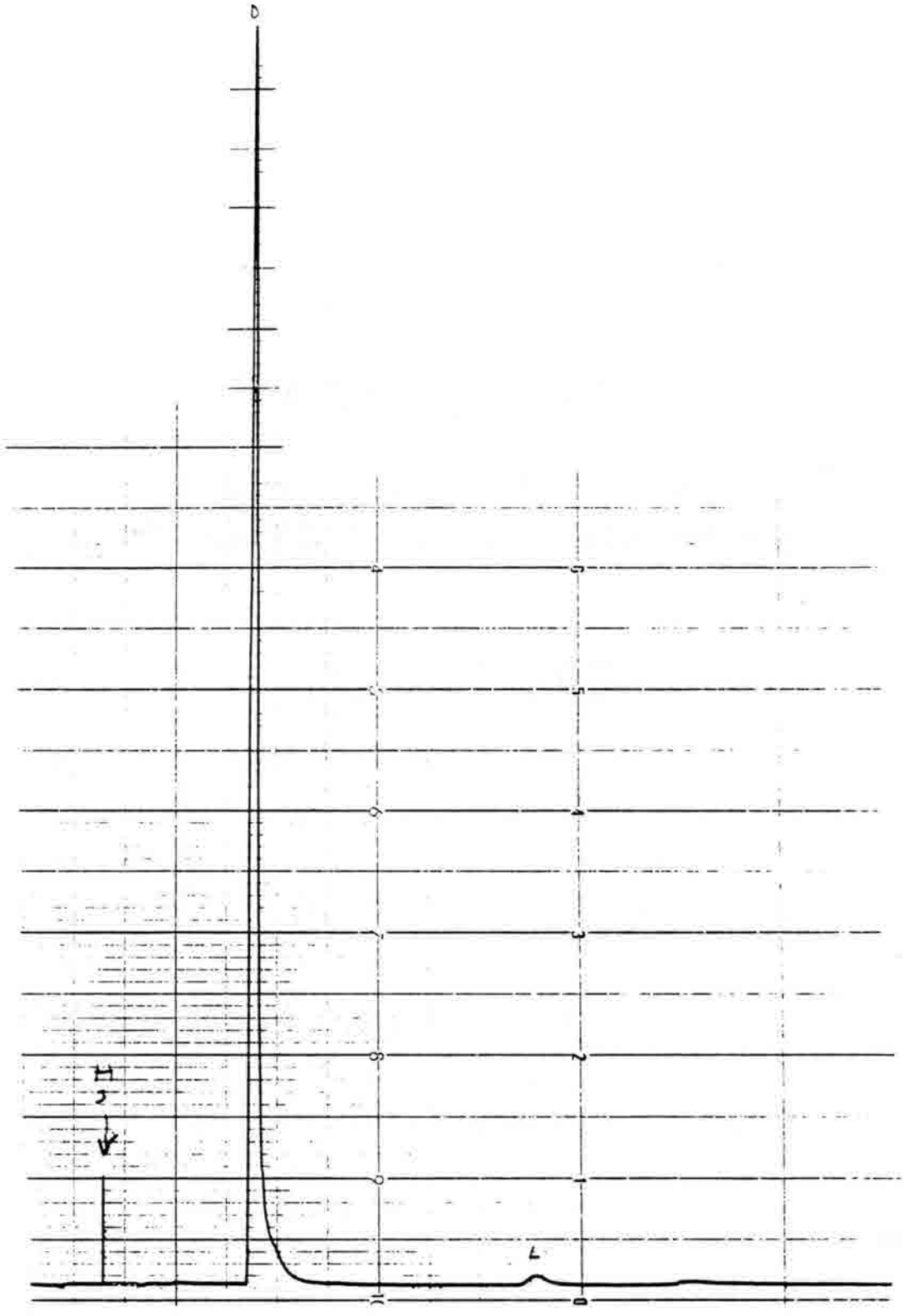
270 MHz ^1H NMR of authentic **194a** in 35 % DCl in D_2O at room temperature.



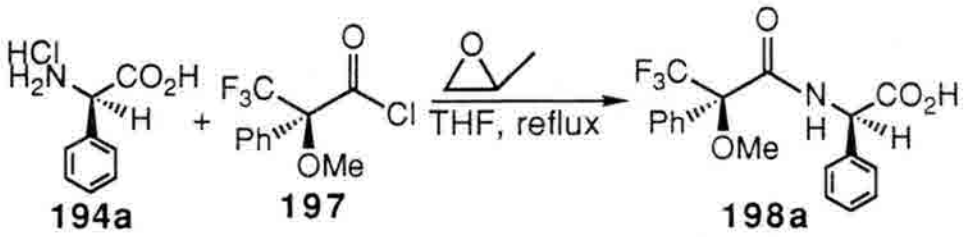
270 MHz ^{1}H NMR of synthetic **194a** in 35 % DCl in D_2O at room temperature.



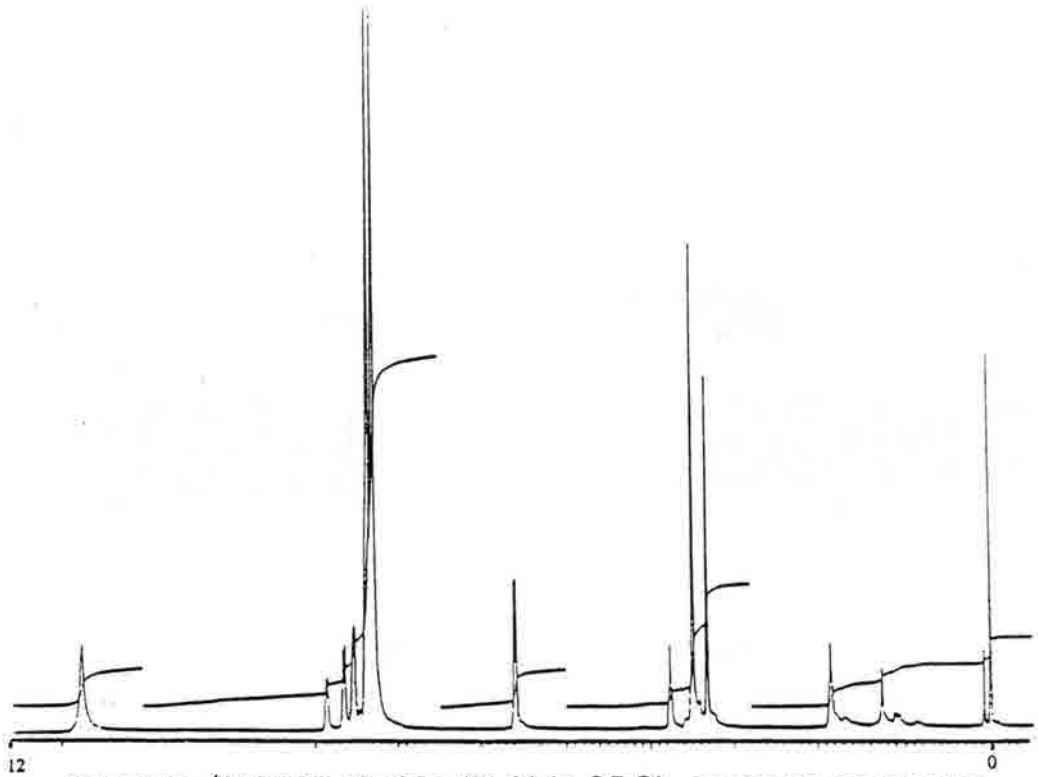
HPLC trace of D,L-Phenylglycine (**194a**), Crownpak CR(+) chiral column; perchloric acid buffer (pH 2); flow rate: 1.00 mL/min.; chart speed: 1.0 cm/s.



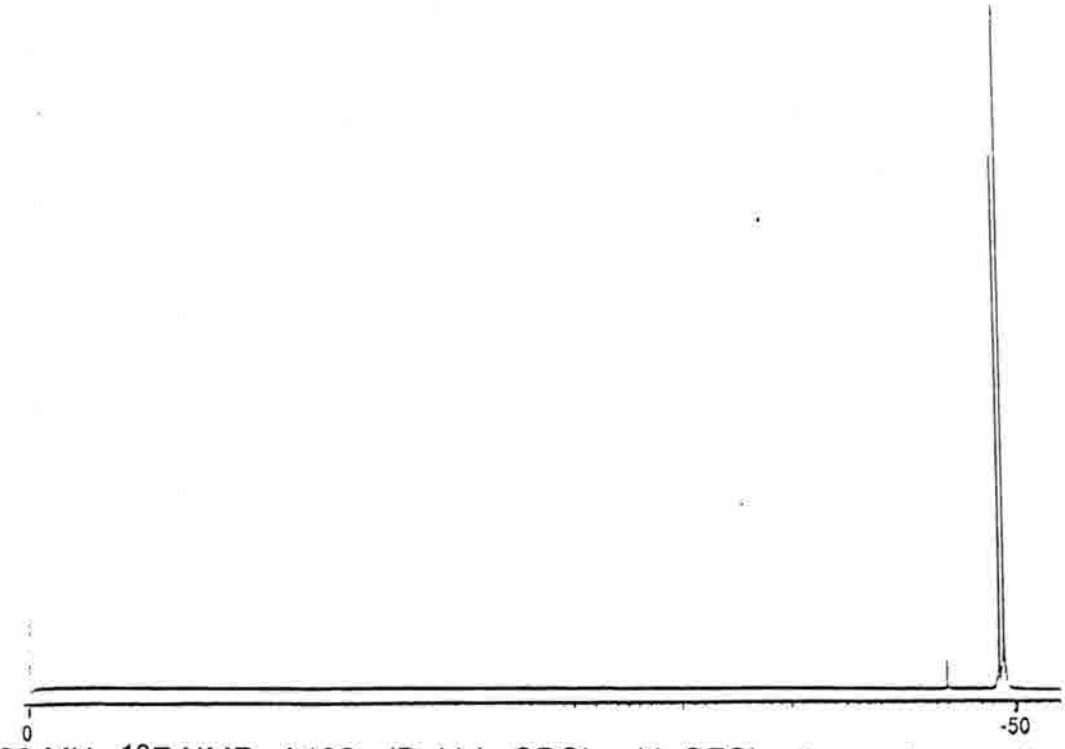
HPLC trace of D-Phenylglycine (**194a**), Crownpak CR(+) chiral column; perchloric acid buffer (pH 2); flow rate: 1.00 mL/min.; chart speed: 1.0 cm/s.



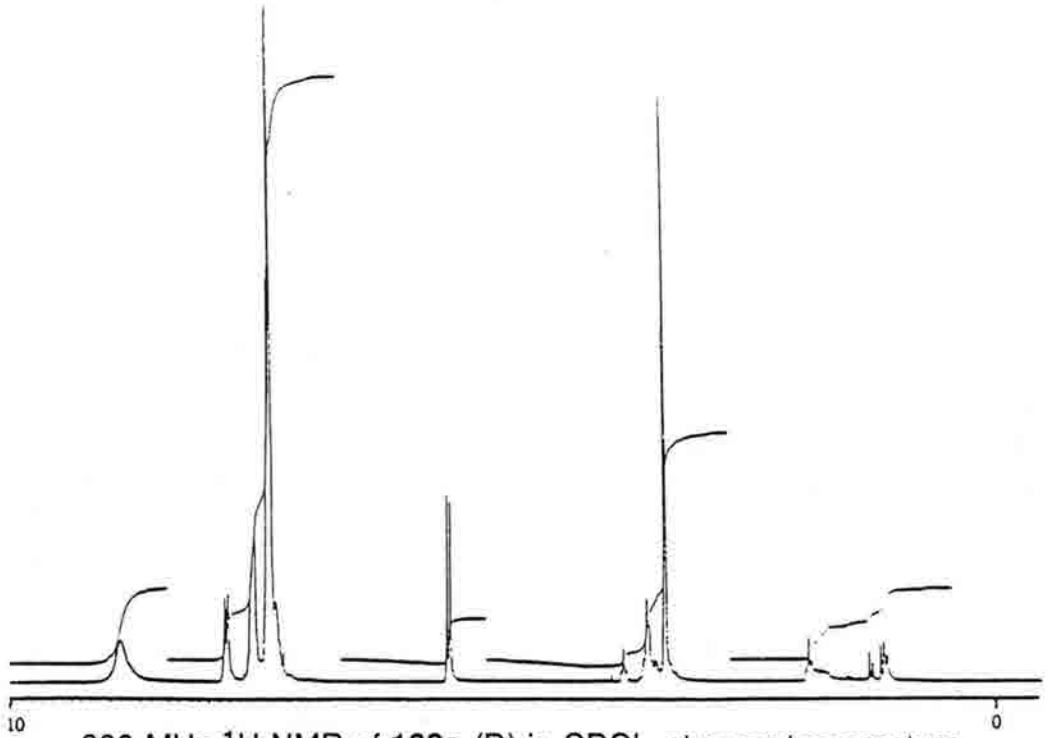
((2-Methoxy-3,3,3-trifluoro-1-oxo-2-phenylpropyl)amino) benzenacetic acid (198a, Ar = Ph).[87] To a stirred suspension of synthetic phenylglycine in a mixture of inorganic salts (2 mg, 0.014 mmoles, 1.00 equiv.) in dry tetrahydrofuran (0.50 mL) was added propylene oxide (4 μL, 0.056 mmoles, 4.00 equiv.) and (S)-(-)-α-methoxy-α-(trifluoromethyl) phenylacetic acid chloride (**197**) (2 μL, 0.014 mmoles, 1.00 equiv.). The resulting suspension was stirred at reflux for 20 min. The resulting mixture was cooled to room temp., filtered and evaporated, yielding 0.6 mg of the desired product as a white solid. Fluorine NMR analysis indicated an 82 % ee of the starting amino acid. ^{1}H NMR: (200 MHz) ($CDCl_3$) δ TMS: 0.88 (br. s, 1 H), 3.56 (s, 3 H), 5.60 (d, J=6.7 Hz, 1 H), 7.26-7.70 (m, 10 H), 11.53 (s, 1 H). ^{19}F NMR: (188 MHz) ($CDCl_3$) δ $CFCl_3$: -47.23 (s, minor peak), -46.98 (s, major peak). **Spectral data for the authentic Mosher (MTPA) Amides of phenylglycine: D,L-phenylglycine Mosher Amide:** ^{1}H NMR: (200 MHz) ($CDCl_3$) δ TMS: 3.32 (s, 1 H), 3.49 (s, 3 H), 5.59 (d, J=6.8, 1 H), 7.23-7.87 (m, 10 H), 10.77 (br. s, 1 H). ^{19}F NMR: (188 MHz) ($CDCl_3$) δ $CFCl_3$: -47.31 (s), -47.06 (s). **D-phenylglycine Mosher Amide:** ^{1}H NMR: (200 MHz) ($CDCl_3$) δ TMS: 1.26 (s, 1 H), 3.34 (s, 3 H), 5.58 (d, J=7.0 Hz, 1 H), 7.25-7.78 (m, 10 H), 9.07 (br. s, 1 H). ^{19}F NMR: (188 MHz) ($CDCl_3$) δ $CFCl_3$: -46.99 (s).



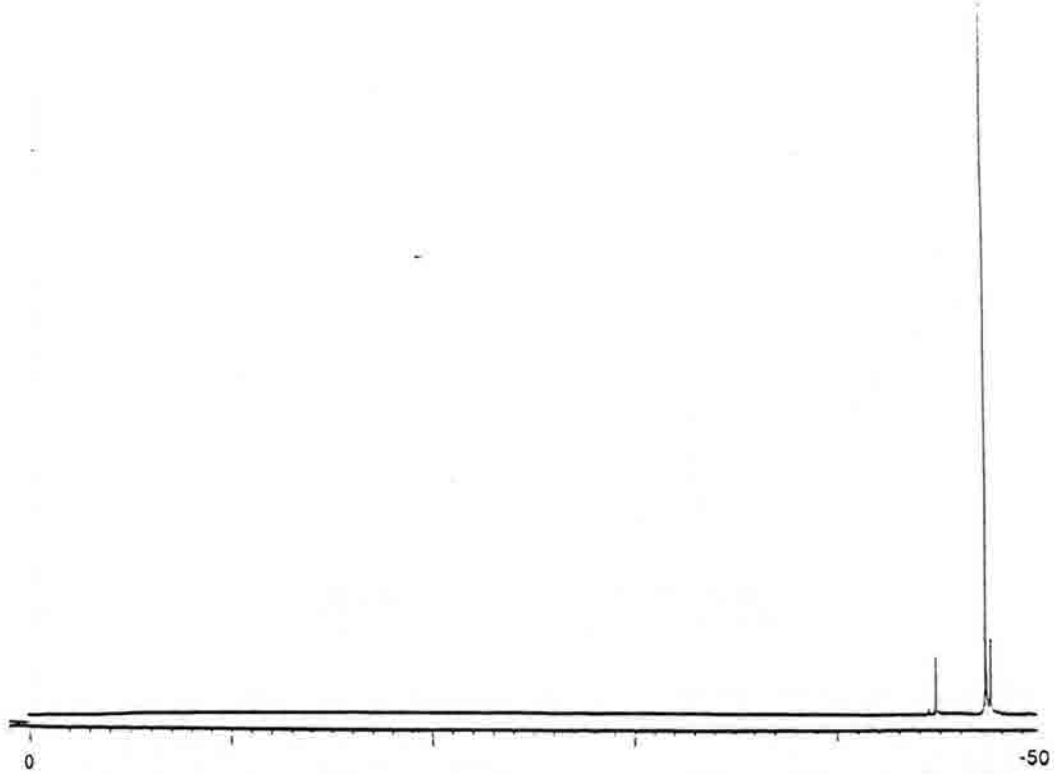
200 MHz ^{1}H NMR of **198a** (D, L) in $CDCl_3$ at room temperature.



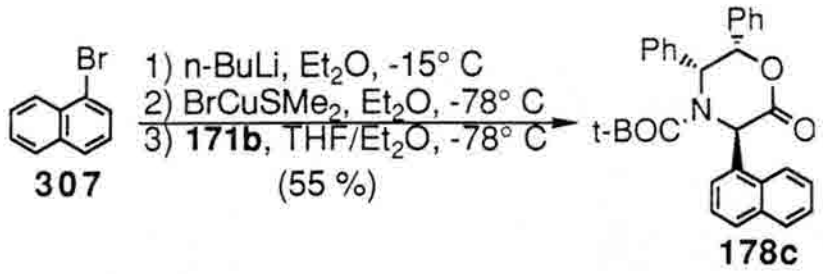
188 MHz ^{19}F NMR of **198a** (D, L) in $CDCl_3$ with $CFCl_3$ at room temperature.



200 MHz ^{1}H NMR of **198a** (D) in $CDCl_3$ at room temperature.



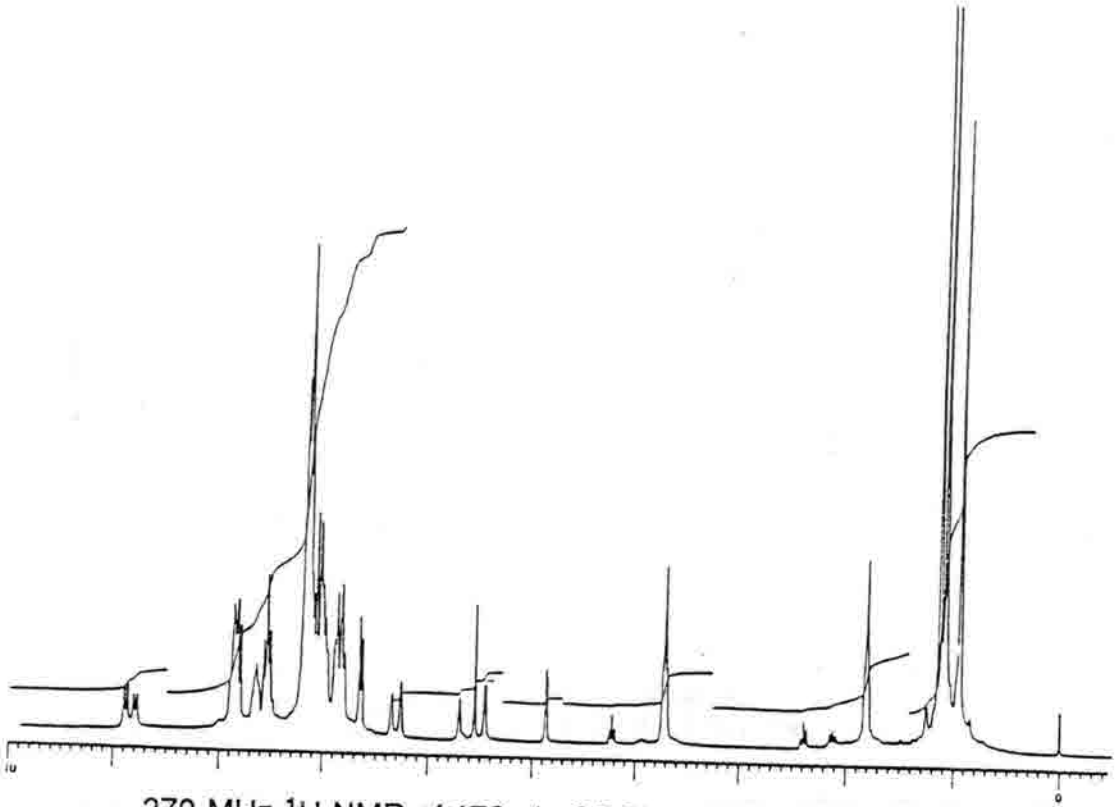
188 MHz ^{19}F NMR of **198a** (D) in $CDCl_3$ with $CFCl_3$ at room temperature.



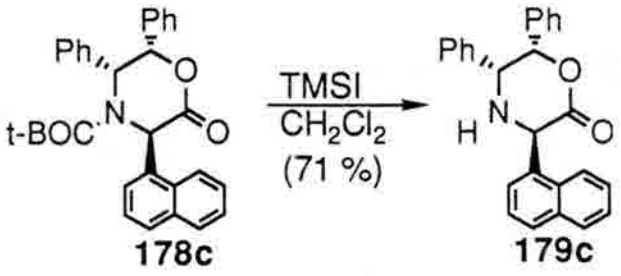
307 178c

(3R,5R,6S)-4-*tert*-butoxycarbonyl-5,6-diphenyl-3-(1'-naphthyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (178c, Ar = 1-napthyl). To a stirred solution of 1-bromonaphthalene (1.68 mL, 12.00 mmoles, 4.00 equiv.) in dry Et_2O (6.00 mL) cooled to -15° C was added *n*-BuLi (7.88 mL, 12.60 mmoles, 4.20 equiv., 1.60 M in hexanes) dropwise. The resulting white suspension was stirred at -15° C for 30 min when additional dry Et_2O (7.50 mL) was added with copper bromide dimethylsulfide (1.233 g, 4.00 mmoles, 2.00 equiv.). To the resulting thick, dark solution was added dry dimethylsulfide (3.00 mL) to aid the solubility of the reactants. The resulting mixture was stirred at -78° C for 3 h when a solution of **171b**[67] (1.296 g, 3.00 mmoles, 1.00 equiv.) in a 1:1 solution of dry Et_2O and dry THF (93.00 mL) was added via cannula. The resulting mixture was stirred at -78° C for 1.5 h when a saturated solution of NH_4Cl (60 mL) was added at -78° C. The resulting mixture was allowed to warm to room temp., separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 60 mL). The combined organic layers were washed with 10% HCl (2 x 60 mL), dried (Na_2SO_4), filtered, and evaporated. The residue was separated via column chromatography (7:2:1, Hex/$CHCl_3$/EtOAc) and recrystallized from EtOAc/Hex yielding 789 mg (55%) of the desired product (**178c**) as a white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 0.97 (s, 3 H), 1.09 (s, 3 H), 1.16 (s, 3 H), 4.88 (s) and 5.58 (s) (1 H), 5.46 (d) and 5.70 (d) (1 H), 6.27 (d) and 6.36 (d) (1 H), 6.64 (d,

J=2.1 Hz, 1 H), 6.86 (m, 2 H), 7.00-7.20 (m, 9 H), 7.55 (t, 1 H), 7.66 (m, 1 H), 7.86 (m, 2 H), 8.86 (dd, J=3.6 Hz, 1 H). IR: (NaCl, $CHCl_3$) 2970, 1740, 1682, 1381, 1359, 1321, 1268, 1245, 1176, 1150, 1112, 1045, 687 cm^{-1}. MS: *m/e* (relative intensity) CI (NH_3): 440 (74.2), 380 (58.7), 334 (21.5), 232 (32.9), 215 (100.0), 196 (32.7), 180 (31.1), 156 (22.5), 106 (52.4), 100 (31.4), 58 (34.2). Anal. Calcd. for $C_{31}H_{29}NO_4$ 1.5 H_2O: C, 73.50; H, 6.37; N, 2.76. Found: C, 73.64; H, 6.31; N, 2.83. Mp: 214-215° C (recryst. EtOAc/hexanes). $[\alpha]^{25}_D$ = +33.9° (*c* 0.99, CH_2Cl_2).

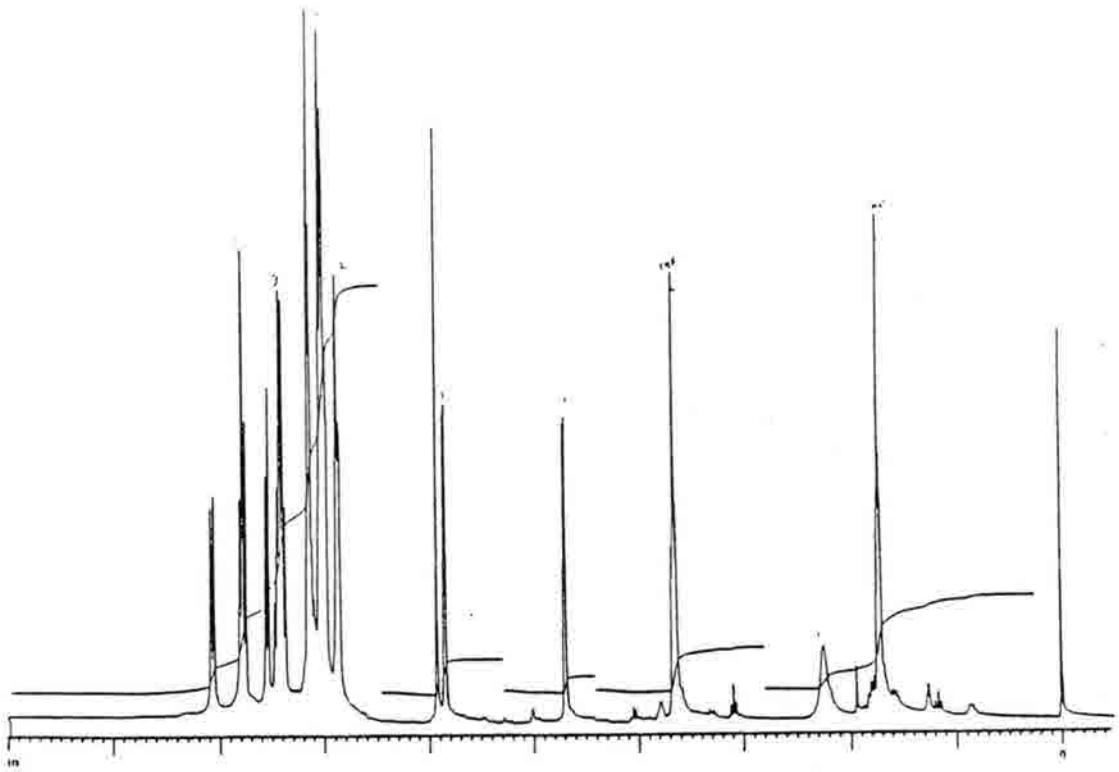


270 MHz ^1H NMR of **178c** in $CDCl_3$ at room temperature.

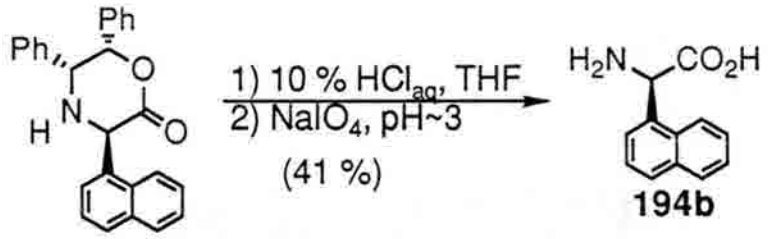


178c **179c**

(3R,5R,6S)-5,6-diphenyl-3-(1'-naphthyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (179c, Ar = 1-naphthyl).[86] To a stirred solution of **178c** (789 mg, 1.65 mmoles, 1.00 equiv.) in dry CH_2Cl_2 (16.50 mL) was added trimethylsilyl iodide (0.56 mL, 3.95 mmoles, 2.40 equiv.). The resulting orange solution was stirred at room temp. for 10 min when the reaction was quenched with the addition of water (25 mL). The resulting mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (4 X 25 mL). The combined organic layers were washed with 1 M $Na_2S_2O_3$ (2 X 40 mL), dried (Na_2SO_4), filtered, and evaporated yielding a crude yellow foam. The resulting mixture was separated via column chromatography (2:2:1, Hex/$CHCl_3$/EtOAc) yielding 443 mg (71 %) of the desired product (**179c**) as a white foam. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 2.28 (br. s, 1 H), 4.70 (d, J=1.2 Hz, 1 H), 5.86 (d, J=1.0 Hz, 1 H), 5.92 (s, 1 H), 6.88 (m, 2 H), 6.99 (m, 5 H), 7.10 (m, 3 H), 7.35 (m, 3 H), 7.56 (d, J=1.6 Hz, 1 H), 7.78 (t, 2 H), 8.06 (d, J=2.1 Hz, 1 H). IR: (NaCl, neat) 3322, 2960, 2850, 1725, 1440, 1220, 1182, 1000, 740, 680 cm^{-1}. MS: *m/e* (relative intensity) CI (NH_3): 287 (0.2), 106 (5.8), 104 (19.1), 88 (83.2), 71 (58.6), 56 (3.6), 35 (100). $[\alpha]^{25}_D$ = +126.7 ° (*c* 0.06, CH_2Cl_2).



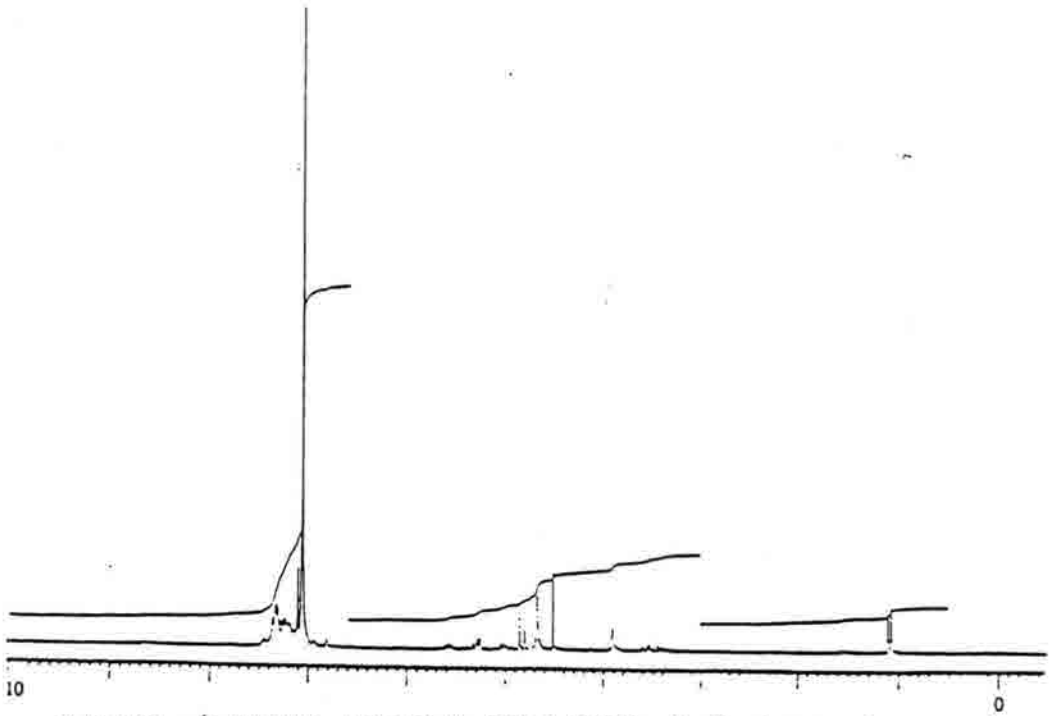
270 MHz ^{1}H NMR of **179c** in $CDCl_3$ at room temperature.



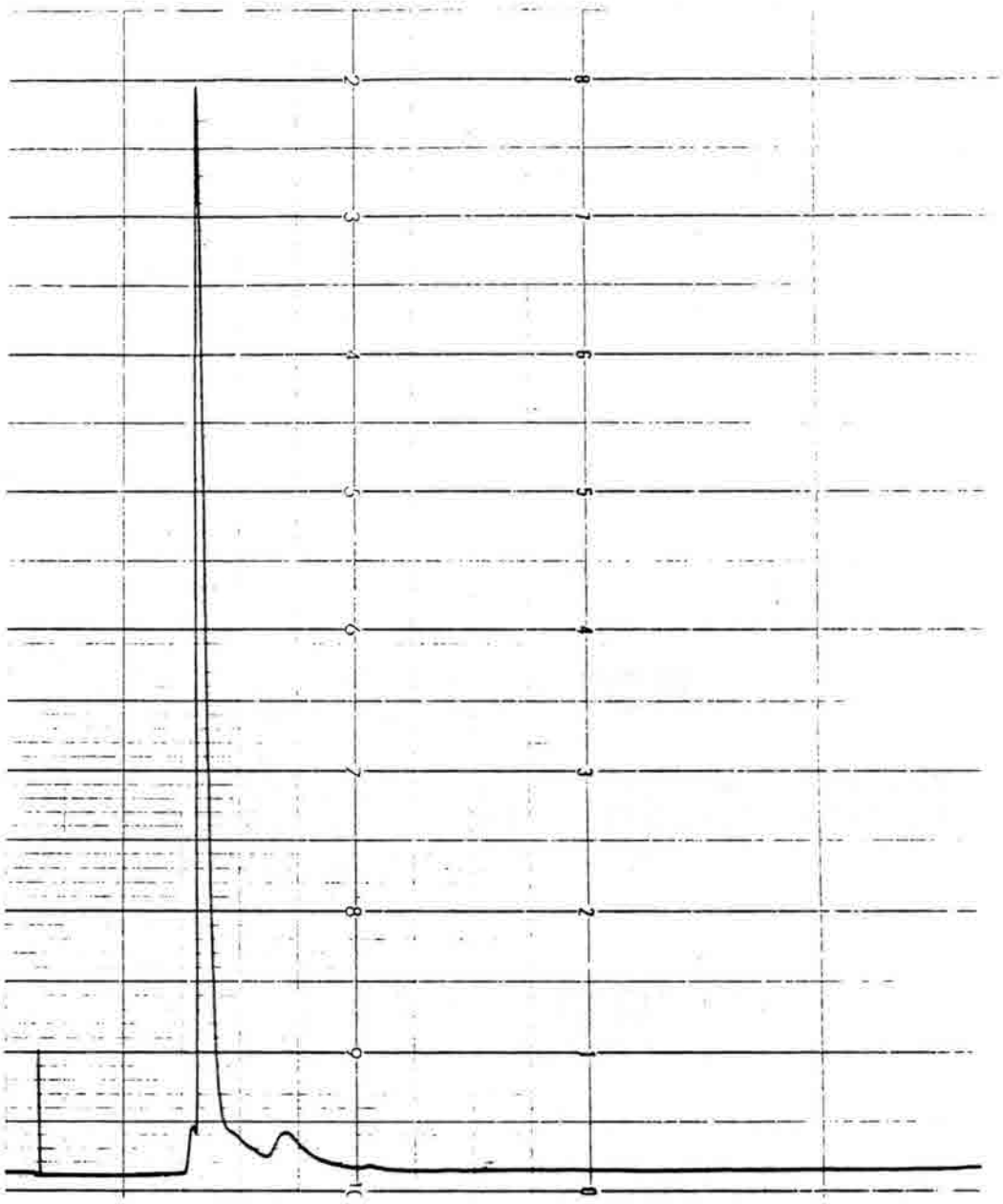
179c **194b**

D-1-Naphthylglycine (194b, Ar = 1-naphthyl).[29, 44] To a stirred solution of **179c** (152 mg, 0.401 mmoles, 1.00 equiv.) in THF (2.5 mL) was added 10% HCl (5.0 mL). The resulting solution was stirred at room temp. for 1 h and evaporated. The white residue was taken up in water (7.0 mL) and THF (5.0 mL). The pH of the resulting suspension was adjusted to 3 with the dropwise addition of 1 N NaOH. To this solution was added sodium periodate (189 mg, 0.882 mmoles, 2.20 equiv.) and the resulting mixture was stirred at

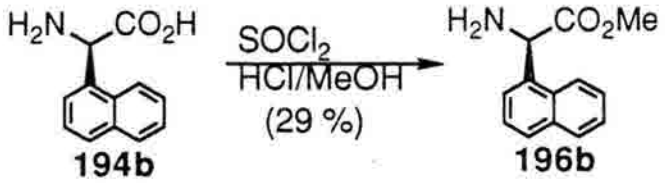
room temperature for 2 days. The pH was then adjusted to 5.5 with the dropwise addition of 1 N NaOH. Several drops of propylene glycol were added (to destroy excess $NaIO_4$). The resulting solution was stirred at room temperature for 15 min and the resulting mixture was washed with EtOAc (3 x 5 mL) and the aqueous layer was evaporated yielding a yellow/white solid mixture which was taken up in water/EtOH and filtered through a C_{18} silica plug and evaporated. This white solid mixture was separated via cation exchange chromatography (eluted with 1N $NH_{3\ (aq)}$, Dowex 50W-X8) yielding 33 mg (41 %) of naphthylglycine (**194b**) as a white solid. ^1H NMR: (270 MHz) (DCl in D_2O) δ HOD: 4.83 (s, 1 H), 7.22-7.53 (m, 7 H). ^1H NMR: (270 MHz) (DMSO-d_6) δ DMSO: 1.13 (m, 2 H), 5.01 (s, 1 H), 7.35-7.98 (m, 7 H), 8.33 (br. s, 1 H). IR: (NaCl, neat) 3380, 3050, 2956, 1594, 1369, 1167, 1047, 1026, 1003, 818 cm^{-1}. MS: *m/e* (relative intensity) CI (NH_3): 171 (20.6), 158 (63.9), 141 (28.8), 128 (3.0), 102 (25.6), 85 (100.0). $[\alpha]^{25}_D$: + 8.0° (*c* 0.05, H_2O).



270 MHz ^1H NMR of **194b** in 35 % DCl in D_2O at room temperature.

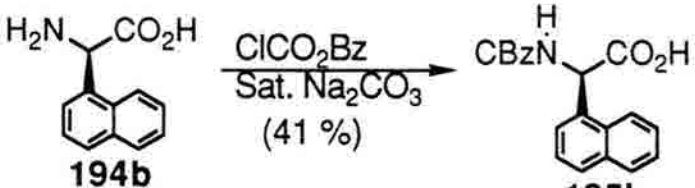


HPLC trace of D-Naphthylglycine (**194b**), Crownpak CR(+) chiral column; perchloric acid buffer (pH 2); flow rate: 0.50 mL/min.; chart speed: 1.0 cm/s.



194b **196b**

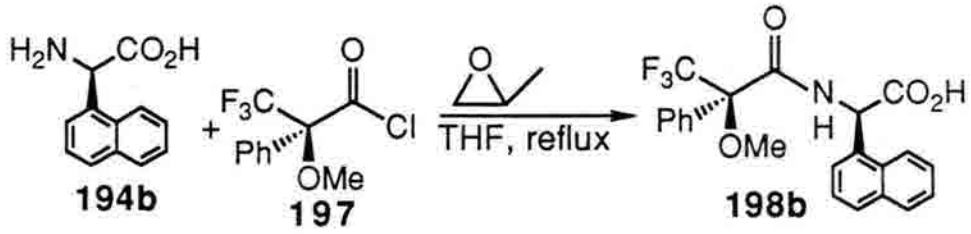
1-Naphthylglycine methyl ester (196b, Ar = 1-naphthyl).[25a] A stirred suspension of the D-1-naphthylglycine (**194b**) (16 mg, 0.078 mmoles, 1.00 equiv.) in a dry MeOH/HCl solution (0.80 mL) was heated until most of the amino acid dissolved. The resulting solution was cooled to 0° C and thionyl chloride (17 μL, 0.242 mmoles, 3.10 equiv.) was added. The resulting solution was stirred at 0° C for 1 h and then at room temp. overnight. The resulting mixture was evaporated and the residue was washed with THF, filtered and the white solid was collected yielding 5 mg (29 %) of the desired product (**196b**). ^{1}H NMR: (270 MHz) (D_2O) δ HOD: 3.68 (s, 3 H), 5.97 (s, 1 H), 7.50 (m, 4 H), 7.98 (m, 3 H). IR (NaCl, $CHCl_3$): 3400, 2922, 2856, 1744, 1722, 1589, 1439, 1133, 1106, 1022, 778 cm^{-1}. MS: *m/e* (relative intensity) CI (NH_3): 216 (0.8), 215 (0.4), 214 (0.8), 200 (2.5), 171 (4.9), 157 (0.9), 153 (4.0), 141 (1.1), 128 (0.5), 102 (37.4), 88 (1.1), 85 (100.0), 74 (0.4), 71 (5.6), 58 (1.6). $[\alpha]^{25}_D$: -50.8° (*c* 0.06, 1:1 EtOH/H_2O).



194b **195b**

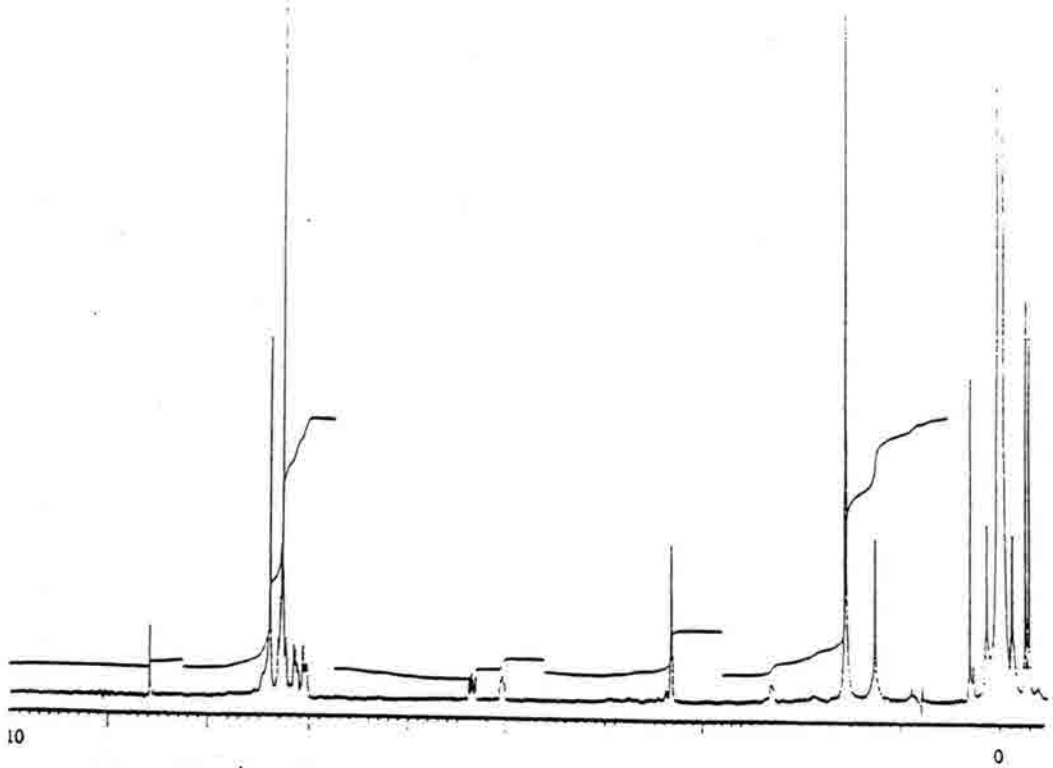
N-Benzyloxycarbonyl-1-naphthylglycine (195b, Ar = 1-naphthyl). To a stirred solution of the D-1-naphthylglycine (**194b**) (12 mg, 0.061 mmoles, 1.00 equiv.) in saturated sodium carbonate (0.50 mL) was added benzyl chloroformate (10 μL, 0.067 mmoles, 1.10 equiv.). The resulting solution was vigorously stirred at room temp. for 2 h and the yellow mixture was thoroughly extracted with CH_2Cl_2 (5 x 2 mL). The combined organic layers were dried

(Na_2SO_4), filtered and evaporated yielding a yellow oil which primarily contained 8 mg (41 %) of the desired product (**195b**). ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 1.56 (s, 1 H), 5.17 (s, 1 H), 5.26 (s, 2 H), 7.25-7.38 (m, 12 H). IR (NaCl, $CHCl_3$): 3333, 2956, 2889, 1828, 1761, 1500, 1456, 1372, 1289, 1261, 1150, 1067, 928, 756, 700 cm^{-1}.

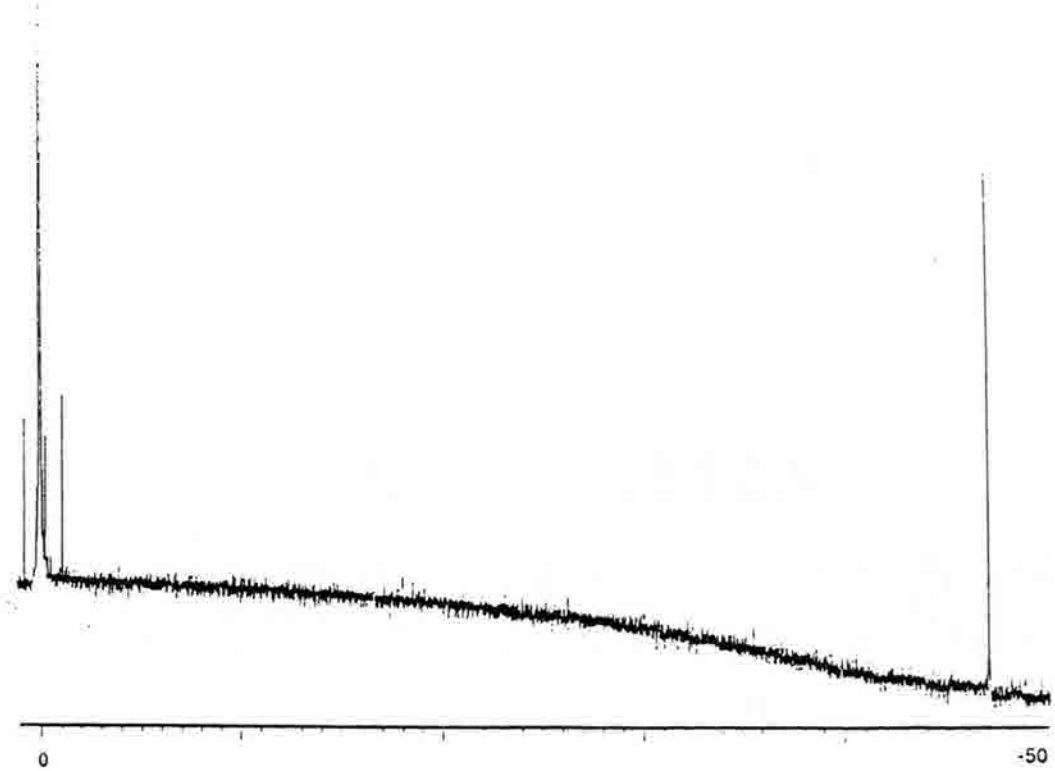


194b **197** **198b**

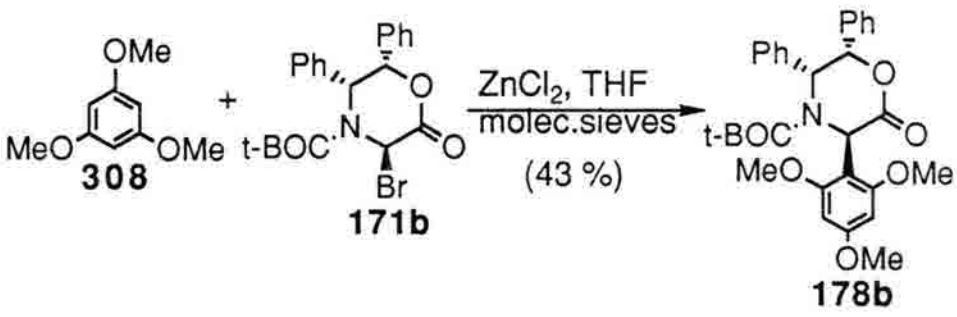
((2'-Methoxy-3',3',3'-trifluoro-1'-oxo-2'-phenylpropyl)amino)-1-naphthalenacetic acid (198b, Ar = 1-naphthyl).[87] To a stirred suspension of L-1-naphthylglycine (**194b**) (3 mg, 0.015 mmoles, 1.000 equiv.) in dry tetrahydrofuran (2.00 mL) was added propylene oxide (4 μL, 0.060 mmoles, 4.000 equiv.) and (S)-(-)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid chloride (**197**) (2 μL, 0.015 mmoles, 1.000 equiv.). The resulting solution was heated at reflux for 30 min, cooled to room temp., filtered and evaporated yielding a clear, colorless oil which was separated via PTLC (7:2:1, Hex/$CHCl_3$/EtOAc) yielding the desired product (**198b**) pure, as a white solid. Fluorine NMR analysis showed 94 % ee of the starting amino acid. ^1H NMR: (200 MHz) ($CDCl_3$) δ TMS: 1.26 (s, 1H), 1.55 (s, 3 H), 3.32 (d, J=1.4 Hz, 1 H), 7.26-7.39 (m, 12 H), 8.59 (s, 1 H). ^{19}F NMR: (188 MHz) ($CDCl_3$) δ $CFCl_3$: -47.09 (s, minor peak), -47.02 (s, major peak). MS: *m/e* (relative intensity) CI (NH_3): 430 (65.7), 412 (57.5), 324 (66.9), 322 (71.1), 251 (100.0), 234 (67.3), 189 (49.1), 106 (85.3), 105 (46.4), 94 (18.3), 78 (10.8), 45 (10.4), 36 (19.3), 29.7 (20.9).



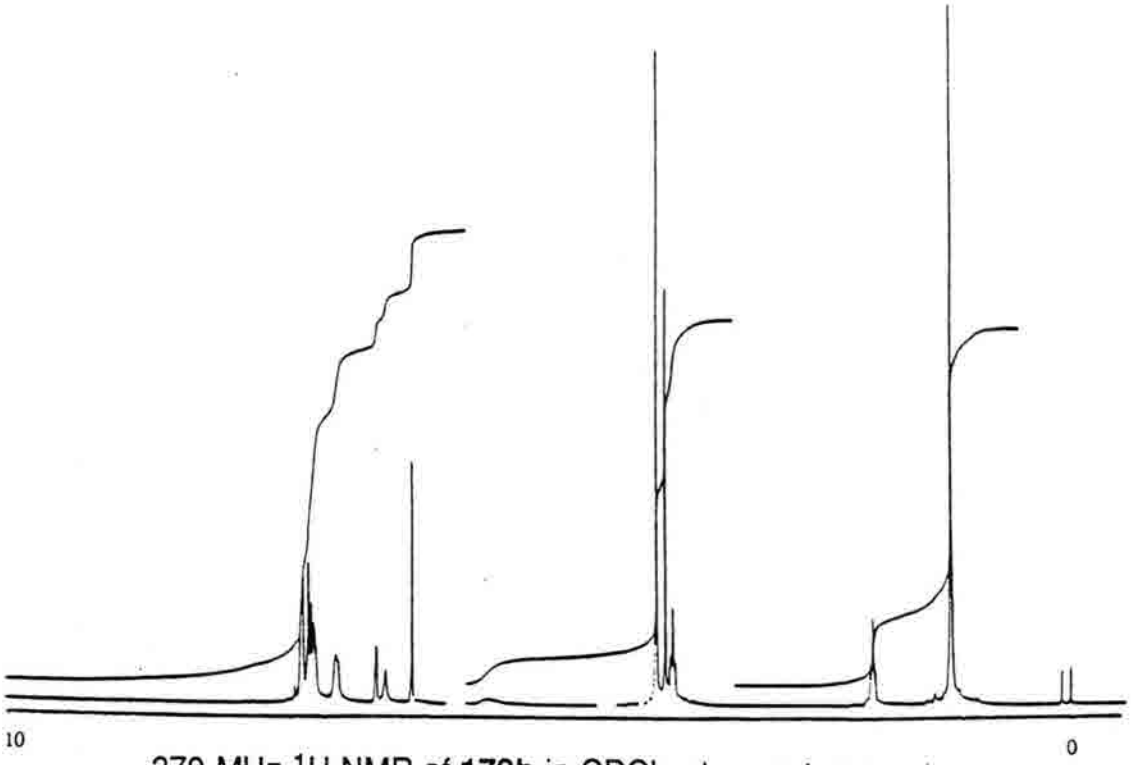
200 MHz ^{1}H NMR of **198b** (D) in $CDCl_3$ at room temperature.



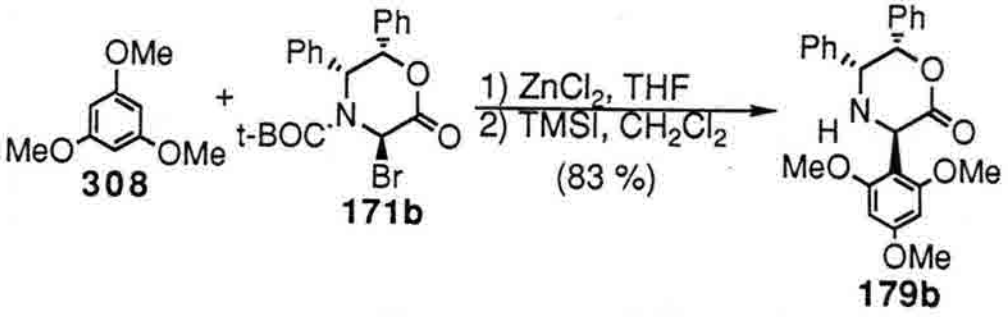
188 MHz ^{19}F NMR of **198b** (D) in $CDCl_3$ with $CFCl_3$ at room temperature.



(3R,5R,6S)-4-*tert*-butoxycarbonyl-5,6-diphenyl-2,3,5,6-tetrahydro-3-(2',4',6'-trimethoxy)phenyl-1,4-oxazin-2-one (178b, Ar = 1,3,5-trimethoxyphenyl). To a stirred solution of **171b**[67] (108 mg, 0.250 mmoles, 1.00 equiv.) and 1,3,5-trimethoxybenzene (505 mg, 3.00 mmoles, 12.0 equiv.) in dry THF (1.50 mL) over 4 Å powdered molec. sieves (0.25 g) was added zinc chloride (0.50 mL, 0.500 mmoles, 2.00 equiv., 1.00 M in THF). The resulting mixture was stirred at room temp. for 3.5 h when the mixture was filtered into water (5 mL). The resulting mixture was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The residue was separated via column chromatography (5:3:2; Hex/$CHCl_3$/EtOAc) yielding 56 mg (43 %) of the desired product (**178b**) as a colorless oil. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 1.11 (s, 9 H), 3.83 (s, 3 H), 3.91 (s, 6 H), 6.18 (s, 1 H), 6.51 (br. s, 1 H), 6.88 (d, J=5.5 Hz, 1 H), 7.09-7.26 (m, 12 H). IR: (NaCl, $CHCl_3$) 2968, 2960, 1745, 1695, 1608, 1460, 1448, 1360, 1345, 1225, 1198, 715, 695 cm^{-1}. MS: *m/e* (relative intensity) CI (NH_3): 520 (0.6), 388 (3.0), 331 (4.0), 306 (3.3), 252 (100.0), 250 (15.0), 196 (14.2), 162 (10.3), 122 (23.3), 106 (26.1), 105 (18.3), 88 (12.4), 58 (12.5), 35 (100.0). Anal. Calcd for $C_{30}H_{33}NO_7$: C, 69.35; H, 6.40; N, 2.70. Found: C, 69.11; H, 6.58; N, 2.48 (obtained as a sticky foam). $[\alpha]^{25}_D$ = + 61.3° (*c* 0.46, CH_2Cl_2).

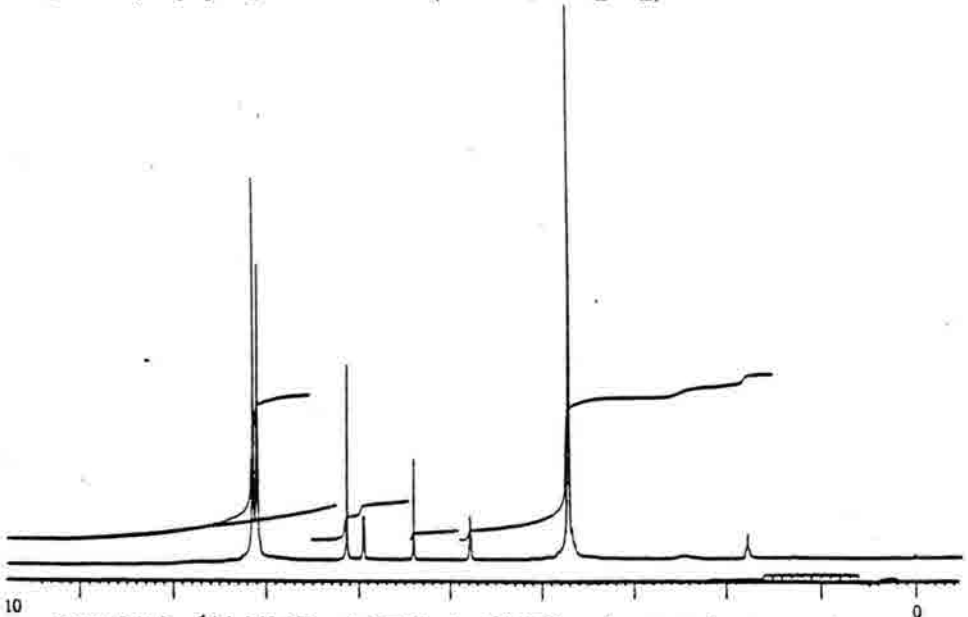


270 MHz ^{1}H NMR of **178b** in $CDCl_3$ at room temperature.

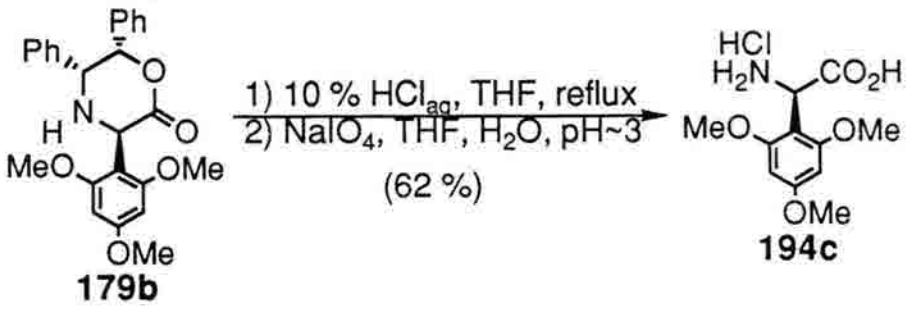


(3R,5R,6S)-5,6-diphenyl-2,3,5,6-tetrahydro-3-(2',4',6'-trimethoxy)phenyl-1,4-oxazin-2-one (179b, Ar = 1,3,5-trimethoxyphenyl). To a stirred solution of **171**[67] (0.432 g, 1.00 mmoles, 1.00 equiv.) in dry THF (7.00 mL) was added 1,3,5-trimethoxybenzene (1.958 g, 11.64 mmoles, 11.64 equiv.) and zinc chloride (1.33 mL, 2.00 mmoles, 2.00 equiv., 1.50 M in THF). The resulting solution was stirred at room temp. for 4.5 h and then poured into water (10 mL). The resulting mixture was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were dried (Na_2SO_4),

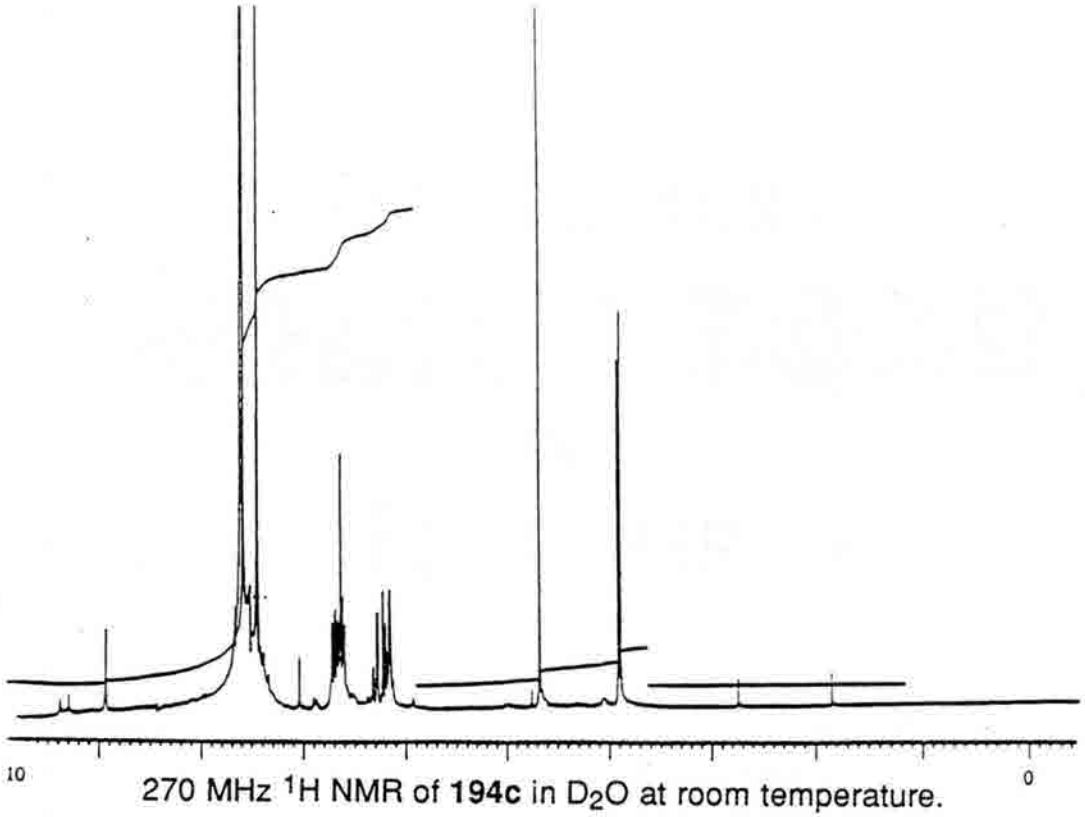
filtered, and evaporated. *Since the residue contained both the t-BOC protected and unprotected coupled products it was found to be most efficient to carry the crude mixture on to the t-BOC deprotection reaction.*[86] To the yellow solid was added dry CH_2Cl_2 (10.00 mL) and trimethylsilyl iodide (0.28 mL, 2.00 mmoles, 2.00 equiv.). The resulting deep red solution was stirred at room temperature for 10 min and water (15 mL) was added. The resulting mixture was separated, and the aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were washed with 1 M $Na_2S_2O_3$ (2 X 10 mL), dried (Na_2SO_4), filtered, and evaporated. The oily residue was separated via silica gel column chromatography (6.5:2.5:1.0, Hex/$CHCl_3$/ EtOAc) yielding 347 mg (83 %) of the desired product (**179b**) as a white foam. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 2.22 (br. s, 1 H), 3.78 (s, 3 H), 3.80 (s, 6 H), 4.79 (d, J=3.8 Hz, 1 H), 5.41 (s, 1 H), 5.94 (d, J=3.8 Hz, 1 H), 7.06-7.21 (m, 12 H). IR: (NaCl, neat) 3315, 2950, 2850, 1734, 1600, 1488, 1456, 1409, 1330, 1220, 1193, 1140, 1110, 1050, 900, 795, 715, 680 cm^{-1}. MS: *m/e* (relative intensity) CI (NH_3): 420 (87.5), 375 (2.6), 285 (2.8), 252 (2.9), 210 (25.6), 196 (25.0), 169 (21.1), 104 (22.7), 88 (14.6), 71 (11.2), 35 (100.0). $[\alpha]^{25}_D$ = + 141.5° (*c* 0.75, CH_2Cl_2).



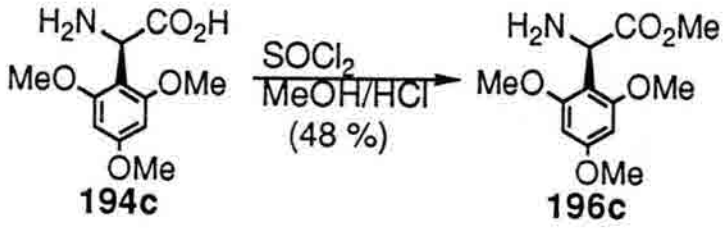
270 MHz ^1H NMR of **179b** in $CDCl_3$ at room temperature.



D-α-amino-2,4,6-trimethoxyphenylacetic acid hydrochloride (194c, Ar =1,3,5-trimethoxyphenyl).[44] A stirred solution of **179b** (184 mg, 0.440 mmoles, 1.00 equiv.) in THF (2.90 mL) and 10% $HCl_{(aq)}$ (5.80 mL) was stirred at mild reflux for 30 min. Upon cooling to room temp., the solution was thoroughly extracted with CH_2Cl_2 (5 x 10 mL), dried (Na_2SO_4), filtered, and evaporated. The resulting residue was taken up in a 1:1 solution of THF and water (9.2 mL) followed by the addition of sodium periodate (207 mg, 0.968 mmoles, 2.20 equiv.). The pH of the resulting mixture was adjusted to approximately 3 and was stirred at room temp. for 2 days. The pH of the resulting mixture was the adjusted to 7 with the dropwise addition of 1 N NaOH. A white precipitate gradually formed with increasing pH. The resulting neutral solution was allowed to precipitate in the refrigerator overnight. The white solid was collected by filtration, taken up in 10 % HCl(aq) and evaporated. The residue was taken up in a minimum amount of 10 % HCl(aq), precipitated with the addition of absolute EtOH, filtered and dried yielding 66 mg (62 %) of the HCl salt of D-α-amino-2,4,6-trimethoxyphenylacetic acid (**194c**) as a yellow solid. ^{1}H NMR: (270 MHz) (D_2O) δ HOD: 3.38 (s, 6 H), 3.54 (s, 3 H), 6.11 (s, 1 H), 7.18 (m, 1 H), 7.36 (m, 1 H). IR: (NaCl, neat) 3387, 2969, 2848, 1609, 1455, 1417, 1384, 1334, 1208, 1153, 1120, 1054, 949, 817, 700 cm^{-1}. MS *m/e* (relative intensity) CI (NH_3): 276 (12.5), 242 (0.3), 210 (17.7), 181 (100.0), 169 (11.2), 106 (20.7), 85 (17.4), 35 (91.8). $[\alpha]^{25}_D$ = -14.0° (*c* 0.05, H_2O).



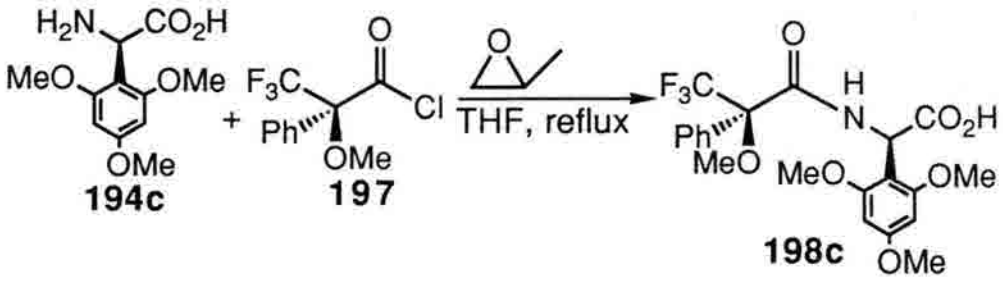
270 MHz ^{1}H NMR of **194c** in D_2O at room temperature.



194c **196c**

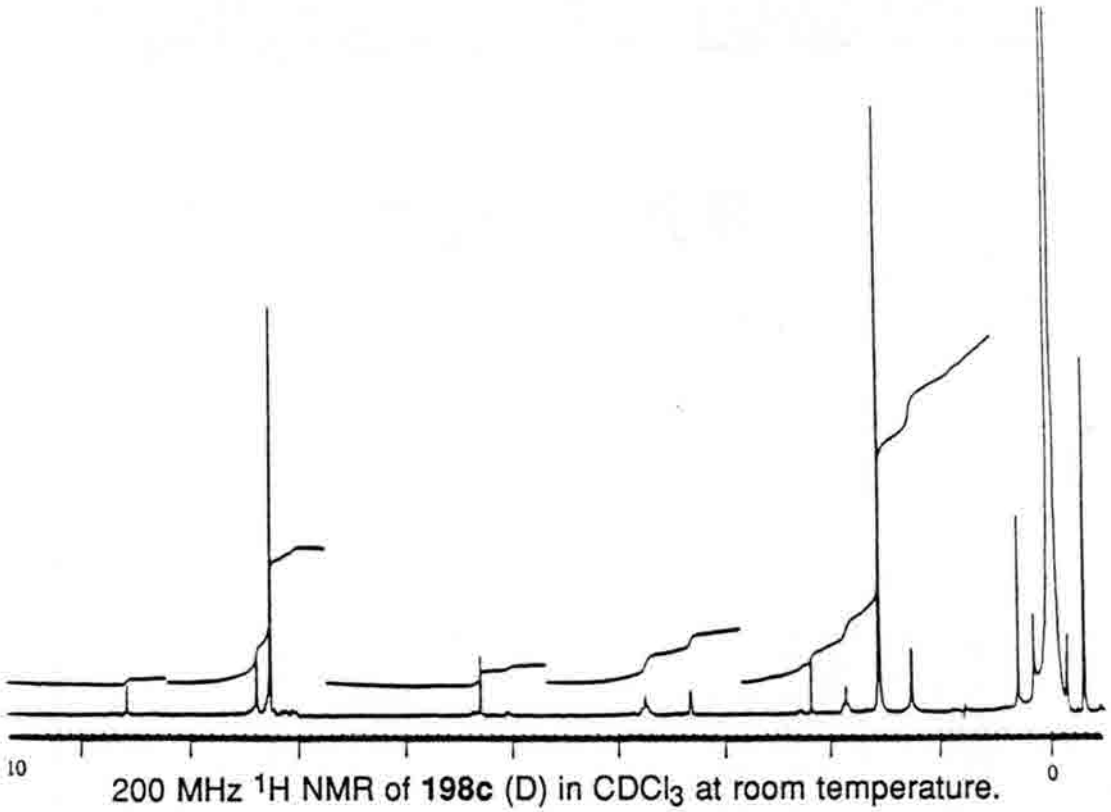
Methyl-(α-amino-2,4,6-trimethoxyphenyl) acetate (196c, Ar = 1,3,5-trimethoxyphenyl).[52] A stirred suspension of D-α-amino-2,4,6-trimethoxyphenylacetic acid (**194c**) (12 mg, 0.048 mmoles, 1.00 equiv.) in a dry MeOH/HCl solution (0.50 mL) was heated until the amino acid completely dissolved. The resulting solution was cooled to 0° C and thionyl chloride (11 μL, 0.148 mmoles, 3.10 equiv.) was added. The resulting solution was stirred at 0° C for 1 h and then at room temp. overnight. The resulting solution was evaporated and the residue was washed with THF, filtered and evaporated yielding 6 mg (48 %) of the desired product (**196c**) as an orange oil. ^{1}H NMR:

(270 MHz) ($CDCl_3$) δ TMS: 1.89 (m, 2 H), 3.63 (s, 3 H), 3.84 (br. s, 9 H), 5.05 (s, 1 H), 6.07 (m, 2 H). IR: (NaCl, neat) 3333, 2956, 2922, 2844, 1722, 1611, 1456, 1361, 1344, 1189, 1156, 1122, 1067, 1033, 956, 928, 850, 706 cm^{-1}. MS: *m/e* (relative intensity) 255 (1.9), 241 (1.1), 197 (2.1), 169 (2.3), 119 (2.1), 104 (26.1), 88 (98.4), 71 (100.0), 56 (15.1). $[\alpha]^{25}_D$ = -17.3° (*c* 0.08, EtOH).

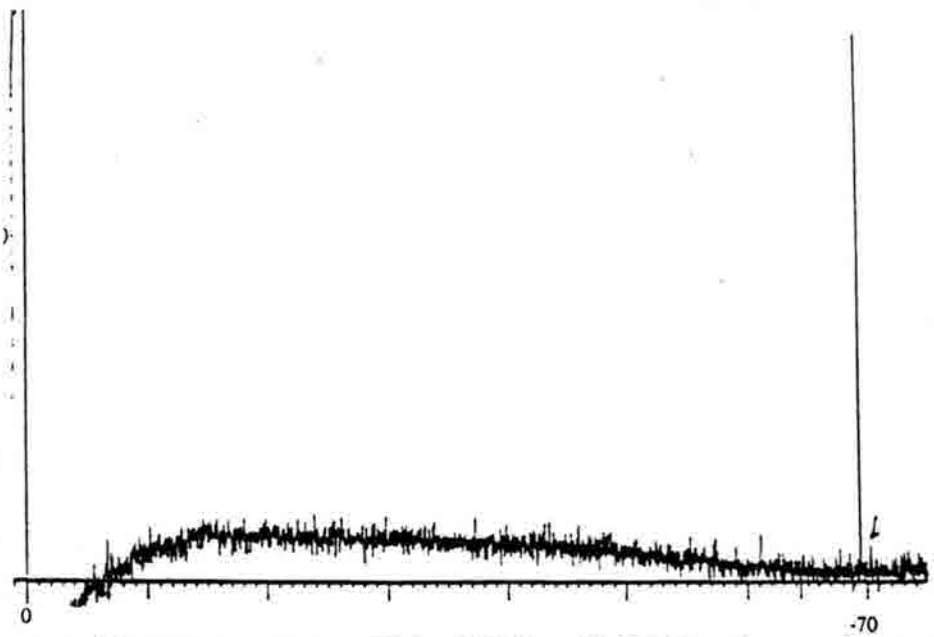


((2-Methoxy-3,3,3-trifluoro-1-oxo-2-phenylpropyl)amino)-(2',4',6'-trimethoxy)phenylacetic acid (198c, Ar =1,3,5-trimethoxyphenyl).[87] To a stirred suspension of L-α-amino-2,4,6-trimethoxyphenylacetic acid (**194c**) (9 mg, 0.040 mmoles, 1.000 equiv.) in dry tetrahydrofuran (2.00 mL) was added propylene oxide (10 μL, 0.148 mmoles, 4.000 equiv.) and (S)-(-)-α-methoxy-α-(trifluoromethyl) phenyl acetic acid chloride (**197**) (6 μL, 0.040 mmoles, 1.000 equiv.). The resulting solution was heated at reflux for 30 min, cooled to room temperature, filtered and evaporated yielding an orange oil which was separated via PTLC (7:2:1, Hex/$CHCl_3$/EtOAc) yielding a pure sample of the desired product as a white solid. Fluorine NMR analysis showed 91 % ee of the starting amino acid. ^1H NMR: (200 MHz) ($CDCl_3$) δ TMS: 1.26 (s, 3 H), 1.55 (s, 9 H), 2.17 (s, 1 H), 5.30 (d, 1 H), 7.26 (s, 5 H), 7.39 (br. s, 2 H), 8.59 (s, 1 H). ^{19}F NMR: (188 MHz) ($CDCl_3$) δ $CFCl_3$: -70.30 (s, minor peak), -69.47 (s, major peak). MS: *m/e* (relative intensity) EI: 230 (0.3), 219 (0.3), 205 (0.5), 189 (6.8), 158 (1.1), 152 (1.6), 149 (4.0), 146 (2.0), 141

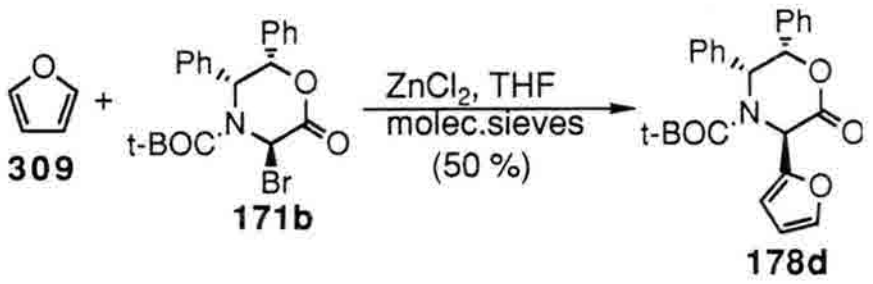
(1.1), 139 (1.6), 137 (1.0), 132 (1.2), 119 (3.0), 105 (18.2), 97 (9.3), 83 (11.4), 77 (13.3), 71 (100), 69 (14.8), 57 (26.7), 55 (17.5), 43 (46.1).



200 MHz ^{1}H NMR of **198c** (D) in $CDCl_3$ at room temperature.

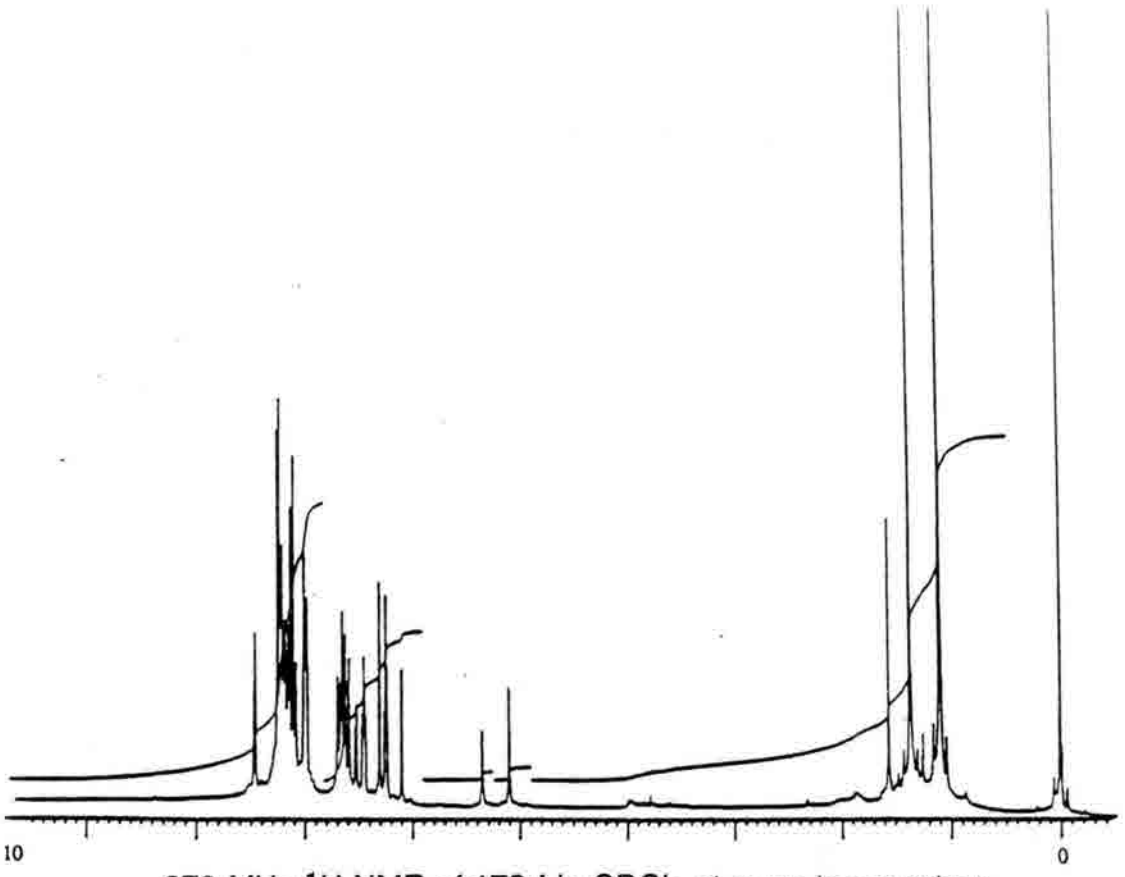


188 MHz ^{19}F NMR of **198c** (D) in $CDCl_3$ with $CFCl_3$ at room temperature.

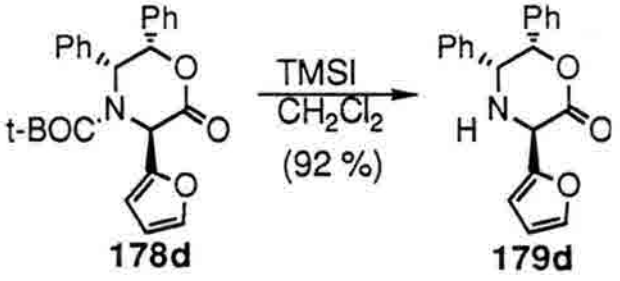


309 **171b** **178d**

(3R,5R,6S)-4-*tert*-butoxycarbonyl-5,6-diphenyl-3-(2'-furyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (178d, Ar = 2-furyl). To a solution of **171b**[67] (0.432 g, 1.00 mmoles, 1.00 equiv.) in THF (10.00 mL) stirred over powdered molec. sieves (0.5 g, 4 Å) was added furan (1.13 mL, 15.60 mmoles, 15.60 equiv.) and zinc chloride (2.00 mL, 2.00 mmoles, 2.00 equiv., 1.0 M in THF). The resulting solution was stirred at room temp. for 5.5 h when the solution was filtered into water (10 mL). The resulting mixture was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The residue was separated via silica gel column chromatography (7:2:1, Hex/$CHCl_3$/EtOAc) yielding 211 mg (50 %) of the desired product (**178d**) as a white solid. ^1H NMR: (270 MHz) $CDCl_3$) δ TMS: 1.10 (s, 5 H), 1.36 (s, 4 H), 5.09 (d, J=3.0 Hz, 1 H), 5.35 (d, J=3.0 Hz, 1 H), 6.09 (s, 1 H), 6.23-6.26 (m, 1 H), 6.31 (s, 1 H), 6.43-6.69 (m, 3 H), 6.97-7.26 (m, 6 H), 7.45-7.47 (m, 2 H). IR: (NaCl, $CHCl_3$) 3130, 2980, 2937, 2874, 1752, 1702, 1501, 1453, 1391, 1350, 1242, 1164, 1055, 952, 883, 757, 716, 701 cm^{-1}. MS: *m/e* (relative intensity) CI (NH_3): 419 (0.2), 381 (11.3), 320 (9.0), 316 (18.0), 274 (100.0), 244 (3.4), 196 (21.9), 106 (8.8), 96 (6.4), 35 (100.0), 32 (34.4). Anal. Calcd for $C_{25}H_{25}NO_5$: C, 71.58; H, 6.01; N, 3.34. Found: C, 71.79; H, 6.11; N, 3.20. Mp: 202-204° C (recryst. EtOAc/hexanes). $[\alpha]^{25}_D$: -2.4° (*c* 1.00, CH_2Cl_2).



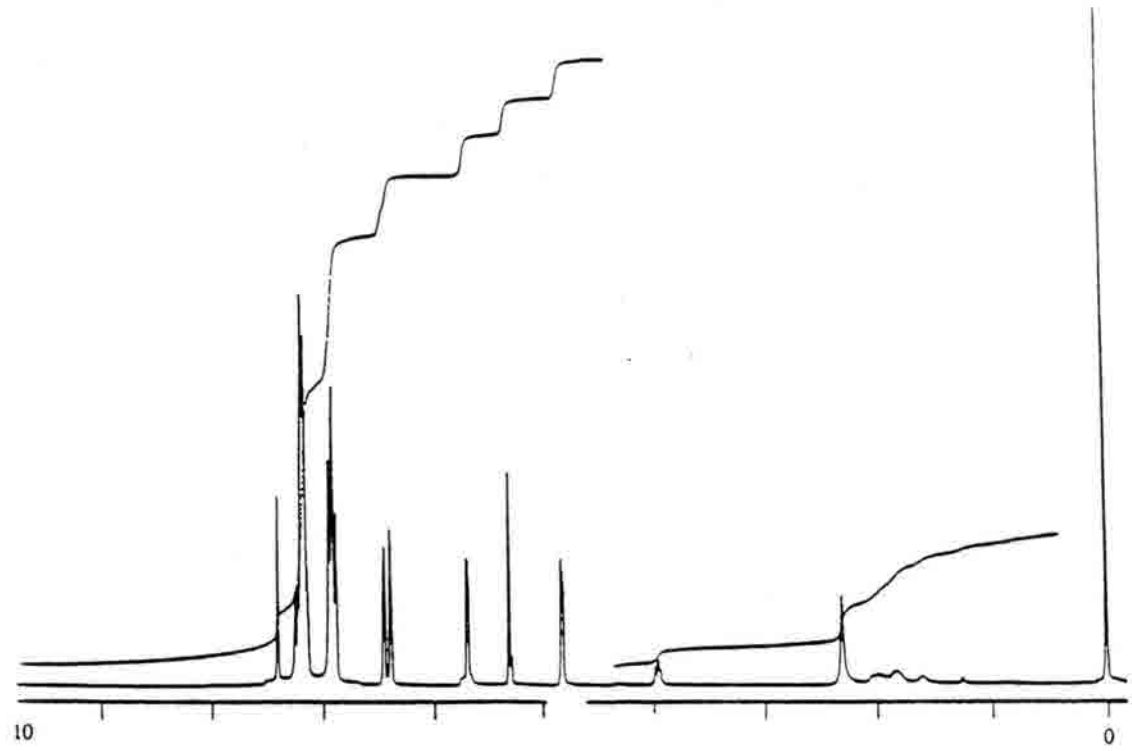
270 MHz ^{1}H NMR of **178d** in $CDCl_3$ at room temperature.



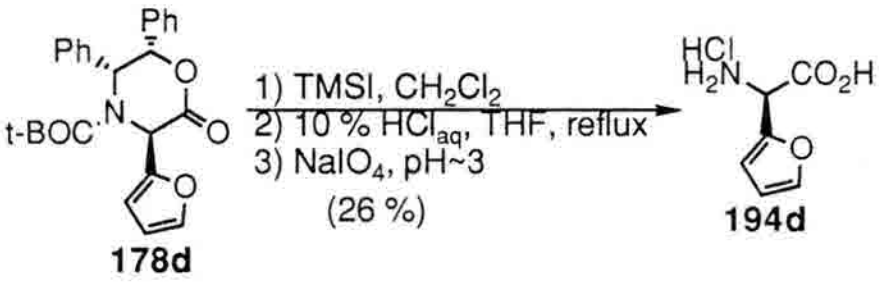
178d **179d**

(3R,5R,6S)-5,6-diphenyl-3-(2'-furyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (179d, Ar = 2-furyl).[86] To a stirred solution of **178d** (43 mg, 0.102 mmoles, 1.00 equiv.) in dry CH_2Cl_2 (1.00 mL) was added trimethylsilyl iodide (35 μL, 0.246 mmoles, 2.40 equiv.). The resulting orange solution was stirred at room temp. for 10 min and the reaction was quenched with the addition of water (1 mL). The resulting mixture was separated and the aqueous

layer was extracted with CH_2Cl_2 (3 X 1 mL). The combined organic layers were washed with brine (3 mL), dried (Na_2SO_4), filtered, and evaporated. The residue was separated via PTLC silica gel (7:2:1, Hex/$CHCl_3$/EtOAc) yielding 30 mg (92 %) of the desired product (**179d**) as colorless oil. The product rapidly decomposed. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 2.31 (br. s, 1 H), 4.83 (d, J=3.9 Hz, 1 H), 5.31 (s, 1 H), 5.69 (d, J=3.9 Hz, 1 H), 6.39-6.41 (m, 3 H), 6.88-7.09 (m, 4 H), 7.13-7.26 (m, 5 H), 7.42 (s, 1 H). IR: (NaCl, neat) 3334, 3030, 1742, 1602, 1498, 1455, 1342, 1214, 1068, 1015, 754, 699 cm^{-1}. MS: *m/e* (relative intensity) CI (NH_3): 320 (17.5), 319 (70.9), 317 (23.3), 315 (14.4), 289 (15.9), 273 (100.0), 210 (9.1), 196 (36.2), 157 (5.6), 121 (4.8), 106 (13.7), 96 (14.4), 71 (5.8), 52 (3.8), 35 (100.0). $[\alpha]^{25}_D$: -174.0° (*c* 1.49, CH_2Cl_2).



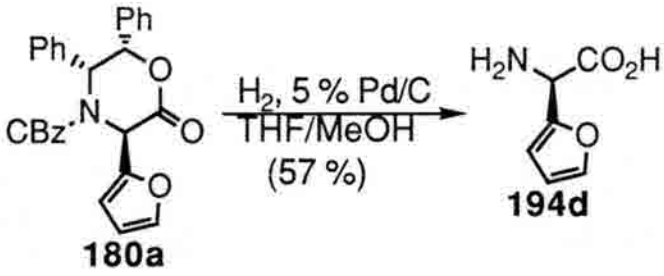
270 MHz ^1H NMR of **179d** in $CDCl_3$ at room temperature.



178d **194d**

D-α-2-Furylglycine hydrochloride (194d, Ar = 2-furyl).[44, 86] To a stirred solution of **178d** (271 mg, 0.646 mmoles, 1.00 equiv.) in dry CH_2Cl_2 (6.50 mL) was added trimethylsilyl iodide (0.22 mL, 1.55 mmoles, 2.40 equiv.). The resulting red solution was stirred at room temp. for 10 min when the reaction was quenched with the addition of water (6.5 mL). The resulting mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (5 x 10 mL) and the combined organic layers were washed with $Na_2S_2O_3$ (2 x 20 mL) and evaporated. Since the product of this reaction, **179d**, rapidly decomposes, the residue was immediately taken up in THF (4.25 mL) and to this solution was added 10% HCl (8.50 mL). The resulting solution was stirred at reflux for 15 min, when, upon cooling to room temp., the pH was adjusted to 3 with the dropwise addition of 1 N NaOH and sodium periodate (0.304 g, 1.42 mmoles, 2.20 equiv.) was added. The resulting solution was stirred at room temp. for 2 days when several drops of ethylene glycol was added to quench the excess sodium periodate. The resulting mixture was stirred at room temp. for 15 min when the mixture was washed with EtOAc (1 x 15 mL). The organic layer was washed with water (1 x 10 mL) and the pH of the combined aqueous layers was adjusted to 7 with the dropwise addition of 1 N NaOH. The resulting solution was evaporated to about a fourth of the original volume and allowed to crystallize in the refrigerator overnight. The resulting mixture was filtered and the solid material was further purified via anion exchange chromatography

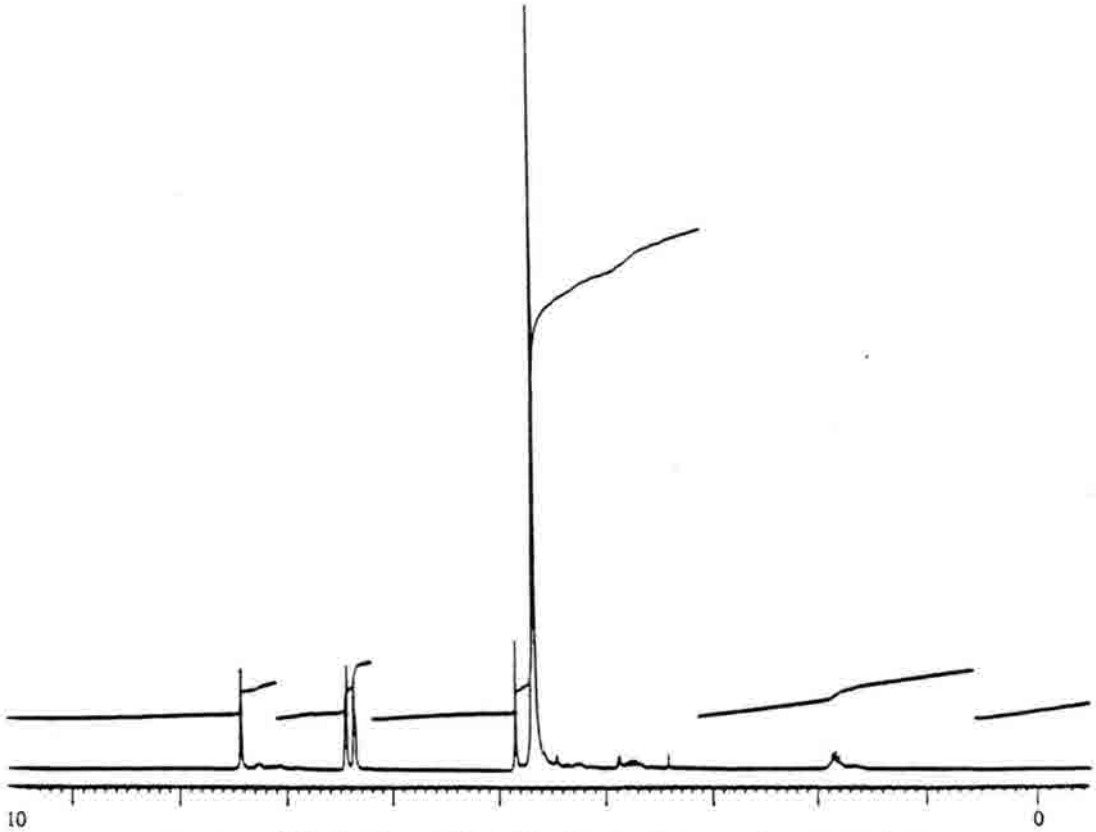
(eluted with 10% HCl, Amberlite IR-45) yielding 30 mg (26 %) of D-α-2-furylglycine hydrochloride (**194d**) as a white amorphous solid. (see data below).



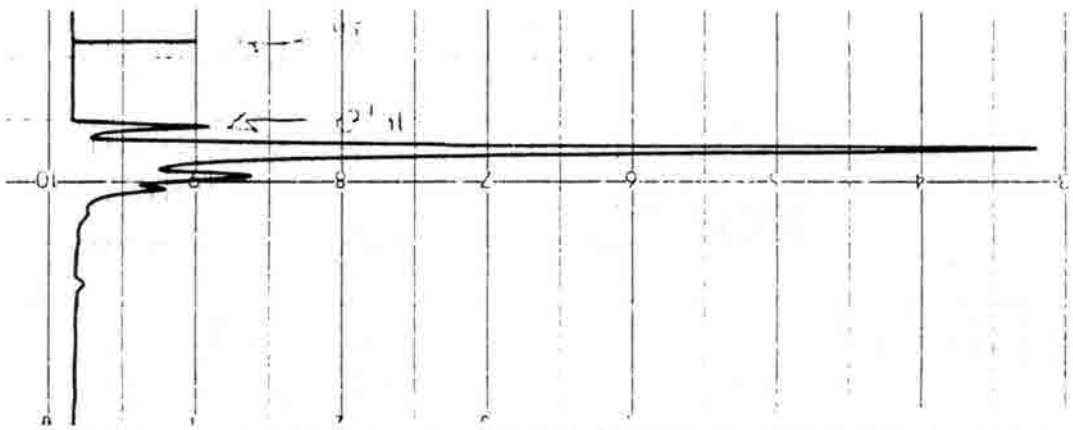
180a **194d**

D-α-2-Furylglycine (194d, Ar = 2-furyl). To a stirred suspension of 5% palladium on activated carbon (75 mg) in absolute MeOH (40.00 mL) charged with hydrogen was added a solution of (3R, 5R, 6S)-4-benzyloxycarbonyl-5,6-diphenyl-3-(2'-furyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (**180a**) (383 mg, 0.846 mmoles, 1.00 equiv.) in dry THF (11.50 mL) via syringe. Compound **180a** was prepared via standard and previously reported conditions.[67] The resulting mixture was stirred at room temp. under hydrogen (1 atm) for 2 h when the resulting mixture was purged with nitrogen, filtered through a plug of celite, and evaporated to dryness. The predominantly white solid was washed with THF, filtered, and the water soluble white solid was collected and dried. This solid was further purified by filtering an aqueous solution through a C_{18} silica plug followed by cation exchange chromatography (eluted with 1N $NH_{3\,(aq)}$, Dowex 50W-X8), and recrystallization from absolute EtOH yielding 68 mg (57 %) of D-α-2-furylglycine (**194d**) as a white solid. ^{1}H NMR: (270 MHz) (D_2O) δ HOD: 4.84 (s, 1 H), 6.36 (q, J=1.2 Hz, 1 H), 6.45 (d, J=3.3 Hz,1 H), 7.43 (d, J=1.5 Hz, 1 H). ^{1}H NMR: (d_6-DMSO) δ DMSO: 1.87 (m, 2 H), 5.05 (s, 1 H), 6.49 (d, J=3.3 Hz, 1 H), 6.57 (d, J=3.2 Hz, 1 H), 7.72 (br. s, 1 H). IR: (NaCl, mineral oil) 3445, 3169, 3015, 2849, 1605, 1513, 1380, 1215, 1159,

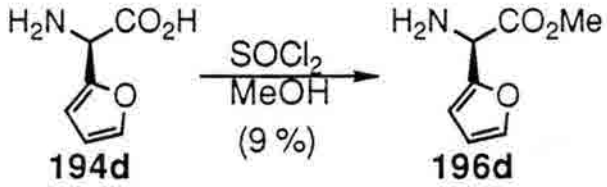
759, 667 cm^{-1}. MS: *m/e* (relative intensity) CI (NH_3): 142 (17.2), 141 (0.5), 125 (1.5), 111 (3.2), 98 (42.3), 96 (100.0), 93 (30.2), 81 (10.9), 69 (2.9), 64 (3.0), 56 (1.3), 54 (1.6), 46 (1.4), 44 (1.6), 39 (4.9), 35 (100.0), 32 (20.2). Mp: 159-161° C (recryst. abs. EtOH). $[\alpha]^{25}_D$: -32.0° (*c* 0.05, H_2O).



270 MHz ^1H NMR of **194d** in D_2O at room temperature.

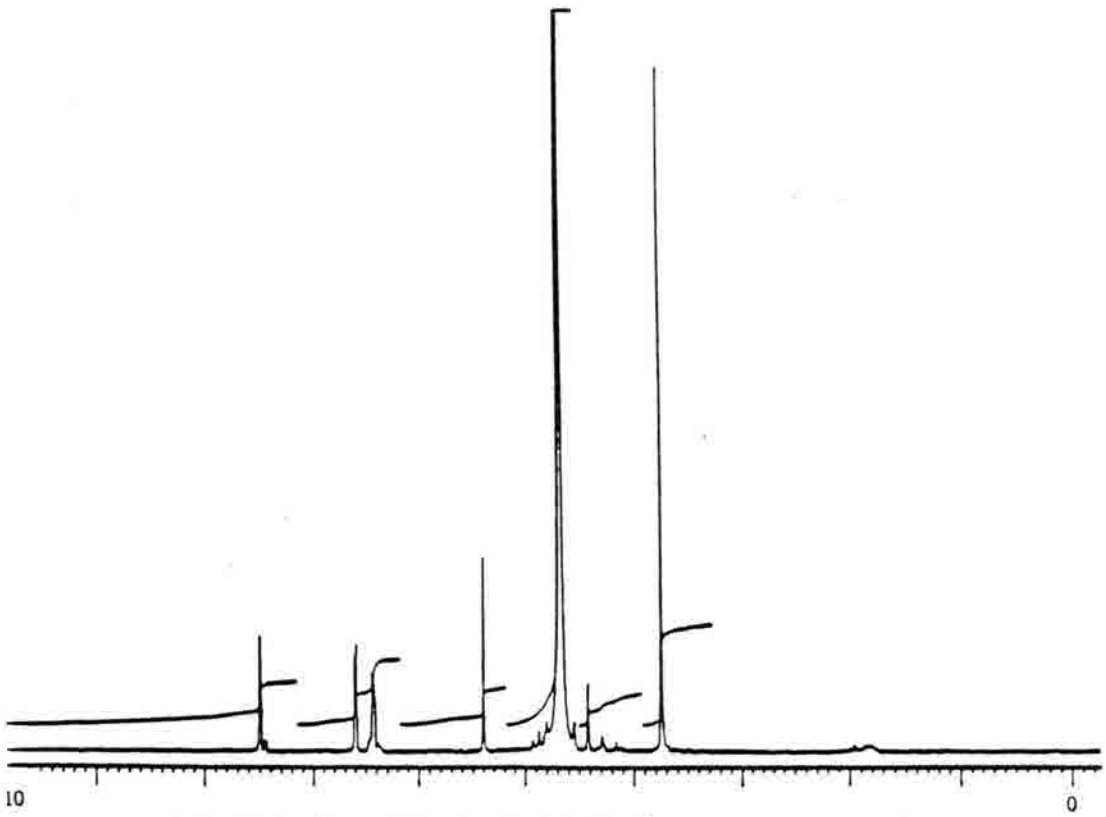


HPLC trace of D-Furylglycine (**194d**), Crownpak CR(+) chiral column; perchloric acid buffer (pH 2); flow rate: 1.00 mL/min.; chart speed: 1.0 cm/s.

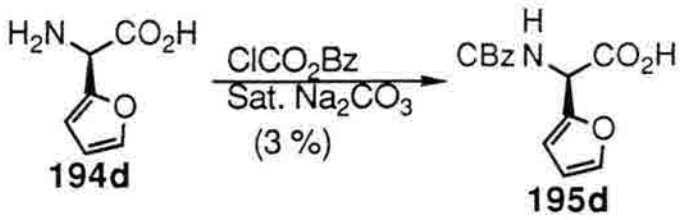


194d **196d**

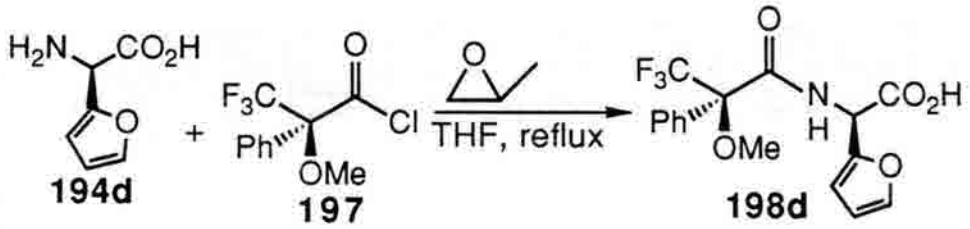
D-α-2-Furylglycine methyl ester (196d, Ar = 2-furyl).[49] To a stirred suspension of D-α-2-furylglycine **194d** (31 mg, 0.22 mmoles, 1.0 equiv.) in absolute methanol (1.00 mL) cooled to 0° C was added thionylchloride (49 μL, 0.68 mmoles, 3.1 equiv.). The resulting solution was stirred at 0° C for 1 hr. and at room temp. overnight. The resulting solution was evaporated, removing the solvent and excess thionylchloride, yielding a crude solid which was recrystallized from EtOAc yielding 3 mg (9 %) of the desired furylglycine methyl ester (**196d**). ^{1}H NMR: (270 MHz) (D_2O) δ HOD: 3.74 (s, 1 H), 5.39 (s, 1 H), 6.43 (m, 1 H), 6.59 (d, J=3.4 Hz, 1 H), 7.49 (d, J=1.5 Hz, 1 H). IR: (NaCl, $CHCl_3$) 3411, 2922, 2850, 1743, 1500, 1247, 1154, 926 cm^{-1}.



200 MHz ^{1}H NMR of **196d** in D_2O at room temperature.

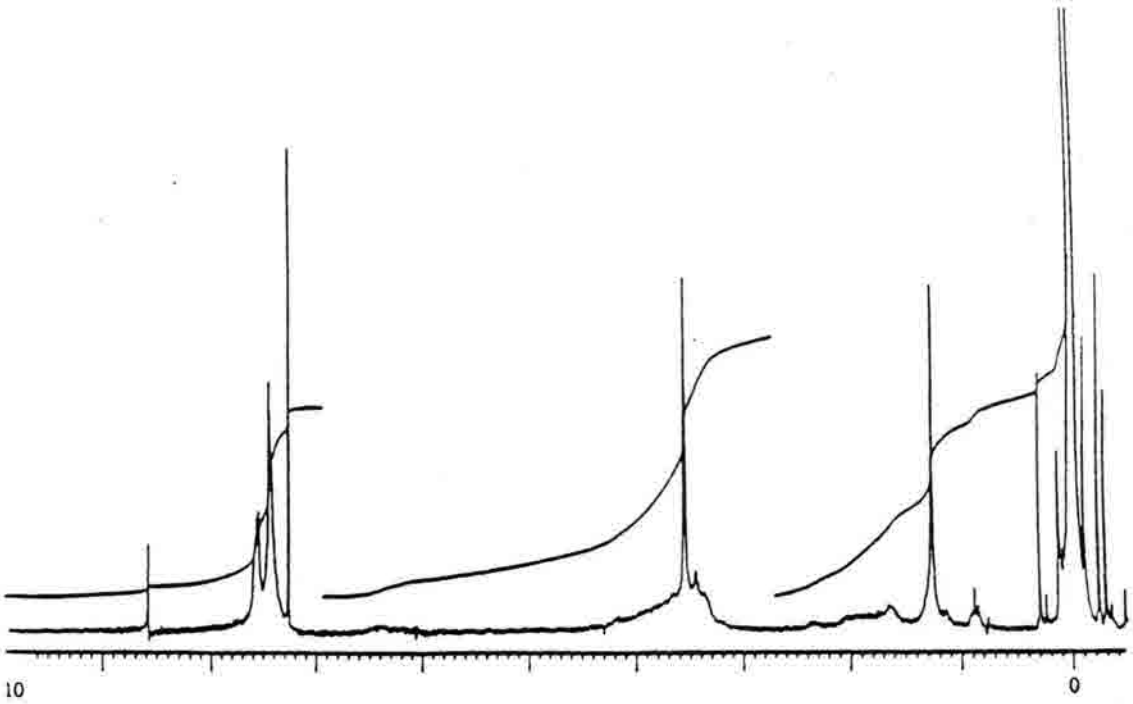


N-Benzyloxycarbonyl-α-2-furylglycine (195d, Ar = 2-furyl).[26b, 88] To a stirred solution of D-α-2-furylglycine (**194d**) (68 mg, 0.482 mmoles, 1.00 equiv.) in saturated sodium carbonate (2.50 mL) was added ethanol to aid in the solubility of the amino acid. To the resulting mixture was added benzyl chloroformate (76 μL, 0.530 mmoles, 1.10 equiv.). The resulting solution was vigorously stirred at room temp. for 2 h when the yellow mixture was thoroughly extracted with CH_2Cl_2 (5 x 4 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The orange, oily residue was triturated with Et_2O and the white solid was collected yielding 4 mg (3 %) of the desired product (**195d**). ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 1.22 (s, 1 H), 5.12 (s, 2 H), 5.29 (d, 1 H), 5.80 (br. s, 1 H), 6.33 (d, 2 H), 7.32 (s, 5 H), 11.53 (s, 1 H). IR (NaCl, $CHCl_3$): 3400, 3067, 3033, 2956, 1744, 1700, 1622, 1494, 1456, 1261, 1217, 1167, 1017, 978, 739, 694 cm^{-1}. MS: *m/e* (relative intensity) CI(NH_3): 276 (21.6), 275 (16.2), 230 (8.3), 211 (2.4), 198 (25.7), 184 (6.1), 168 (10.8), 141 (1.1), 126 (10.4), 106 (100.0), 88 (30.7), 71 (17.8), 52 (13.3). $[\alpha]^{25}_D$: -31.1° (*c* 0.09, CH_2Cl_2).

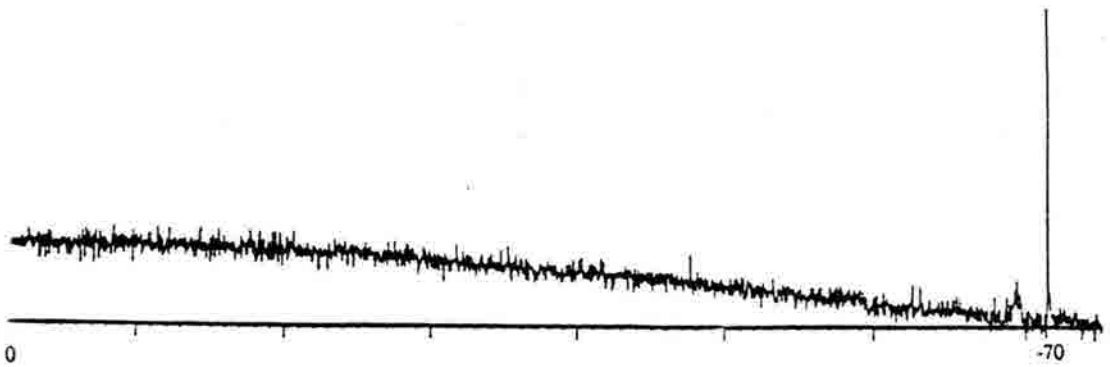


((2-Methoxy-3,3,3-trifluoro-1-oxo-2-phenylpropyl)amino)-2'-furylacetic acid (198d, Ar = 2-furyl).[87] To a stirred suspension of D-α-2-furylglycine (**194d**) (30 mg, 0.170 mmoles, 1.00 equiv.) in dry THF (1.00 mL)

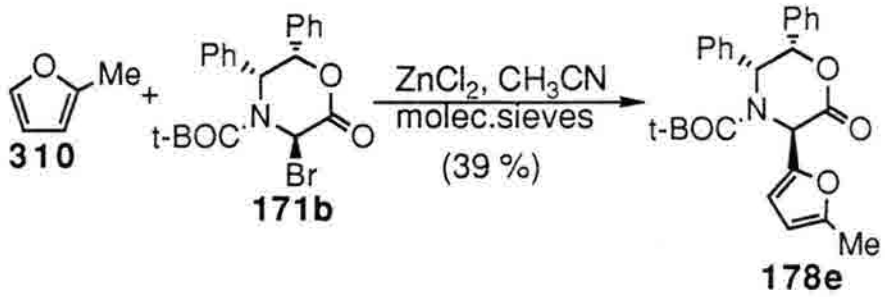
was added propylene oxide (48 μL, 0.680 mmoles, 4.00 equiv.) and (S)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride (**197**) (26 μL, 0.170 mmoles, 1.00 equiv.). The resulting mixture was heated at reflux for 20 min, cooled to room temp., filtered, and evaporated yielding a crude mixture which was separated via PTLC (7:2:1, Hex/$CHCl_3$/EtOAc) yielding 2 mg of the desired Mosher Amide. ^1H NMR: (200 MHz) ($CHCl_3$) δ TMS: 1.26 (br. s, 1 H), 1.54 (s, 3 H), 3.32 (s, 1 H), 6.97-7.39 (m, 8 H). ^{19}F NMR: (188 MHz) ($CDCl_3$) δ $CFCl_3$ -69.47 (s). 90 % ee of D-α-2-furylglycine.



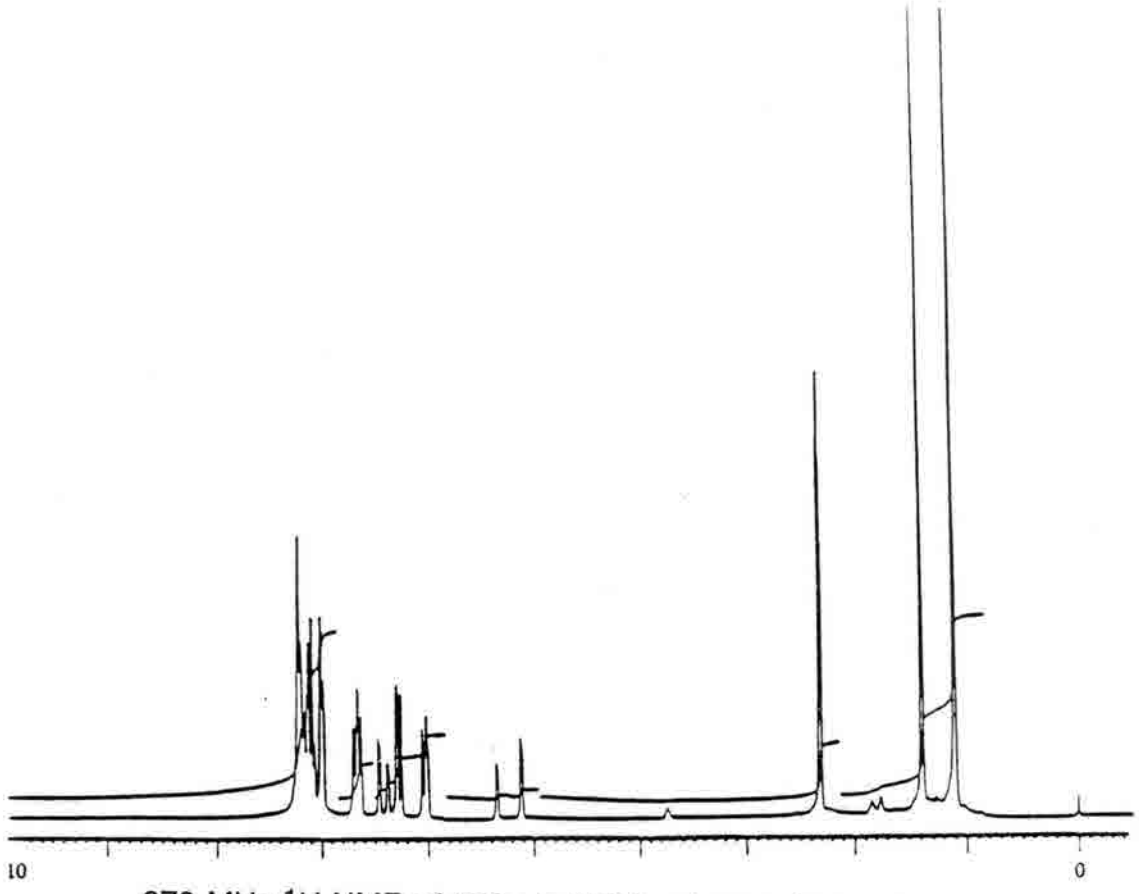
200 MHz ^1H NMR of **198d** (D) in $CDCl_3$ at room temperature.



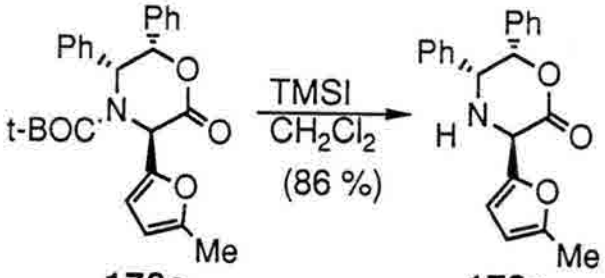
188 MHz ^{19}F NMR of **198d** (D) in $CDCl_3$ with $CFCl_3$ at room temperature.



(3R,5R,6S)-4-*tert*-butoxycarbonyl-5,6-diphenyl-3-(2'-(5'-methyl)furyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (178e, Ar = 2-(5'-methyl)furyl). To a solution of **171b**[67] (0.432 g, 1.00 mmoles, 1.00 equiv.) in CH_3CN (7.00 mL) stirred over powdered molec. sieves (1 g, 4 Å) was added 2-methylfuran (1.35 mL, 15.00 mmoles, 15.00 equiv.) and zinc chloride (2.00 mL, 2.00 mmoles, 2.00 equiv., 1.0 M in THF). The resulting solution was stirred at room temp. for 4 h and the solution was filtered into water (20 mL). The resulting mixture was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The residue was separated via column chromatography (7:2:1, Hex/$CHCl_3$/EtOAc) yielding 170 mg (39 %) of the desired product (**178e**) as a white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 1.09 (s, 5 H), 1.38 (s, 4 H), 2.29 (s, 3 H), 5.11 (d, J=2.7 Hz, 1 H), 5.35 (d, J=2.0 Hz, 1 H), 6.01-6.05 (m, 1 H), 6.25-6.29 (m, 1 H), 6.38 (d, J=2.8 Hz, 1 H), 6.44 (d, J=2.9 Hz, 1 H), 6.63-6.69 (m, 2 H), 6.98-7.22 (m, 7 H). IR: (NaCl, $CHCl_3$) 3058, 3021, 2970, 2909, 1758, 1742, 1685, 1591, 1572, 1489, 1445, 1365, 1268, 1211, 1195, 1170, 1160, 1010, 744, 688, 650, 579 cm^{-1}. MS: *m/e* (relative intensity) CI (NH_3): 434 (0.5), 430 (1.6), 429 (8.8), 428 (29.5), 395 (10.8), 378 (2.5), 334 (7.5), 289 (14.6), 252 (11.4), 214 (29.7), 197 (100), 105 (65.6), 95 (46.1). Anal. Calcd for $C_{26}H_{27}NO_5$: C, 72.04; H, 6.28; N, 3.23. Found: C, 72.02; H, 6.40; N, 3.13. Mp: 213-215° C (recryst. EtOAc/Hex). $[\alpha]^{25}_D$: -21.2 ° (*c* 1.00, CH_2Cl_2).



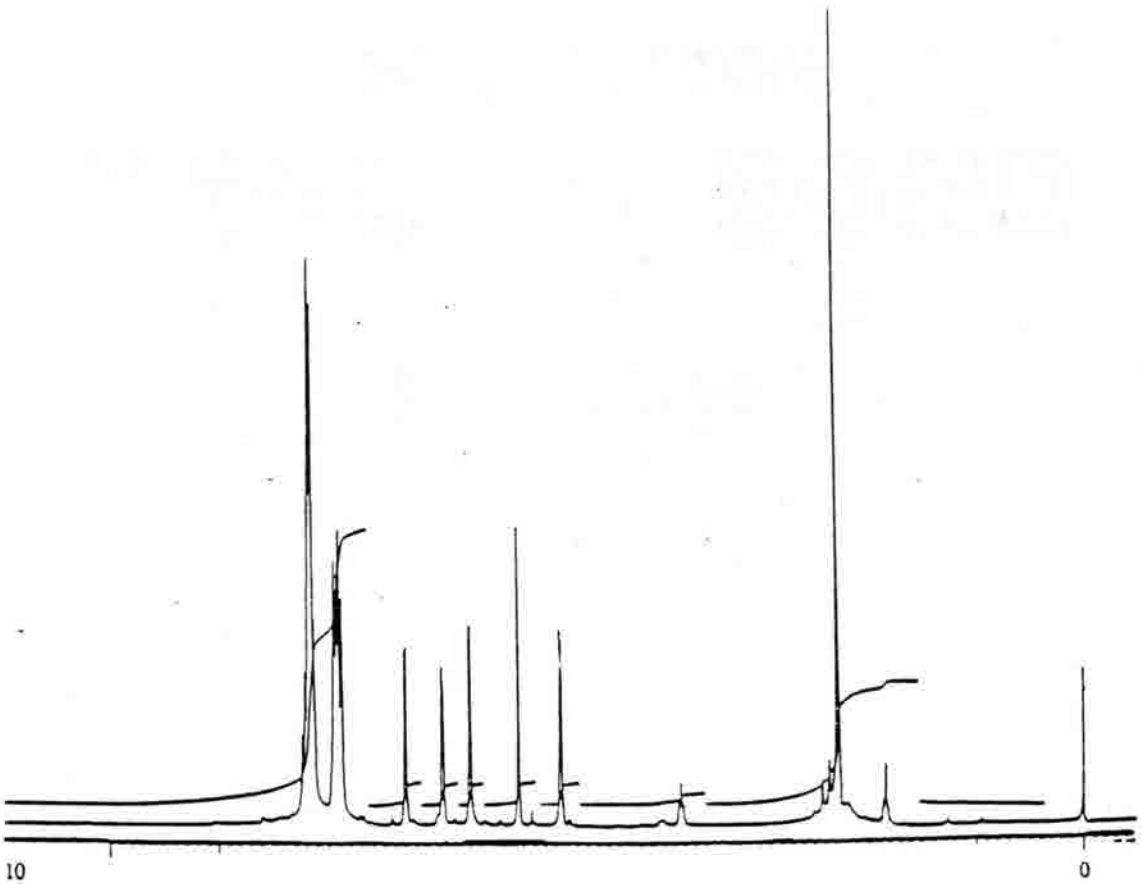
270 MHz ^{1}H NMR of **178e** in $CDCl_3$ at room temperature.



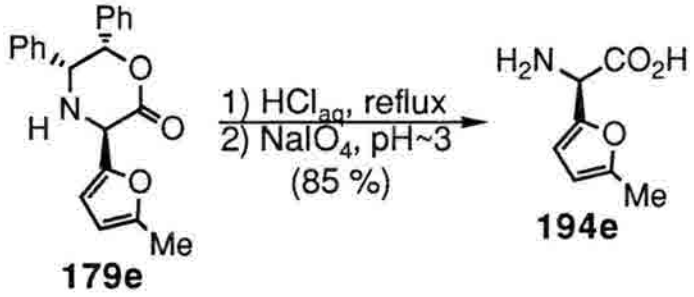
178e **179e**

(3R,5R,6S)-5,6-diphenyl-3-(2'-(5'-methyl)furyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (179e, Ar = 2-(5'-methyl)furyl).[86] To a stirred solution of **178e** (108 mg, 0.249 mmoles, 1.00 equiv.) in dry CH_2Cl_2 (2.50 mL) was added trimethylsilyl iodide (85 μL, 0.598 mmoles, 2.40 equiv.). The resulting orange solution was stirred at room temp. for 10 min and the reaction was quenched with the addition of water (5 mL). The resulting mixture

was separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with 1 M $Na_2S_2O_3$ (2 x 5 mL), dried (Na_2SO_4), filtered, and evaporated. The resulting oil was separated via PTLC silica gel (7:2:1, Hex/$CHCl_3$/EtOAc) yielding 71 mg (86 %) of the desired product **179e** as an amber oil. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 2.27 (br. s, 1 H), 4.85 (d, J=4.0 Hz, 1 H), 5.24 (s, 1 H), 5.69 (d, J=4.0 Hz, 1 H), 5.96 (d, J=0.9 Hz, 1 H), 6.30 (d, J=3.1 Hz, 1 H), 6.87-7.21 (m, 10 H). IR: (NaCl, neat) 3330, 3030, 2920, 1750, 1734, 1491, 1448, 1210, 1200, 1195, 1012, 760, 692, 686 cm^{-1}. MS: *m/e* (relative intensity) CI (NH_3): 334 (2.5), 333 (0.5), 332 (2.6), 288 (2.9), 214 (47.5), 197 (100.0), 105 (51.9), 95 (2.6), 35 (97.3). $[\alpha]^{25}_D$: -150.9 ° (*c* 0.84, CH_2Cl_2).

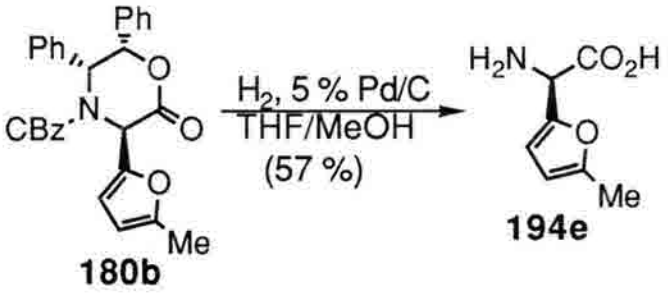


270 MHz ^1H NMR of **179e** in $CDCl_3$ at room temperature.



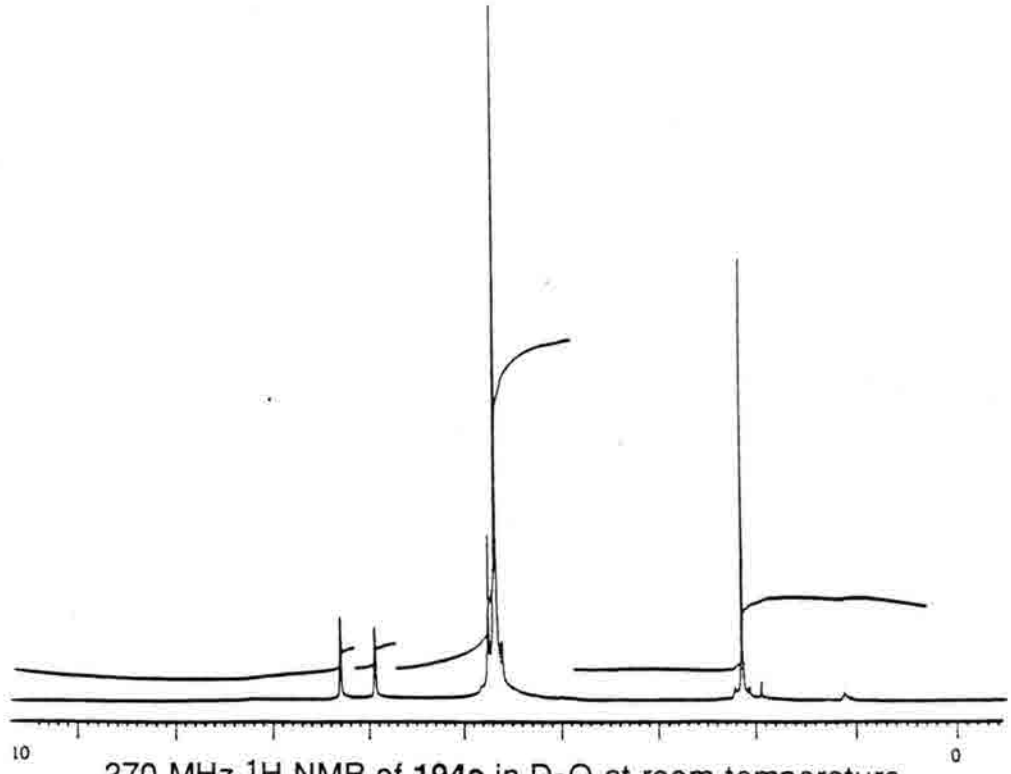
179e **194e**

D-α-amino-2-(5'-methyl)furylacetic acid (194e, Ar = 2-(5'-methyl)furyl).[44] A stirred suspension of **179e** (174 mg, 0.521 mmoles, 1.00 equiv.) in water (4.50 mL) and 10 % hydrochloric acid (1.75 mL) was heated at reflux for 30 min. When most of the organic material went into solution, the mixture was cooled to room temp., washed with CH_2Cl_2 (3 x 3 mL) and the aqueous layer was evaporated. The resulting white solid was taken up in water (10.60 mL) and sodium periodate (245 mg, 1.15 mmoles, 2.20 equiv.) was then added. The pH of the resulting suspension was adjusted to 3 with the dropwise addition of 1 N NaOH. The resulting mixture was stirred at room temp. for 36 h when the pH was adjusted to 5.5 with the dropwise addition of 1 N NaOH and several drops of propylene glycol were added (to destroy excess $NaIO_4$). The resulting solution was stirred at room temp. for 15 min and the resulting mixture was washed with EtOAc (3 x 5 mL) and the aqueous layer was evaporated yielding a pure white solid mixture. This white solid mixture was separated via cation exchange chromatography (eluted with 1N $NH_{3\ (aq)}$, Dowex 50W-X8) yielding 69 mg (85 %) of D-α-amino-2-(5'-methyl)furylacetic acid (**194e**) as a white solid. (Spectral data is given below).

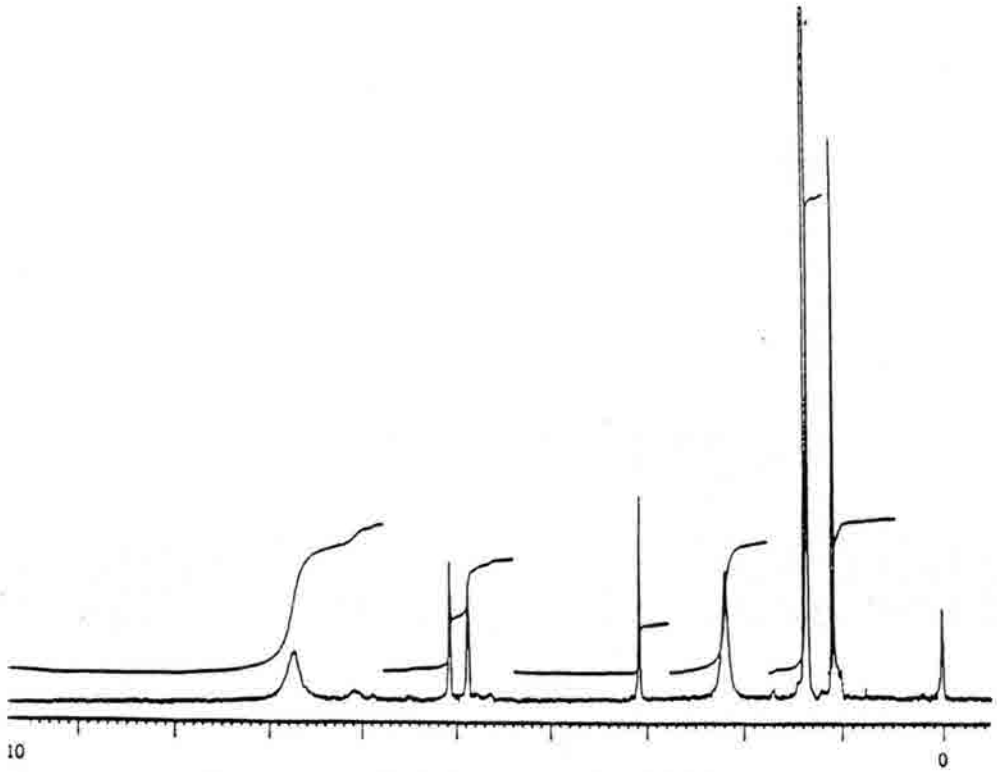


180b **194e**

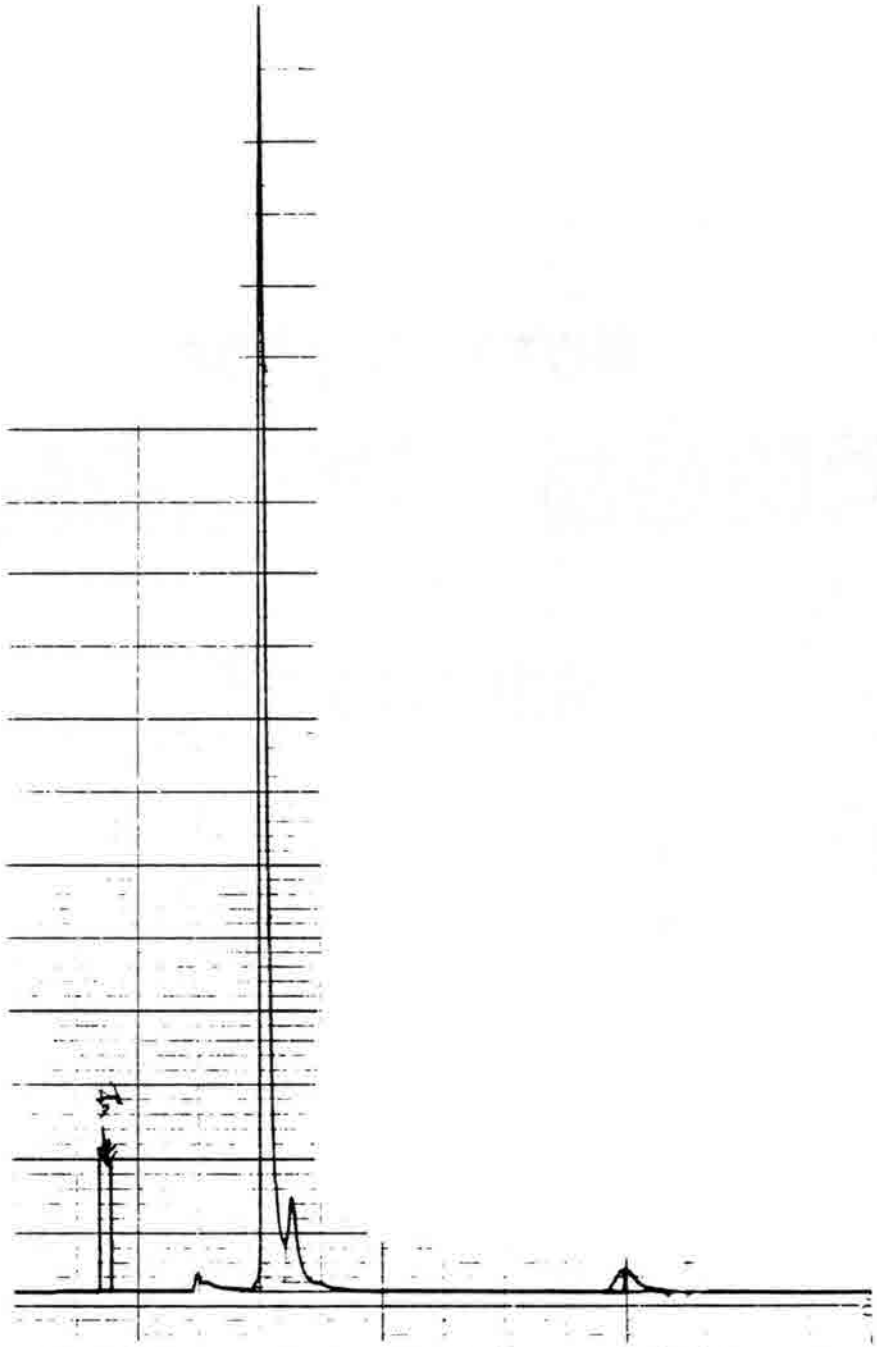
D-α-amino-2-(5'-methyl)furylacetic acid (194e, Ar = 2-(5'-methyl)furyl). To a stirred suspension of 5% palladium on activated carbon (177 mg) in absolute MeOH (75.00 mL) charged with hydrogen was added a solution of (3R, 5R, 6S)-4-benzyloxycarbonyl-5,6-diphenyl-3-(2'-(5'-methyl)furyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (**180b**) (798 mg, 1.71 mmoles, 1.00 equiv.) in dry THF (25.00 mL) via syringe. Compound **180b** was prepared via standard and previously reported conditions.[67] The resulting mixture was stirred at room temp. under hydrogen (1 atm) for 5 h and the resulting mixture was purged with nitrogen, filtered through a plug of celite, and evaporated to dryness. The predominately white solid was washed with THF, filtered, and the water soluble white solid was collected and dried yielding 216 mg (82%) of D-α-amino-2-(5'-methyl)furylacetic acid (**194e**) as a white solid. ^{1}H NMR: (270 MHz) (d_6-DMSO) δ DMSO: 2.22 (s, 3 H), 3.31 (br. s, 2 H), 4.20 (s, 1 H), 6.01 (br. s, 1 H), 6.19 (d, J=2.8 Hz, 1 H), 7.87 (br. s, 1 H). IR: (NaCl, mineral oil) 3413, 3178, 2919, 2849, 2625, 2355, 1608, 1501, 1455, 1378, 1108, 1020, 785, 720 cm^{-1}. MS: *m/e* (relative intensity) CI (NH_3): 156 (2.3), 155 (0.3), 139 (4.8), 125 (15.7), 110 (52.3), 95 (5.5), 83 (1.1), 52 (7.3), 36 (13.7), 35 (100.0), 32 (20.3). Anal. Calcd for $C_7H_9NO_3$: C, 59.19; H, 5.85; N, 9.03. Found: C, 54.31; H, 6.05; N, 9.18. Mp: 161-163° C (recryst. EtOH). $[\alpha]^{25}_D$: -22.3° (*c* 1.00, H_2O).



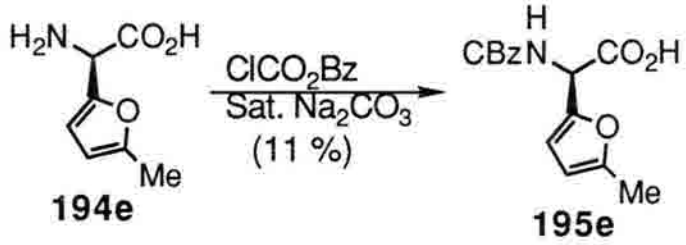
270 MHz ^{1}H NMR of **194e** in D_2O at room temperature.



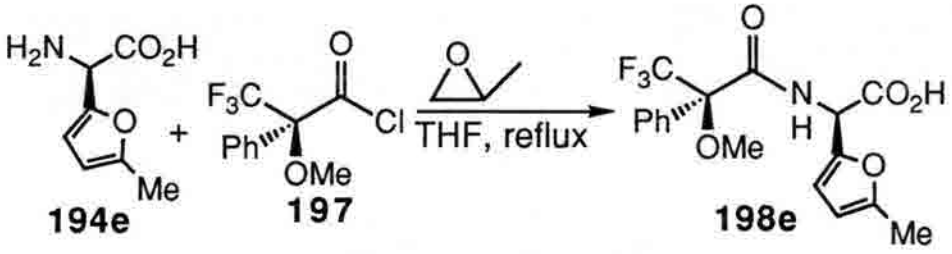
270 MHz ^{1}H NMR of **194e** in d_6-DMSO at room temperature.



HPLC trace of D-5-Methylfurylglycine (194e), Crownpak CR(+) chiral column; perchloric acid buffer (pH 2); flow rate: 1.00 mL/min.; chart speed: 1.0 cm/s.

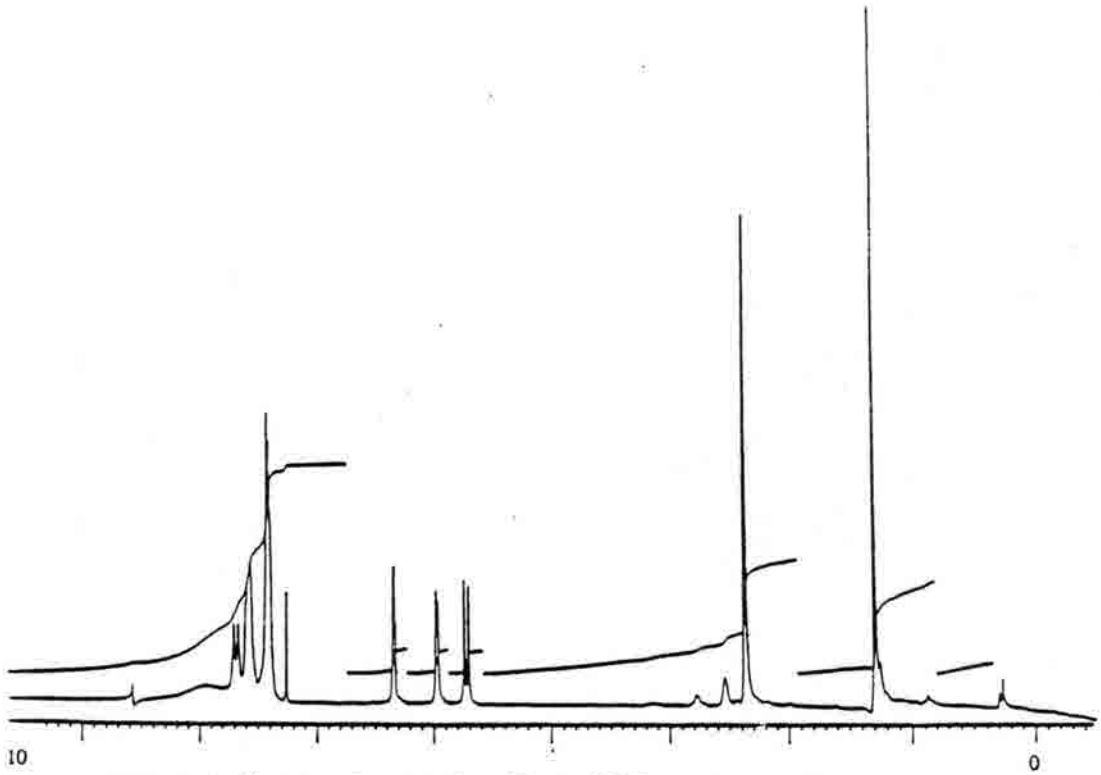


N-Benzyloxycarbonyl-2-(5'-methyl)furylacetic acid (195e, Ar = 2-(5'-methyl)furyl).[26b, 88] To a stirred solution of D-α-amino-2-(5'-methyl)furylacetic acid (**194e**) (20 mg, 0.129 mmoles, 1.00 equiv.) in saturated sodium carbonate (0.50 mL) was added benzyl chloroformate (19 μL, 0.136 mmoles, 1.10 equiv.). The resulting solution was vigorously stirred at room temp. for 2 h when the resulting yellow mixture was thoroughly extracted with CH_2Cl_2 (4 x 2 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The oily residue was purified via PTLC (5:3:2; hexanes/$CHCl_3$/EtOAc) yielding 4 mg (11 %) of the desired product (**195e**) as a clear, colorless oil. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 1.25 (br. s, 1 H), 2.23 (s, 3 H), 5.12 (s, 2 H), 5.45 (d, J=7.7 Hz, 1 H), 5.91 (d, J=1.2 Hz, 1 H), 6.20 (d, J=2.9 Hz, 1 H), 7.34 (s, 5 H). IR: (NaCl, neat) 3333, 2956, 2889, 1750, 1722, 1456, 1344, 1322, 1194, 1067, 967, 928, 733, 700 cm^{-1}. MS: *m/e* (relative intensity) CI (NH_3): 288 (0.3), 146 (5.7), 104 (0.5), 88 (17.2), 71 (22.8), 58 (14.3), 56 (13.1).

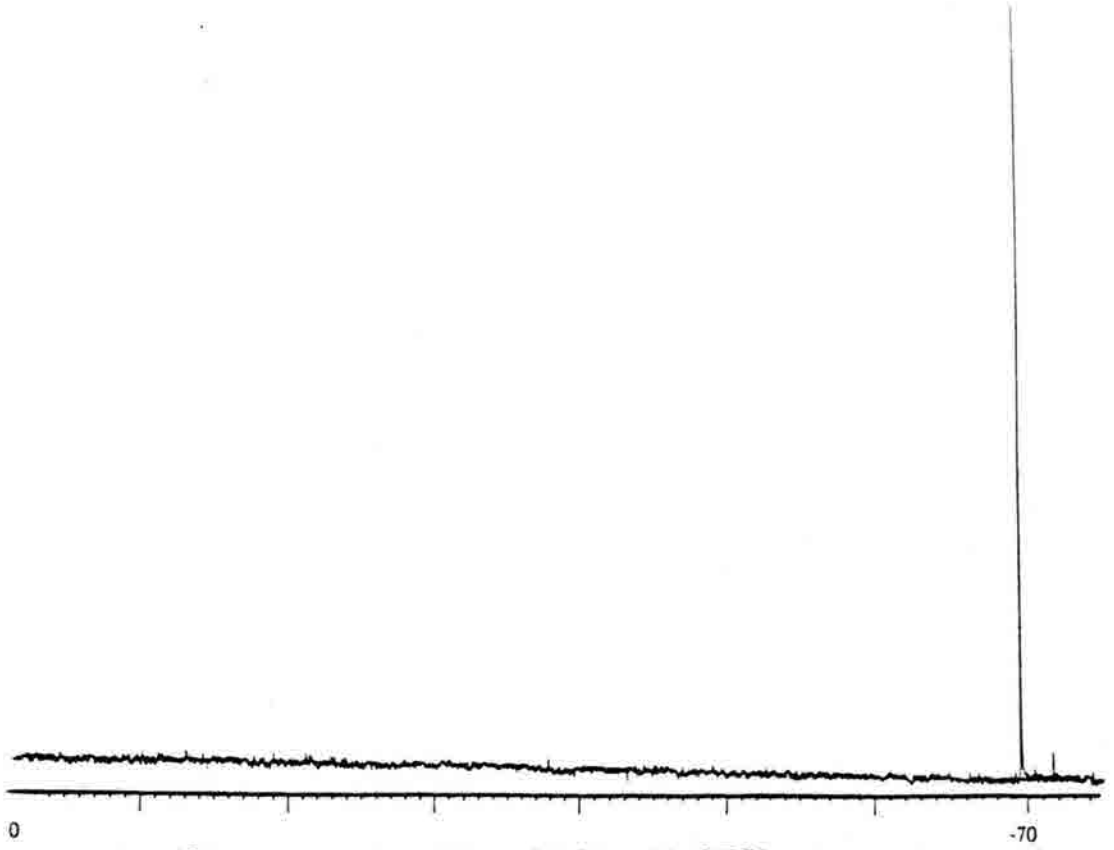


((2-Methoxy-3,3,3-trifluoro-1-oxo-2-phenylpropyl)amino)-2'-(5''-methyl)furylacetic acid (198e, Ar = 2-(5'-methyl)furyl).[87] To a stirred suspension of D-α-amino-2-(5'-methyl)furylacetic acid (20 mg, 0.129 mmoles,

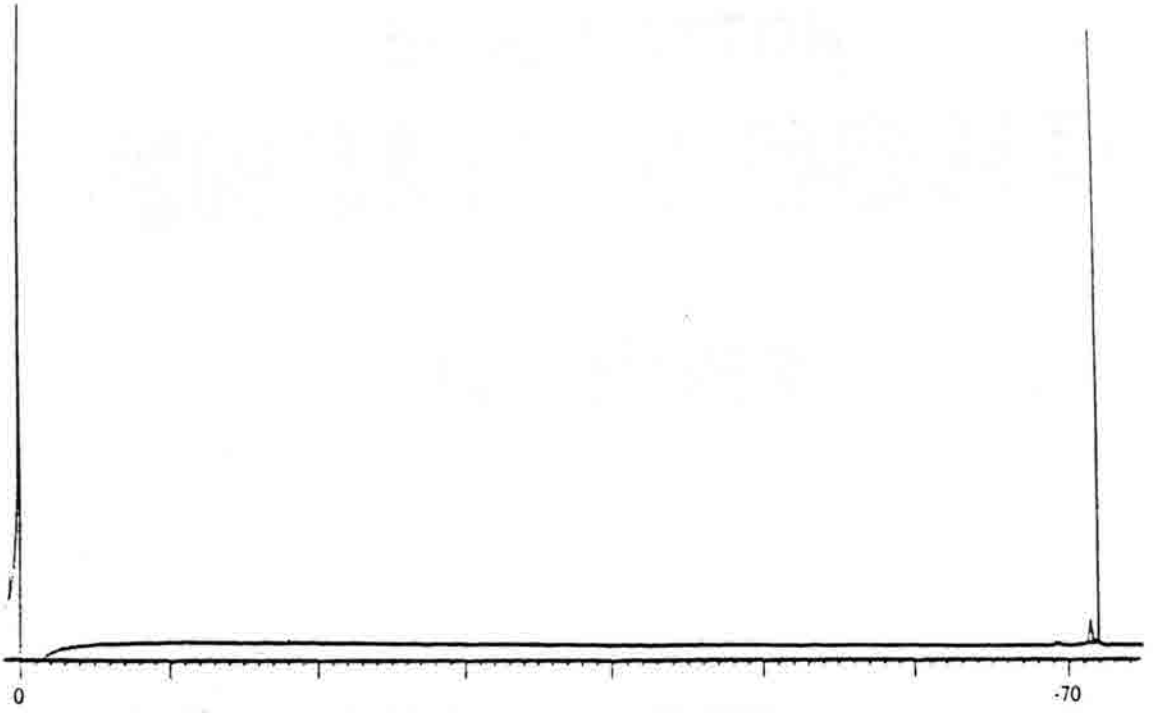
1.00 equiv.) in dry THF (1.00 mL) was added propylene oxide (31 μL, 0.516 mmoles, 4.00 equiv.) and (S)-(-)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid chloride (**197**) (19 μL, 0.129 mmoles, 1.00 equiv.). The resulting mixture was heated at reflux for 20 min, cooled to room temp., filtered, and evaporated yielding 23 mg (43 %) of the desired product (**198e**) as a white solid. ^{1}H NMR: (200 MHz) ($CHCl_3$) δ TMS: 1.28 (br. s, 1 H), 2.29 (s, 3 H), 3.37 (s, 3 H), 5.72 (d, J=7.7 Hz, 1 H), 5.97 (d, J=2.5 Hz, 1 H), 6.34 (d, J=3.0 Hz, 1 H), 7.26-7.71 (m, 5 H), 8.60 (br. s, 1 H). ^{19}F NMR: (188 MHz) ($CDCl_3$) δ $CFCl_3$: -71.71 (s, minor peak), -69.60 (s, major peak). 93 % ee of the D-α-amino-2(5'-methyl)furylacetic acid.



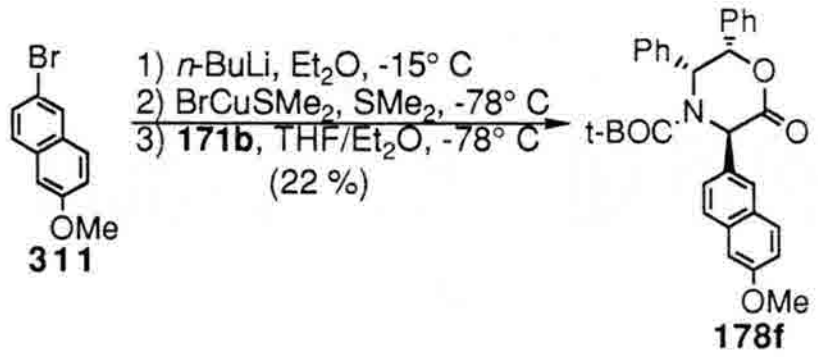
200 MHz ^{1}H NMR of **198e** (D) in $CDCl_3$ at room temperature.



188 MHz ^{19}F NMR of **198e** (D) in $CDCl_3$ with $CFCl_3$ at room temperature.

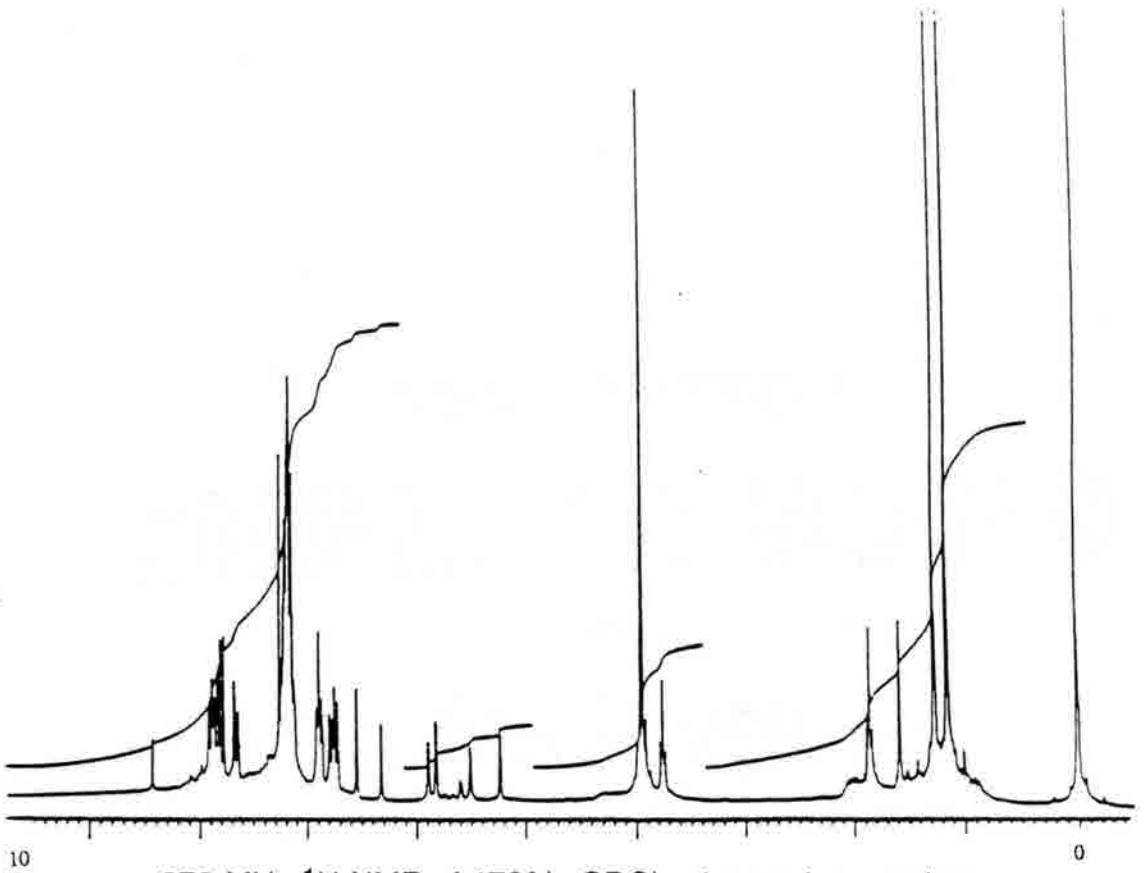


188 MHz ^{19}F NMR of **198e** (L) in $CDCl_3$ with $CFCl_3$ at room temperature.

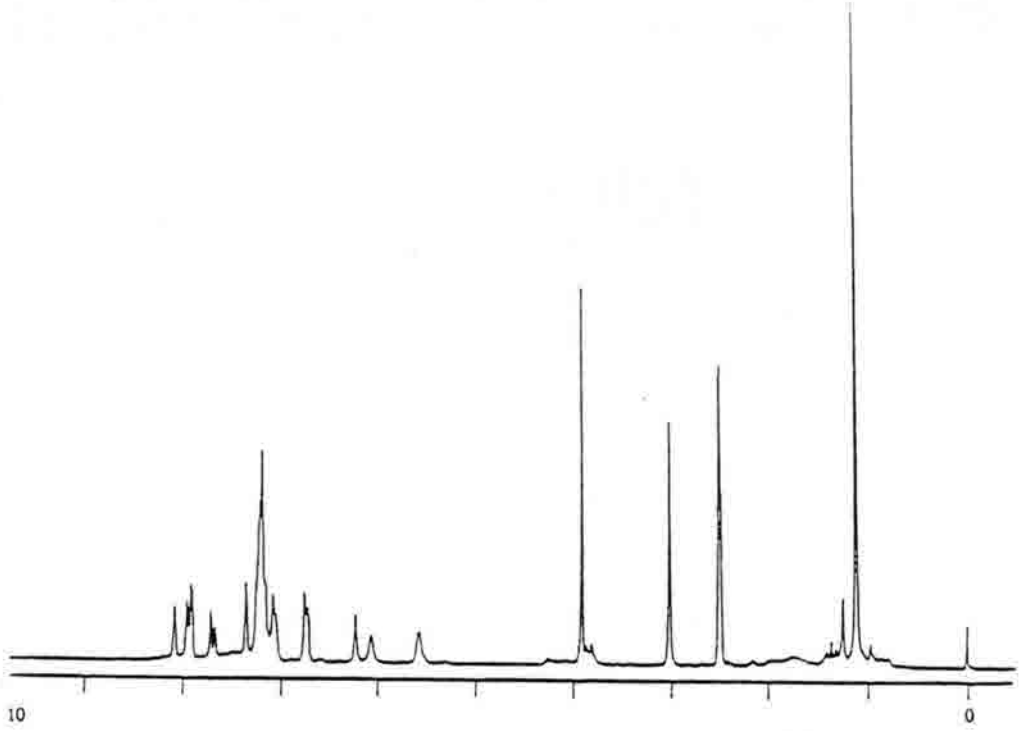


(3R,5R,6S)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-3-(2'-(6'-methoxy)naphthyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (178f, Ar = 2-(6'-methoxy)naphthyl). To a stirred suspension of 2-bromo-6-methoxynaphthalene (95 mg, 0.400 mmoles, 4.00 equiv.) in dry Et_2O (1.00 mL) cooled to -15° C was added *n*-BuLi (0.26 mL, 0.420 mmoles, 4.20 equiv., 1.6 M in Hex) dropwise. The resulting suspension was stirred at -15° C for 30 min when copper bromide dimethylsulfide (41 mg, 0.200 mmoles, 2.00 equiv.) and dry SMe_2 (0.10 mL) were added. The resulting mixture was stirred at -78° C for 4 h when a solution of **171b**[67] (43 mg, 0.100 mmoles, 1.00 equiv.) in a 1:1 solution of dry Et_2O and dry THF (3.10 mL) was added via cannula. The resulting mixture was stirred at -78° C for 2 h when a saturated solution of NH_4Cl (2 mL) was added at -78° C. The resulting mixture was allowed to warm to room temp., separated and the aqueous layer was extracted with CH_2Cl_2 (5 x 5 mL). The combined organic layers were washed with 10% HCl (2 x 10 mL), dried (Na_2SO_4), filtered, and evaporated. The residue was separated via PTLC (7:2:1, Hex/$CHCl_3$/EtOAc) yielding 11 mg (22 %) of the desired product (**178f**) as a white solid. ^{1}H NMR: (270 MHz) ($CDCl_3$) δ TMS: 1.15 (s, 6 H), 1.27 (s, 3 H), 3.94 (s, 3 H), 5.23 (d, J=3.1 Hz) and 5.51 (d, J=3.1 Hz) (1 H), 5.82 (d, J=3.1 Hz) and 5.89 (d, J=3.0 Hz) (1 H), 6.32 (s) and 6.54 (s) (1 H), 6.71-6.91 (m, 2 H), 7.12-7.30 (m, 8 H), 7.63-7.91 (m, 6 H). ^{1}H NMR: (200 MHz) (DMSO-d_6 at 385 K)

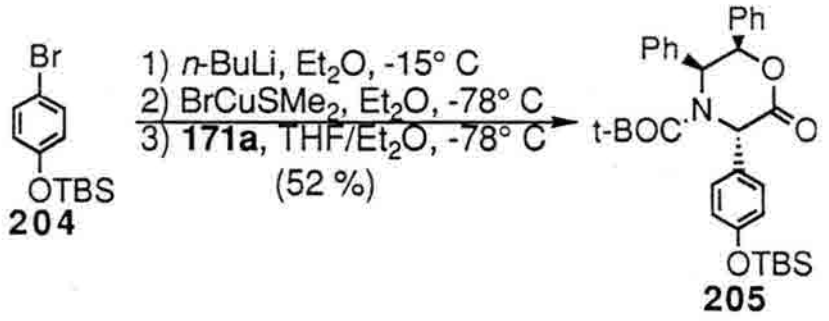
δ DMSO: 1.12 (s, 9 H), 3.90 (s, 3 H), 5.58 (d, J=5.6 Hz, 1 H), 6.07 (br. s,1 H), 6.23 (s, 1 H), 6.72-6.76 (m, 2 H), 7.06-7.26 (m, 9 H), 7.36 (d, J=2.3 Hz, 1 H), 7.67-7.72 (m, 1 H), 7.91 (d, J=3.4 Hz, 1 H), 7.96 (d, J=4.0 Hz, 1 H), 8.09 (s, 1 H). IR: (NaCl, $CHCl_3$) 2978, 2937, 1746, 1700, 1632, 1604, 1485, 1462, 1381, 1347, 1272, 1230, 1167, 1059, 787, 700 cm^{-1}.



270 MHz ^1H NMR of **178f** in $CDCl_3$ at room temperature.

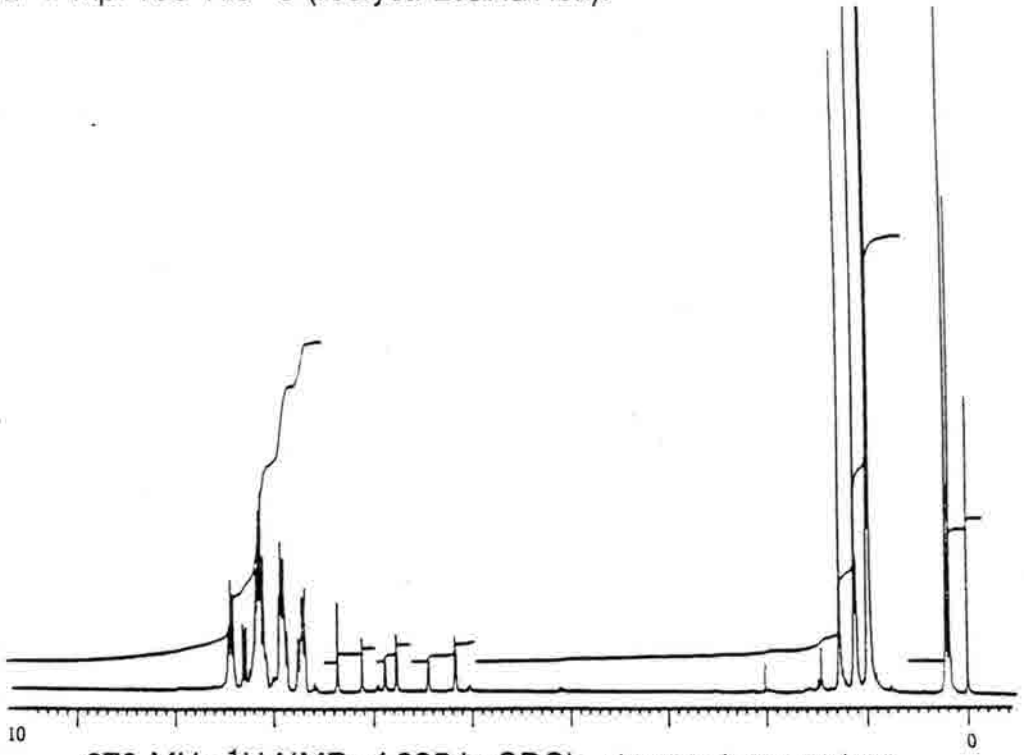


200 MHz ^{1}H NMR of **178f** in d_6-DMSO at 385 K.

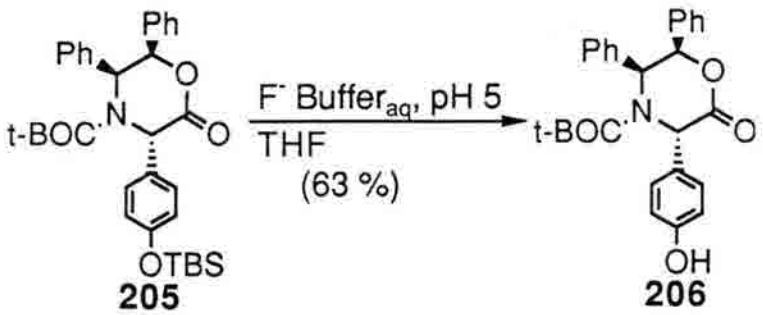


(3S,5S,6R)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-3-(4'-*tert*-butyldimethylsiloxy)phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (205, Ar = 4-*tert*-butyldimethylsiloxyphenyl). To a stirred solution of 4-*tert*-butyldimethylsiloxybromobenzene[89] (**204**) (3.44 g, 12.00 mmoles, 4.00 equiv.) in dry Et_2O (6.00 mL) cooled to -15° C was added *n*-BuLi (7.90 mL, 12.60 mmoles, 4.20 equiv., 1.6 M in Hex) dropwise. The resulting solution was stirred at -15° C for 30 min when additional dry Et_2O (7.50 mL) was added with copper bromide dimethylsulfide (1.23 g, 6.00 mmoles, 2.00 equiv.). The

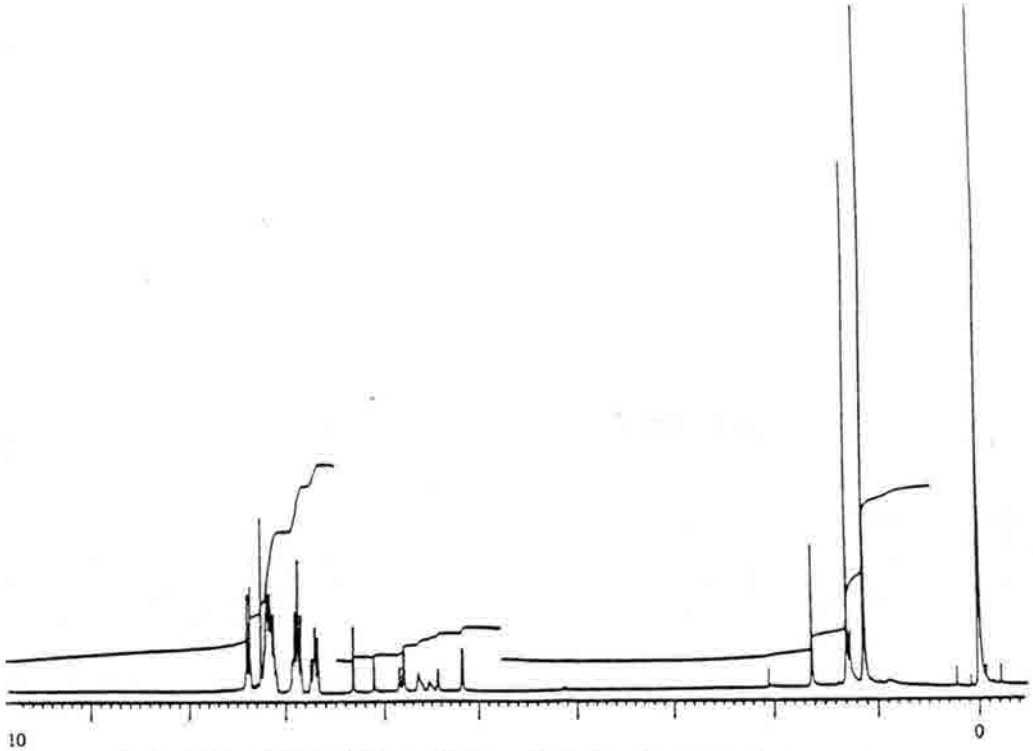
resulting mixture was stirred at -78° C for 4 h when a solution of **171a**[67] (1.30 g, 3.00 mmoles, 1.00 equiv.) in a 1:1 solution of dry Et_2O and dry THF (93.00 mL) was added via cannula. The resulting mixture was stirred at -78° C for 1.5 h when a saturated solution of NH_4Cl (60 mL) was added at -78° C. The resulting mixture was allowed to warm to room temp., separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 60 mL). The combined organic layers were washed with 10% HCl (2 x 90 mL), dried (Na_2SO_4), filtered, and evaporated. The residue was separated via column chromatography (7:2:1, Hex/$CHCl_3$/EtOAc) yielding 866 mg (52 %) of the desired product (**205**) as a white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 0.99 (s, 9 H), 1.12 (s, 3 H), 1.27 (s, 3 H), 1.43 (s, 7 H), 1.57 (s, 2 H), 5.15 (d, J=1.9 Hz) and 5.43 (d, J=1.2 Hz) (1 H), 5.76 (d, J=2.8 Hz) and 5.87 (d, J=2.7 Hz) (1 H), 6.11 (s) and 6.34 (s) (1 H), 6.67-7.44 (m, 14 H). IR: (NaCl, $CHCl_3$) 2954, 2845, 1752, 1703, 1676, 1589, 1507, 1491, 1431, 1393, 1365, 1267, 1218, 1164, 1066, 919, 826, 782, 700 cm^{-1}. Mp: 165-170° C (recryst. EtOAc/Hex).



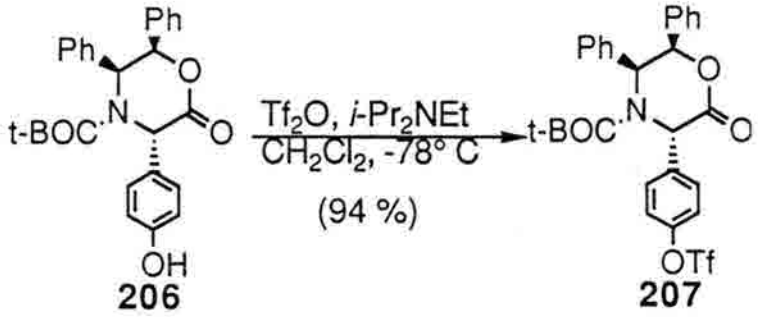
270 MHz ^1H NMR of **205** in $CDCl_3$ at room temperature.



(3S,5S,6R)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-3-(4'-hydroxy)phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (206, Ar = 4-phenol). To a stirred solution of **205** (842 mg, 1.505 mmoles, 1.00 equiv.) in THF (11.60 mL) was added a fluoride buffer solution (4.10 mL, aqueous buffer, pH 5).[74] The resulting solution was stirred at room temp. for 24 h when the mixture was extracted with CH_2Cl_2 (4 x 5 mL) and the combined organic layers were washed with water (20 mL), dried (Na_2SO_4), filtered and evaporated. The residue was separated via column chromatography (5:3:2; Hex/$CHCl_3$/EtOAc) yielding 421 mg (63 %) of the desired product (**206**) as a white solid. ^{1}H NMR: (270 MHz) ($CDCl_3$) δ TMS: 1.14 (s, 6 H), 1.30 (s, 3 H), 5.18 (d, J=2.7 Hz) and 5.44 (d, J=2.5 Hz) (1 H), 5.81 (d, J=2.7 Hz) and 5.86 (d, J=2.5 Hz) (1 H), 6.10 (s) and 6.32 (s) (1 H), 6.32 (br. s, 1 H), 6.68-7.37 (m, 14 H). IR: (NaCl, $CHCl_3$) 3355, 2928, 1742, 1677, 1514, 1455, 1394, 1367, 1272, 1162, 1118, 1057, 755, 698 cm^{-1}. Mp: 212-215° C (recryst. from EtOAc).



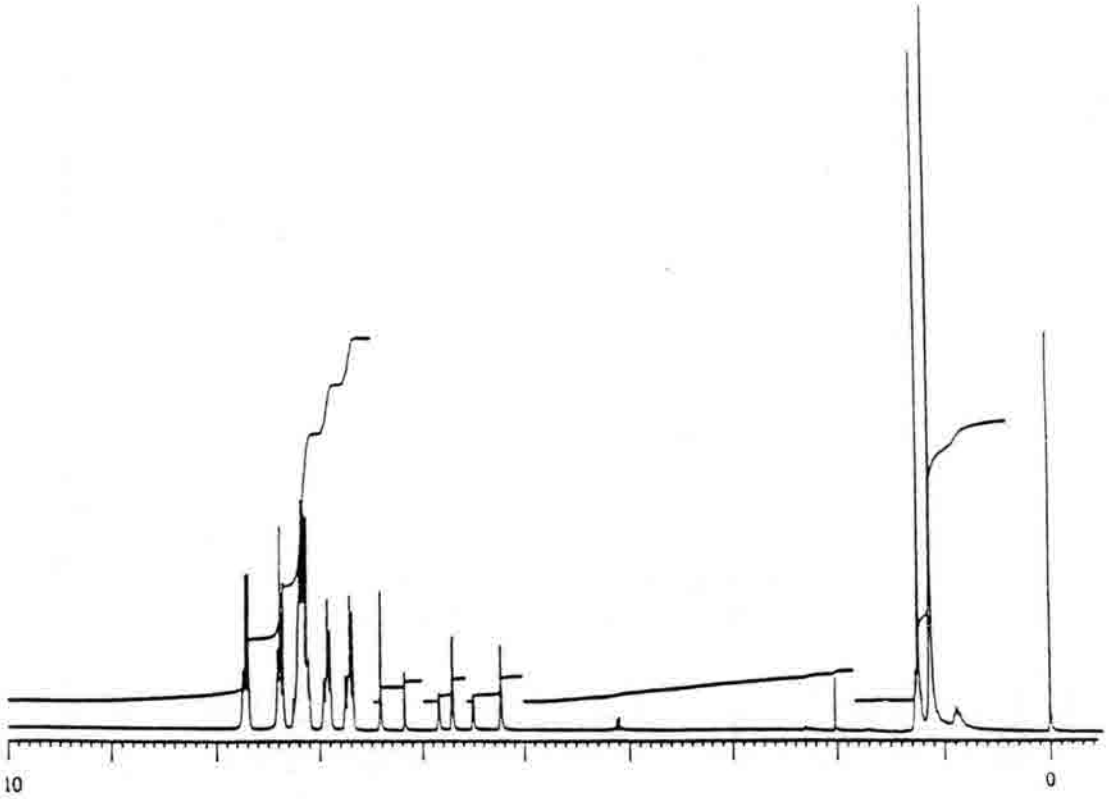
270 MHz ^{1}H NMR of **206** in $CDCl_3$ at room temperature.



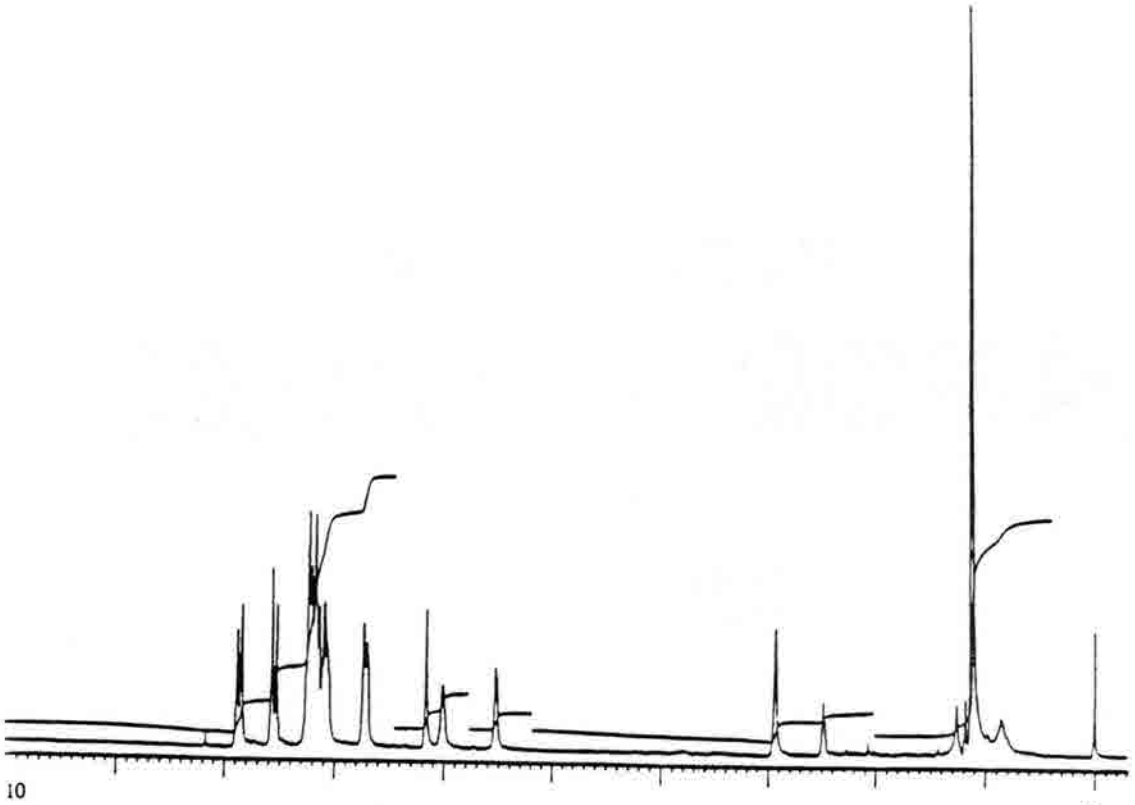
206 **207**

(3S,5S,6R)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-3-(4'-trifluoromethanesulfonato)phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (207, Ar = 4-phenyltriflate).[75] To a stirred solution of **206** (511 mg, 1.147 mmoles, 1.00 equiv.) and dry N,N-diisopropylethylamine (0.60 mL, 3.442 mmoles, 3.00 equiv.) in dry CH_2Cl_2 (17.60 mL) cooled to -78° C was added triflic anhydride (0.24 mL, 1.494 mmoles, 1.25 equiv.). The resulting solution was stirred at -78° C for 6 h when water (12 mL) was added. Upon warming to

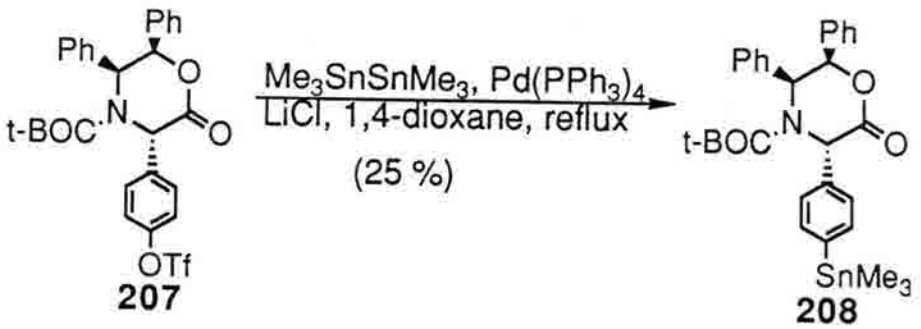
room temp., the mixture was extracted with CH_2Cl_2 (4 x 20 mL) and the combined organic layers were washed with water (60 mL), 10 % $HCl_{(aq)}$ (2 x 60 mL) and water (60 mL), dried (Na_2SO_4), filtered and evaporated. The residue was separated via column chromatography (7:2:1; Hex/$CHCl_3$/EtOAc) yielding 623 mg (94 %) of the desired product (**207**) as a white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 1.13 (s, 5 H), 1.25 (s, 4 H), 5.21 (d, J=2.9 Hz) and 5.49 (d) (1 H), 5.69 (d, J=3.0 Hz) and 5.82 (d, J=2.8 Hz) (1 H), 6.16 (s) and 6.40 (s) (1 H), 6.70 (m, 2 H), 6.93 (m, 2 H), 7.21 (m, 6 H), 7.40 (m, 2 H), 7.71 (m, 2 H). ^1H NMR: (200 MHz) (DMSO-d_6) (390 K) δ TMS: 1.11 (s, 9 H), 5.53 (br. s, 1 H), 6.01 (br. s, 1 H), 6.16 (s, 1 H), 6.73 (m, 2 H), 7.07-7.26 (m, 8 H), 7.55 (d, J=8.8 Hz, 2 H), 7.86 (d, J=8.7 Hz, 2 H). IR: (NaCl, $CHCl_3$) 3029, 2979, 2931, 1746, 1699, 1501, 1428, 1379, 1350, 1219, 1165, 1140, 1058, 890, 767, 701 cm^{-1}. Mp: 209-210° C (recryst. from EtOAc).



270 MHz ^1H NMR of **207** in $CDCl_3$ at room temperature.



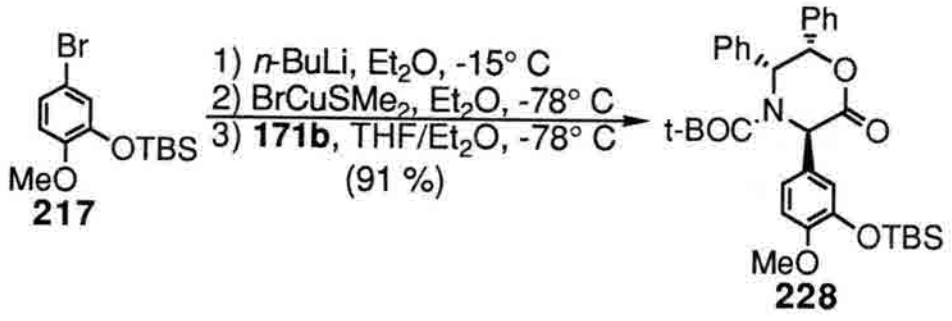
200 MHz ^{1}H NMR of **207** in d_6-DMSO at 390 K.



207 **208**

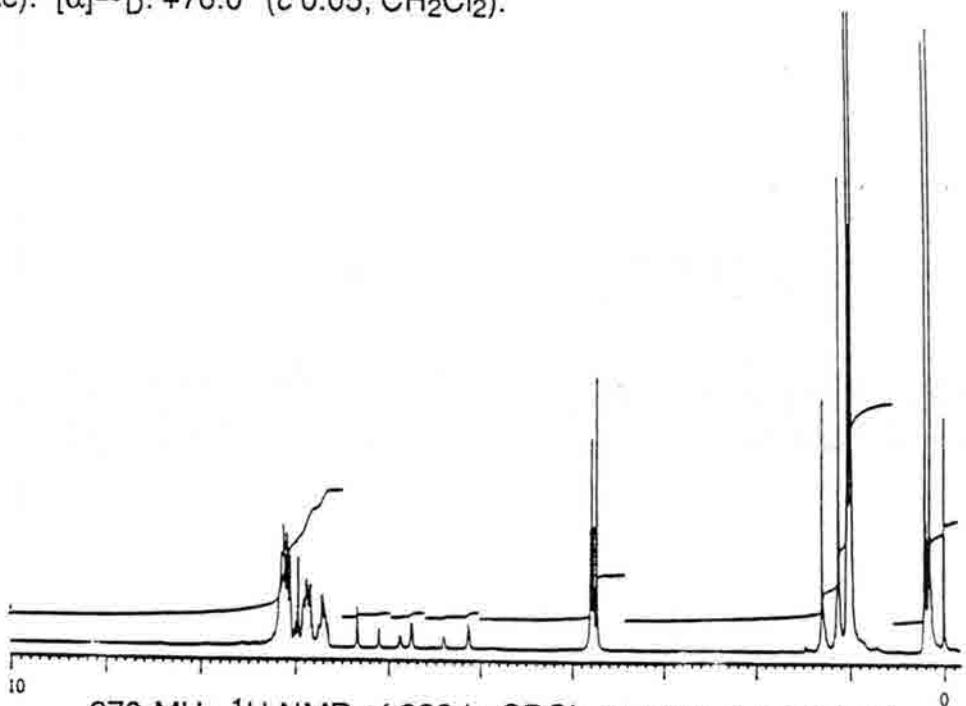
(3S,5S,6R)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-3-(4'-trimethylstannyl)phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (208, Ar = 4-phenyl trimethyltin).[76] To a stirred solution of **207** (289 mg, 0.500 mmoles, 1.00 equiv.) in dry 1,4-dioxane (5.00 mL) was added hexamethylditin (94 µL, 0.500 mmoles, 1.00 equiv.), LiCl (65 mg, 1.525 mmoles, 3.05 equiv.) and $Pd(PPh_3)_4$ (13 mg, 0.011 mmoles, 0.022 equiv.). The resulting mixture

was stirred at a mild reflux for 36 h when, upon cooling to room temp., the dark mixture was partitioned between CH_2Cl_2 (20 mL) and water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL) and the combined organic layers were washed with 10 % $NH_{3\ (aq)}$ (20 mL), water (20 mL), brine (20 mL), dried (Na_2SO_4), filtered, and evaporated. The residue was separated via column chromatography (7:2:1; Hex/$CHCl_3$/EtOAc) yielding 72 mg (25 %) of the desired product (**208**) as a very insoluble white solid. ^{1}H NMR: (200 MHz) (DMSO-d_6) (410 K) δ TMS: 1.18 (s, 9 H), 1.28 (s, 9H), 5.47 (s) and 5.51 (br. s) (1 H), 5.94 (br. s) and 6.01 (s) (1 H), 6.09 (s) and 6.18 (s) (1 H), 6.76 (m, 2 H), 7.08 (m, 2 H), 7.14-7.28 (m, 6 H), 7.58-7.85 (m, 4 H). IR: (NaCl, $CHCl_3$) 2971, 2925, 1743, 1704, 1454, 1381, 1350, 1274, 1164, 1117, 1058, 953, 771, 700 cm^{-1}.

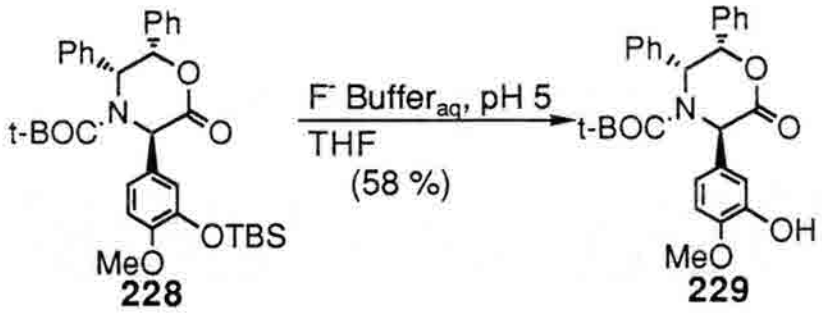


(3R,5R,6S)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-3-(3'-*tert*-butyldimethylsiloxy-4'-methoxy)phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (228, Ar = 3-*tert*-butyldimethylsiloxy-4-methoxy phenyl). To a stirred solution of 4-bromo-2-*tert*-butyldimethylsiloxyanisole (**217**) (1.39 mL, 4.00 mmoles, 4.00 equiv.) in dry Et_2O (2.00 mL) cooled to -15° C was added *n*-BuLi (2.63 mL, 4.20 mmoles, 4.20 equiv., 1.60 M in Hex). The resulting white suspension was stirred at -15° C for 30 min when additional dry Et_2O (2.50 mL) and copper bromide dimethylsulfide (411 mg, 2.00 mmoles,

2.00 equiv.) were added. The resulting dark mixture was stirred at -78° C for 3.5 h when a solution of **171b**[67] (432 mg, 1.00 mmoles, 1.00 equiv.) in a 1:1 solution of dry THF and dry Et_2O (31.00 mL) was added via cannula. The resulting solution was stirred at -78° C for 2 h when sat. $NH_4Cl_{(aq)}$ (16 mL) was added at -78° C. Upon warming to room temp., the mixture was extracted with CH_2Cl_2(4 x 20 mL). The combined organic layers were washed with 10 % $HCl_{(aq)}$ (2 x 80 mL) and the resulting pink solution was dried (Na_2SO_4), filtered and evaporated. The residue was separated via column chromatography (7:2:1; Hex/$CHCl_3$/EtOAc) and recrystallized from EtOAc yielding 539 mg (91 %) of the desired product (**228**) as a white solid. ^1H NMR: (200 MHz) ($CDCl_3$) δ TMS: 0.20 (s, 6 H), 1.03 (s, 9 H), 1.12 (s, 6 H), 1.30 (s, 3 H), 3.81 (s, 3 H), 5.12 (d, J=3.0 Hz) and 5.39 (d, J=2.9 Hz) (1 H), 5.75 (d, J=3.1 Hz) and 5.87 (d, J=2.9 Hz) (1 H), 6.10 (s) and 6.32 (s) (1 H), 6.68-7.25 (m, 13 H). IR: (NaCl, $CHCl_3$) 2930, 2857, 1759, 1704, 1605, 1584, 1511, 1455, 1378, 1269, 1164, 1115, 1058, 1031, 991, 940, 840, 784, 699 cm^{-1}. Mp: 214-217° C (recryst. from EtOAc). $[\alpha]^{25}_D$: +76.0° (*c* 0.05, CH_2Cl_2).

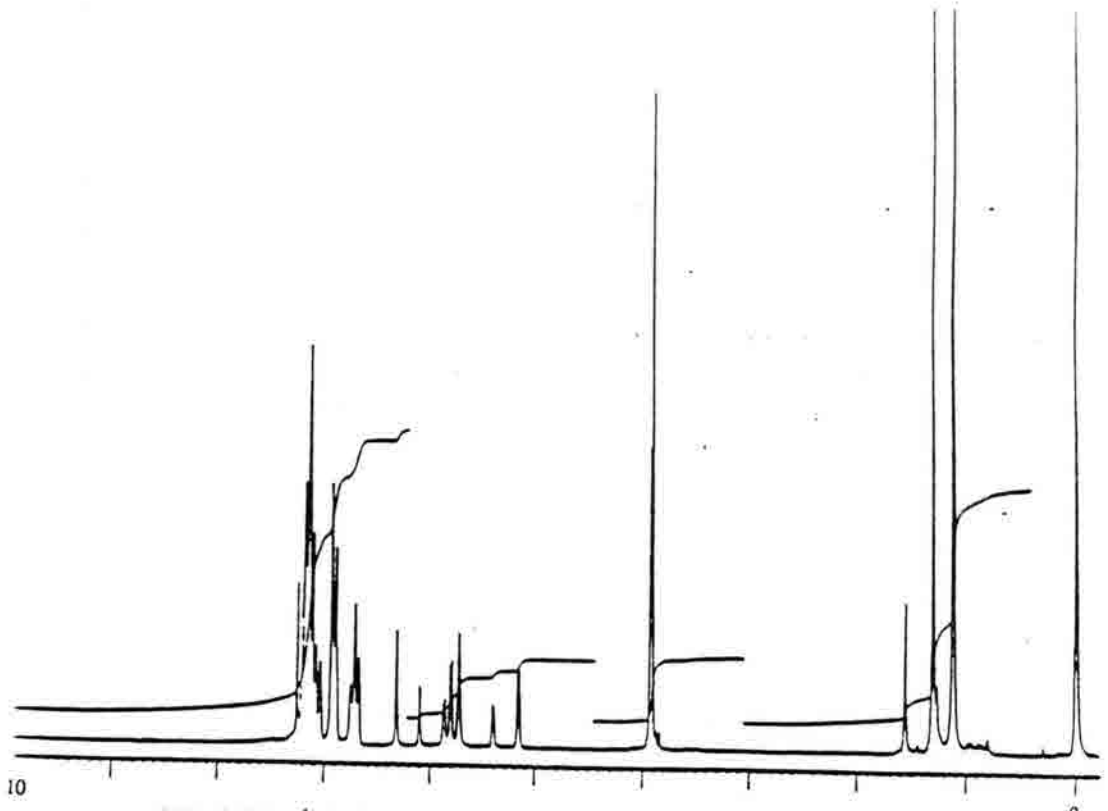


270 MHz ^1H NMR of **228** in $CDCl_3$ at room temperature.

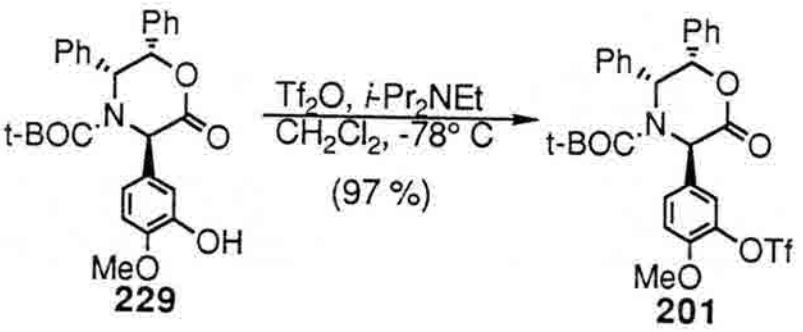


228 **229**

(3R,5R,6S)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-3-(3'-hydroxy-4'-methoxy)phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (229, Ar = 3-hydroxy-4-methoxyphenyl). To a stirred solution of **228** (539 mg, 0.914 mmoles, 1.00 equiv.) in THF (7.00 mL) was added a fluoride buffer solution (2.50 mL, aqueous buffer, pH 5).[74] The resulting solution was stirred at room temp. for 24 h when the mixture was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The residue was separated via column chromatography (2:2:1; Hex/$CHCl_3$/EtOAc) yielding 250 mg (58 %) of the desired product (**229**) as a white solid. ^{1}H NMR: (270 MHz) ($CDCl_3$) δ TMS: 1.12 (s, 5 H), 1.30 (s, 4 H), 3.90 (s) and 3.92 (s) (3 H), 5.16 (d, J=3.0 Hz) and 5.40 (d, J=2.9 Hz) (1 H), 5.80 (d, J=3.4 Hz) and 5.87 (d, J=3.0 Hz) (1 H), 5.85 (br. s, 1 H), 6.10 (s) and 6.32 (s) (1 H), 6.70 (m, 2 H), 6.92 (m, 3 H), 7.04-7.19 (m, 8 H). IR: (NaCl, $CHCl_3$) 3423, 3016, 2985, 2939, 1744, 1683, 1513, 1455, 1392, 1272, 1216, 1167, 1125, 1060, 1031, 909, 754, 669 cm^{-1}. Mp: 204-206° C (recryst. from EtOAc). Anal. Calcd for $C_{28}H_{29}NO_6$: C, 70.72; H, 6.15; N, 2.95. Found: C, 70.57; H, 6.39; N, 2.92. $[\alpha]^{25}_D$: +69.8° (*c* 0.28, CH_2Cl_2).

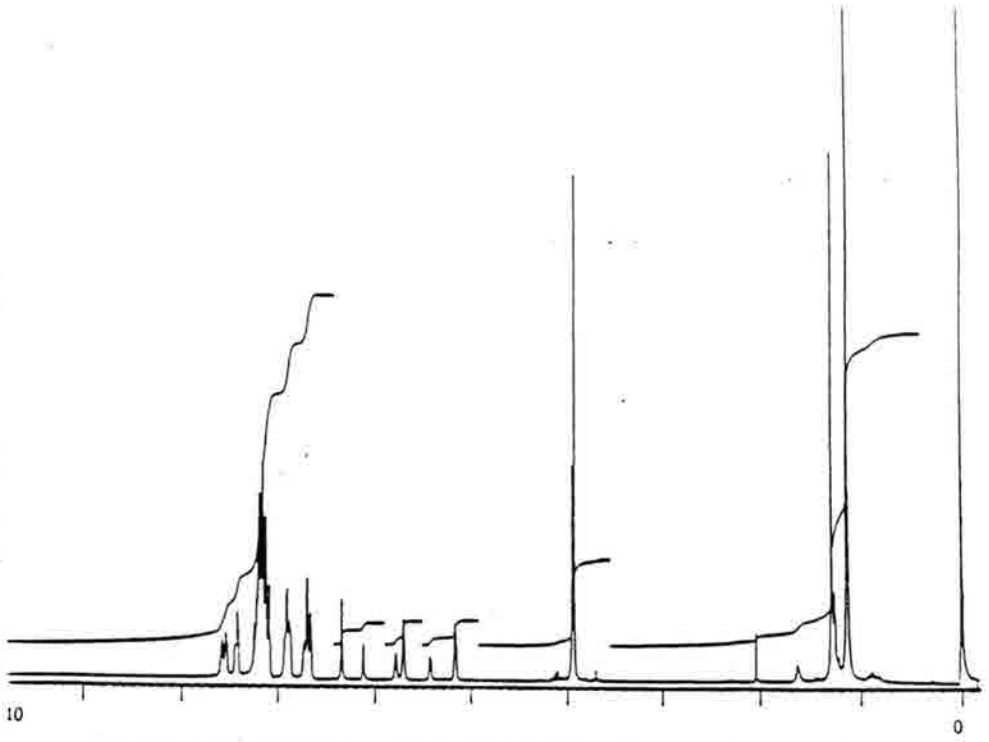


200 MHz ^{1}H NMR of **229** in $CDCl_3$ at room temperature.

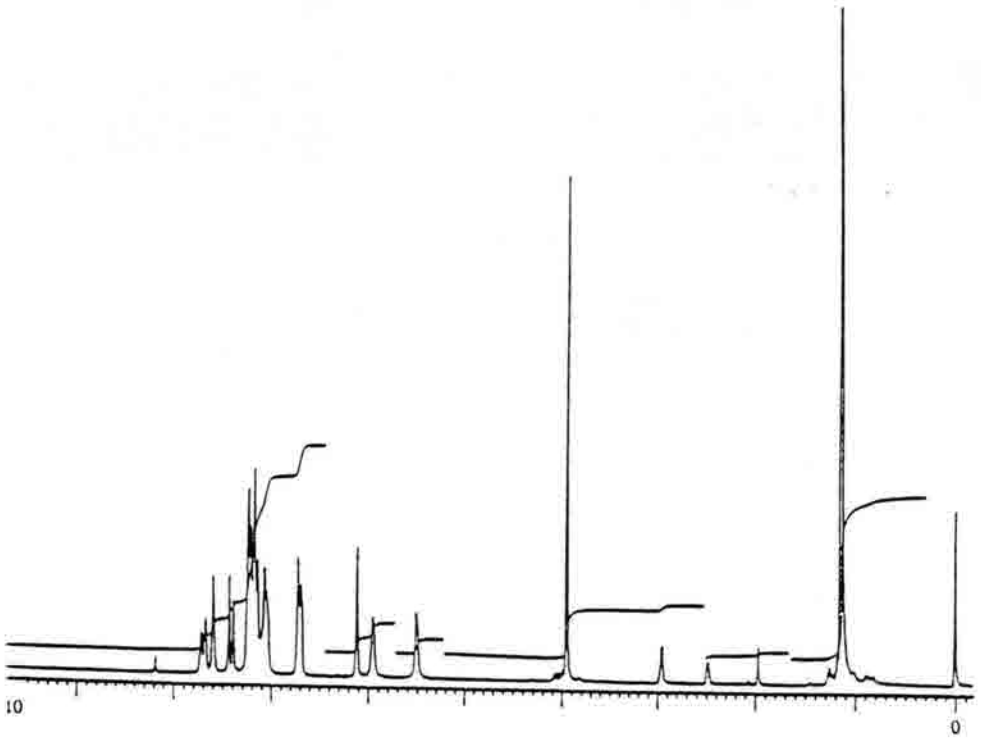


(3R,5R,6S)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-3-(4'-methoxy-3'-trifluoromethanesulfonato)phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (201, Ar = 4-methoxy-3-trifluoromethanesulfonatophenyl).[75] To a stirred solution of **229** (1.14 g, 2.40 mmoles, 1.00 equiv.) and dry N,N-diisopropyl ethylamine (1.25 mL, 7.19 mmoles, 3.00 equiv.) in dry CH_2Cl_2

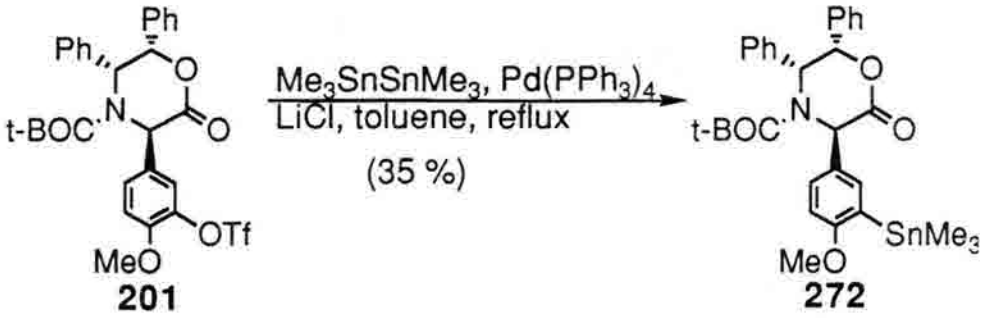
(24.00 mL) cooled to -78° C was added triflic anhydride (0.45 mL, 2.66 mmoles, 1.11 equiv.). The resulting solution was stirred at -78° C for 30 min when water (24 mL) was added. Upon warming to room temp., the mixture was extracted with CH_2Cl_2 (4 x 24 mL) and the combined organic layers were washed with water (60 mL), 10 % $HCl_{(aq)}$ (60 mL) and water (60 mL), dried (Na_2SO_4), filtered and evaporated. The residue was separated via column chromatography (5:3:2; Hex/$CHCl_3$/EtOAc) yielding 1.41 g (97 %) of the desired product (**201**) as a white solid. ^{1}H NMR: (270 MHz) ($CDCl_3$) δ TMS: 1.14 (s, 6 H), 1.29 (s, 3 H), 3.92 (s) and 3.94 (s) (3 H), 5.17 (d, J=3.0 Hz) and 5.44 (d, J=2.8 Hz) (1 H), 5.71 (d, J=3.1 Hz) and 5.80 (d, J=2.9 Hz) (1 H), 6.12 (s) and 6.34 (s) (1 H), 6.70 (m, 2 H), 6.90 (m, 2 H), 7.10-7.26 (m, 7 H), 7.43 (m, 1 H), 7.56 (m, 1 H). ^{1}H NMR: (200 MHz) (DMSO-d_6) (390 K) δ TMS: 1.14 (s, 9 H), 3.94 (s, 3 H), 5.51 (br. s, 1 H), 5.95 (br. s, 1 H), 6.11 (s, 1 H), 6.70 (d, J=7.1 Hz, 2 H), 7.05-7.24 (m, 8 H), 7.41 (d, J=8.7 Hz, 1 H), 7.60 (s, 1 H), 7.71 (d, J=8.6 Hz, 1 H). IR: (NaCl, $CHCl_3$) 3031, 2981, 2937, 1746, 1704, 1516, 1423, 1380, 1349, 1301, 1271, 1221, 1166, 1141, 1098, 1058, 1027, 968, 947, 881, 851, 768, 720, 699 cm^{-1}. MS: *m/e* (relative intensity) CI(NH_3): 625 (6.7), 624 (10.3), 569 (100.0), 507 (18.0), 462 (11.8), 419 (7.3), 372 (7.9), 296 (8.8), 196 (24.0), 180 (26.1), 106 (11.1), 58 (4.8). Mp: 198-199° C (recryst. from DMSO). Anal. Calcd. for $C_{29}H_{28}NSO_8F_3$: C, 57.33; H, 4.64; N, 2.31. Found: C, 57.18; H, 4.69; N, 2.26. $[\alpha]^{25}_D$: +47.8° (*c* 1.00, CH_2Cl_2).



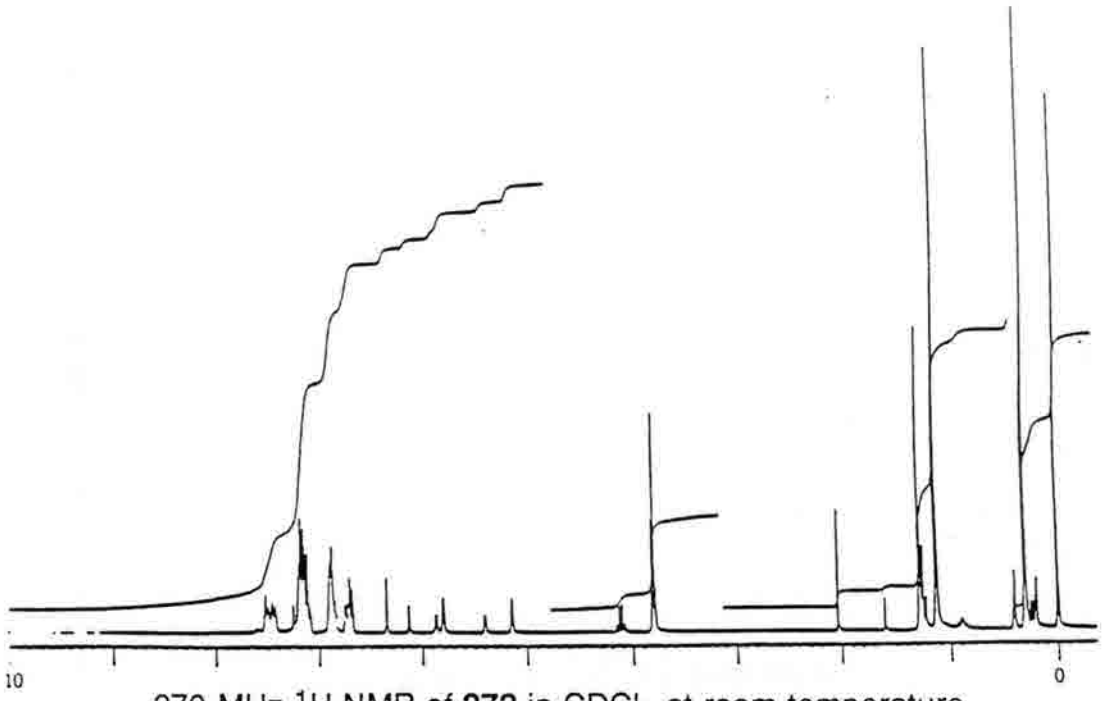
200 MHz ^{1}H NMR of **201** in $CDCl_3$ at room temperature.



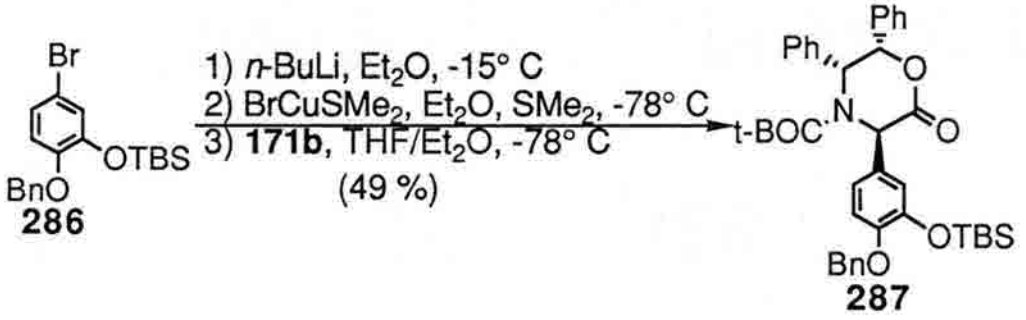
200 MHz ^{1}H NMR of **201** in d_6-DMSO at 390 K.



(3R,5R,6S)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-3-(4'-methoxy-3'-trimethylstannyl)phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (272, Ar = 4-methoxy-3-trimethylstannylphenyl).[76] To a stirred suspension of **201** (121 mg, 0.200 mmoles, 1.00 equiv.) in dry toluene (2.00 mL) was added hexamethylditin (79 mg, 0.240 mmoles, 1.20 equiv.), $Pd(PPh_3)_4$ (35 mg, 0.030 mmoles, 0.15 equiv.) and LiCl (25 mg, 0.600 mmoles, 3.00 equiv.). The resulting mixture was stirred at reflux for 24 h when, upon cooling to room temp., the dark mixture was filtered through celite with CH_2Cl_2 and evaporated. The residue was taken up in CH_3CN (5 mL) and washed with hexanes (2 x 5 mL). The CH_3CN layer was partitioned between water (5 mL) and CH_2Cl_2 (5 mL) and separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried (Na_2SO_4), filtered and evaporated. The residue was separated via PTLC (7:2:1; Hex/$CHCl_3$/EtOAc) yielding 43 mg (35 %) of the desired product (**272**) as a white solid and 33 mg of starting material (**201**). ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 0.30 (s) and 0.31 (s) (9 H), 1.14 (s, 6 H), 1.29 (s, 3 H), 3.80 (s) and 3.82 (s) (3 H), 5.15 (d) and 5.41 (d) (J=3.0 Hz, 1 H), 5.81 (d, J=3.1 Hz) and 5.87 (d, J=3.0 Hz) (1 H), 6.13 (s) and 6.35 (s) (1 H), 6.71 (m, 2 H), 6.88 (m, 3 H), 7.18 (m, 6 H), 7.49 (m, 2 H). IR: (NaCl, $CHCl_3$) 3032, 2928, 2832, 1759, 1704, 1477, 1459, 1368, 1238, 1164, 1118, 1060, 1026, 952, 852, 757, 698 cm^{-1}.

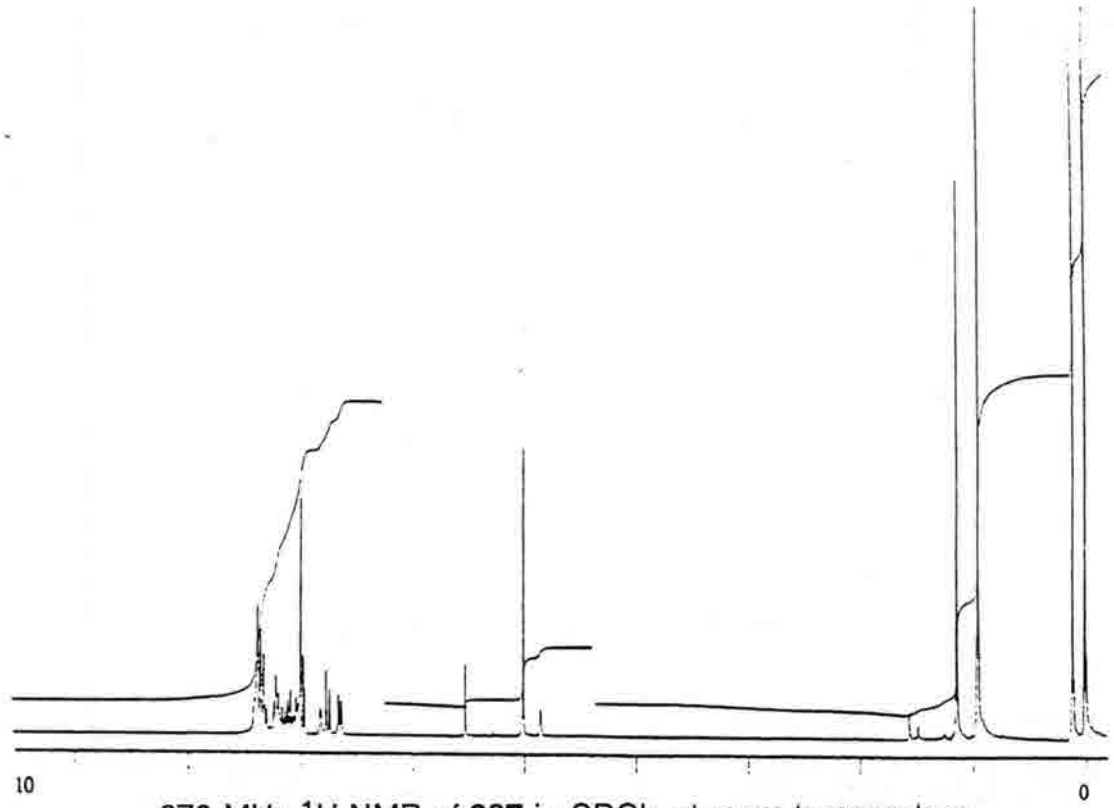


270 MHz ^{1}H NMR of **272** in $CDCl_3$ at room temperature.

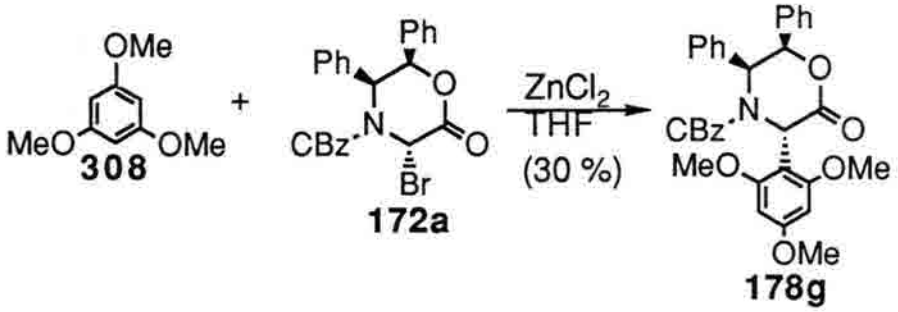


(3R,5R,6S)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-3-(4'-benzyloxy-3'-*tert*-butyldimethylsiloxy)phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (287, Ar = 4-benzyloxy-3-*tert*-butyldimethylsiloxy phenyl). To a stirred solution of 4-benzyloxy-3-*tert*-butyldimethylsiloxy bromobenzene (**286**) (1.57 g, 4.00 mmoles, 4.00 equiv.) in dry Et_2O (2.00 mL) cooled to -15° C was added *n*-BuLi (2.63 mL, 4.20 mmoles, 4.20 equiv., 1.60 M in Hex) dropwise. The resulting solution was stirred at -15° C for 30 min when copper bromide dimethylsulfide (411 mg, 2.00 mmoles, 2.00 equiv.), dry Et_2O (2.50 mL) and dry SMe_2 (4.00 mL) was added. The resulting mixture was

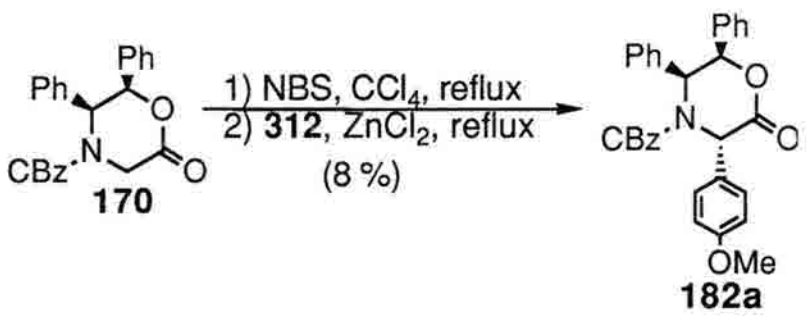
stirred at -78° C for 3 h when a solution of **171b**[67] (432 mg, 1.00 mmoles, 1.00 equiv.) in a 1:1 solution of dry THF and dry Et_2O (31.00 mL) was added via cannula. The resulting mixture was stirred at -78° C for 2 h when sat. NH_4Cl_{aq} (20 mL) was added at -78° C. The resulting mixture was allowed to warm to room temp. and the mixture was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were washed with 10 % HCl_{aq} (2 x 50 mL), dried (Na_2SO_4), filtered, and evaporated. The residue was separated via column chromatography (7:2:1; Hex/$CHCl_3$/EtOAc) and recrystallized from Hex/EtOAc yielding 323 mg (49 %) of the desired product (**287**) as a white solid. ^{1}H NMR: (270 MHz) ($CDCl_3$) δ TMS: 0.11 (s, 6 H), 0.95 (s, 13 H), 1.15 (s, 5 H), 4.85 (d, J=3.2 Hz, 1/2 H), 5.00 (s, 2 H), 5.53 (s, 1/2 H), 6.64 (d, J=7.0 Hz, 1 H), 6.75 (d, J=8.8 Hz, 1 H), 6.82 (d, J=3.2 Hz, 1/2 H), 6.96-7.42 (m, 17 1/2 H). IR: (NaCl, $CHCl_3$) 3018, 2931, 2854, 1746, 1686, 1493, 1396, 1254, 1125, 1062, 932, 668 cm^{-1}. Mp: 227-234° C (recryst. from EtOAc/Hex).



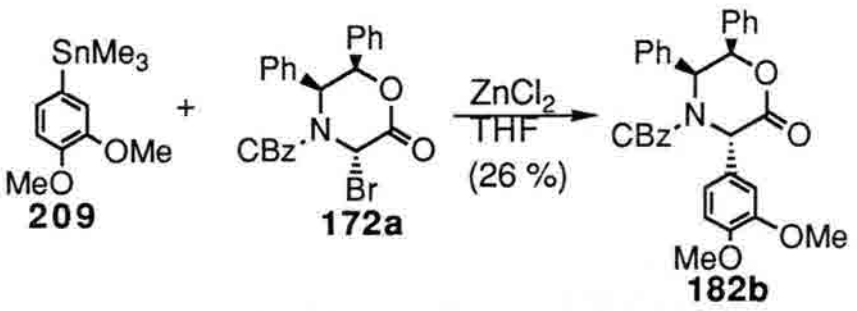
270 MHz ^{1}H NMR of **287** in $CDCl_3$ at room temperature.



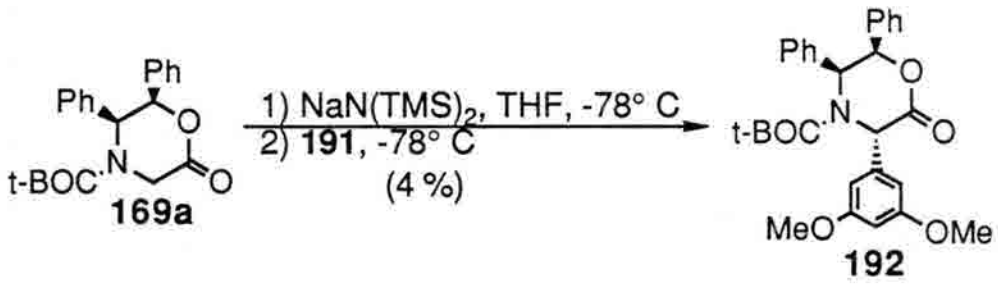
(3S,5S,6R)-4-benzyloxcarbonyl-5,6-diphenyl-2,3,5,6-tetrahydro-3-(2',4',6'-trimethoxy)phenyl-1,4-oxazin-2-one (178g, Ar = 1,3,5-trimethoxyphenyl). To a stirred solution of (3S,5S,6R)-4-benzyloxcarbonyl-3-bromo-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (**172a**) (117 mg, 0.250 mmoles, 1.00 equiv.) and 1,3,5-trimethoxybenzene (505 mg, 3.00 mmoles, 12.0 equiv.) in dry THF (1.50 mL) was added zinc chloride (0.50 mL, 0.500 mmoles, 2.00 equiv., 1.00 M in THF). Compound **172a** was synthesized by standard and previously reported methodology.[67] The resulting mixture was stirred at room temp. for 3 h when the mixture was poured into water (5 mL). The resulting mixture was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The residue was separated via column chromatography (5:3:2; Hex/$CHCl_3$/EtOAc) yielding 42 mg (30 %) of the desired product (**178g**) as a white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.83 (s, 9 H), 4.99 (d, J=3.4 Hz, 1 H), 6.19 (br. s, 2 H), 6.52 (d, J=2.0 Hz, 1 H), 6.85 (s, 1 H), 7.01-7.43 (m, 17 H). IR: (NaCl, CH_2Cl_2) 3033, 2944, 2844, 1744, 1700, 1600, 1456, 1394, 1228, 1127, 972, 733, 700 cm^{-1}. MS: *m/e* (relative intensity) CI (NH_3): 556 (19.1), 555 (36.3), 554 (100.0), 420 (12.3), 342 (15.5), 225 (19.3), 196 (22.7), 169 (39.6), 106 (62.2), 88 (17.7).



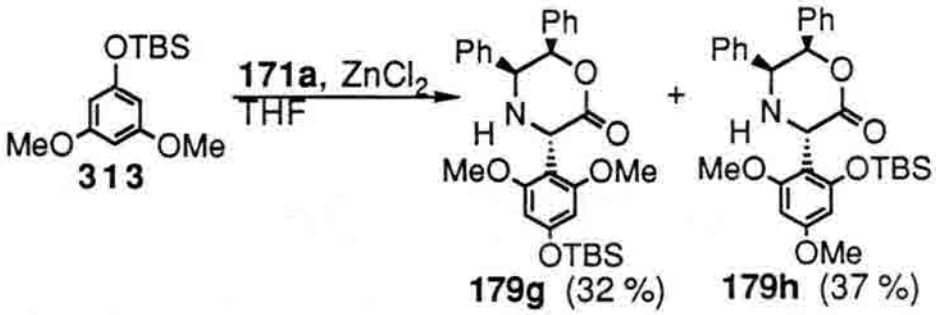
(3S,5S,6R)-4-Benzyloxycarbonyl-5,6-diphenyl-3-(4'-methoxy phenyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (182a, 4-methoxy phenyl). A suspension of (5S,6R)-4-benzyloxycarbonyl-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (**170a**) (97 mg, 0.250 mmoles, 1.00 equiv.) in dry CCl_4 (18.75 mL) was warmed until complete dissolution. Compound **170a** was synthesized by standard and previously reported methodology.[67] To the resulting solution was added NBS (53 mg, 0.300 mmoles, 1.20 equiv.) and the mixture was heated at reflux for 1 h. Upon cooling to room temp., the mixture was filtered, to remove succinimide. To the resulting solution was added (4-methoxyphenyl)trimethylstannane[90] (**312**) (0.17 mL, 0.350 mmoles, 1.40 equiv.) and zinc chloride (0.25 mL, 0.250 mmoles, 1.00 equiv., 1.00 M in THF). The resulting solution was stirred at reflux for 2.5 h when the reaction was quenched with the addition of water (4 mL) at reflux. Upon cooling to room temp., the resulting mixture was extracted with CH_2Cl_2 (4 x 10), dried (Na_2SO_4), filtered and evaporated. The residue was separated via PTLC (7:2:1; Hex/$CHCl_3$/EtOAc) yielding 10 mg (8 %) of the desired product (**182a**) as a white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.87 (s, 3 H), 4.96 (s, 2 H), 5.29 (d, J=1.8 Hz) and 5.42 (br. s) (1 H), 5.82 (m) and 6.26 (d, J=2.0 Hz) (1 H), 6.32 (s) and 6.40 (s) (1 H), 6.64-7.59 (m, 19 H).



(3S,5S,6R)-4-Benzyloxycarbonyl-3-(3',4'-dimethoxy)phenyl-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (182b, Ar = 3,4-dimethoxyphenyl).[70] To (3,4-dimethoxyphenyl)trimethylstannane (**209**) (376 mg, 1.250 mmoles, 5.00 equiv.) was added a solution of **172a**[67] (117 mg, 0.250 mmoles, 1.00 equiv.) in dry THF (1.50 mL) via cannula. To the resulting yellow solution was added zinc chloride (0.25 mL, 0.250 mmoles, 1.00 equiv., 1.00 M in THF). The resulting solution was stirred at room temp. for 3.5 h when the yellow solution was poured into water (3 mL). The mixture was extracted with CH_2Cl_2 (4 x 5 mL) and the combined organic layers were washed with 10 % $NH_{3\ (aq)}$ (2 x 15 mL), water (15 mL) and brine (15 mL), dried (Na_2SO_4), filtered, and evaporated. The residue was separated via PTLC (5:3:2; Hex/$CHCl_3$/EtOAc) yielding 35 mg (26 %) of the desired product (**182b**) as a white solid. ^1H NMR: (200 MHz) ($CDCl_3$) δ TMS: 3.73 (s, 3 H), 3.81 (s, 3 H), 4.86 (d, J=3.0 Hz) and 5.25 (d, J=3.0 Hz) (1 H), 4.92 (s) and 4.97 (s) (2 H), 5.03 (d, J=3.0 Hz) and 5.14 (d, J=3.0 Hz) (1 H), 6.46 (s) and 6.58 (s) (1 H), 6.62-7.42 (m, 18 H). IR: (NaCl, $CHCl_3$) 3066, 3033, 2942, 1770, 1723, 1598, 1499, 1455, 1397, 1271, 1174, 1112, 1053, 969, 754, 699 cm^{-1}.

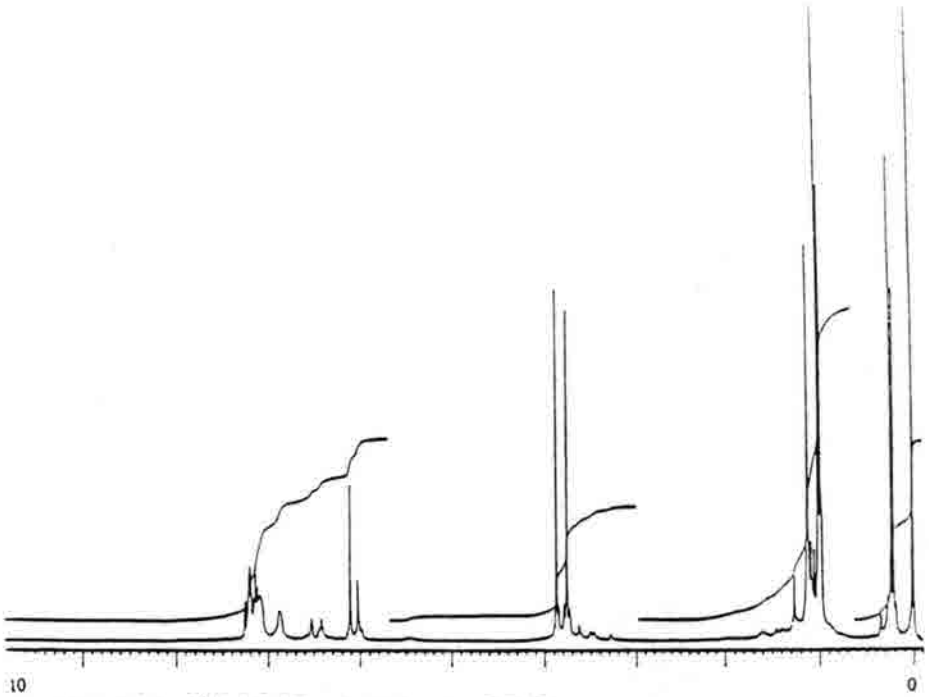


(3S,5S,6R)-4-*tert*-butoxycarbonyl-3-(3',5'-dimethoxy)phenyl-5,6-diphenyl-2,3,5,6-tetrahydro-3-1,4-oxazin-2-one (192, Ar = 3,5-dimethoxyphenyl).[69] To a stirred solution of (5S,6R)-4-*tert*-butoxycarbonyl-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one **169a**[67] (71 mg, 0.200 mmoles, 1.00 equiv.) in dry THF (2.50 mL) at -78° C was added $NaN(TMS)_2$ (0.20 mL, 0.200 mmoles, 1.00 equiv., 1.00 M in THF). The resulting solution was stirred at -78° C for 30 min when 3,5-dimethoxyphenyl trifluoromethanesulfonate (**191**) (0.21 mL, 1.00 mmoles, 5.00 equiv.) was added. The resulting solution was stirred at -78° C for 3 h when water (2 mL) was added at -78° C. Upon warming to room temp., the mixture was extracted with CH_2Cl_2 (4 x 5 mL) and the combined organic layers were washed with brine (25 mL), dried (Na_2SO_4), filtered and evaporated. The residue was separated via column chromatography (7:2:1; Hex/$CHCl_3$/EtOAc) yielding 3 mg (4 %) of the desired product (**192**) as a white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 1.26-1.55 (m, 9 H), 3.80 (s, 6 H), 4.59 (br. s) and 4.83 (br. s) (1 H), 4.98 (d, J=3.1 Hz) and 5.06 (d, J=3.1 Hz) (1 H), 5.01 (d, J=3.4 Hz) and 5.09 (d, J=3.4 Hz) (1 H), 5.94 (s) and 6.09 (s) (1 H), 6.40-7.26 (m, 12 H).

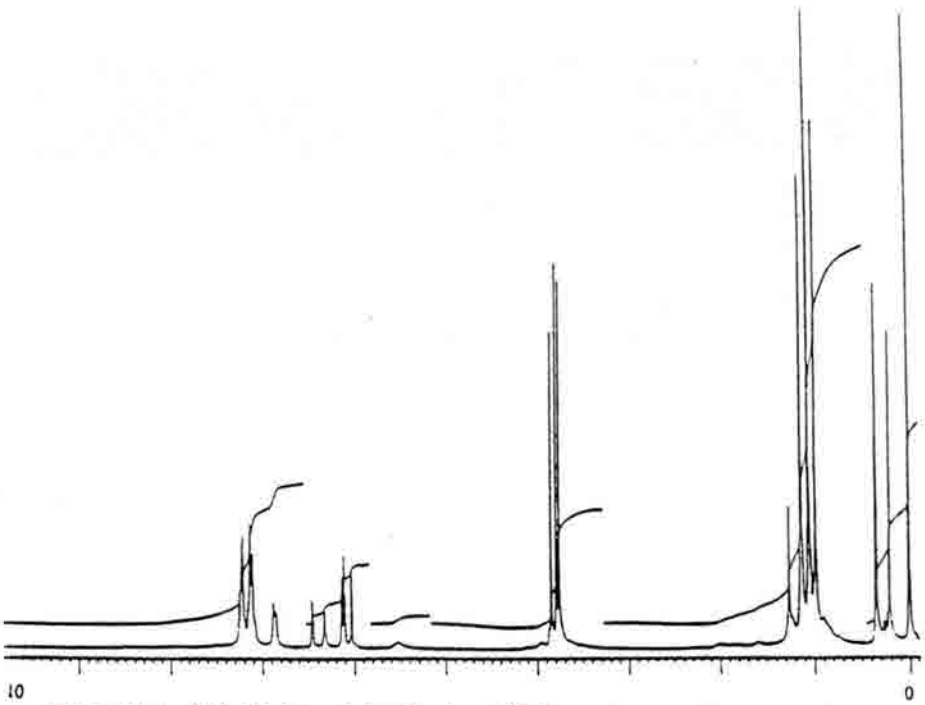


(3S,5S,6R)-5,6-diphenyl-3-(2',6'-dimethoxy-4'-*tert*-butyldimethylsiloxy)phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (179g, Ar = 2,6-dimethoxy-4-*tert*-butyldimethylsiloxyphenyl and **(3S,5S,6R)-5,6-diphenyl-3-(4',6'-dimethoxy-2'-*tert*-butyldimethylsiloxy)phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (179h, Ar = 4,6-dimethoxy-2-*tert*-butyldimethylsiloxyphenyl).** To a stirred solution of **171a**[67] (117 mg, 0.250 mmoles, 1.00 equiv.) and 3,5-dimethoxy-*tert*-butyldimethylsiloxybenzene (**313**)[91] (0.78 mL, 2.90 mmoles, 11.60 equiv.) in dry THF (1.50 mL) was added zinc chloride (0.50 mL, 0.500 mmoles, 2.00 equiv., 1.00 M in THF). The resulting mixture was stirred at room temp. for 4 h when the mixture was poured into water (2 mL). The resulting mixture was extracted with CH_2Cl_2 (4 x 3 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The residue was separated via column chromatography (7:2:1; Hex/$CHCl_3$/EtOAc) yielding 41 mg (32 %) of **179g** and 48 mg (37 %) of **179h**. **179g:** ^{1}H NMR: (270 MHz) ($CDCl_3$) δ TMS: 0.21 (s, 3 H), 0.24 (s, 3 H), 0.98 (s, 3 H), 1.01 (s, 3 H), 1.12 (s, 3 H), 1.26 (br. s, 1 H), 3.75 (s, 3 H), 3.87 (s, 3 H), 6.03 (d, 1 H), 6.11 (s, 1 H), 6.42 (d, J=3.4 Hz) and 6.53 (d, J=7.3 Hz) (1 H), 6.88 (m, 2 H), 7.08 to 7.26 (m, 10 H). IR: (NaCl, CH_2Cl_2) 3344, 2956, 1744, 1706, 1594, 1456, 1417, 1344, 1222, 1122, 1067, 839, 739, 706 cm^{-1}. **179h:** ^{1}H NMR: (270 MHz) ($CDCl_3$) δ TMS: 0.21 (s, 3 H), 0.34 (d, 3 H), 0.98 (s, 3 H), 1.05 (s, 3 H), 1.13 (s, 3 H), 1.26, (br. s, 1 H), 3.75 (s, 3 H), 3.78 (s) and 3.84 (s) (3 H), 6.02 (br. s) and 6.45 (d, J=3.2 Hz) (1 H), 6.12 (m,

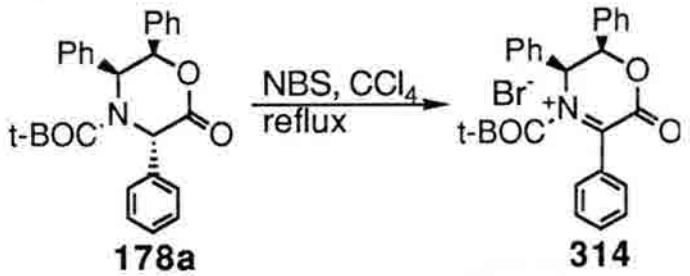
1 H), 6.32 (s, 1 H), 6.87 (d, J=3.0 Hz, 2 H), 7.11-7.26 (m, 10 H). IR: (NaCl, CH_2Cl_2) 3344, 2956, 1744, 1706, 1594, 1456, 1417, 1344, 1222, 1122, 1067, 839, 739, 706 cm^{-1}.



270 MHz ^1H NMR of **179g** in $CDCl_3$ at room temperature.

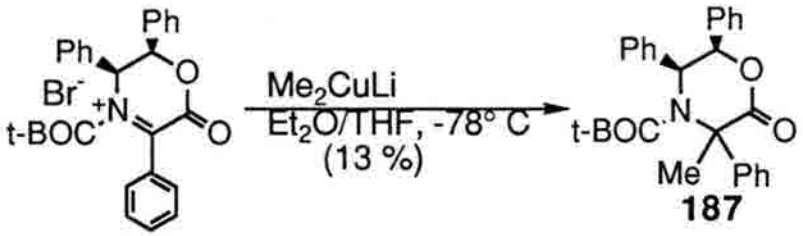


270 MHz ^1H NMR of **179h** in $CDCl_3$ at room temperature.



178a 314

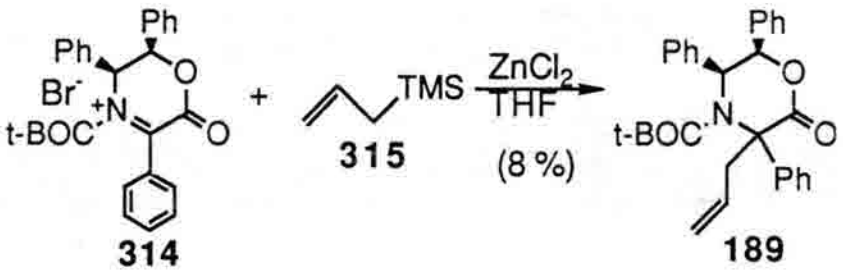
(5S,6R)-3-Bromo-4-*tert*-butoxycarbonyl-2,3,5,6-tetrahydro-3,5,6-triphenyl-1,4-oxazin-2-one (314, Ar = Ph). A stirred suspension of **178a** (43 mg, 0.100 mmoles, 1.00 equiv.) in dry CCl_4 (5.60 mL) was heated to complete dissolution. To the resulting clear, colorless solution was added NBS (21 mg, 0.120 mmoles, 1.20 equiv.). The resulting mixture was heated at reflux for 45 min when the resulting deep red solution was cooled to room temp. The resulting orange solution was held under nitrogen for 2 h, filtered, to remove succinimide, and evaporated yielding an orange oil/ white foam mixture which was used without further purification.



314 187

(5S,6R)-4-*tert*-Butoxycarbonyl-3-methyl-2,3,5,6-tetrahydro-3,5,6-triphenyl-1,4-oxazin-2-one (187, Ar = Ph). To a stirred suspension of copper (I) iodide (38 mg, 0.200 mmoles, 2.00 equiv.) in dry Et_2O (0.40 mL) was added MeLi (0.27 mL, 0.380 mmoles, 3.80 equiv., 1.4 M in Et_2O). The resulting clear, colorless solution was cooled to -78° C and stirred for 4 h. The solution gradually became orange when a solution of **314** (51 mg, 0.100 mmoles, 1.00 equiv.) in a 1:1 solution of dry THF and dry Et_2O (3.10 mL) was added via

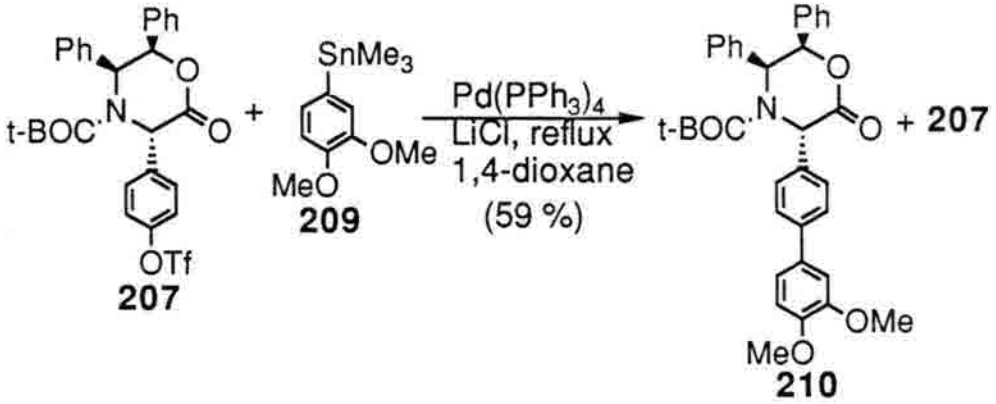
cannula. The resulting solution was stirred at -78° C for 2 h when saturated NH_4Cl (2 mL) was added at -78° C. The resulting mixture was allowed to warm to room temp., separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 3 mL). The combined organic layers were washed with 10% HCl (2 x 5 mL), dried (Na_2SO_4), filtered and evaporated yielding a crude yellow solid mixture which was separated via PTLC (7:2:1, Hex/$CHCl_3$/EtOAc) yielding 6 mg (13 %) of the desired product (**187**) as a white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ (TMS): 1.26-1.68 (m, 9 H), 5.52 (d, 1 H), 5.96 (d, 1 H), 6.46-7.64 (m, 15 H). MS: *m/e* (relative intensity) CI (NH_3): 446 (0.6), 429 (0.2), 390 (8.6), 373 (0.7), 327 (3.1), 297 (3.4), 284 (2.1), 194 (1.8), 121 (2.9), 106 (6.5), 105 (2.4), 58 (2.5), 35 (100.0), 32 (8.4).



314 189

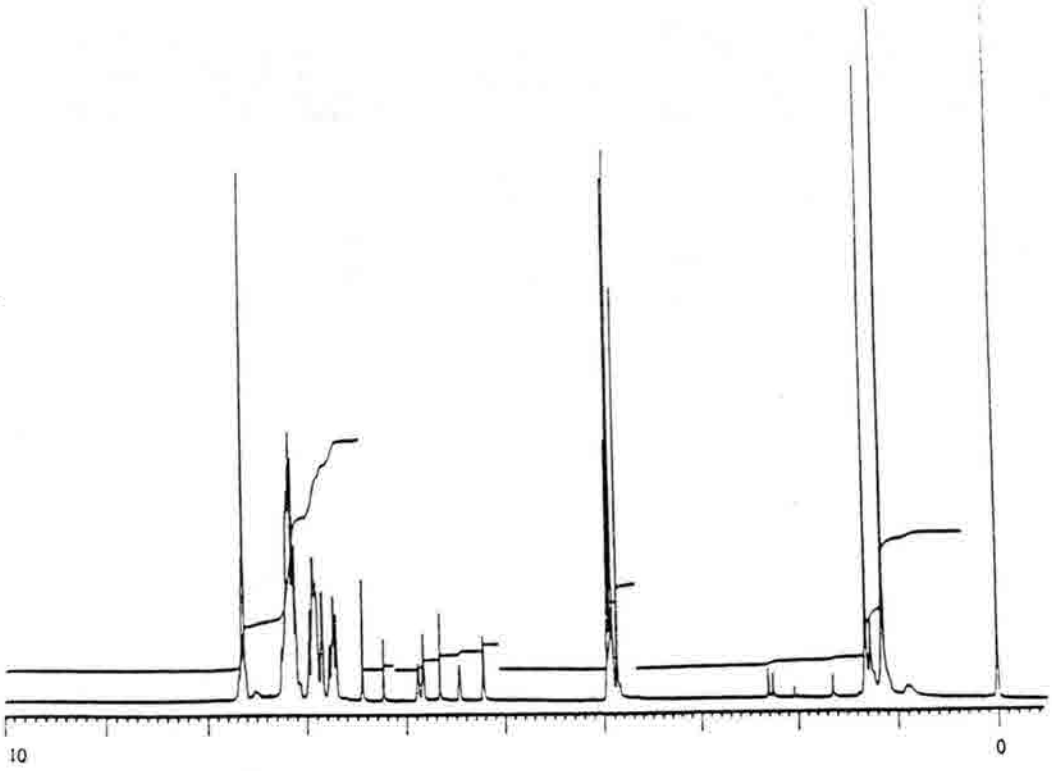
(5S,6R)-4-*tert*-Butoxycarbonyl-3-(2'-propenyl)-2,3,5,6-tetrahydro-3,5,6-triphenyl-1,4-oxazin-2-one (189, Ar = Ph). To a stirred solution of **314** (68 mg, 0.135 mmoles, 1.00 equiv.) and allyltrimethylsilane (**315**) (86 μL, 0.538 mmoles, 4.00 equiv.) in dry THF (1.60 mL) was added zinc chloride (0.18 mL, 0.269 mmoles, 2.00 equiv., 1.5 M in THF). The resulting yellow solution was stirred at room temp. for 60 h when the resulting white/yellow suspension was poured into water (5 mL). The resulting mixture was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated yield 5 mg (8 %) of the desired product (**189**) as a white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ (TMS): 1.09-1.83 (m, 9 H), 5.52 (d, 1 H), 5.95 (d, 1

H), 6.69-7.60 (m, 15 H). MS:*m/e* (relative intensity) CI (NH_3): 447 (0.5), 391 (10.4), 328 (14.4), 308 (20.9), 285 (6.8), 228 (63.3), 197 (23.4), 177 (85.5), 139 (32.1), 122 (100.0), 105 (100.0), 88 (63.9), 71 (61.3), 35 (100.0).

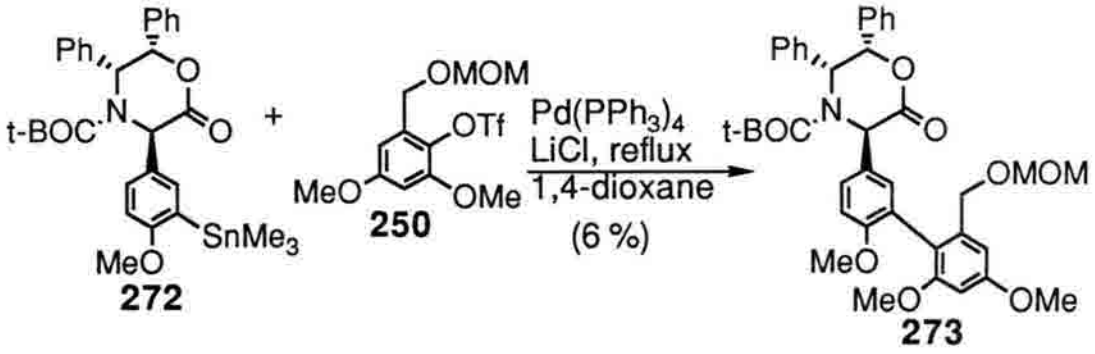


(3S,5S,6R)-4-*tert*-Butoxycarbonyl-3-(4'-(3'',4''-dimethoxy)phenyl)phenyl-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (210, Ar = 4-(3',4'-dimethoxyphenyl)phenyl.[72] To a stirred solution of **207** (115 mg, 0.200 mmoles, 1.00 equiv.) and (3,4-dimethoxyphenyl) trimethylstannane (**209**) (53 µL, 0.242 mmoles, 1.21 equiv.) in dry 1,4-dioxane (2.00 mL) was added LiCl (26 mg, 0.606 mmoles, 3.03 equiv.) and $Pd(PPh_3)_4$ (7 mg, 0.006 mmoles, 0.03 equiv.). The resulting mixture was stirred at a mild reflux for 24 h when, upon cooling to room temp., the reaction mixture was filtered through a plug of celite with CH_2Cl_2. The solution was evaporated, taken up in CH_2Cl_2 (5 mL) and washed with water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The residue was separated via column chromatography (5:3:2; Hex/$CHCl_3$/EtOAc) yielding 66 mg (59 %, 78 % based on unreacted S.M.) of the desired product (**210**) as a white solid and 28 mg of the triflate starting material (**207**). ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 1.15 (s, 5 H), 1.31 (s, 4 H), 3.92 (s, 3 H), 3.95 (s, 3 H), 5.22 (d,

J=2.9 Hz) and 5.47 (d, J=2.7 Hz) (1 H), 5.83 (d, J=2.9 Hz) and 5.88 (d, J=2.8 Hz) (1 H), 6.24 (s) and 6.44 (s) (1 H), 6.71-6.98 (m, 6 H), 7.11-7.25 (m, 7 H), 7.64 (m, 4 H). ^{1}H NMR: (200 MHz) (DMSO-d_6) (400 K) δ TMS: 1.15 (s, 9 H), 3.81 (s, 3 H), 3.86 (s, 3 H), 5.51 (d, J=2.4, 1 H), 5.99 (d, J=2.7 Hz, 1 H), 6.15 (s, 1 H), 6.71 (d, J=1.7 Hz, 1 H), 6.75 (s, 2 H), 7.02-7.25 (m, 10 H), 7.70 (q, J=5.7 Hz, 4 H). IR: (NaCl, $CHCl_3$) 3026, 2968, 2361, 1744, 1701, 1600, 1503, 1456, 1380, 1257, 1167, 1116, 1057, 1026, 951, 911, 854, 804, 753, 703 cm^{-1}.

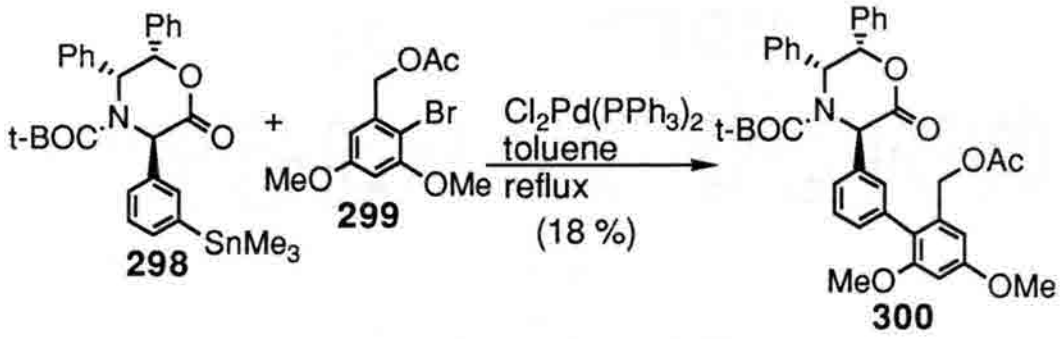


270 MHz ^{1}H NMR of **210** in $CDCl_3$ at room temperature.



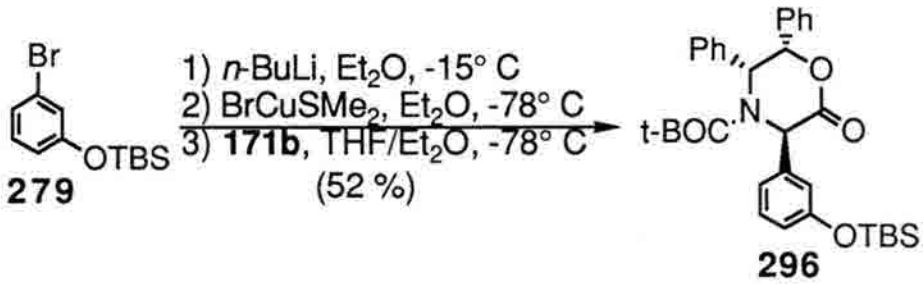
(3R,5R,6S)-4-*tert*-Butoxycarbonyl-5,6-diphenyl-3-(4'-methoxy-(4'',6''-dimethoxy-2''-((methoxy)methoxy)methyl)phenyl)phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (273, Ar = (4-methoxy(4',6'-dimethoxy-2'-((methoxy)methoxy)methyl)phenyl)phenyl).[72, 82e] To a stirred solution of 4,6-dimethoxy-2(((methoxy)methoxy)methylphenyl) trifluoromethane sulfonate (**250**) (60 µL, 0.200 mmoles, 1.00 equiv.) and (**272**) (140 mg, 0.225 mmoles, 1.13 equiv.) in dry 1,4-dioxane (1.00 mL) was added $Pd(PPh_3)_4$ (29 mg, 0.025 mmoles, 0.05 equiv.) and LiCl (25 mg, 0.600 mmoles, 3.00 equiv.). The resulting mixture was stirred at reflux for 48 h when, upon cooling to room temp., the mixture was filtered through a plug of celite with CH_2Cl_2 and evaporated. The residue was partitioned between CH_2Cl_2 (5 mL) and water (5 mL), separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with 10 % $NH_{3\,(aq)}$ (2 x 20 mL), and brine (20 mL), dried (Na_2SO_4), filtered and evaporated. The residue was separated via PTLC (7:2:1; Hex/$CHCl_3$/EtOAc) yielding 9 mg (6 %) of the desired product (**273**) as a white solid. ^1H NMR: (200 MHz) (d_6-DMSO) (440 K) δ TMS: 1.14 (s, 9 H), 3.10 (br. s, 3 H), 3.58 (s) and 3.63 (s) (3 H), 3.68 (s, 3 H), 3.82 (s, 3 H), 4.23 (s) and 4.42 (s) (2 H), 5.43 (br. s, 1 H), 5.93 (br. s, 1 H), 6.06 (s, 1 H), 6.58 (d, J=5.8, 1 H), 6.72 (m, 3 H), 7.01 (m, 2 H), 7.21 (m, 7 H), 7.51 (d, J=8.2 Hz, 2 H). IR: (NaCl, $CHCl_3$) 2937, 1759, 1704, 1605, 1487, 1455,

1380, 1324, 1266, 1162, 1117, 1043, 926, 850, 755 cm^{-1}. MS: *m/e* (relative intensity) CI (NH_3): 670 (1.3), 669 (2.4), 608 (4.8), 570 (28.8), 552 (18.9), 524 (17.2), 508 (10.4), 407 (4.5), 373 (6.3), 345 (3.9), 313 (8.8), 282 (9.3), 257 (100.0), 252 (10.3), 206 (5.8), 196 (22.5), 194 (9.8), 180 (9.0), 106 (29.2), 71 (8.0), 58 (13.7), 56 (8.3).



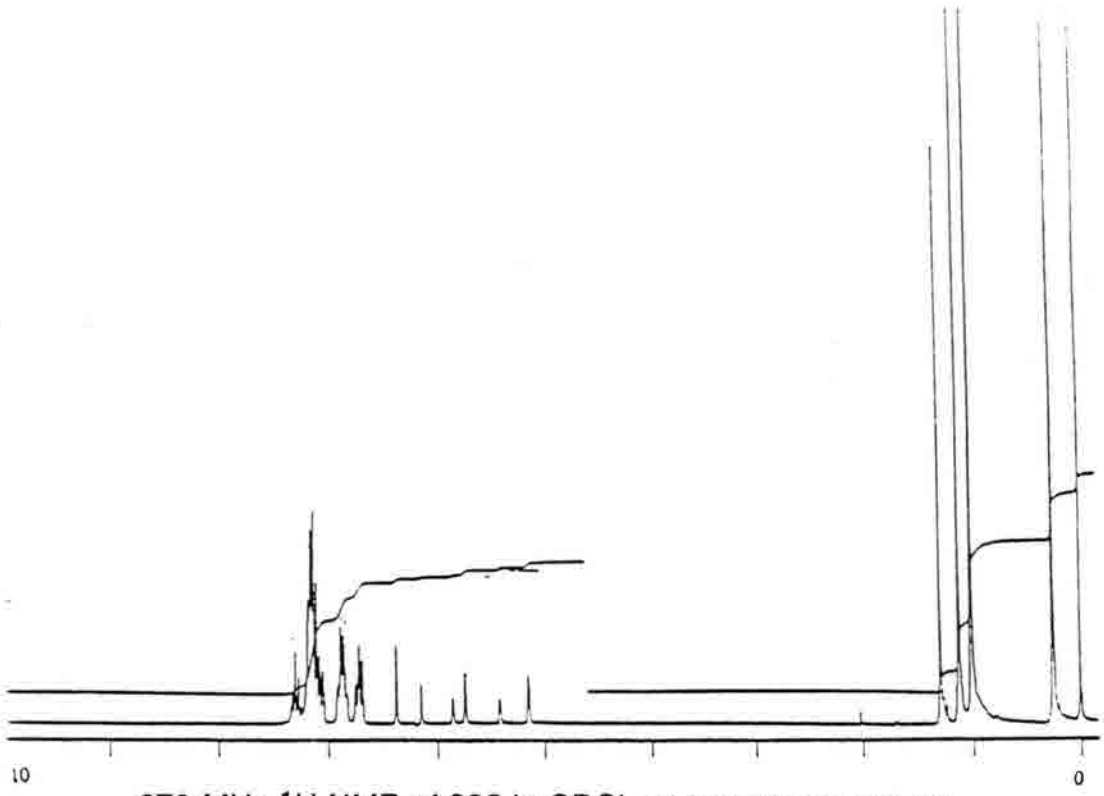
(3R,5R,6S)-4-*tert*-Butoxycarbonyl-5,6-diphenyl-3-(3'-(4'',6''-dimethoxy-2''-acetoxymethyl)phenyl)phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (300, Ar = (3-(4',6'-dimethoxy-2'-acetoxymethyl) phenyl)phenyl).[72, 82c] To a stirred solution of (3R,5R,6S)-4-(tert-Butoxycarbonyl)-5,6-diphenyl-3-(3'-trimethylstannyl)phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (**298**) (35 mg, 0.0588 mmoles, 1.00 equiv.) and 2-bromo-3,5-dimethoxybenzyl acetate (**299**) (34 mg, 0.118 mmoles, 2.00 equiv.) in dry toluene (1.00 mL) was added $Cl_2Pd(PPh_3)_2$ (2 mg, 0.003 mmoles, 0.05 equiv.). The resulting mixture was stirred at reflux for 48 h when, upon cooling to room temp., the mixture was evaporated and the residue was partitioned between CH_2Cl_2 (5 mL) and water (5 mL), separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with 10 % $NH_{3\,(aq)}$ (2 x 20 mL), and brine (20 mL), dried (Na_2SO_4), filtered and evaporated. The residue was separated via PTLC (7:2:1; Hex/$CHCl_3$/EtOAc) yielding 7 mg (18 %) of the desired product (**300**) as a white solid. ^1H NMR:

(200 MHz) ($CDCl_3$) δ TMS: 1.10 (s, 5 H), 1.28 (s, 4 H), 2.03 (br. s, 3 H), 3.67 (br. s, 3 H), 3.87 (s) and 3.88 (s) (3 H), 4.82 (m, 2 H), 5.17 (br. s) and 5.41 (br. s) (1 H), 5.87 (m, 1 H), 6.22 (s) and 6.46 (s) (1 H), 6.54 to 6.75 (m, 4 H), 6.93 (m, 2 H), 7.15 (m, 7 H), 7.25 (m, 3 H). IR: (NaCl, $CHCl_3$) 3010, 2976, 2842, 1756, 1704, 1609, 1587, 1455, 1381, 1324, 1233, 1163, 1118, 1062, 1031, 953, 847, 757, 708, 667 cm^{-1}.

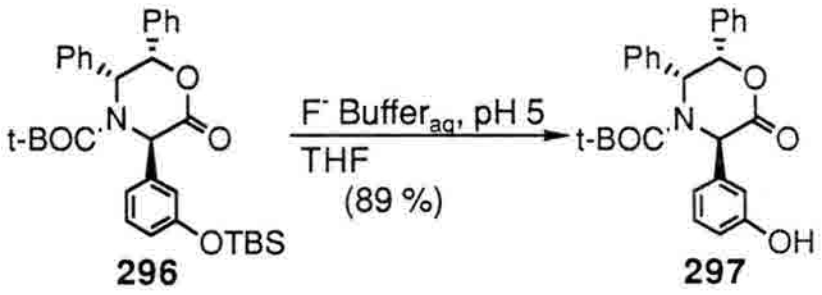


(3R,5R,6S)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-3-(3'-*tert*-butyldimethylsiloxy)phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (296, Ar = 3-*tert*-butyldimethylsiloxyphenyl). To a stirred solution of 3-*tert*-butyldimethylsiloxybromobenzene (**279**)[92] (9.99 g, 34.82 mmoles, 4.00 equiv.) in dry Et_2O (17.40 mL) cooled to -15° C was added *n*-BuLi (22.85 mL, 36.56 mmoles, 4.20 equiv., 1.60 M in Hex) dropwise. The resulting solution was stirred at -15° C for 30 min when copper bromide dimethylsulfide (3.58 g, 17.41 mmoles, 2.00 equiv.) and dry Et_2O (21.75 mL) was added. The resulting mixture was stirred at -78° C for 3 h when a solution of **171b**[67] (3.76 g, 8.71 mmoles, 1.00 equiv.) in a 1:1 solution of dry THF and dry Et_2O (270.00 mL) was added via cannula. The resulting mixture was stirred at -78° C for 2.5 h when sat. NH_4Cl_{aq} (175 mL) was added at -78° C. The resulting mixture was allowed to warm to room temp. and the mixture was extracted with CH_2Cl_2 (4 x 175 mL). The combined organic layers were washed with 10 % HCl_{aq} (2 x 520 mL), dried (Na_2SO_4), filtered, and evaporated. The residue was separated via column

chromatography (7:2:1; Hex/$CHCl_3$/EtOAc) and recrystallized from Hex/EtOAc yielding 2.54 g (52 %) of the desired product (**296**) as a white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 0.25 (s, 6 H), 1.01 (s, 9 H), 1.13 (s, 6 H), 1.29 (s, 3 H), 5.15 (d, J=3.1 Hz) and 5.42 (d, J=2.9 Hz) (1 H), 5.74 (d, J=3.2 Hz) and 5.86 (d, J=3.0 Hz) (1 H), 6.15 (s) and 6.38 (s) (1 H), 6.72 (m, 2 H), 6.89 (m, 3 H), 7.13 (m, 8 H), 7.30 (m, 1 H). IR: (NaCl, $CHCl_3$) 3032, 2931, 2859, 1761, 1706, 1600, 1487, 1455, 1380, 1273, 1163, 1117, 1059, 986, 940, 840, 757, 697 cm^{-1}. Mp: 146-149° C (recryst. from EtOH). Anal. Calcd. for $C_{33}H_{41}NSiO_5$: C, 70.81; H, 7.38; N, 2.50. Found: C, 71.00; H, 7.46; N, 2.41. $[\alpha]^{25}_D$: +63.8° (*c* 1.05, CH_2Cl_2).

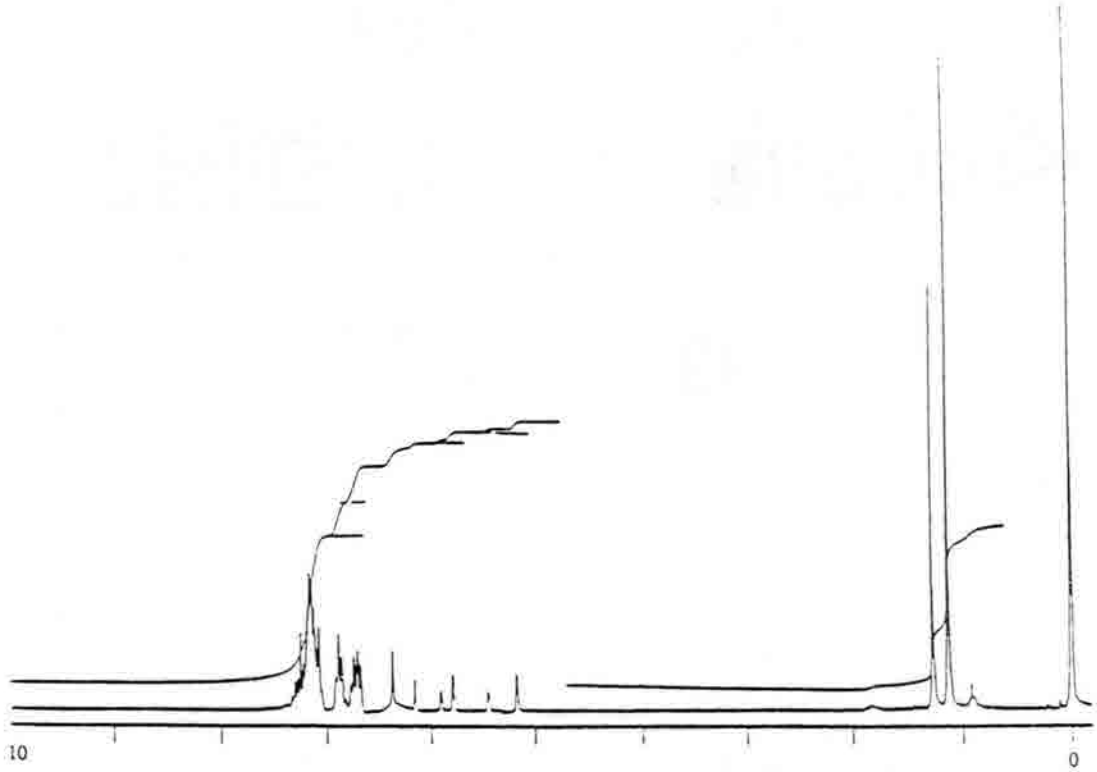


270 MHz ^1H NMR of **296** in $CDCl_3$ at room temperature.

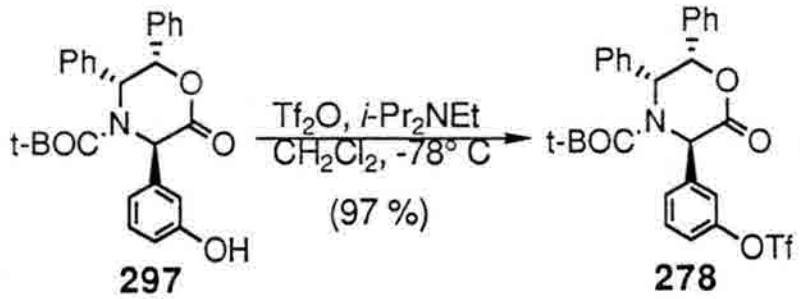


296 **297**

(3R,5R,6S)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-3-(3'-hydroxy)phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (297, Ar = 3-phenol). To a stirred solution of **296** (2.54 g, 4.52 mmoles, 1.00 equiv.) in THF (34.60 mL) was added a fluoride buffer solution (12.40 mL, pH 5).[74] The resulting mixture was stirred at room temp. for 24 h when the mixture was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (2:2:1; Hex/$CHCl_3$/EtOAc) yielding 1.79 g (89 %) of the desired product (**297**) as a white solid. ^{1}H NMR: (270 MHz) ($CDCl_3$) δ TMS: 1.13 (s, 6 H), 1.28 (s, 3 H), 5.17 (d, J=2.7 Hz) and 5.45 (d, J=2.4 Hz) (1 H), 5.79 (d, J=2.8 Hz) and 5.91 (d, J=2.5 Hz) (1 H), 6.16 (s) and 6.37 (s) (1 H), 6.30 (br. s, 1 H), 6.71 (m, 2 H), 6.89 (m, 3 H), 7.17 (m, 9 H). IR: (NaCl, $CHCl_3$) 3390, 3018, 2975, 2931, 1755, 1701, 1602, 1455, 1384, 1367, 1274, 1160, 1056, 925 cm^{-1}. Mp: 96-99° C (recryst. from EtOH). Anal. Calcd. for $C_{27}H_{27}NO_5$: C, 72.79; H, 6.11; N, 3.14. Found: C, 72.84; H, 6.34; N, 3.15. $[\alpha]^{25}_D$: +77.2° (*c* 1.00, CH_2Cl_2).



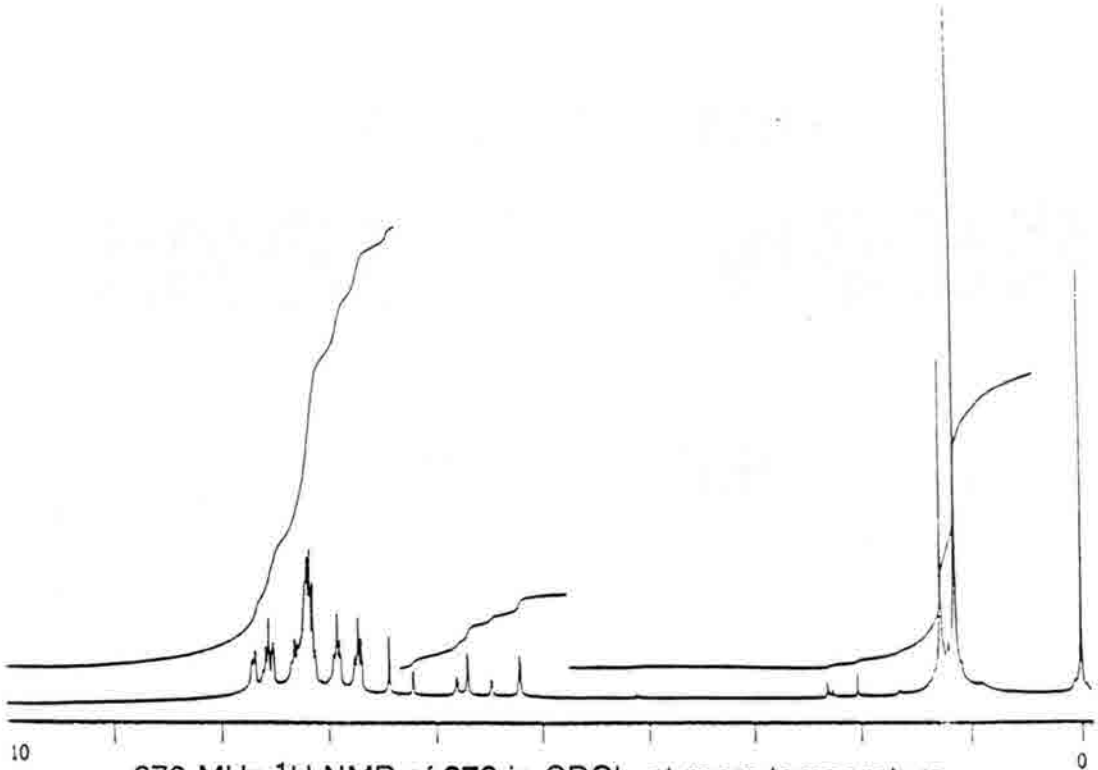
270 MHz ^{1}H NMR of **297** in $CDCl_3$ at room temperature.



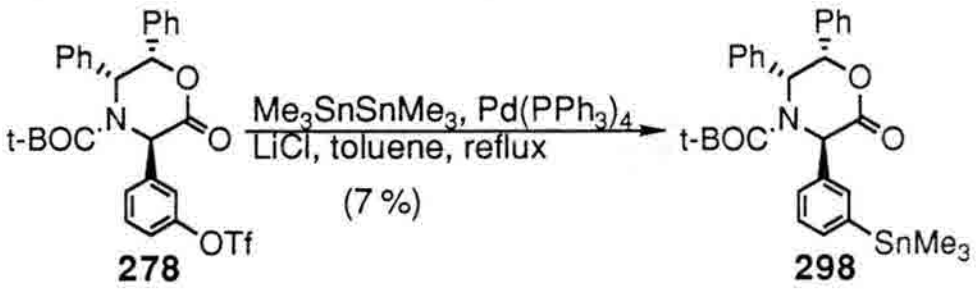
297 **278**

(3R,5R,6S)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-3-(3'-trifluoromethanesulfonato)phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (278, Ar = 3-phenyl triflate).[75] To a stirred solution of **297** (1.12 g, 2.526 mmoles, 1.00 equiv.) in dry CH_2Cl_2 (38.80 mL) cooled to -78° C was added diisopropylethyl amine (1.32 mL, 7.579 mmoles, 3.00 equiv.) and triflic anhydride (0.47 mL, 2.804 mmoles, 1.11 equiv.). The resulting mixture was stirred at -78° C for 2 h when water (38.8 mL) was added at -78° C. Upon warming to room temp., the mixture was separated and the aqueous layer was

extracted with CH_2Cl_2 (4 x 55 mL). The combined organic layers were washed with water (110 mL), 10 % HCl_{aq} (2 x 110 mL), water (110 mL) and brine (110 mL), dried (Na_2SO_4), filtered and evaporated. The residue was separated via column chromatography (7:2:1; Hex/$CHCl_3$/EtOAc) yielding 1.42 g (97 %) of the desired product (**278**) as a white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 1.14 (s, 6 H), 1.27 (s, 3 H), 5.21 (d, J=2.8 Hz) and 5.47 (d, J=2.5 Hz) (1 H), 5.70 (d, J=2.9 Hz) and 5.80 (d, J=2.7 Hz) (1 H), 6.20 (s) and 6.42 (s) (1 H), 6.71 (m, 2 H), 6.94 (m, 3 H), 7.16 (m, 6 H), 7.54 (m, 2 H), 7.67 (m, 1 H). IR: (NaCl, $CHCl_3$) 3033, 2983, 2927, 1747, 1694, 1611, 1586, 1487, 1428, 1383, 1349, 1218, 1137, 1084, 1059, 971, 914, 852 cm^{-1}. Mp: 186-188° C (recryst. from EtOH). Anal. Calcd. for $C_{28}H_{26}NF_3SO_7$: C, 58.23; H, 4.54; N, 2.43. Found: C, 58.30; H, 4.75; N, 2.45. $[\alpha]^{25}_D$: +49.3° (*c* 1.10, CH_2Cl_2).

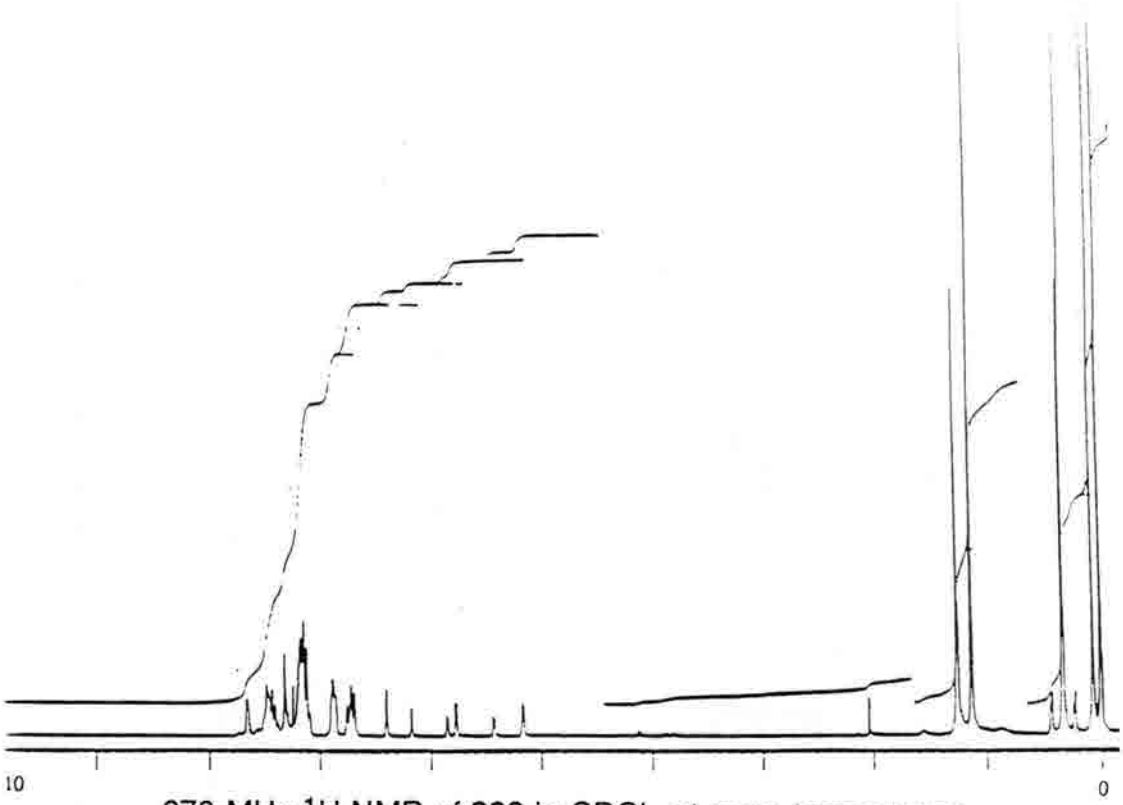


270 MHz ^1H NMR of **278** in $CDCl_3$ at room temperature.

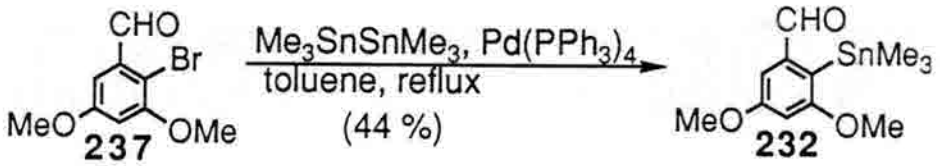


278 **298**

(3R,5R,6S)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-3-(3'-trimethylstannyl)phenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (298, Ar = 3-phenyl trimethyltin).[76] To a stirred solution of **278** (500 mg, 0.867 mmoles, 1.00 equiv.) in dry toluene (6.10 mL) was added hexamethylditin (0.19 mL, 1.040 mmoles, 1.20 equiv.), $Pd(PPh_3)_4$ (150 mg, 0.130 mmoles, 0.15 equiv.) and dry lithium chloride (294 mg, 6.932 mmoles, 8.00 equiv.). The resulting mixture was stirred at reflux for 17 h when, upon slight cooling, the mixture was filtered through a plug of celite and evaporated. The residue was taken up in CH_3CN (5 mL) and washed with hexanes (3 x 5 mL). The CH_3CN layer was partitioned between CH_2Cl_2 (5 mL) and water (5 mL), separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and evaporated. The residue was separated via column chromatography (7:2:1; Hex/$CHCl_3$/EtOAc) yielding 35 mg (7 %) of the desired product (**298**) as a white solid and 237 mg of starting material. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 0.33 (s) and 0.34 (s) (9 H), 1.14 (s, 6 H), 1.27 (s, 3 H), 5.17 (d, J = 3.1) and 5.44 (d, J = 2.9 Hz) (1 H), 5.78 (d, J = 3.1 Hz) and 5.86 (d, J = 3.0 Hz) (1 H), 6.18 (s) and 6.40 (s) (1 H), 6.72 (m, 2 H), 6.89 (m, 2 H), 7.15 (m, 6 H), 7.33 (m, 1 H), 7.45 (m, 2 H), 7.67 (m, 1 H).

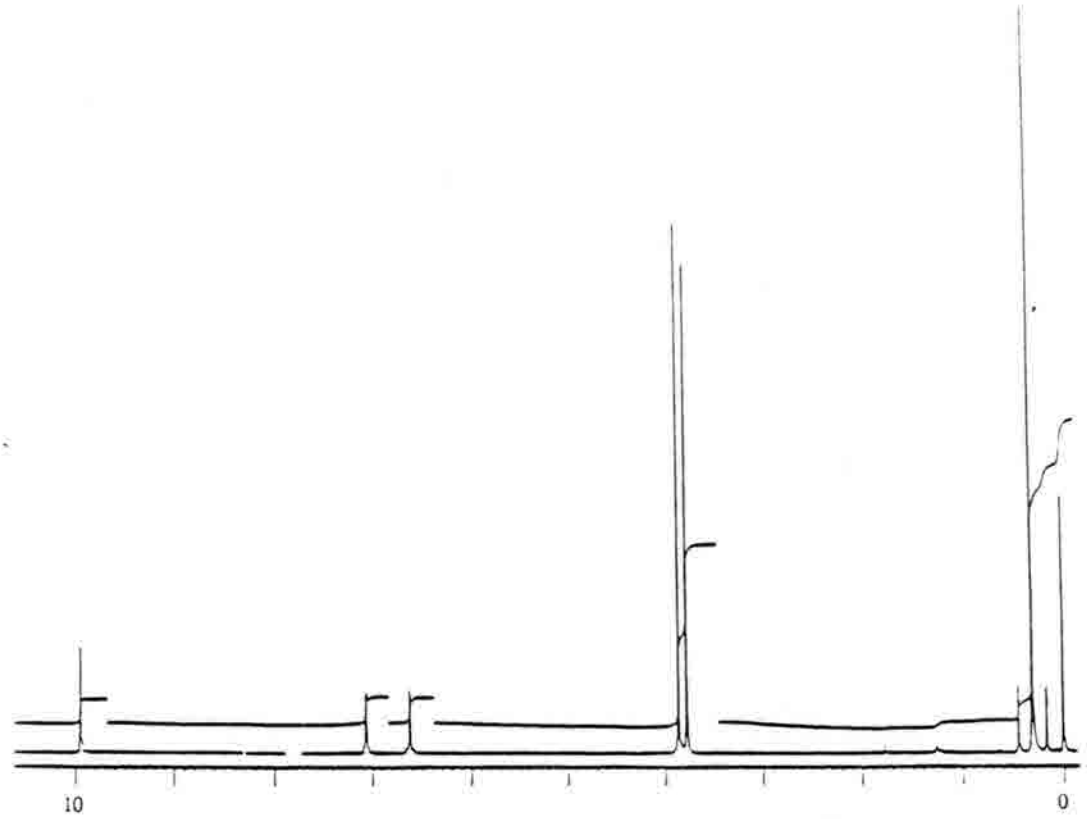


270 MHz ^{1}H NMR of **298** in $CDCl_3$ at room temperature.

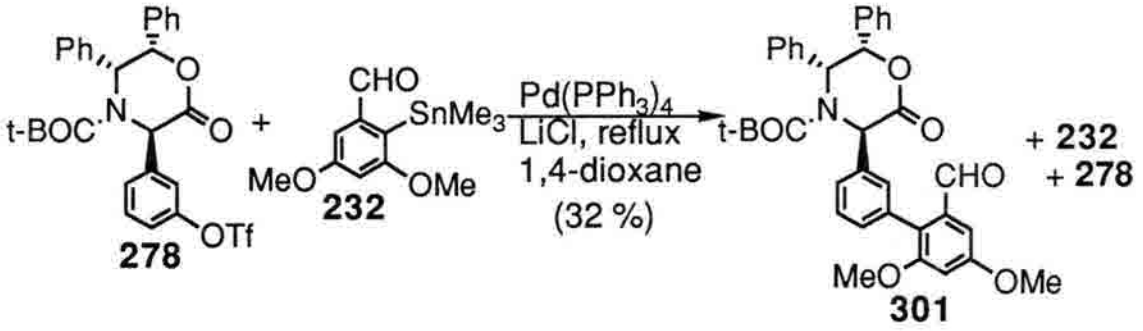


3,5-Dimethoxy-2-trimethylstannyl benzaldehyde (232).[76] To a stirred solution of 2-bromo-3,5-dimethoxybenzaldehyde (**237**)[81] (2.00 g, 8.16 mmoles, 1.00 equiv.) in dry toluene (16.40 mL) was added hexamethylditin (3.20 g, 9.80 mmoles, 1.20 equiv.) and $Pd(PPh_3)_4$ (160 mg, 0.14 mmoles, 0.017 equiv.). The resulting mixture was stirred at reflux overnight when, upon cooling to room temp., the yellow solution was evaporated, precipitated with pentane and filtered. The yellow solid was thoroughly washed with pentane and the filtrated was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column

chromatography (4:1; Hex/EtOAc) yielding 1.18 g (44 %) of the desired product (**232**) as a pale, yellow solid. ^{1}H NMR: (270 MHz) ($CDCl_3$) δ TMS: 0.30 (s, 9 H), 3.78 (s, 3 H), 3.87 (s, 3 H), 6.62 (d, J = 2.2 Hz, 1 H), 7.07 (d, J = 2.2 Hz, 1 H), 9.95 (s, 1 H). IR: (NaCl) 2965, 2938, 2912, 2838, 1694, 1587 1454, 1384, 1324, 1281, 1213, 1156, 1071, 952, 847, 774 cm^{-1}. MS: *m/e* (relative intensity) EI: 319 (16.6), 317 (15.5), 316 (11.4), 315 (100.0), 314 (35.0), 313 (75.1), 312 (28.3), 311 (43.8), 285 (44.2), 283 (33.4), 281 (20.2), 227 (4.0), 118 (3.1), 77 (2.0), 63 (2.1), 44 (45.0).

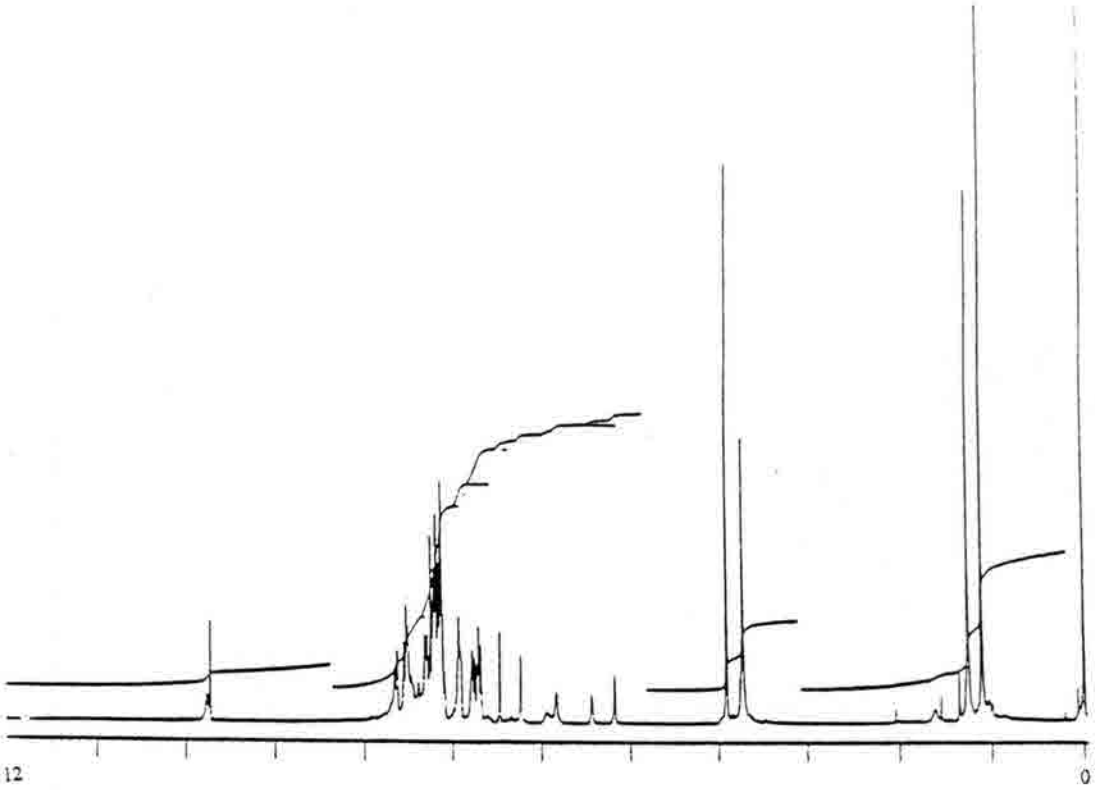


200 MHz ^{1}H NMR of **232** in $CDCl_3$ at room temperature.

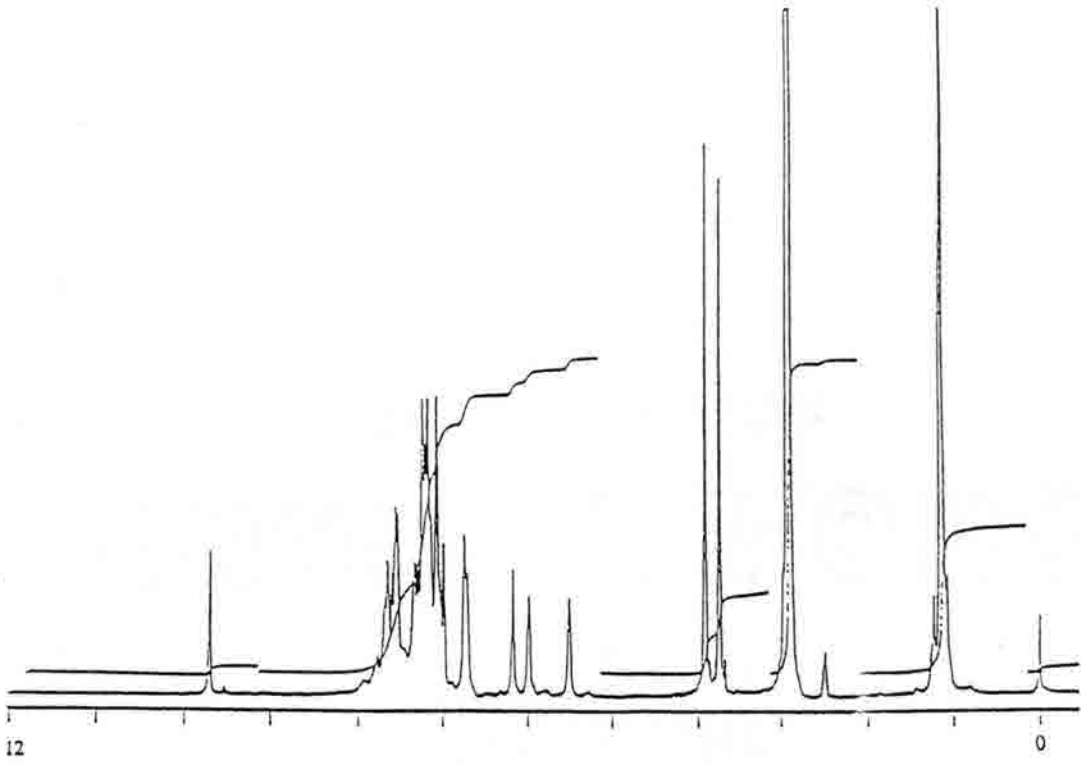


(3R,5R,6S)-4-*tert*-Butoxycarbonyl-3-(3'-(4'',6''-dimethoxy-2''-formyl)phenyl)phenyl-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (301, Ar = (3-(4',6'-dimethoxy-2'-formyl)phenyl)phenyl).[72] To a stirred solution of **278** (115 mg, 0.200 mmoles, 1.00 equiv.) and **232** (79 mg, 0.240 mmoles, 1.20 equiv.) in dry 1,4-dioxane (2.00 mL) was added $Pd(PPh_3)_4$ (29 mg, 0.025 mmoles, 0.125 equiv.) and LiCl (25 mg, 0.600 mmoles, 3.00 equiv.). The resulting mixture was stirred at reflux for 48 h when, upon cooling to room temp., the mixture was filtered through a plug of celite with CH_2Cl_2 and evaporated. The residue was partitioned between CH_2Cl_2 (5 mL) and water (5 mL), separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with 10 % $NH_{3\,(aq)}$ (2 x 20 mL), and brine (20 mL), dried (Na_2SO_4), filtered and evaporated. The residue was separated via PTLC (7:2:1; Hex/$CHCl_3$/EtOAc) yielding 38 mg (32 %, 56 % based on recovered S.M.) of the desired product (**301**) as a white solid / foam. Also recovered were 49 mg of **278**, 39 mg of **232**, and 7 mg of 3,5-dimethoxybenzaldehyde (**302**). ^{1}H NMR: (270 MHz) ($CDCl_3$) δ TMS: 1.10 (s, 6 H), 1.25 (s, 3 H), 3.73 (s, 3 H), 3.91 (s) and 3.92 (s) (3 H), 5.18 (d, J = 2.8 Hz) and 5.44 (d, J=2.6 Hz) (1 H), 5.84 (br. s) and 5.94 (br. s) (1 H), 6.23 (s) and 6.47 (s) (1 H), 6.75 (m, 4 H), 6.91 (m, 2 H), 7.14 (m, 6 H), 7.53 (m, 3 H), 7.64 (m, 1 H), 9.74 (s) and 9.77 (br. s) (1 H). ^{1}H NMR: (200 MHz) (d_6-DMSO) (410 K) δ TMS:

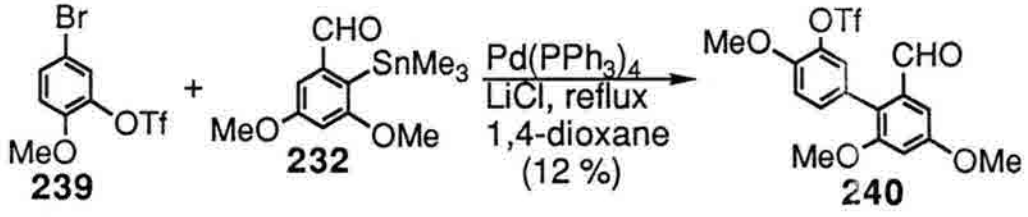
1.13 (s, 9 H), 3.73 (s, 3 H), 3.90 (s, 3 H), 5.50 (br. s, 1 H), 5.98 (br. s, 1 H), 6.17 (s, 1 H), 6.74 (m, 2 H), 7.05-7.39 (m, 10 H), 7.55 (m, 4 H), 9.69 (s, 1 H). IR: (NaCl, $CHCl_3$) 2983, 1738, 1706, 1604, 1456, 1373, 1242, 1161, 1117, 1047, 918, 848, 734, 702 cm^{-1}. MS: *m/e* (relative intensity) CI (NH_3): 610 (12.7), 609 (32.4), 535 (7.8), 341 (12.7), 328 (8.8), 284 (16.7), 278 (73.5), 262 (48.0), 213 (14.7), 195 (88.2), 121 (14.7), 106 (100.0), 94 (21.6), 72 (21.6), 58 (64.7). Mp: d 182° C (recryst. from EtOH). Anal. Calcd. for $C_{36}H_{35}NO_7$: C, 72.83; H, 5.94; N, 2.36. Found: C, 72.71; H, 5.81; N, 2.37. $[\alpha]^{25}_D$: +34.0° (*c* 1.00, CH_2Cl_2).



270 MHz ^1H NMR of **301** in $CDCl_3$ at room temperature.

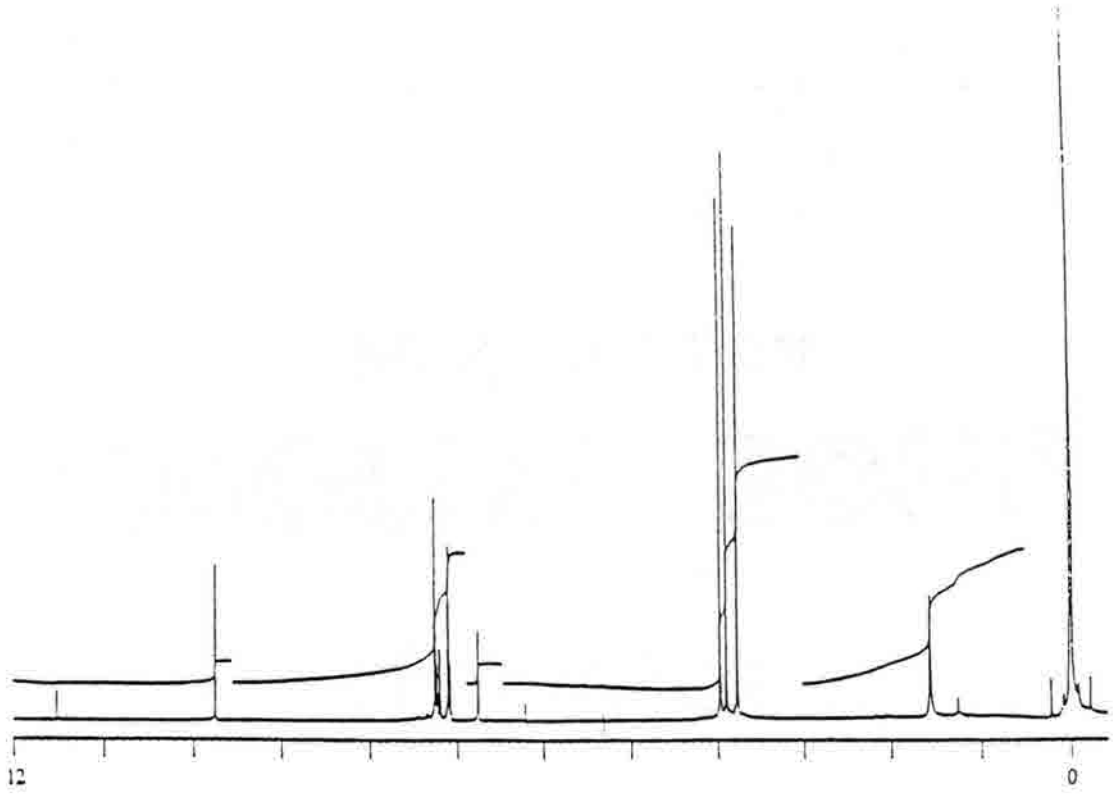


200 MHz ^{1}H NMR of **301** in d_6-DMSO at 410 K.

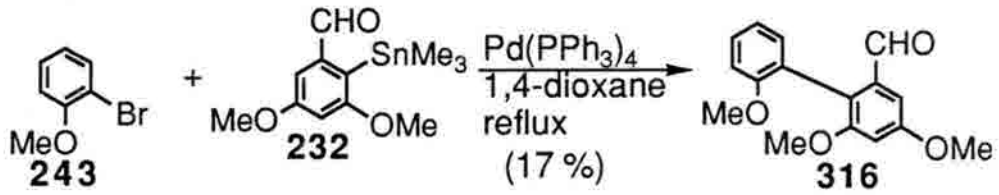


2-(4'-Methoxy-3'-trifluoromethanesulfonato)phenyl-3,5-dimethoxybenzaldehyde (240).[72] To a stirred solution of 5-bromo-2-trifluoromethanesulfonato anisole (**239**) (57 μL, 0.200 mmoles, 1.00 equiv.) and **232** (80 mg, 0.240 mmoles, 1.20 equiv.) in dry 1,4-dioxane (1.00 mL) was added $Pd(PPh_3)_4$ (7 mg, 0.006 mmoles, 0.031 equiv.), LiCl (26 mg, 0.606 mmoles, 3.03 equiv.) and a grain of 2,6-di-tert-butyl-4-methylphenol as a radical inhibitor. The resulting mixture was stirred at reflux for 36 h when, upon cooling to room temp., the mixture was filtered through a plug of celite with CH_2Cl_2 and

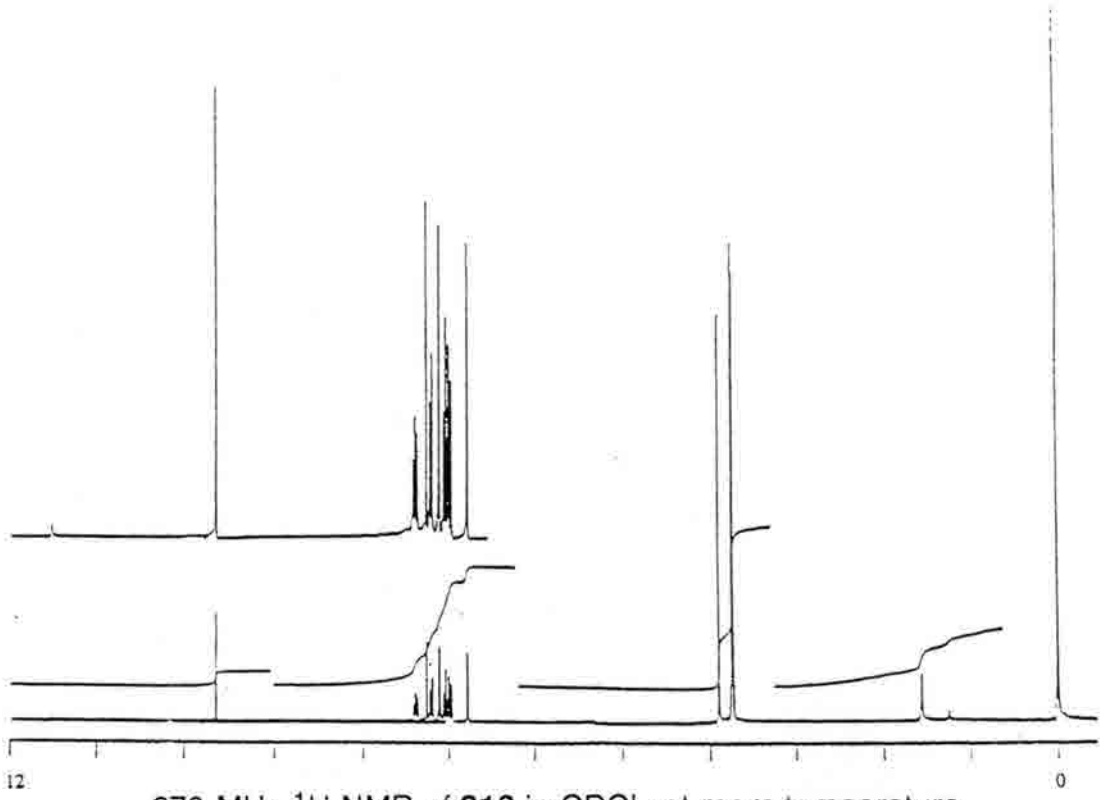
evaporated. The residue was partitioned between CH_2Cl_2 (5 mL) and water (5 mL), separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with 10 % $NH_{3\ (aq)}$ (2 x 15 mL), water (15 mL), 10 % $HCl_{(aq)}$ (15 mL) and brine (15 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via PTLC (4:1; Hex/EtOAc) yielding 10 mg (12 %) of **240** as a white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.77 (s, 3 H), 3.90 (s, 3 H), 3.97 (s, 3 H), 6.75 (d, J=2.4 Hz, 1 H), 7.10 (m, 2 H), 7.26 (m, 3 H), 9.75 (s, 1 H). IR: (NaCl, $CHCl_3$) 3424, 2942, 2847, 1687, 1603, 1520, 1466, 1422, 1333, 1294, 1203, 1141, 1106, 1065, 1022, 932, 914, 819, 753 cm^{-1}. MS: *m/e* (relative intensity) CI(NH_3): 423 (1.2), 422 (8.1), 421 (20.2), 420 (100.0), 288 (17.8), 287 (64.8), 259 (72.9), 244 (50.2), 231 (12.5), 227 (26.6), 216 (26.3), 203 (25.7), 201 (23.9), 188 (10.0), 173 (12.2), 145 (13.1), 122 (17.3), 115 (18.1), 102 (10.7), 69 (20.3), 43 (44.4).



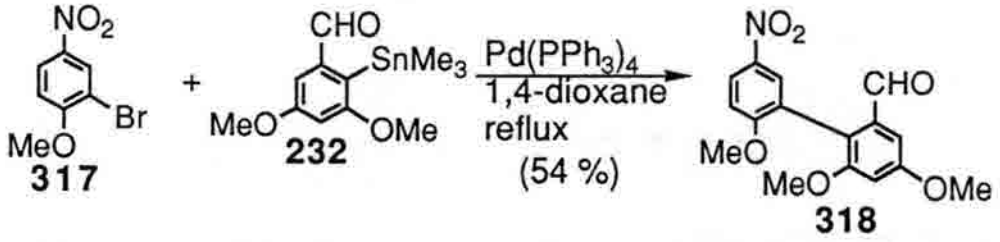
270 MHz ^1H NMR of **240** in $CDCl_3$ at room temperature.



2-(2'-Methoxy)phenyl-3,5-dimethoxybenzaldehyde (316).[72, 82a] To a stirred solution of 2-bromoanisole (25 μL, 0.200 mmoles, 1.00 equiv.) and **232** (79 mg, 0.240 mmoles, 1.20 equiv.) in dry 1,4-dioxane (2.00 mL) was added $Pd(PPh_3)_4$ (29 mg, 0.025 mmoles, 0.05 equiv.). The resulting mixture was stirred at reflux for 36 h when, upon cooling to room temp., the mixture was filtered through a plug of celite with CH_2Cl_2 and evaporated. The residue was partitioned between CH_2Cl_2 (5 mL) and water (5 mL), separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with 10 % $NH_{3\ (aq)}$ (2 x 15 mL), and brine (15 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via PTLC (4:1; Hex/EtOAc) yielding 9 mg (17 %) of the desired product (**316**) as a white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.73 (s, 3 H), 3.75 (s, 3 H), 3.90 (s, 3 H), 6.78 (d, J=2.5 Hz, 1 H), 7.02 (m, 2 H), 7.11 (d, J=2.5, 1 H), 7.21 (dd, J=5.8 Hz, 1 H), 7.39 (m, 1 H), 9.64 (s 1 H). IR: (NaCl, $CHCl_3$) 3003, 2938, 2838, 1687, 1599, 1464, 1393, 1334, 1288, 1257, 1200, 1155, 1063, 1026, 1000, 927, 845, 756 cm^{-1}.

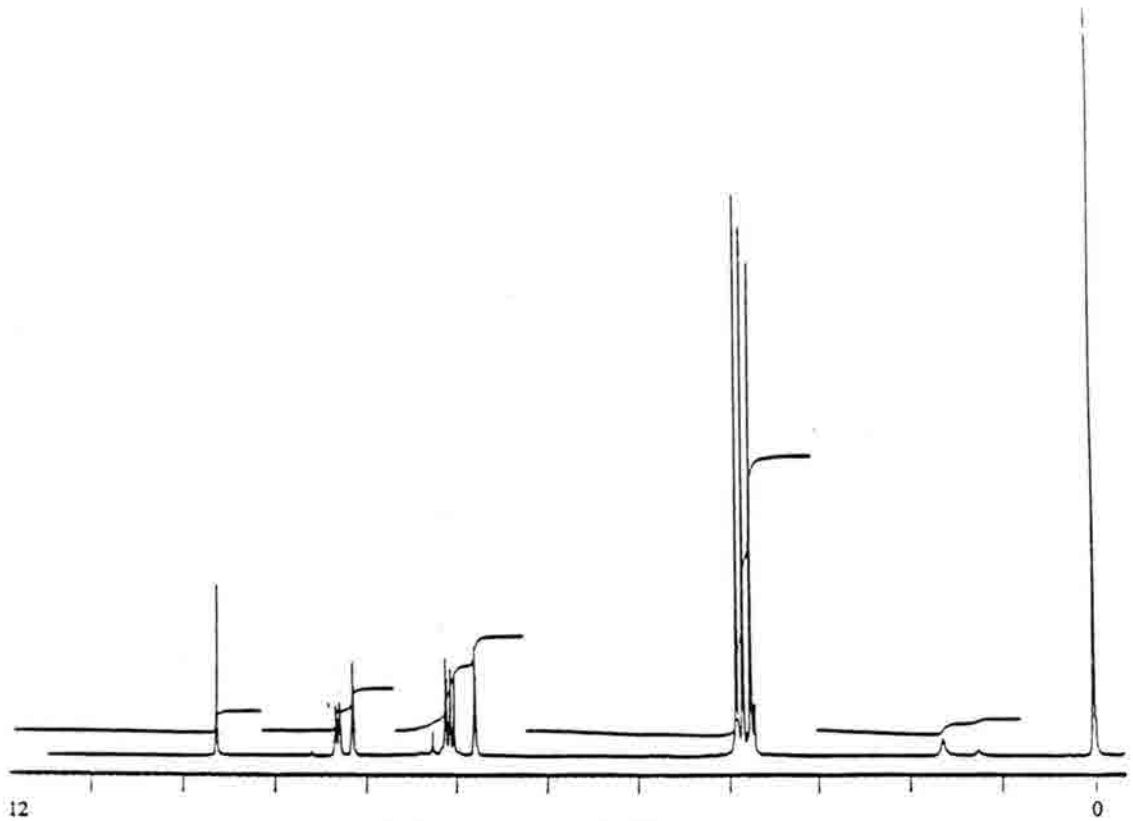


270 MHz ^1H NMR of **316** in $CDCl_3$ at room temperature.

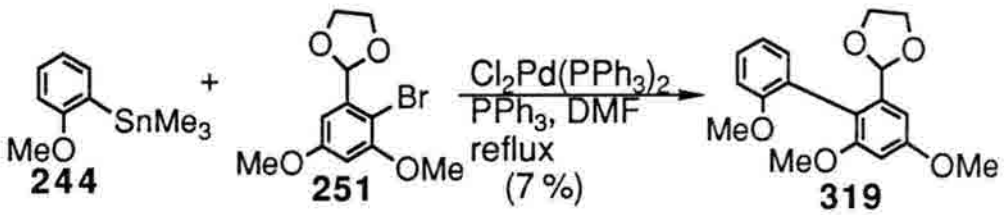


2-(2'-Methoxy-5'-nitro)phenyl-3,5-dimethoxybenzaldehyde (318).[72] To a stirred solution of 2-bromo-4-nitroanisole (46 mg, 0.200 mmoles, 1.00 equiv.) and **232** (79 mg, 0.240 mmoles, 1.20 equiv.) in dry 1,4-dioxane (2.00 mL) was added $Pd(PPh_3)_4$ (29 mg, 0.025 mmoles, 0.05 equiv.). The resulting mixture was stirred at reflux for 48 h when, upon cooling to room temp., the mixture was filtered through a plug of celite with CH_2Cl_2 and evaporated. The residue was partitioned between CH_2Cl_2 (5 mL) and water (5 mL), separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with 10 % $NH_{3\,(aq)}$ (2 x 15 mL), and

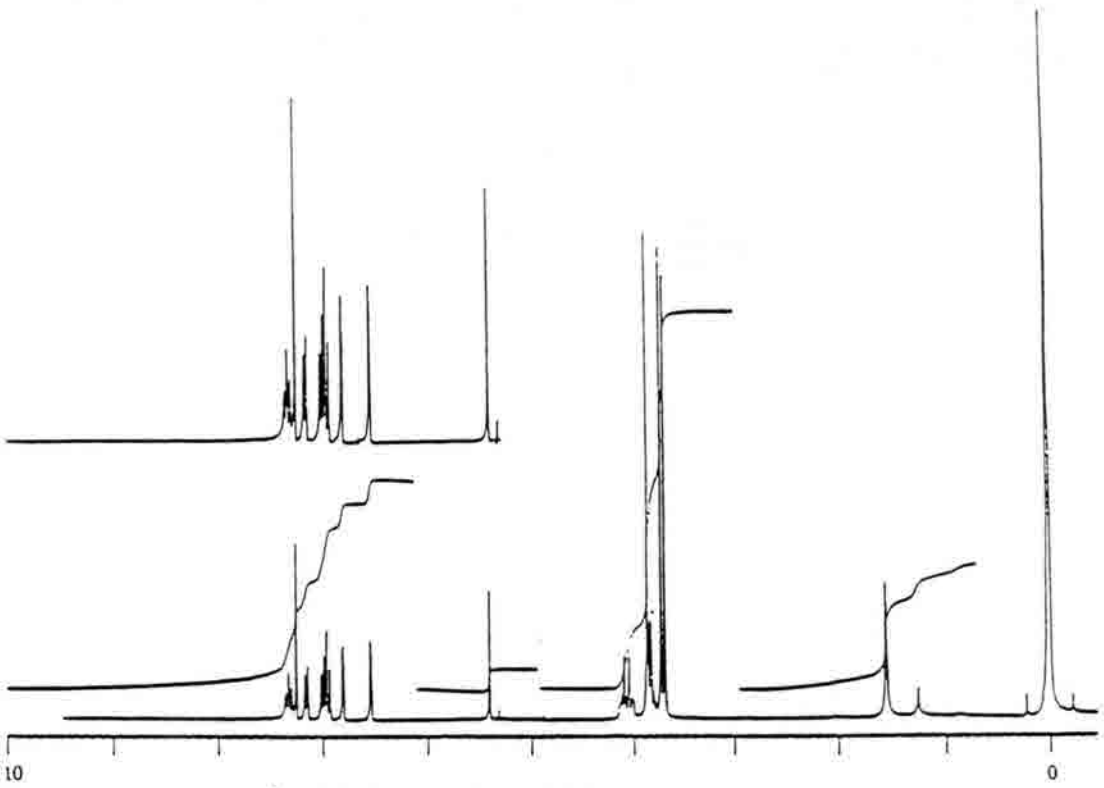
brine (15 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via PTLC (4:1; Hex/EtOAc) yielding 34 mg (54 %) of the desired product (**318**) as a pale yellow solid. ^1H NMR: (200 MHz) ($CDCl_3$) δ TMS: 3.75 (s, 3 H), 3.84 (s, 3 H), 3.91 (s, 3 H), 6.80 (d, J=2.4 Hz, 1 H), 7.05 (d, J=9.1 Hz, 1 H), 7.12 (d, J=2.4, 1 H), 8.15 (d, J=2.9 Hz, 1 H), 8.32 (dd, J=6.2 Hz, 1 H), 9.63 (s 1 H). IR: (NaCl, $CHCl_3$) 3020, 2942, 2844, 1691, 1602, 1520, 1464, 1343, 1268, 1216, 1157, 1106, 1062, 1026, 930, 849, 758 cm^{-1}.



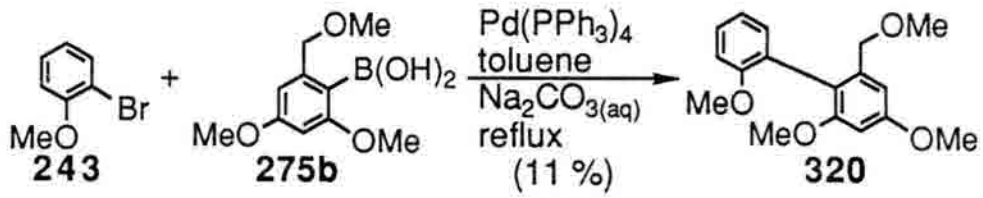
200 MHz ^1H NMR of **318** in $CDCl_3$ at room temperature.



2-(2'-(2''-Methoxy)phenyl-3',5'-dimethoxy)phenyl-1,3-dioxolane (319).[72] To a stirred solution of 2-(2'-bromo-3',5'-dimethoxy)phenyl-1,3-dioxolane (**251**) (54 mg, 0.200 mmoles, 1.00 equiv.) and 2-methoxyphenyl trimethylstannane (**244**)[93] (54 μL, 0.240 mmoles, 1.20 equiv.) in dry DMF (2.00 mL) was added $Cl_2Pd(PPh_3)_2$ (21 mg, 0.030 mmoles, 0.15 equiv.) and PPh_3 (21 mg, 0.080 mmoles, 0.40 equiv.). The resulting mixture was stirred at reflux for 48 h when, upon cooling to room temp., the mixture was filtered through a plug of celite with CH_2Cl_2 and evaporated. The residue was partitioned between CH_2Cl_2 (5 mL) and water (5 mL), separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with 10 % $NH_{3\ (aq)}$ (2 x 15 mL), and brine (15 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via PTLC (4:1; Hex/EtOAc) yielding 4 mg (7 %) of the desired product (**319**) as a white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.69 (s, 3 H), 3.73 (s, 3 H), 3.83 (m, 2 H), 3.87 (s, 3 H), 4.07 (m, 2 H), 5.41 (s, 1 H), 6.55 (d, J=2.4 Hz, 1 H), 6.82 (d, J=2.4, 1 H), 6.97 (m, 2 H), 7.16 (d, J=7.3 Hz, 1 H), 7.33 (m, 1 H). IR: (NaCl, $CHCl_3$) 2937, 2890, 2836, 1610, 1598, 1464, 1392, 1322, 1256, 1201, 1156, 1064, 960, 840, 756 cm^{-1}.

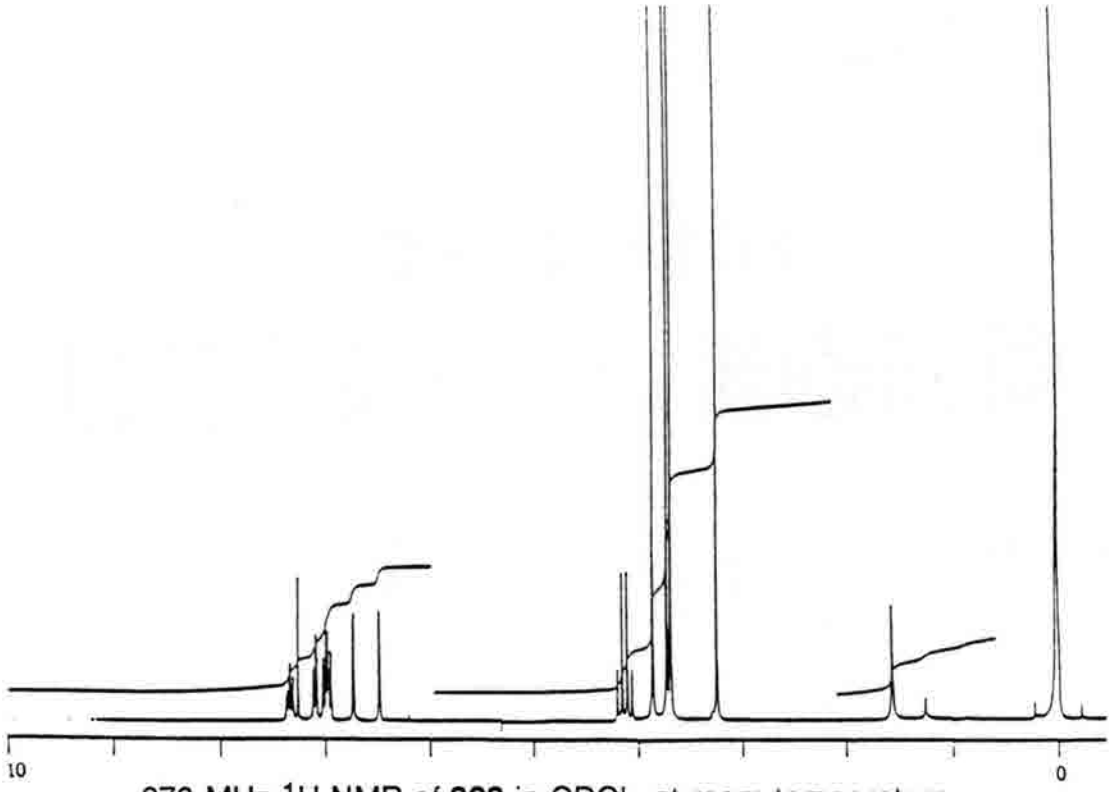


270 MHz ^{1}H NMR of **319** in $CDCl_3$ at room temperature.

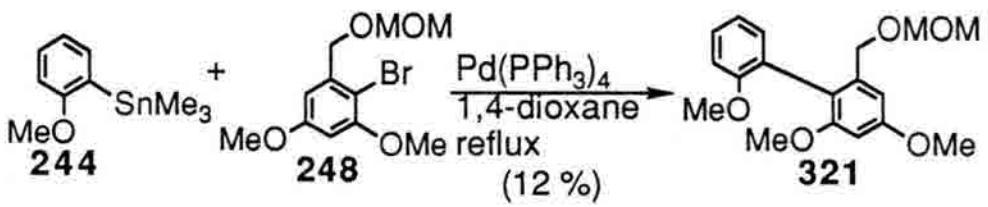


2-(2',4'-Dimethoxy-6'-methoxymethyl)phenyl anisole (320).[83] To a stirred solution of 2-bromoanisole (25 μL, 0.200 mmoles, 1.00 equiv.) and $Pd(PPh_3)_4$ (7 mg, 0.006 mmoles, 0.03 equiv.) in toluene (5.00 mL) was added 6,4-dimethoxy-2-methoxymethylphenylboronic acid (**275b**) (50 mg, 0.220 mmoles, 1.10 equiv.), ethanol (1.00 mL) and 2 M $Na_2CO_{3(aq)}$ (0.22 mL). The resulting mixture was stirred at reflux for 20 h when, upon cooling to room temp., the mixture was filtered and evaporated. The residue was partitioned between CH_2Cl_2 (5 mL) and water (5 mL), separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried

($MgSO_4$), filtered and evaporated. The residue was separated via PTLC (4:1; Hex/EtOAc) yielding 6 mg (11 %) of the desired product (**320**) as a white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.24 (s, 3 H), 3.69 (s, 3 H), 3.73 (s, 3 H), 3.86 (s, 3 H), 4.09 (1/2 ABq, J=22.6 Hz, 1 H), 4.17 (1/2 ABq, J=22.6 Hz, 1 H), 6.49 (d, J=2.5 Hz, 1 H), 6.74 (d, J=2.4, 1 H), 6.99 (m, 2 H), 7.05 (dd, J=15.4 Hz, 1 H), 7.34 (m, 1 H). IR: (NaCl, $CHCl_3$) 2997, 2934, 2836, 1598, 1463, 1322, 1256, 1200, 1154, 1077, 1002, 836, 755 cm^{-1}.

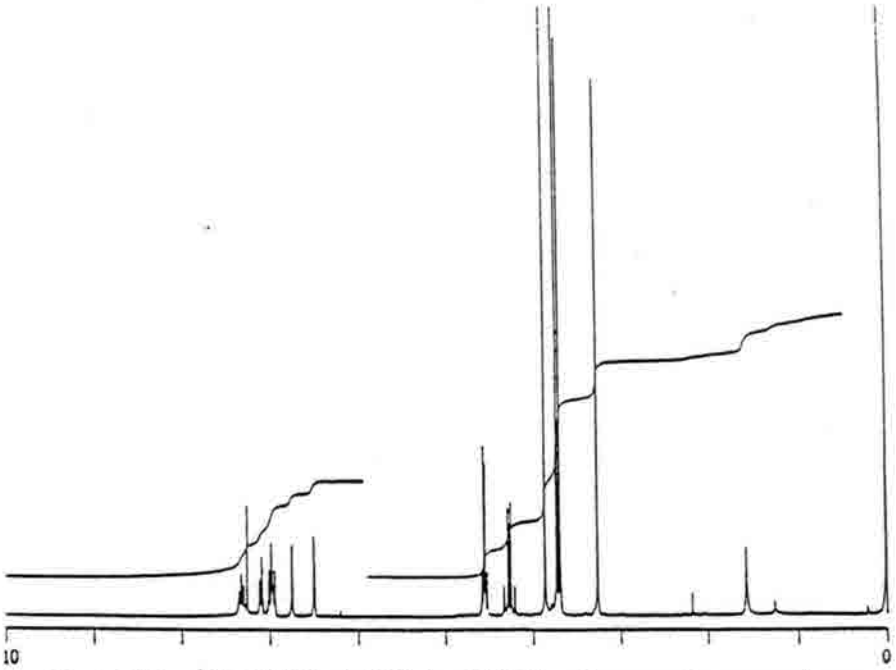


270 MHz ^1H NMR of **320** in $CDCl_3$ at room temperature.

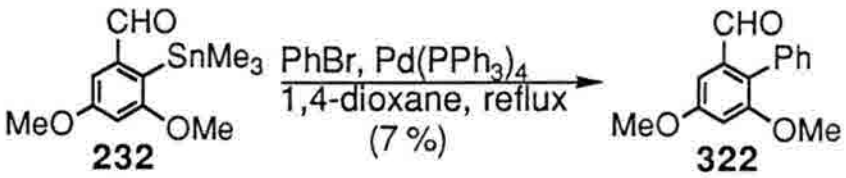


2-(2',4'-Dimethoxy-6'-(methoxy)methoxymethyl)phenyl anisole (321).[72] To a stirred solution of 4,6-dimethoxy-2-(methoxy)methoxymethyl

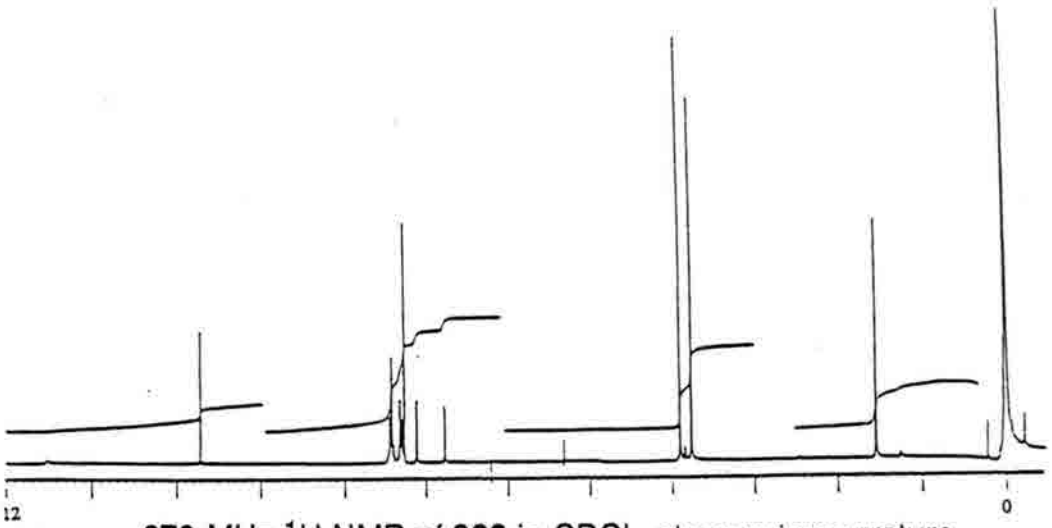
bromobenzene (**248**) (39 μL, 0.200 mmoles, 1.00 equiv.) and 2-methoxyphenyl trimethylstannane (**244**)[76] (54 μL, 0.240 mmoles, 1.20 equiv.) in dry 1,4-dioxane (1.00 mL) was added $Pd(PPh_3)_4$ (29 mg, 0.025 mmoles, 0.05 equiv.). The resulting mixture was stirred at reflux for 48 h when, upon cooling to room temp., the mixture was filtered through a plug of celite with CH_2Cl_2 and evaporated. The residue was partitioned between CH_2Cl_2 (5 mL) and water (5 mL), separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with 10 % $NH_{3\ (aq)}$ (2 x 15 mL), and brine (15 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via PTLC (4:1; Hex/EtOAc) yielding 8 mg (12 %) of the desired product (**321**) as a clear, colorless oil. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.26 (s, 3 H), 3.69 (s, 3 H), 3.73 (s, 3 H), 3.86 (s, 3 H), 4.24 (1/2 ABq, J=12.4 Hz, 1 H), 4.30 (1/2 ABq, J=12.3 Hz, 1 H), 4.52 (1/2 ABq, J=6.5 Hz, 1 H), 4.58 (1/2 ABq, J=6.4 Hz, 1 H), 6.50 (d, J=2.4 Hz, 1 H), 6.75 (d, J=2.3 Hz, 1 H), 6.98 (m, 2 H), 7.10 (dd, J=5.7 Hz, 1 H), 7.32 (m, 1 H). IR: (NaCl, $CHCl_3$) 2938, 2837, 1598, 1463, 1323, 1200, 1154, 1045, 1002, 922, 836, 755 cm^{-1}.



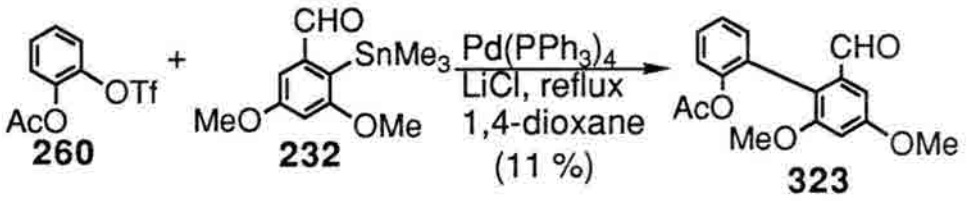
270 MHz ^1H NMR of **321** in $CDCl_3$ at room temperature.



3,5-Dimethoxy-2-phenylbenzaldehyde (322).[72] To a stirred solution of bromobenzene (21 μL, 0.200 mmoles, 1.00 equiv.) and **232** (79 mg, 0.240 mmoles, 1.20 equiv.) in dry 1,4-dioxane (2.00 mL) was added $Pd(PPh_3)_4$ (29 mg, 0.025 mmoles, 0.05 equiv.). The resulting mixture was stirred at reflux for 48 h when, upon cooling to room temp., the mixture was filtered through a plug of celite with CH_2Cl_2 and evaporated. The residue was partitioned between CH_2Cl_2 (5 mL) and water (5 mL), separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with 10 % $NH_{3\,(aq)}$ (2 x 20 mL), and brine (20 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via PTLC (4:1; Hex/EtOAc) yielding 4 mg (7 %) of the desired product (**322**) as a white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.76 (s, 3 H), 3.90 (s, 3 H), 6.77 (d, J=2.5 Hz, 1 H), 7.11 (d, J=2.5 Hz, 1 H), 7.26 (s, 1 H), 7.32 (m, 1 H), 7.42 (m, 3 H), 9.71 (s, 1 H). IR: (NaCl, $CHCl_3$) 2965, 2933, 2857, 1682, 1602, 1456, 1395, 1335, 1288, 1199, 1155, 1063, 842, 747, 705 cm^{-1}.

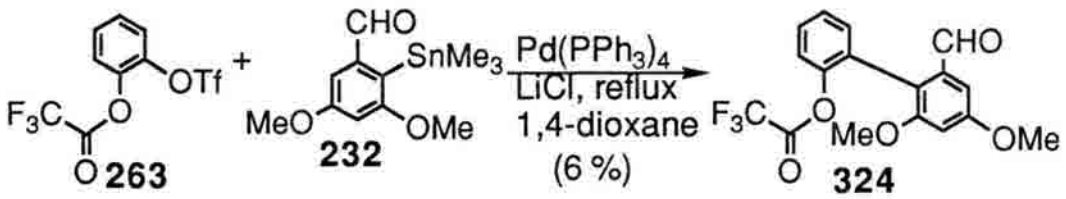


270 MHz ^1H NMR of **322** in $CDCl_3$ at room temperature.

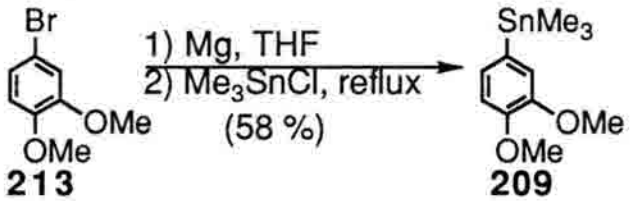


260 232 323

3,5-Dimethoxy-2-(2'-acetoxy)phenylbenzaldehyde (323).[72] To a stirred solution of 2-acetoxyphenyl trifluoromethanesulfonate (**260**) (33 mg, 0.116 mmoles, 1.00 equiv.) and **232** (79 mg, 0.240 mmoles, 2.07 equiv.) in dry 1,4-dioxane (2.00 mL) was added $Pd(PPh_3)_4$ (29 mg, 0.025 mmoles, 0.215 equiv.) and LiCl (25 mg, 0.600 mmoles, 5.16 equiv.). The resulting mixture was stirred at reflux for 48 h when, upon cooling to room temp., the mixture was filtered through a plug of celite with CH_2Cl_2 and evaporated. The residue was partitioned between CH_2Cl_2 (5 mL) and water (5 mL), separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with 10 % $NH_{3\,(aq)}$ (2 x 20 mL), and brine (20 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via PTLC (4:1; Hex/EtOAc) yielding 4 mg (11 %) of the desired product (**323**) as a white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 1.94 (s, 3 H), 3.74 (s, 3 H), 3.90 (s, 3 H), 6.75 (d, J=2.4 Hz, 1 H), 7.11 (d, J=2.4 Hz, 1 H), 7.26 (m, 3 H), 7.32 (m, 1 H), 9.67 (s, 1 H). IR: (NaCl, $CHCl_3$) 3052, 2932, 2856, 1765, 1689, 1600, 1469, 1436, 1333, 1188, 1155, 1097, 1061, 911, 846, 745, 693 cm^{-1}. MS: *m/e* (relative intensity) CI (NH_3): 302 (5.7), 301 (28.5), 300 (9.9), 279 (8.3), 264 (19.7), 263 (100.0), 258 (11.6), 257 (13.7), 253 (12.9), 241 (82.2), 212 (26.7), 201 (11.1), 183 (8.7), 147 (6.8), 129 (7.6), 78 (5.6).

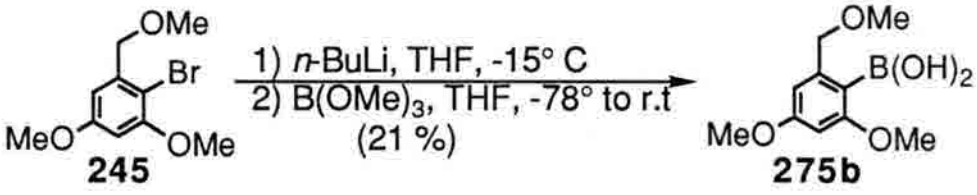


3,5-Dimethoxy-2-(2'-trifluoroacetoxy)phenylbenzaldehyde (324).[72] To a stirred solution of 2-trifluoroacetoxyphenyltrifluoromethane sulfonate (**263**) (65 mg, 0.200 mmoles, 1.00 equiv.) and **232** (79 mg, 0.240 mmoles, 1.20 equiv.) in dry 1,4-dioxane (2.00 mL) was added $Pd(PPh_3)_4$ (29 mg, 0.025 mmoles, 0.125 equiv.) and LiCl (25 mg, 0.600 mmoles, 3.00 equiv.). The resulting mixture was stirred at reflux for 48 h when, upon cooling to room temp., the mixture was filtered through a plug of celite with CH_2Cl_2 and evaporated. The residue was partitioned between CH_2Cl_2 (5 mL) and water (5 mL), separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with 10 % $NH_{3\,(aq)}$ (2 x 20 mL), and brine (20 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via PTLC (4:1; Hex/EtOAc) yielding 5 mg (6 %) of the desired product (**324**) as a white solid. ^1H NMR: (200 MHz) ($CDCl_3$) δ TMS: 3.77 (s, 3 H), 3.92 (s, 3 H), 6.77 (d, J=2.4 Hz, 1 H), 7.15 (d, J=2.4 Hz, 1 H), 7.26-7.53 (m, 4 H), 9.69 (s, 1 H).



(3,4-dimethoxyphenyl)trimethylstannane (209).[93, 94] To a stirred suspension of magnesium (612 mg, 25.17 mmoles, 1.07 equiv.) in dry THF (18.10 mL) was added 4-bromoveretrol (**213**) (3.00 mL, 23.52 mmoles, 1.00 equiv.). The resulting mixture was warmed slightly, with the palm of the hand,

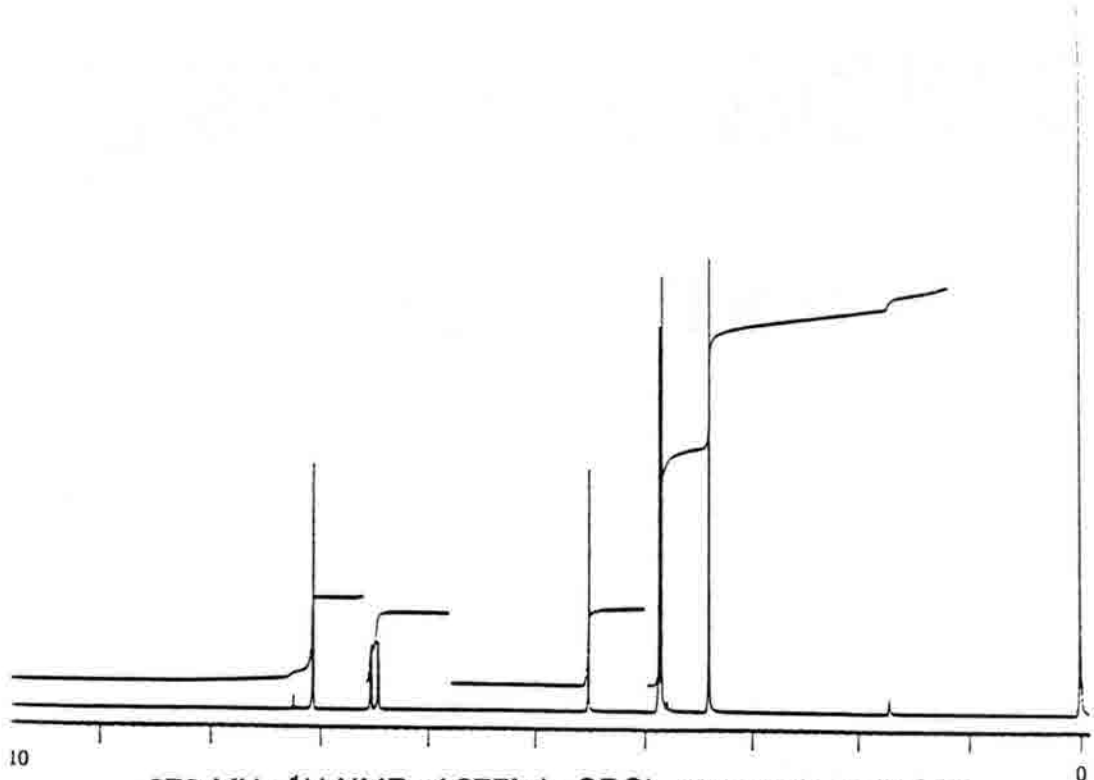
until the mixture began to reflux spontaneously. The suspension was stirred at room temp. for 2 h total when trimethyltin chloride (4.686 g, 23.52 mmoles, 1.00 equiv.) was added. The resulting mixture was stirred at reflux overnight. Upon cooling to room temp., the mixture was partitioned between Et_2O (100 mL) and sat. NH_4Cl (100 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and evaporated. The crude yellow oil was purified via Kugelrohr distillation yielding 4.14 g (58 %) of the desired product (**209**) as a clear, colorless oil. ^1H NMR: (200 MHz) ($CDCl_3$) δ TMS: 0.29 (s, 9 H), 3.84 (s, 3 H), 3.89 (s, 3 H), 6.82-7.05 (m, 3 H).



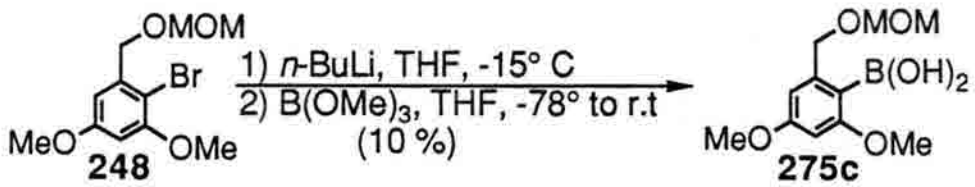
245 **275b**

4,6-Dimethoxy-2-methoxymethylphenylboronic acid (275b).[83a] To a stirred solution of 4,6-dimethoxy-2-methoxymethylbromobenzene (**245**) (94 μL, 0.383 mmoles, 1.00 equiv.) in dry THF (0.38 mL) cooled to -15° C was added *n*-BuLi (0.38 mL, 0.613 mmoles, 1.60 equiv., 1.60 M in Hex) dropwise. The resulting solution was stirred at -15° C for 30 min when it was added dropwise to a solution of trimethylborate (52 μL, 0.460 mmoles, 1.20 equiv.) in dry THF (0.12 mL) cooled to -78° C. The resulting mixture was gradually allowed to warm to room temp. over 2 h when the mixture was partitioned between Et_2O (2 mL) and 10 % $HCl_{(aq)}$ (2 mL). The organic layer was washed with water (2 mL), dried ($MgSO_4$), filtered and evaporated. The residue was recrystallized from Et_2O/Hex yielding 18 mg (21 %) of the desired product (**275b**) as a pure, white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.41 (s, 3 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 4.53 (s, 2 H), 6.47 (d, J=2.1 Hz, 1 H), 6.54 (d,

J=2.1 Hz, 1 H), 7.08 (s, 2 H). IR: (NaCl, $CHCl_3$) 3333, 3019, 2935, 2841, 1601, 1574, 1455, 1422, 1384, 1310, 1216, 1156, 1072, 758, 668 cm^{-1}.

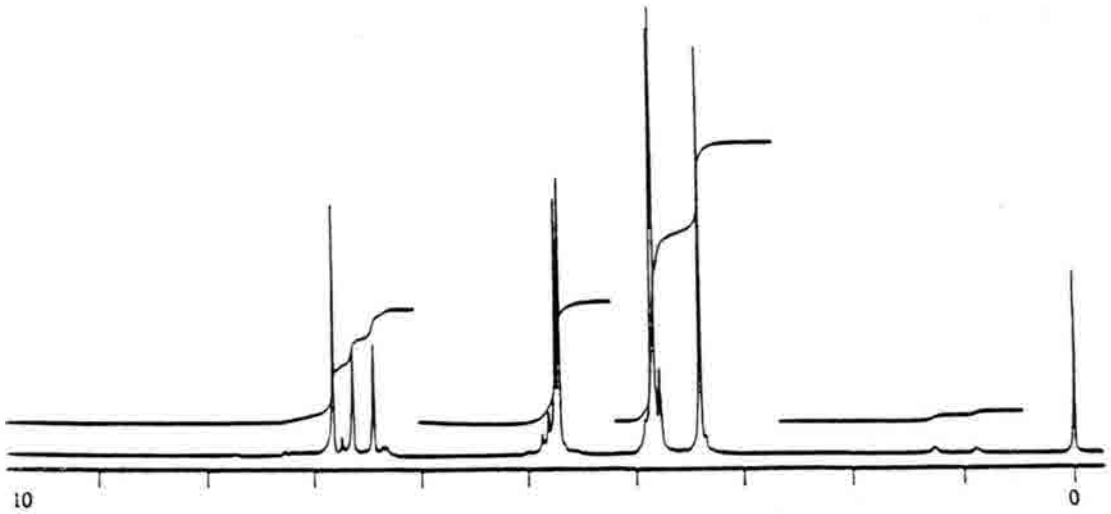


270 MHz ^1H NMR of **275b** in $CDCl_3$ at room temperature.

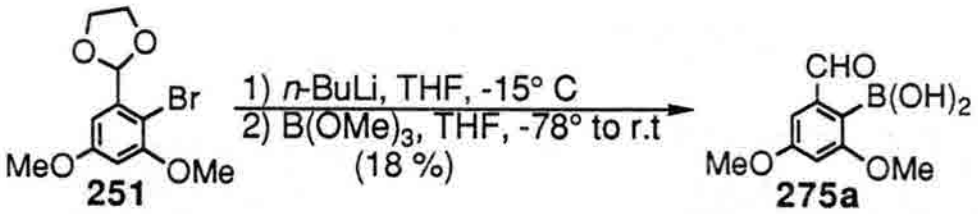


4,6-Dimethoxy-2-(methoxy)methoxymethylphenylboronic acid (275c).[83a] To a stirred solution of 4,6-dimethoxy-2-(methoxy)methoxymethyl bromobenzene (**248**) (1.00 g, 3.436 mmoles, 1.00 equiv.) in dry THF (3.40 mL) cooled to -15° C was added *n*-BuLi (3.44 mL, 5.498 mmoles, 1.60 equiv., 1.60 M in Hex) dropwise. The resulting solution was stirred at -15° C for 30 min when it was added dropwise to a solution of trimethylborate (0.59 mL, 5.155 mmoles, 1.50 equiv.) in dry THF (1.00 mL) cooled to -78° C. The resulting mixture was gradually allowed to warm to room temp. over 4 h when the mixture

was partitioned between Et_2O (20 mL) and 10 % $HCl_{(aq)}$ (20 mL) and separated. The organic layer was washed with water (10 mL), dried ($MgSO_4$), filtered and evaporated. The residue was recrystallized from Et_2O/Hex yielding 88 mg (10 %) of the desired product (**275c**) as a white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.41 (s, 3 H), 3.84 (s, 3 H), 3.86 (s, 3 H), 4.71 (s, 2 H), 4.74 (s, 2 H), 6.44 (s, 1 H), 6.63 (s, 1 H), 6.82 (s, 2 H). IR: (NaCl, $CDCl_3$) 3418, 2941, 2845, 1602, 1463, 1426, 1311, 1200, 1153, 1096, 1044, 912, 834, 732 cm^{-1}.

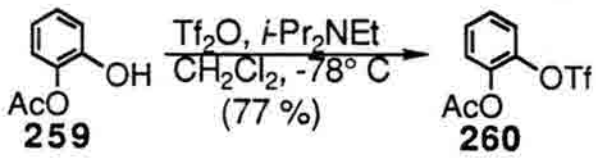


270 MHz ^1H NMR of **275c** in $CDCl_3$ at room temperature.



4,6-Dimethoxy-2-formylphenylboronic acid (275a).[83a] To a stirred solution of 2-(2'-bromo-3',5'-dimethoxy)phenyl-1,3-dioxolane (**251**) (500 mg, 1.730 mmoles, 1.00 equiv.) in dry THF (1.75 mL) cooled to -15° C was added *n*-BuLi (1.19 mL, 1.903 mmoles, 1.10 equiv., 1.60 M in Hex) dropwise. The resulting solution was stirred at -15° C for 30 min when it was added dropwise

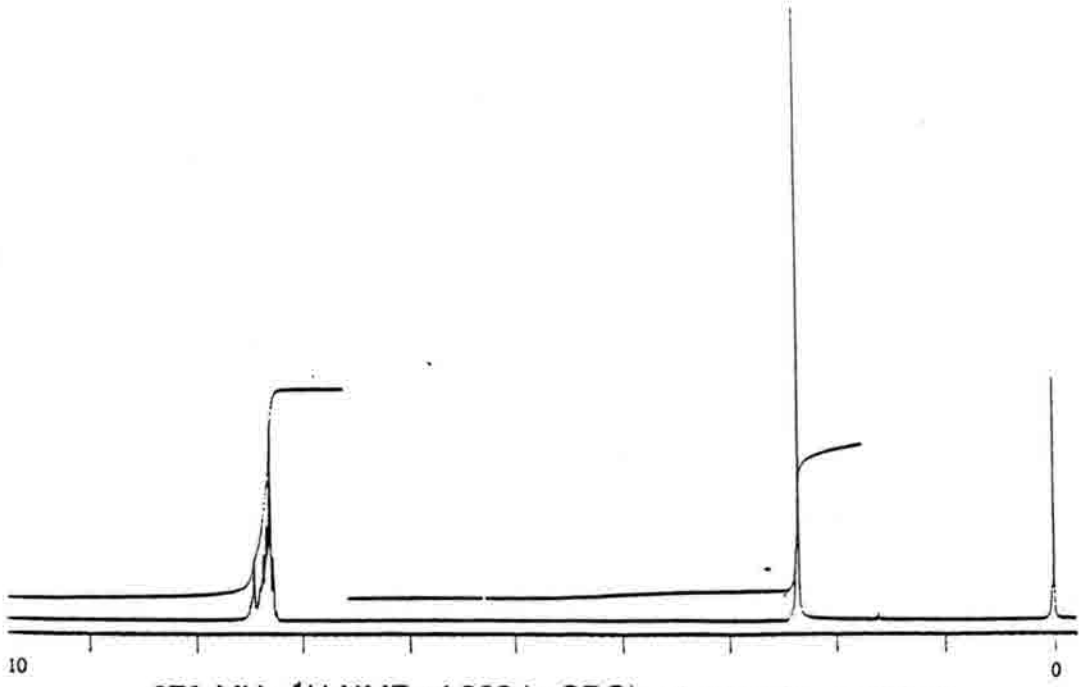
to a solution of trimethylborate (0.30 mL, 2.595 mmoles, 1.50 equiv.) in dry THF (0.50 mL) cooled to -78° C. The resulting mixture was gradually allowed to warm to room temp. over 4 h when the mixture was partitioned between Et_2O (10 mL) and 10 % $HCl_{(aq)}$ (10 mL). The organic layer was washed with water (10 mL), dried ($MgSO_4$), filtered and evaporated. The residue was recrystallized from Et_2O/Hex yielding 66 mg (18 %) of **275a** as a white solid / yellow oil. ^1H NMR: (200 MHz) ($CDCl_3$) δ TMS: 3.82 (s, 3 H), 3.83 (s, 3 H), 6.36 (d, J=1.5 Hz, 1 H), 6.66 (d, J=1.7 Hz, 1 H), 7.01 (d, J = 2.3 Hz, 2 H), 9.89 (s, 1 H). IR: (NaCl) 3444, 3215, 2943, 2845, 1693, 1599, 1454, 1425, 1311, 1207, 1153, 1060, 1022, 837 cm^{-1}.



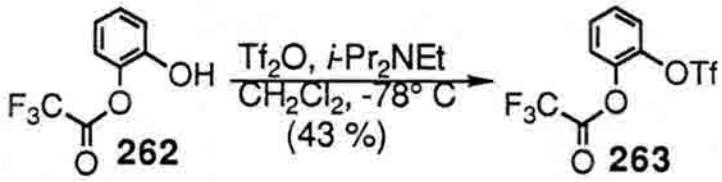
259 **260**

2-Acetoxyphenyltrifluoromethanesulfonate (260).[75, 95] To a stirred solution of 2-acetoxyphenol (**259**)[96] (2.00 g, 13.16 mmoles, 1.00 equiv.) in dry CH_2Cl_2 (116.25 mL) cooled to -78° C was added diisopropylethyl amine (6.88 mL, 39.47 mmoles, 3.00 equiv.) and triflic anhydride (2.46 mL, 14.61 mmoles, 1.11 equiv.). The resulting mixture was stirred at -78° C for 4 h when water (75 mL) was added at -78° C. Upon warming to room temp., the mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 75 mL). The combined organic layers were washed with water (300 mL), 10 % HCl_{aq} (2 x 300 mL), water (300 mL) and brine (300 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (4:1; Hex/EtOAc) yielding 2.87 g (77 %) of the desired product (**260**) as a white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 2.34 (s, 3 H), 7.38 (m, 4 H). IR: (NaCl)

3075, 2988, 1782, 1740, 1492, 1425, 1372, 1211, 1138, 1092, 1033, 1010, 911, 888, 858, 816, 768 cm^{-1}. Mp: 53-54° C.

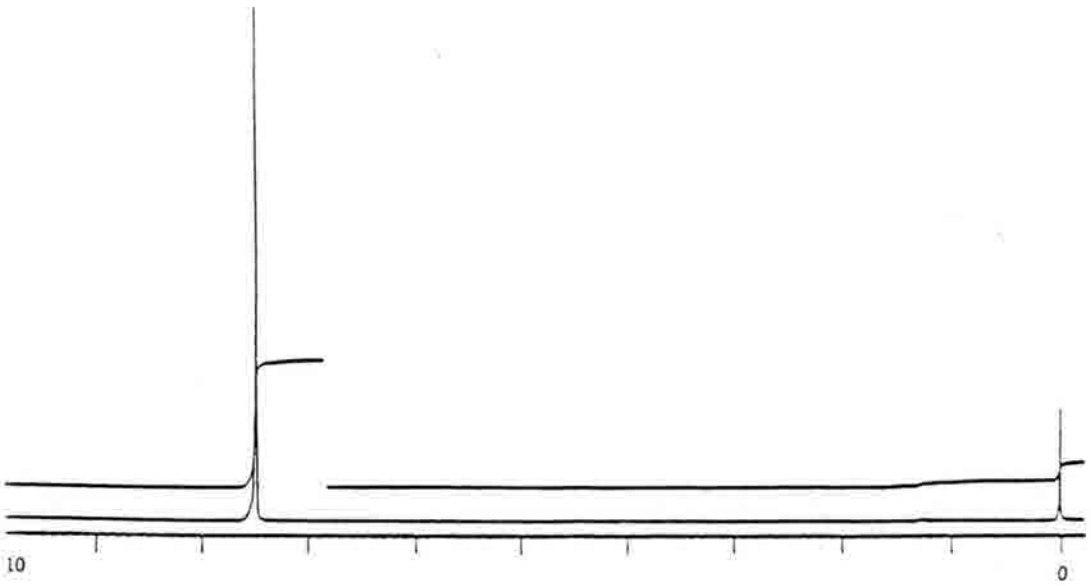


270 MHz ^1H NMR of **260** in $CDCl_3$ at room temperature.

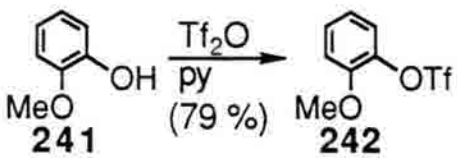


2-Trifluoroacetoxyphenyltrifluoromethanesulfonate (263).[75] To a stirred solution of 2-trifluoroacetoxyphenol (**263**) (430 mg, 2.087 mmoles, 1.00 equiv.) in dry CH_2Cl_2 (18.44 mL) cooled to -78° C was added diisopropylethyl amine (1.10 mL, 6.262 mmoles, 3.00 equiv.) and triflic anhydride (0.39 mL, 2.317 mmoles, 1.11 equiv.). The resulting mixture was stirred at -78° C for 2 h when water (15 mL) was added at -78° C. Upon warming to room temp., the mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 15 mL). The combined organic layers were washed with water (50 mL), 10 %

HCl_{aq} (2 x 50 mL), water (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (4:1; Hex/EtOAc) yielding 293 mg (43 %) of the desired product (**263**) as a clear, colorless oil. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 7.49 (s, 4 H). IR: (NaCl) 3117, 2360, 1738, 1591, 1443, 1494, 1218, 1135, 1085, 900, 857, 784, 767, 737 cm^{-1}.

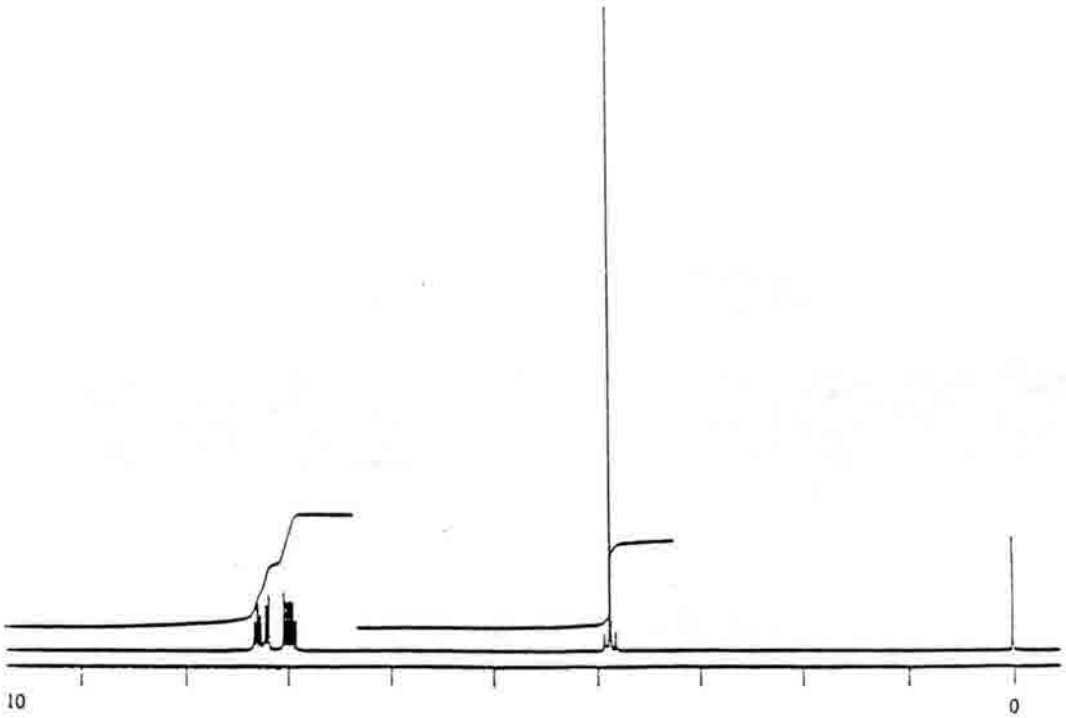


270 MHz ^1H NMR of **263** in $CDCl_3$ at room temperature.

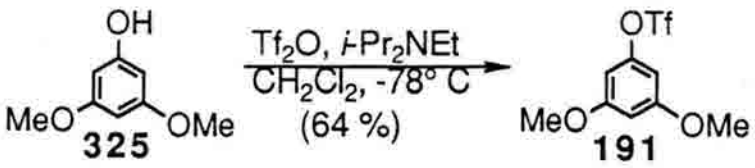


2-Methoxyphenyltrifluoromethanesulfonate (242).[75] To a stirred solution of guaiacol (**241**) (0.89 mL, 8.06 mmoles, 1.00 equiv.) in pyridine (4.35 mL) cooled to 0° C was added triflic anhydride (1.50 mL, 8.94 mmoles, 1.11 equiv.) dropwise. The resulting solution was stirred at 0° C for 10 min and at room temp. overnight when water (6 mL) was added. The mixture was

extracted with Et_2O (4 x 6 mL) and the combined organic layers were washed sequentially with water (10 mL), 10 % $HCl_{(aq)}$ (2 x 10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (4:1, Hex/ EtOAc) yielding 1.64 g (79 %) of the desired product (**242**) as a clear, colorless oil. ^1H NMR: (200 MHz) ($CDCl_3$) δ TMS: 3.84 (s, 3 H), 6.89-7.03 (m, 2 H), 7.18-7.32 (m, 2 H). IR: (NaCl) 2950, 2847, 1614, 1504, 1423, 1285, 1207, 1140, 1101, 1025, 890, 796, 754, 716 cm^{-1}.

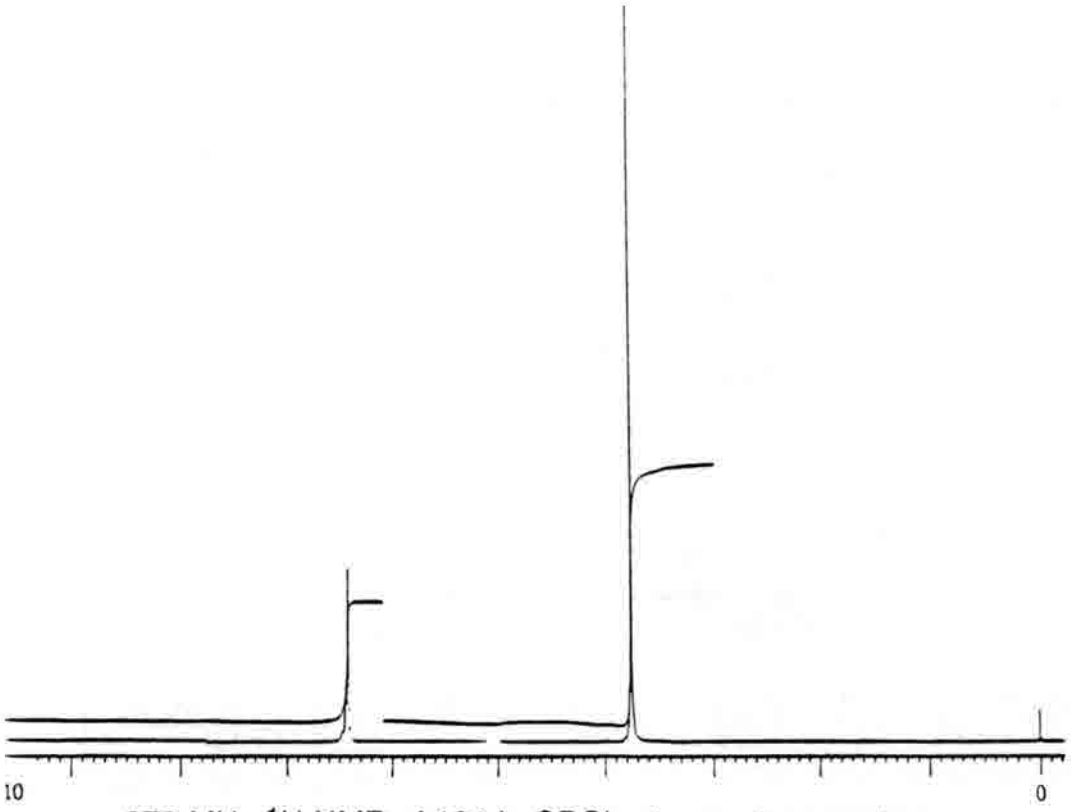


270 MHz ^1H NMR of **242** in $CDCl_3$ at room temperature.

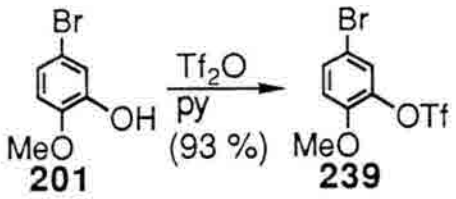


3,5-Dimethoxyphenyltrifluoromethanesulfonate (191).[75] To a stirred solution of 3,5-dimethoxyphenol (1.00 g, 6.49 mmoles, 1.00 equiv.) and

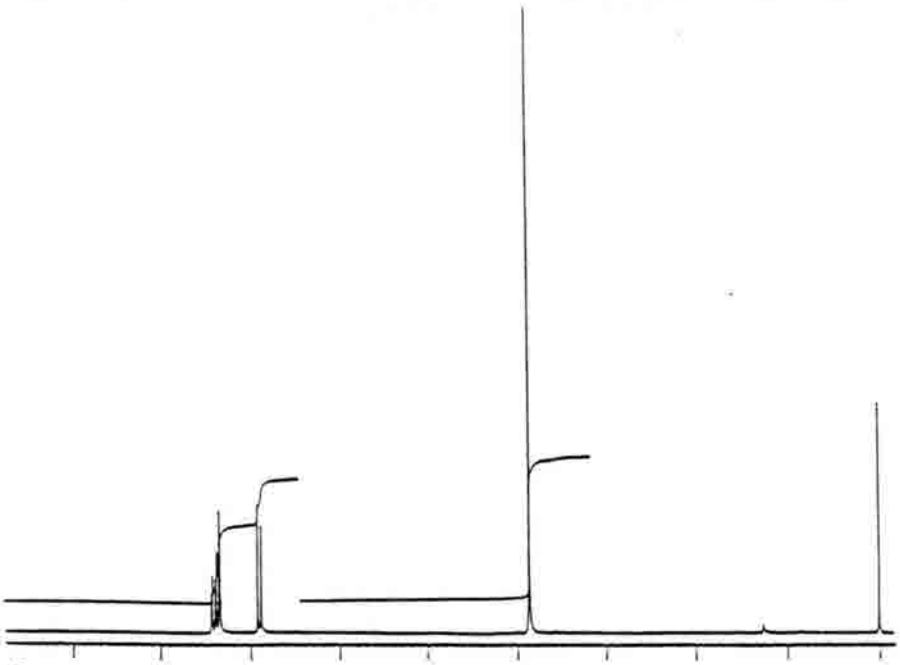
N,N-diisopropylethylamine (3.39 mL, 19.47 mmoles, 3.00 equiv.) in dry CH_2Cl_2 (3.50 mL) cooled to -78° C was added triflic anhydride (1.21 mL, 7.20 mmoles, 1.11 equiv.). The resulting suspension was stirred at -78° C for 1.5 h when the mixture was poured into water (5 mL) and extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with water (10 mL), 10 % $HCl_{(aq)}$ (2 x 10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (4:1; Hex/EtOAc) yielding 1.19 g (64 %) of the desired product (**191**) as a pale yellow oil. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.76 (s, 6 H), 6.42 (m, 3 H). IR: (NaCl) 3124, 2946, 2846, 1691, 1606, 1467, 1419, 1221, 1141, 1120, 975, 810, 762, 698 cm^{-1}. MS: *m/e* (relative intensity) CI(NH_3): 300 (1.0), 289 (1.1), 288 (6.8), 287 (21.9), 286 (100.0), 285 (79.5), 270 (1.6), 170 (2.1), 155 (6.3), 139 (13.0), 125 (77.3), 52 (20.4).



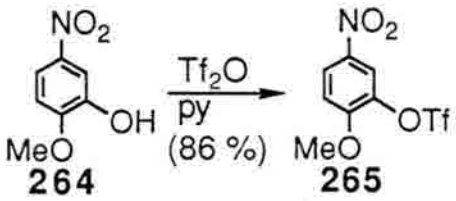
270 MHz ^1H NMR of **191** in $CDCl_3$ at room temperature.



5-Bromo-2-trifluoromethanesulfonatoanisole (239).[75] To a stirred solution of 5-bromoguaiacol (**201**) (500 mg, 2.46 mmoles, 1.00 equiv.) in pyridine (1.50 mL) cooled to 0° C was added triflic anhydride (0.46 mL, 2.73 mmoles, 1.11 equiv.) dropwise. The resulting solution was stirred at 0° C for 2 h when the mixture was poured into water (2 mL) and extracted with Et_2O (4 x 2 mL). The combined organic layers were washed with water (5 mL), 10 % $HCl_{(aq)}$ (2 x 5 mL), water (5 mL), and brine (5 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (4:1; Hex/EtOAc) yielding 767 mg (93 %) of the desired product (**239**) as a clear, colorless oil. ^1H NMR: (200 MHz) ($CDCl_3$) δ TMS: 3.87 (s, 3 H), 6.90 (d, J=8.7 Hz, 1 H), 7.35 (d, J=2.3 Hz, 1 H), 7.41 (dd, J=6.6 Hz, 1 H). IR: (NaCl) 3083, 2950, 2847, 1496, 1426, 1297, 1248, 1211, 1139, 1120, 1024, 909, 807 cm^{-1}.

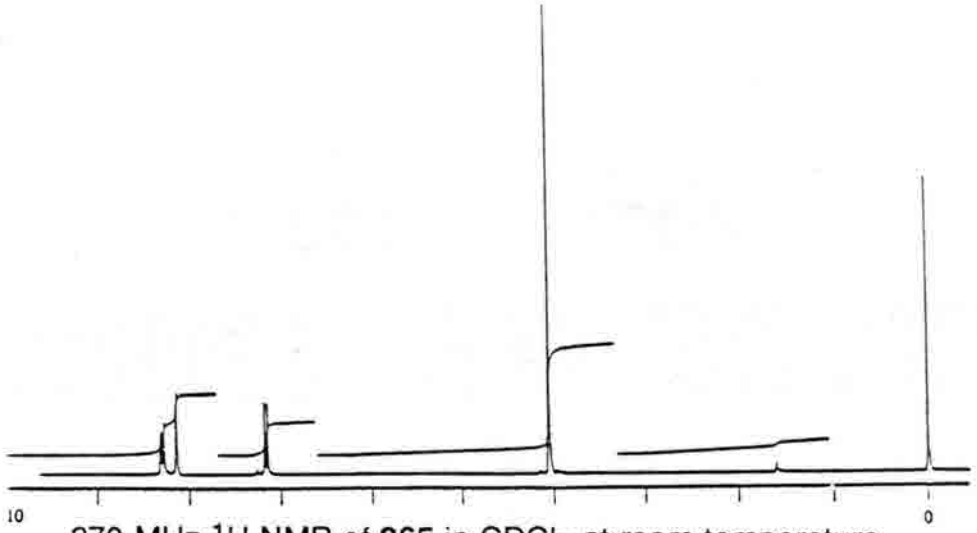


[10] 270 MHz ^1H NMR of **239** in $CDCl_3$ at room temperature. [0]

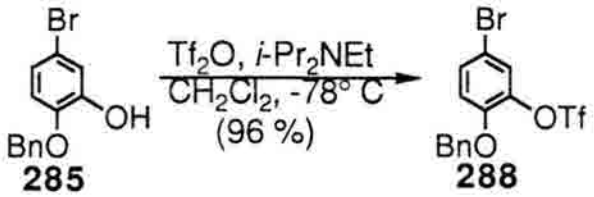


264 **265**

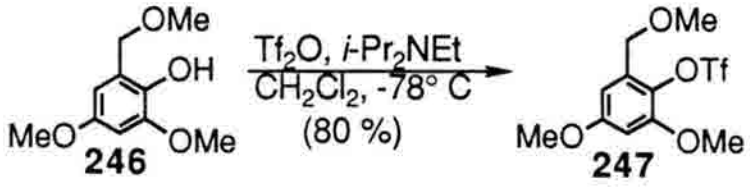
2-Methoxy-5-nitrophenyltrifluoromethanesulfonate (265).[75] To a stirred solution of 2-methoxy-5-nitrophenol (5.00 g, 29.56 mmoles, 1.00 equiv.) in pyridine (18.00 mL) cooled to 0° C was added triflic anhydride (5.52 mL, 32.81 mmoles, 1.11 equiv.) dropwise. The resulting solution was stirred at 0° C for 10 min, and then at room temp. for 4 h when the mixture was poured into water (30 mL) and extracted with Et_2O (4 x 50 mL). The combined organic layers were washed with water (150 mL), 10 % $HCl_{(aq)}$ (2 x 150 mL), water (150 mL), and brine (150 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (3:2; Hex/EtOAc) yielding 7.62 g (86 %) of the desired product (**265**) as a clear, yellow oil. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 4.06 (s, 3 H), 7.17 (d, J=9.2 Hz, 1 H), 8.15 (d, J=2.5 Hz, 1 H), 8.30 (dd, J=6.6 Hz, 1 H). IR: (NaCl) 3094, 2956, 2852, 1601, 1538, 1505, 1428, 1348, 1289, 1210, 1138, 1075, 1017, 949, 843, 795, 744, 635 cm^{-1}.



270 MHz ^1H NMR of **265** in $CDCl_3$ at room temperature.

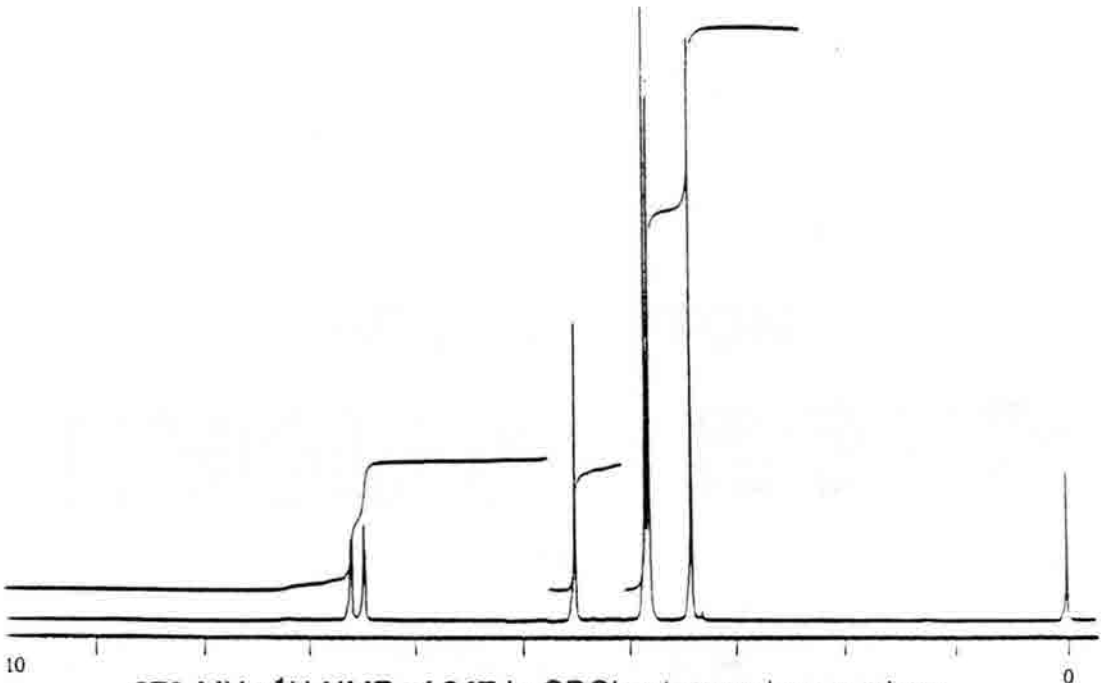


2-Benzyloxy-5-bromophenyltrifluoromethanesulfonate (288).[75] To a stirred solution of 2-benzyloxy-5-bromophenol (**285**) (360 mg, 1.272 mmoles, 1.00 equiv.) in dry CH_2Cl_2 (19.54 mL) cooled to -78° C was added diisopropylethyl amine (0.66 mL, 3.816 mmoles, 3.00 equiv.) and triflic anhydride (0.24 mL, 1.412 mmoles, 1.11 equiv.). The resulting mixture was stirred at -78° C for 3 h when water (20 mL) was added at -78° C. Upon warming to room temp., the mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were washed with water (50 mL), 10 % HCl_{aq} (2 x 50 mL), water (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and evaporated yielding 504 mg (96 %) of the desired product (**288**) as an amber oil. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 5.11 (s, 2 H), 6.92 (m, 1 H), 7.36 (m, 7 H). IR: (NaCl) 3069, 3036, 2929, 2884, 1601, 1493, 1426, 1294, 1211, 1140, 1117, 1004, 908, 808, 738, 696, 600 cm^{-1}.

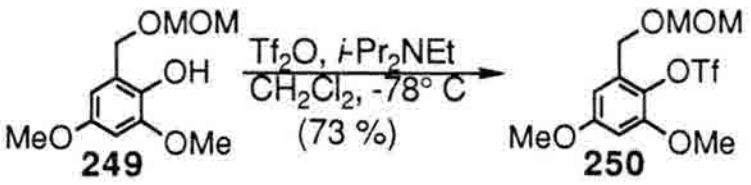


4,6-Dimethoxy-2-methoxymethylphenyltrifluoromethanesulfonate (247).[75] To a stirred solution of 4,6-dimethoxy-2-methoxymethylphenol (**246**) (402 mg, 2.030 mmoles, 1.00 equiv.) in dry CH_2Cl_2 (150 mL) cooled to -78° C was added N,N-diisopropylethylamine (1.06 mL, 6.091 mmoles, 3.00 equiv.) and triflic anhydride (0.38 mL, 2.254 mmoles, 1.11 equiv.). The resulting solution was stirred at -78° C for 4 h when water (10 mL) was added at -78° C.

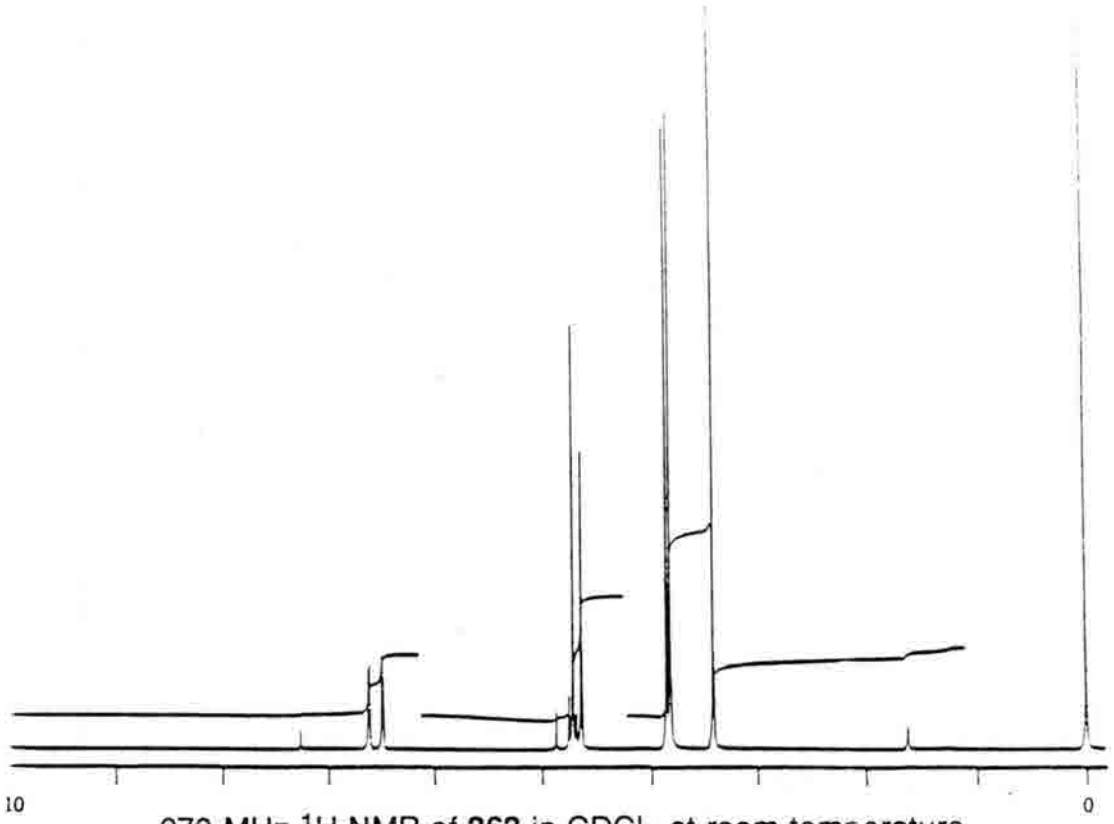
Upon warming to room temp., the mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with water (20 mL), 10 % $HCl_{(aq)}$ (2 x 20 mL), water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (3:2; Hex/EtOAc) yielding 538 mg (80 %) of the desired product (**247**) as a pale yellow oil. ^1H NMR: (200 MHz) ($CDCl_3$) δ TMS: 3.42 (s, 3 H), 3.81 (s, 3 H), 3.85 (s, 3 H), 4.51 (s, 2 H), 6.48 (d, J=2.8 Hz, 1 H), 6.60 (d, J=2.7 Hz, 1 H). IR: (NaCl) 2942, 2847, 1599, 1471, 1416, 1347, 1205, 1168, 1136, 1081, 1051, 874, 749, 612 cm^{-1}.



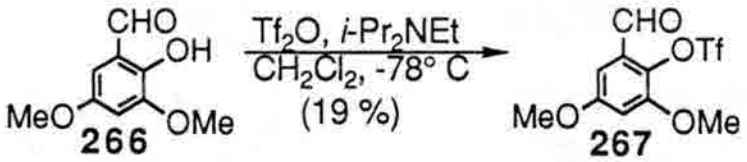
270 MHz ^1H NMR of **247** in $CDCl_3$ at room temperature.



4,6-Dimethoxy-2-(methoxy)methoxymethylphenyl trifluoromethanesulfonate (250).[75] To a stirred solution of 4,6-dimethoxy-2-(methoxy)methoxymethylphenol (**249**) (389 mg, 1.706 mmoles, 1.00 equiv.) in dry CH_2Cl_2 (15.00 mL) cooled to -78° C was added N,N-diisopropylethylamine (0.89 mL, 5.118 mmoles, 3.00 equiv.) and triflic anhydride (0.32 mL, 1.894 mmoles, 1.11 equiv.). The resulting solution was stirred at -78° C for 2 h when water (10 mL) was added at -78° C. Upon warming to room temp., the mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with water (20 mL), 10 % $HCl_{(aq)}$ (2 x 20 mL), water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (3:2; Hex/EtOAc) yielding 449 mg (73 %) of the desired product (**250**) as an amber oil. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.42 (s, 3 H), 3.82 (s, 3 H), 3.86 (s, 3 H), 4.65 (s, 2 H), 472 (s, 2 H), 6.49 (d, J=2.9 Hz, 1 H), 6.62 (d, J=2.8 Hz, 1 H). IR: (NaCl) 2949, 2845, 1598, 1470, 1416, 1348, 1204, 1169, 1135, 1048, 925, 874 cm^{-1}.

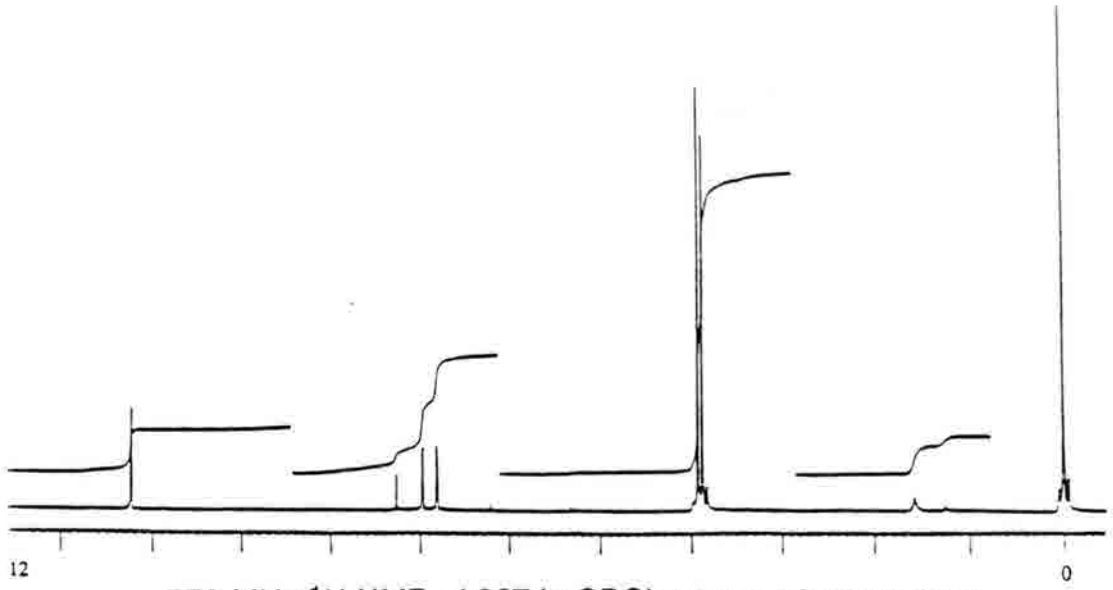


270 MHz ^{1}H NMR of **263** in $CDCl_3$ at room temperature.

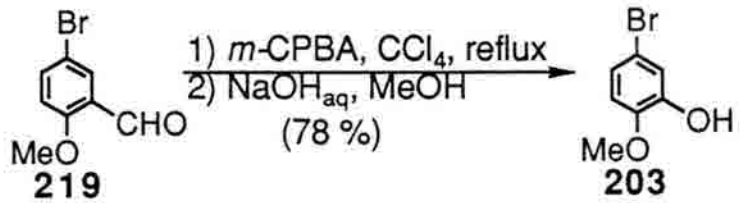


3,5-Dimethoxy-2-trifluoromethanesulfonatobenzaldehyde (267).[75] To a stirred solution of 3,5-dimethoxy-2-hydroxybenzaldehyde (**266**)[97] (42 mg, 0.200 mmoles, 1.00 equiv.) in dry CH_2Cl_2 (2.00 mL) cooled to -78° C was added N,N-diisopropylethylamine (105 µL, 0.600 mmoles, 3.00 equiv.) and triflic anhydride (37 µL, 0.222 mmoles, 1.11 equiv.). The resulting solution was stirred at -78° C for 4 h when water (2 mL) was added at -78° C. The resulting mixture was allowed to warm to room temp. and was extracted with CH_2Cl_2 (4 x 2 mL). The combined organic layers were washed with water (5 mL), 10 % $HCl_{(aq)}$ (5 mL), water (5 mL), dried (Na_2SO_4), filtered and

evaporated. The residue was separated via PTLC (4:1; Hex/EtOAc) yielding 12 mg (19 %) of the desired product (**267**) as a pale yellow solid and 8 mg of starting material. ^{1}H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.87 (s, 3 H), 3.93 (s, 3 H), 6.81 (d, J=2.9 Hz, 1 H), 6.97 (d, J=2.9 Hz, 1 H), 10.23 (s, 1 H). IR: (NaCl, $CHCl_3$) 3096, 2953, 2853, 1709, 1596, 1460, 1421, 1343, 1211, 1138, 1047, 948, 849, 751 cm^{-1}.



270 MHz ^{1}H NMR of **267** in $CDCl_3$ at room temperature.

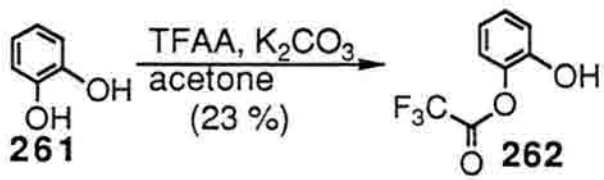


219 **203**

5-Bromoguaiacol (203).[78] To a stirred suspension of *m*-CPBA (8.67 g, 25.11 mmoles, 1.08 equiv.) in dry CCl_4 (38.75 mL) cooled to 0° C was added 5-bromo-*o*-anisaldehyde (**219**) (5.00 g, 23.25 mmoles, 1.00 equiv.). The resulting mixture was allowed to warm to room temp. and then heated at reflux for 18 h. Upon cooling to room temp., the mixture was washed with sat. $NaHCO_3$ (8 x 20 mL) and $Na_2S_2O_3$ (25 mL). The organic layer was evaporated

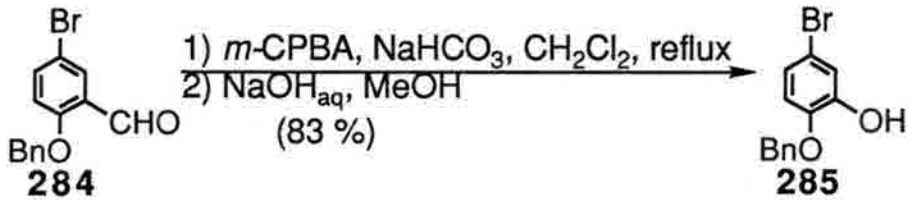
and the dark, oily residue was taken up in MeOH (20 mL) and stirred at room temp. with 1.0 M $NaOH_{(aq)}$ (20 mL) for 1.5 h The pH of the resulting mixture was adjusted to 5 with the dropwise addition of 10 % $HCl_{(aq)}$ and extracted with CH_2Cl_2 (4 x 40 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was separated via column chromatography (3:2; Hex/EtOAc) yielding 3.67 g (78 %) of 5-bromoguaiacol (**203**)[77] as a yellow solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.79 (s, 3 H), 5.89 (br. s, 1 H), 6.65 (d, J=8.6 Hz, 1 H), 6.92 (ABq, J=2.4 Hz, 1 H), 7.04 (d, J=2.4 Hz, 1 H). IR: (NaCl, $CHCl_3$) 3424, 2926, 2850, 1592, 1494, 1441, 1285, 1262, 1219, 1126, 1026, 879, 793, 761 cm^{-1}. Mp: 56-57° C.

270 MHz ^1H NMR of **203** in $CDCl_3$ at room temperature.



2-Trifluoroacetoxyphenol (262).[98] To a stirred suspension of catechol (**261**) (1.00 g, 9.082 mmoles, 1.00 equiv.) and potassium carbonate (6.28 g,

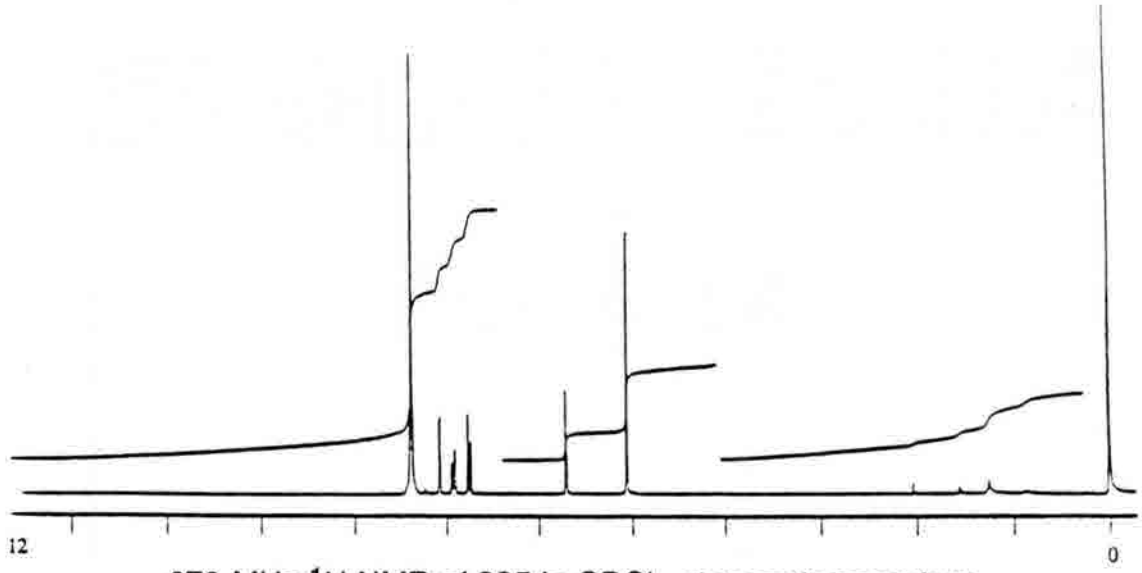
45.41 mmoles, 5.00 equiv.) in dry acetone (36.40 mL) was added trifluoroacetic anhydride (1.28 mL, 9.082 mmoles, 1.00 equiv.). The resulting mixture spontaneously boiled for a few minutes and was stirred at room temp. for 1 h when the mixture was filtered, acidified with 10 % HCl_{aq}, partitioned between CH_2Cl_2 (40 mL) and water (40 mL) and separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL) and the combined organic layers were washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (3:2; Hex/EtOAc) yielding 430 mg (23 %) of the desired product (**262**) as a white, crystalline solid with some catechol and di-acetylated catechol. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 6.50 (br. s, 1 H), 6.78 (m, 2 H), 6.86 (m, 2 H). IR: (NaCl, $CHCl_3$) 3332, 3020, 2978, 1727, 1708, 1618, 1599, 1511, 1470, 1364, 1254, 1216, 1188, 1095, 1041, 910, 848 cm^{-1}.



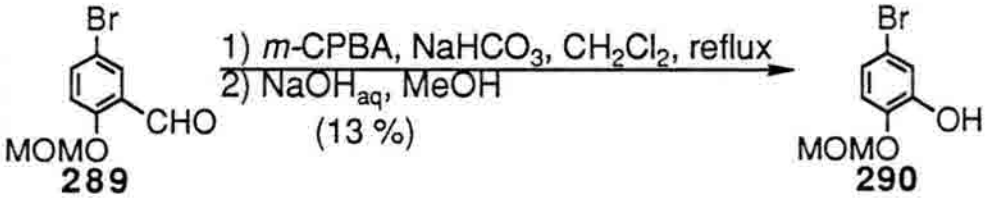
284 **285**

2-Benzyloxy-5-bromophenol (285).[78] To a mechanically stirred suspension of *m*-CPBA (7.38 g, 21.38 mmoles, 1.08 equiv.) and $NaHCO_3$ (2.00 g, 23.75 mmoles, 1.20 equiv.) in dry CH_2Cl_2 (53.10 mL) cooled to 0° C was added a solution of 2-benzyloxy-5-bromobenzaldehyde (**284**)[83d, 99] (5.76 g, 19.79 mmoles, 1.00 equiv.) in dry CH_2Cl_2 (15.35 mL) via cannula. The resulting mixture was allowed to warm to room temp. and then was stirred at reflux for 36 h when, upon cooling to room temp., the mixture was washed with water (3 x 35 mL), sat. $NaHCO_{3(aq)}$ (6 x 30 mL), 1 M $Na_2S_2O_3$ (35 mL) and evaporated. The dark oil was taken up in absolute methanol (54.67 mL) and

reacted with 1 M $NaOH_{aq}$ (27.33 mL). The resulting mixture was stirred at room temp. for 2 h when the mixture was acidified with 10 % HCl_{aq} and extracted with CH_2Cl_2 (4 x 70 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (3:2; Hex/EtOAc) yielding 4.60 g (83 %) of the desired product (**285**) as a yellow oil / white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 5.06 (s, 2 H), 5.71 (s, 1 H), 6.75 (d, J=8.5 Hz, 1 H), 6.93 (dd, J=6.5 Hz, 1 H), 7.08 (d, J=2.2 Hz, 1 H), 7.38 (s, 5 H). IR: (NaCl) 3518, 3067, 3033, 2928, 1592, 1495, 1455, 1382, 1330, 1284, 1260, 1213, 1125, 1007, 880, 854, 791, 746, 697 cm^{-1}.



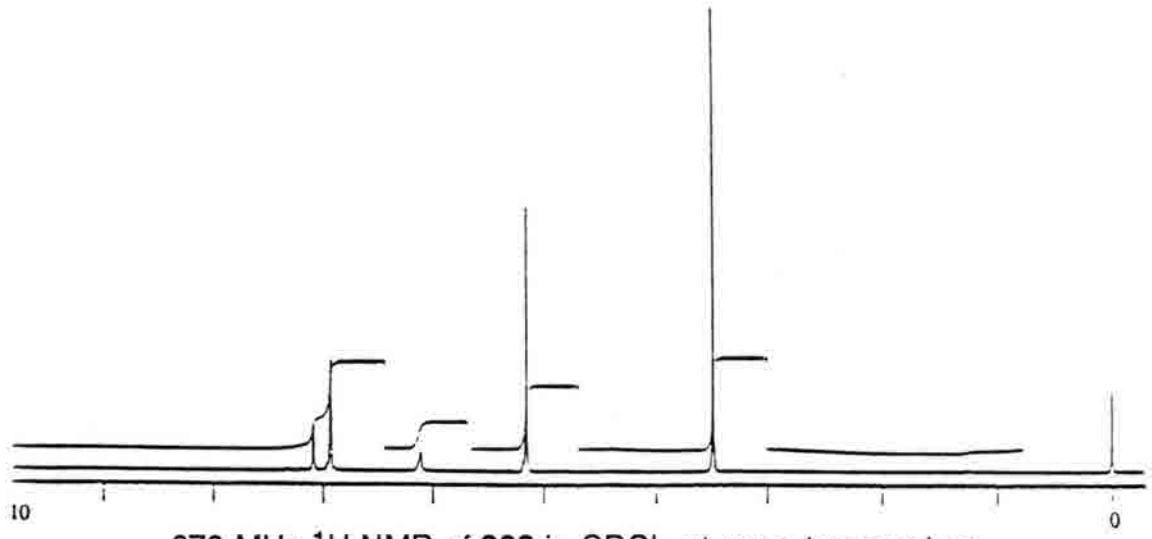
270 MHz ^1H NMR of **285** in $CDCl_3$ at room temperature.



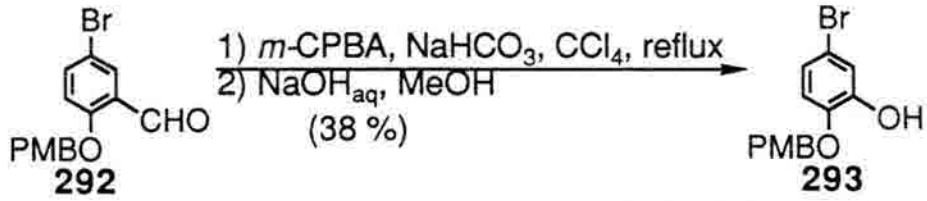
289 **290**

5-Bromo-2-(methoxy)methoxyphenol (290).[78] To a mechanically stirred suspension of *m*-CPBA (4.29 g, 12.44 mmoles, 1.08 equiv.) and $NaHCO_3$ (1.16 g, 13.82 mmoles, 1.20 equiv.) in dry CH_2Cl_2 (20.00 mL) cooled to 0° C was added a solution of 5-bromo-2-(methoxy)methoxybenzaldehyde

(**289**)[100] (2.82 g, 11.52 mmoles, 1.00 equiv.) in dry CH_2Cl_2 (19.80 mL) via cannula. The resulting mixture was allowed to warm to room temp. and then was stirred at reflux for 22 h when, upon cooling to room temp., the mixture was washed with water (3 x 30 mL), sat. $NaHCO_{3(aq)}$ (5 x 30 mL), 1 M $Na_2S_2O_3$ (30 mL) and evaporated. The dark oil was taken up in absolute methanol (31.80 mL) and reacted with 1 M $NaOH_{aq}$ (15.90 mL). The resulting mixture was stirred at room temp. for 2 h when the mixture was acidified with 10 % HCl_{aq} and extracted with CH_2Cl_2 (4 x 40 mL). The combined organic layers were extracted with 1 M $NaOH_{aq}$ (3 x 40 mL) and the combined base extracts were acidified with conc. HCl_{aq}. The resulting mixture was extracted with CH_2Cl_2 (4 x 40) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (3:2; Hex/EtOAc) yielding 357 mg (13 %) of the desired product (**290**) as a pale, yellow oil. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.49 (s, 3 H), 5.15 (s, 2 H), 6.11 (br. s, 1 H), 6.93 (m, 2 H), 7.09 (d, J=1.9 Hz, 1 H). IR: (NaCl) 3417, 2930, 2834, 1590, 1492, 1263, 1155, 1122, 1081, 983, 879, 798 cm^{-1}.

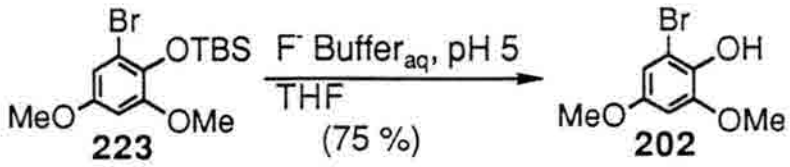


270 MHz ^1H NMR of **290** in $CDCl_3$ at room temperature.

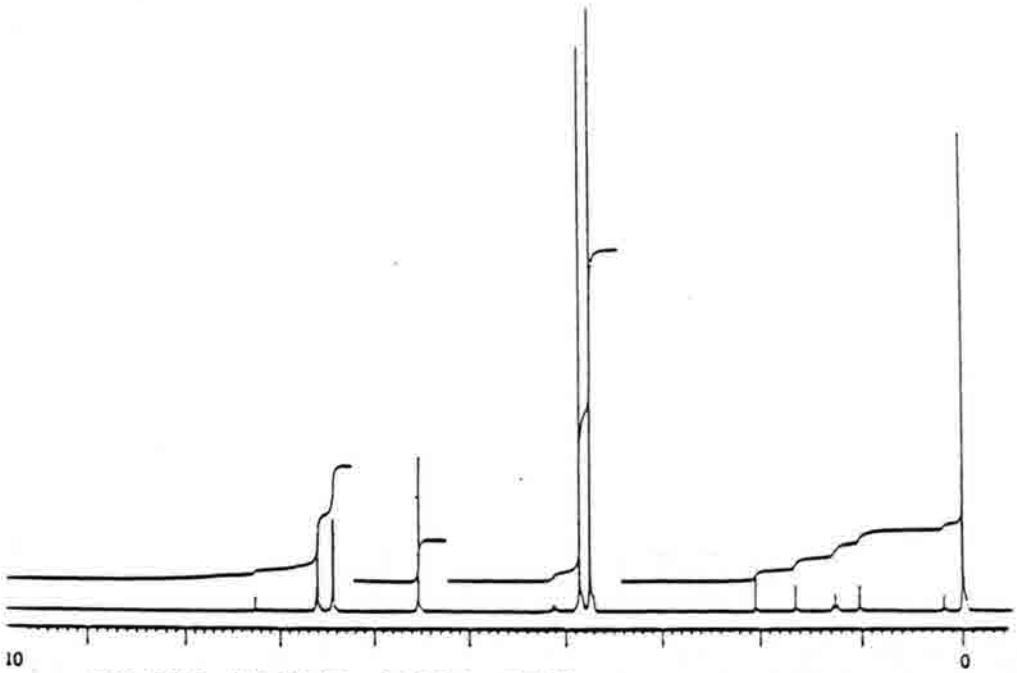


292 **293**

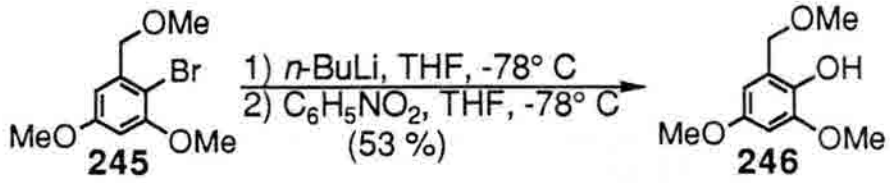
5-Bromo-2-(4'-methoxy)benzyloxyphenol (293).[78] To a mechanically stirred suspension of *m*-CPBA (5.07 g, 14.70 mmoles, 1.08 equiv.) and $NaHCO_3$ (1.37 g, 16.33 mmoles, 1.20 equiv.) in dry CCl_4 (40.00 mL) cooled to 0° C was added a solution of 5-bromo-2-(4'-methoxy)benzyloxybenzaldehyde (**292**) (4.37 g, 13.61 mmoles, 1.00 equiv.) in dry CH_2Cl_2 (20.00 mL) via cannula. The resulting mixture was allowed to warm to room temp. and then was stirred at reflux for 18 h when, upon cooling to room temp., the mixture was washed with water (6 x 50 mL), sat. $NaHCO_{3(aq)}$ (6 x 50 mL), 1 M $Na_2S_2O_3$ (50 mL) and evaporated. The dark oil was taken up in absolute methanol (37.70 mL) and reacted with 1 M $NaOH_{aq}$ (18.80 mL). The resulting mixture was stirred at room temp. for 2 h when the mixture was acidified with 10 % HCl_{aq} and extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (4:1; Hex/EtOAc) yielding 1.60 g (38 %) of the desired product (**293**) as a pale, yellow oil and 1.61 g of starting material (**292**). ^1H NMR: (200 MHz) ($CDCl_3$) δ TMS: 3.82 (s, 3 H), 5.00 (s, 2 H), 5.69 (s, 1 H), 6.78 (d, J=8.6 Hz, 1 H), 6.94 (m, 3 H), 7.07 (d, J=2.3 Hz, 1 H), 7.31 (m, 2 H). IR: (NaCl) 3508, 3001, 2934, 2836, 1732, 1682, 1614, 1589, 1514, 1495, 1463, 1380, 1250, 1175, 1124, 1033, 998, 864, 823, 748, 642 cm^{-1}.



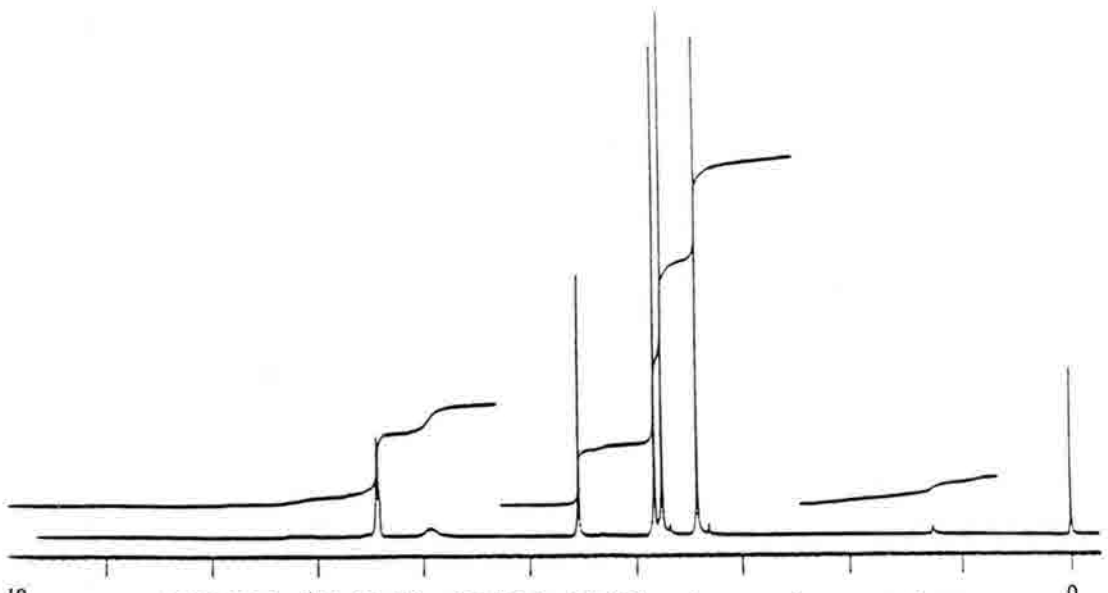
2-Bromo-4,6-dimethoxyphenol (202). To a stirred solution of 2-*tert*-butyldimethylsiloxy-3,5-dimethoxybromobenzene (**223**) (363 mg, 1.144 mmoles, 1.00 equiv.) in THF (8.80 mL) was added a fluoride buffer solution (3.10 mL, aqueous buffer, pH 5).[74] The resulting solution was stirred at room temp. for 3 days when the mixture was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (3:2; Hex/EtOAc) yielding 200 mg (75 %) of 2-bromo-4,6-dimethoxyphenol (**202**) as a white, crystalline solid. ^{1}H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.74 (s, 3 H), 3.85 (s, 3 H), 5.59 (s, 1 H), 6.44 (d, J=2.6 Hz, 1 H), 6.60 (d, J=2.7 Hz, 1 H). IR: (NaCl, $CHCl_3$) 3394, 2946, 2840, 1613, 1586, 1499, 1449, 1421, 1364, 1274, 1212, 1172, 1137, 1051, 1032, 928, 836, 776 cm^{-1}. Mp: 106-109° C.



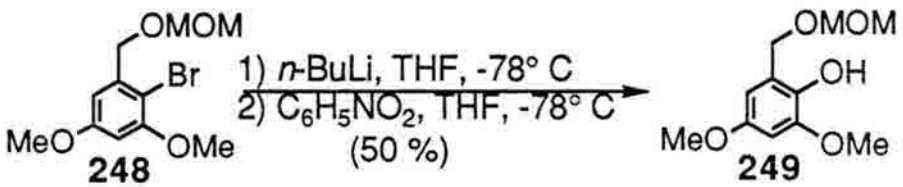
270 MHz ^{1}H NMR of **202** in $CDCl_3$ at room temperature.



4,6-Dimethoxy-2-methoxymethylphenol (246).[97] To a stirred solution of 4,6-dimethoxy-2-methoxymethyl bromobenzene (**245**) (1.00 g, 3.831 mmoles, 1.00 equiv.) in dry THF (13.50 mL) cooled to -78° C was added *n*-BuLi (3.83 mL, 6.130 mmoles, 1.60 equiv., 1.60 M in Hex) dropwise. The resulting yellow solution was stirred at -78° C for 35 min, when a solution of nitrobenzene (1.10 mL, 10.727 mmoles, 2.80 equiv.) in dry THF (2.00 mL) was added dropwise via an addition funnel. The resulting blue solution was stirred at -78° C for 4 h when, upon warming to room temp., the mixture was partitioned between 10 % HCl_{aq} (50 mL) and Et_2O (50 mL), separated and the aqueous layer was extracted with Et_2O (4 x 50 mL). The combined organic layers were extracted with 1 M $NaOH_{(aq)}$ (4 x 50 mL). The combined basic extracts were acidified with conc. $HCl_{(aq)}$ and extracted with CH_2Cl_2 (4 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated yielding 402 mg (53 %) of the desired product (**246**) as a deep, red oil. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.43 (s, 3 H), 3.76 (s, 3 H), 3.85 (s, 3 H), 4.55 (s, 2 H), 5.89 (s, 1 H), 6.41 (d, J=2.8 Hz, 1 H), 6.45 (d, J=2.8 Hz, 1 H). IR: (NaCl) 3416, 2936, 2840, 1614, 1499, 1468, 1432, 1383, 1231, 1198, 1151, 1077, 1055, 923, 836, 800 cm^{-1}.

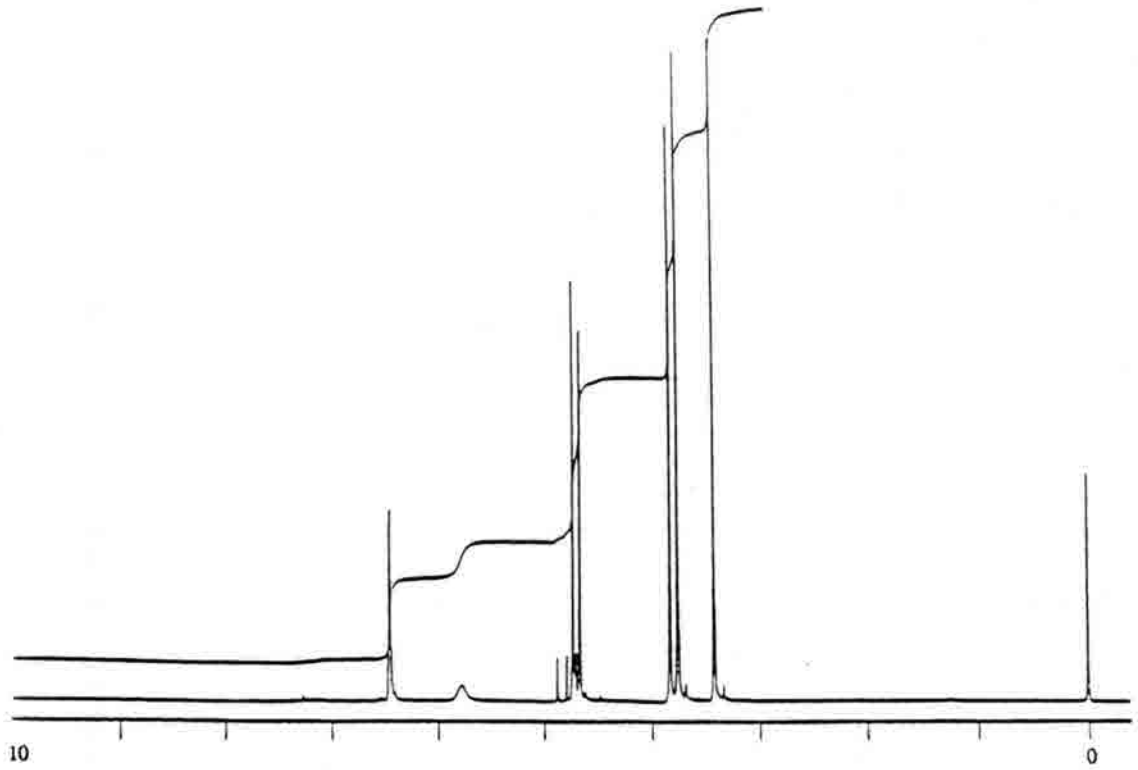


270 MHz ^{1}H NMR of **246** in $CDCl_3$ at room temperature.

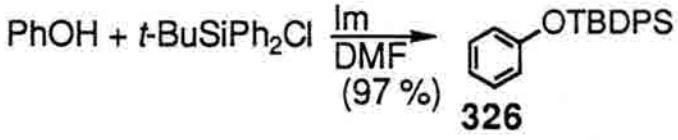


4,6-Dimethoxy-2-(methoxy)methoxymethylphenol (249).[97] To a stirred solution of 4,6-dimethoxy-2-(methoxy)methoxymethyl bromobenzene (**248**) (1.00 g, 3.436 mmoles, 1.00 equiv.) in dry THF (12.10 mL) cooled to -78° C was added *n*-BuLi (3.44 mL, 5.498 mmoles, 1.60 equiv., 1.60 M in Hex) dropwise. The resulting solution was stirred at -78° C for 30 min, when a solution of nitrobenzene (1.00 mL, 9.622 mmoles, 2.80 equiv.) in dry THF (1.80 mL) was added dropwise via an addition funnel. The resulting blue solution was stirred at -78° C for 4 h when, upon warming to room temp., the mixture was partitioned between 10 % $HCl_{(aq)}$ (50 mL) and Et_2O (50 mL), separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic layers were extracted with 1 M $NaOH_{(aq)}$ (4 x 50 mL). The combined basic extracts were acidified with conc. $HCl_{(aq)}$ and extracted with CH_2Cl_2 (4 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and

evaporated yielding 389 mg (50 %) of the desired product (**249**) as a dark oil. ^{1}H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.43 (s, 3 H), 3.76 (s, 3 H), 3.83 (s, 3 H), 4.67 (s, 2 H), 4.73 (s, 2 H), 5.78 (br. s, 1 H), 6.46 (s, 2 H). IR: (NaCl) 3418, 2943, 2842, 1614, 1499, 1469, 1433, 1383, 1231, 1198, 1151, 1086, 1044, 920, 836, 802 cm^{-1}.



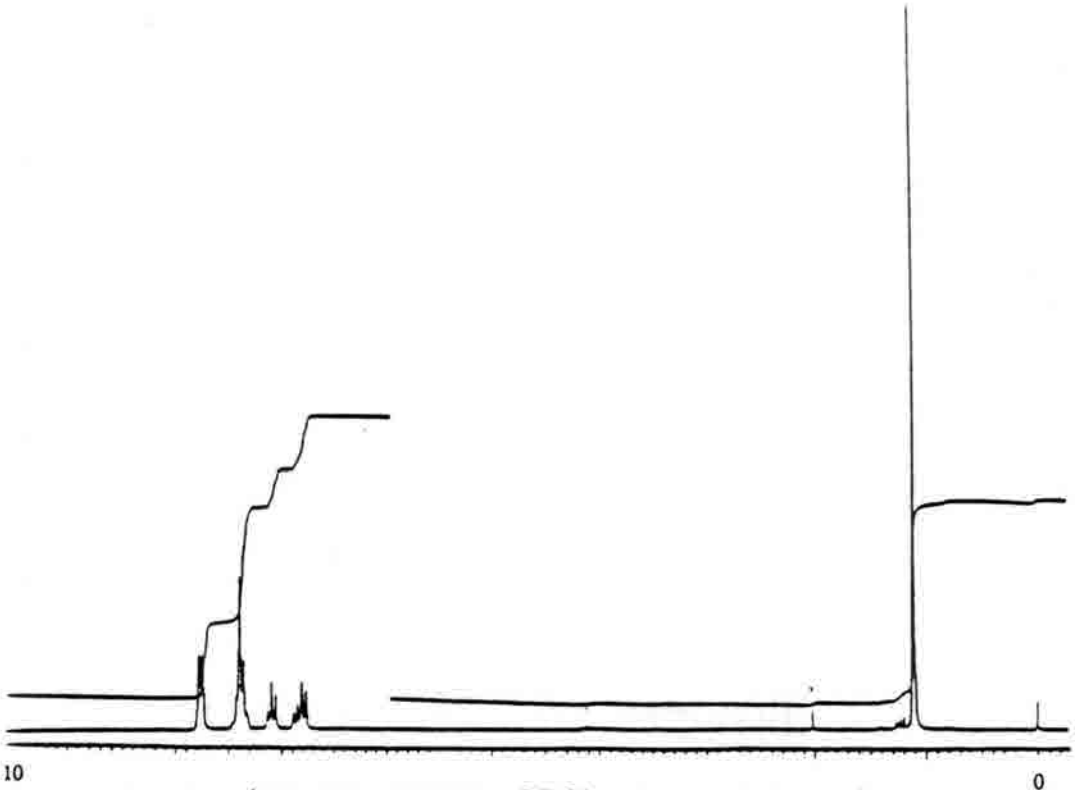
270 MHz ^{1}H NMR of **249** in $CDCl_3$ at room temperature.



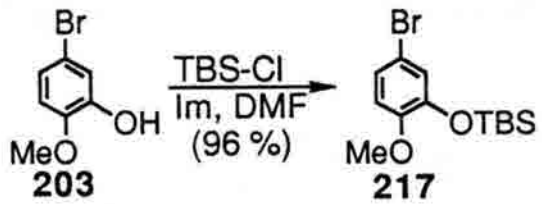
326

***tert*-Butyldiphenylsiloxybenzene (326).**[101] To a stirred solution of phenol (1.000 g, 10.626 mmoles, 1.00 equiv.) and imidazole (2.537 g, 37.261 mmoles, 3.50 equiv.) in dry DMF (5.00 mL) was added *tert*-butyldiphenylsilyl chloride (3.00 mL, 11.688 mmoles, 1.10 equiv.). The resulting solution was stirred at room temp. overnight when the solution was partitioned between Et_2O

(100 mL) and water (30 mL). The aqueous layer was extracted with Et_2O (4 x 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The resulting crude oil was separated via column chromatography (4:1, Hex/EtOAc) yielding 3.42 g (97 %) of the desired product (**326**) as a yellow oil. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 1.11 (s, 9 H), 6.85-6.75 (m, 3 H), 7.06 (t, 3 H), 7.35 (q, J=1.6 Hz, 5 H), 7.71 (d, J=7.4 Hz, 4 H). IR: (NaCl) 3072, 2961, 2863, 1596, 1492, 1431, 1259, 1105, 921, 823, 761, 700, 608 cm^{-1}.



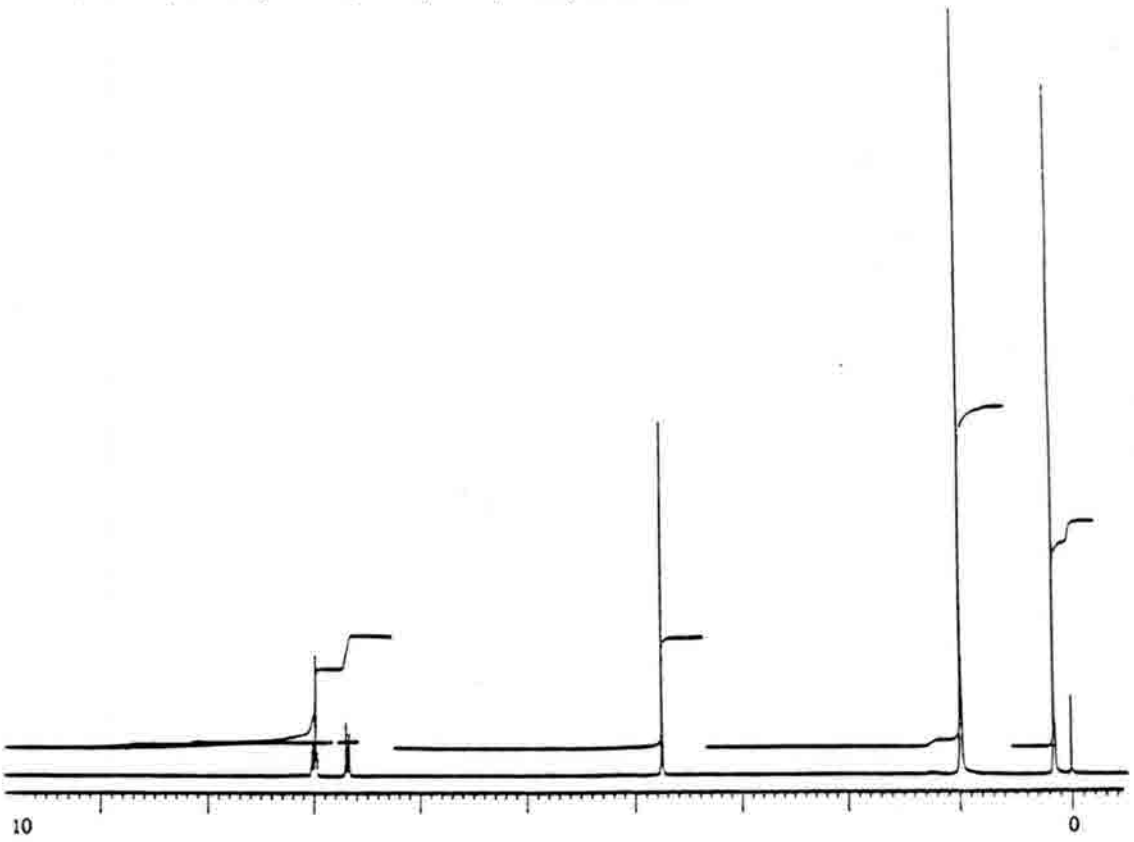
270 MHz ^1H NMR of **326** in $CDCl_3$ at room temperature.



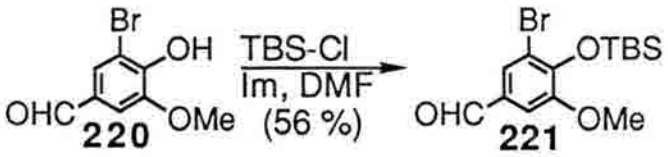
203 **217**

4-Bromo-2-*tert*-butyldimethylsiloxyanisole (217).[101] To a stirred solution of the 5-bromoguaiacol (**203**) (13.42 g, 66.11 mmoles, 1.00 equiv.) in

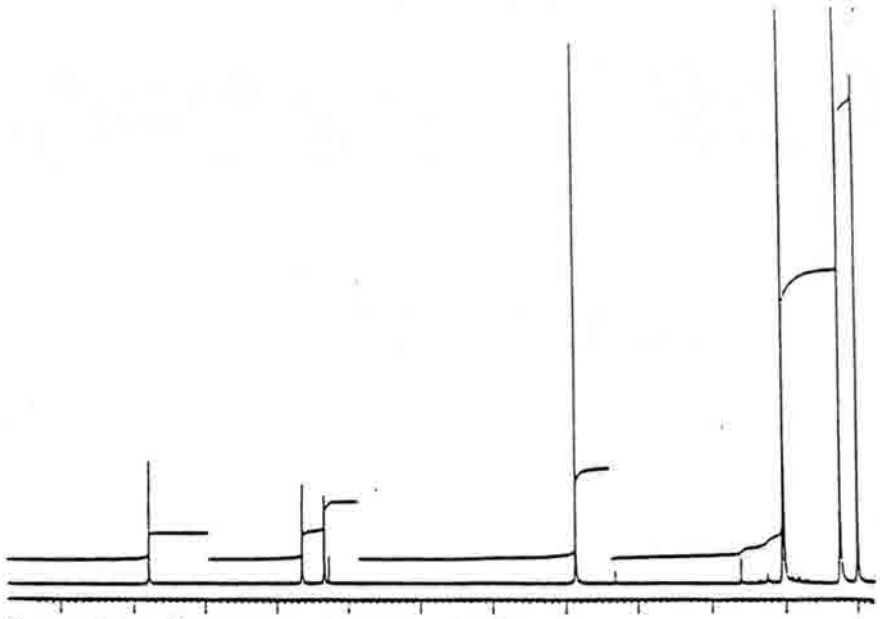
dry DMF (57.20 mL) was added *tert*-butyldimethylsilyl chloride (10.96 g, 72.72 mmoles, 1.10 equiv.) and imidazole (15.75 g, 231.38 mmoles, 3.50 equiv.). The resulting solution was stirred at room temp. overnight when the mixture was partitioned between Et_2O (1.075 L) and water (360 mL). The organic layer was washed with H_2O (3 x 360 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (20:1; Hex/EtOAc) yielding 20.13 g (96 %) of the desired product (**217**) as a pale yellow oil. ^1H NMR: (200 MHz) ($CDCl_3$) δ TMS: 0.15 (s, 6 H), 0.99 (s, 9 H), 3.76 (s, 3 H), 6.69 (d, J=8.1 Hz, 1 H), 6.98 (s) and 7.03 (d, J=2.9 Hz) (2 H). IR: (NaCl) 2933, 2856, 1583, 1494, 1400, 1272, 1228, 1133, 933, 833, 783, 622 cm^{-1}.



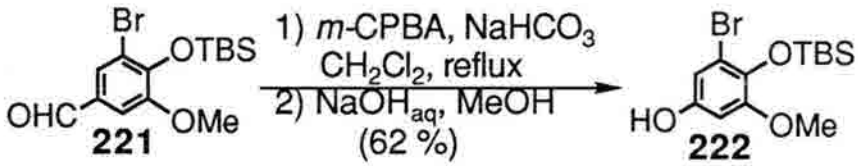
270 MHz ^1H NMR of **217** in $CDCl_3$ at room temperature.



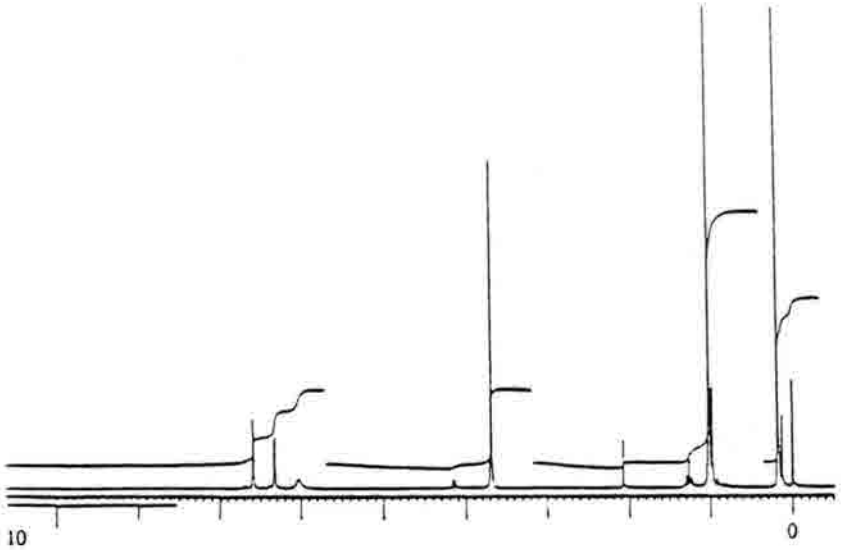
3-Bromo-4-*tert*-butyldimethylsiloxy-5-methoxybenzaldehyde (221).[101] To a stirred solution of the 5-bromovanillin (**220**) (5.00 g, 21.64 mmoles, 1.00 equiv.) in dry DMF (18.72 mL) was added *tert*-butyldimethylsilyl chloride (3.59 g, 23.80 mmoles, 1.10 equiv.) and imidazole (5.16 g, 75.74 mmoles, 3.50 equiv.). The resulting solution was stirred at room temp. overnight when the mixture was partitioned between Et_2O (500 mL) and water (150 mL). The organic layer was washed with H_2O (3 x 125 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (4:1; Hex/EtOAc) yielding 4.19 g (56 %) of the desired product (**221**) as a white, sticky solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 0.24 (s, 6 H), 1.04 (s, 9 H), 3.86 (s, 3 H), 7.30 (d, J=1.8 Hz, 1 H), 7.58 (d, J=1.9 Hz, 1 H), 9.76 (s, 1 H). IR: (NaCl, $CHCl_3$) 2933, 2858, 1696, 1588, 1487, 1416, 1387, 1293, 1253, 1139, 1046, 903, 843, 787, 720, 683, 586 cm^{-1}. Mp: 53-57° C.



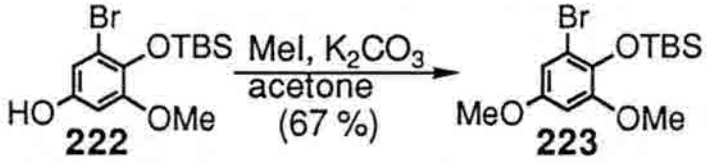
[12] 200 MHz ^1H NMR of **221** in $CDCl_3$ at room temperature.[0]



3-Bromo-4-*tert*-butyldimethylsiloxy-5-methoxyphenol (222).[78] To a stirred suspension of *m*-CPBA (2.784 g, 8.066 mmoles, 1.08 equiv., 50-55 %) and $NaHCO_3$ (0.753 g, 8.962 mmoles, 1.20 equiv.) in dry CH_2Cl_2 (20.00 mL) cooled to 0° C was added a solution of **221** (2.577 g, 7.468 mmoles, 1.00 equiv.) in dry CH_2Cl_2 (5.80 mL) via cannula. The resulting mixture was allowed to warm to room temp. and then heated at reflux for 36 h. Upon cooling to room temp., the mixture was washed with sat. $NaHCO_3$ (8 x 10 mL) and $Na_2S_2O_3$ (15 mL). The organic layer was evaporated and the dark, oily residue was taken up in MeOH (20 mL) and stirred at room temp. with 1.0 M $NaOH_{(aq)}$ (10 mL) for 30 min. The pH of the resulting solution was adjusted to 5 with the dropwise addition of 10 % $HCl_{(aq)}$ and extracted with CH_2Cl_2 (4 x 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was separated via column chromatography (3:2; Hex/EtOAc) yielding 1.524 g (62 %) of the desired product (**222**) as a yellow oil. ^1H NMR: (200 MHz) ($CDCl_3$) δ TMS: 0.18 (s, 6 H), 1.02 (s, 9 H), 3.69 (s, 3 H), 6.04 (br. s, 1 H), 6.33 (d, J=2.8 Hz, 1 H), 6.59 (d, J=2.9 Hz, 1 H). IR: (NaCl) 3376, 2930, 2857, 1606, 1586, 1494, 1434, 1362, 1317, 1250, 1145, 1047, 1023, 976, 907, 826, 782, 694 cm^{-1}.

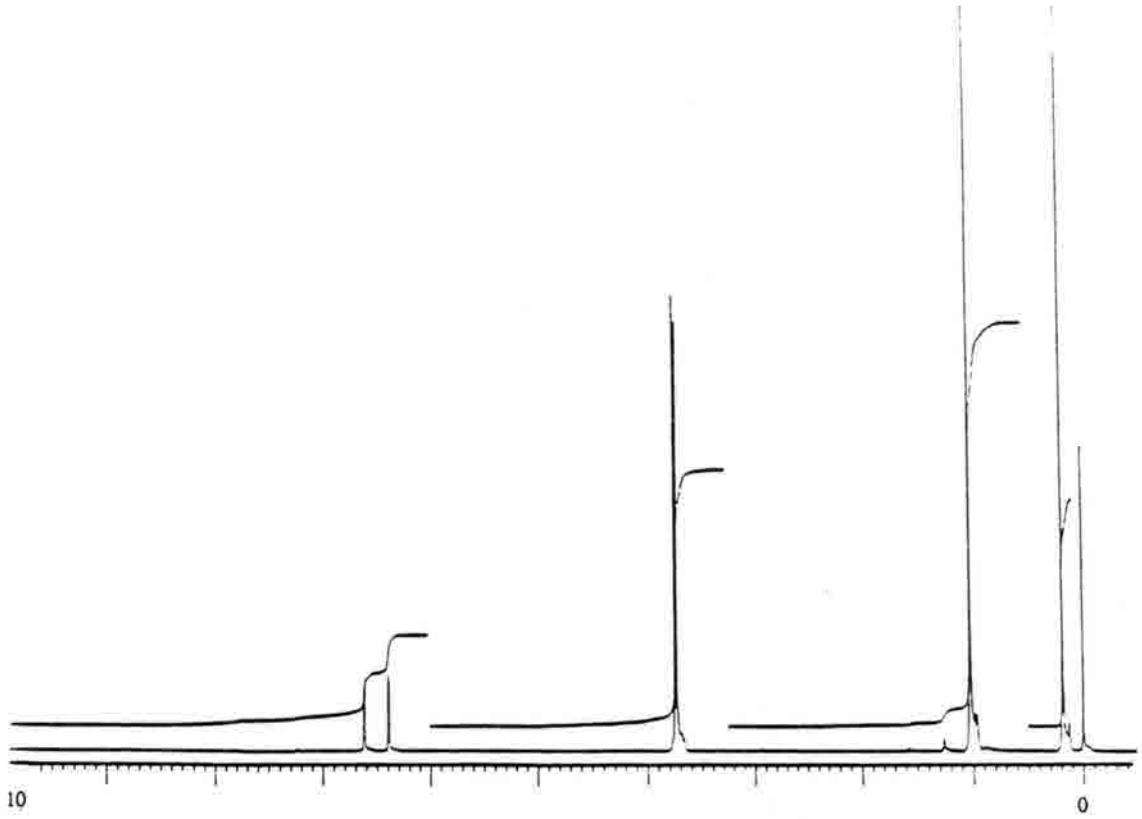


200 MHz ^{1}H NMR of **222** in $CDCl_3$ at room temperature.

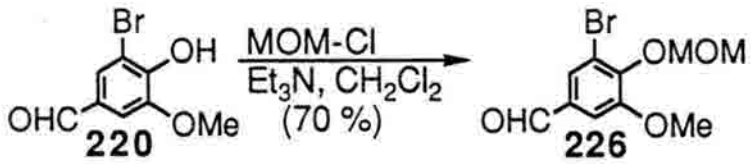


2-*tert*-Butyldimethylsiloxy-3,5-dimethoxybromobenzene (223).[102] To a stirred solution of **222** (1.542 g, 4.632 mmoles, 1.00 equiv.) in dry acetone (7.05 mL) was added potassium carbonate (0.653 g, 4.274 mmoles, 1.02 equiv.) and methyl iodide (2.88 mL, 46.32 mmoles, 10.00 equiv.). The resulting mixture was stirred at reflux overnight when the resulting mixture was cooled to room temp., acidified with the addition of 10 % $H_2SO_{4\ aq}$ and partitioned between water (45 mL) and CH_2Cl_2 (45 mL). The aqueous layer was extracted with CH_2Cl_2 (4 x 45 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated. The resulting oily residue was separated via column chromatography (4:1; Hex/EtOAc) yielding 1.084 g (67 %) of the desired product (**223**) as a pale yellow oil. ^{1}H NMR: (270 MHz) ($CDCl_3$) δ TMS: 0.19 (s, 6 H), 1.03 (s, 9 H), 3.73 (s, 3 H), 3.75 (s, 3 H), 6.40 (d, J=2.9 Hz, 1 H), 6.62 (d, J=2.8

Hz, 1 H). IR: (NaCl) 2930, 2857, 1739, 1602, 1573, 1494, 1470, 1436, 1415, 1245, 1213, 1153, 1057, 1043, 905, 840, 782, 733, 691 cm^{-1}.

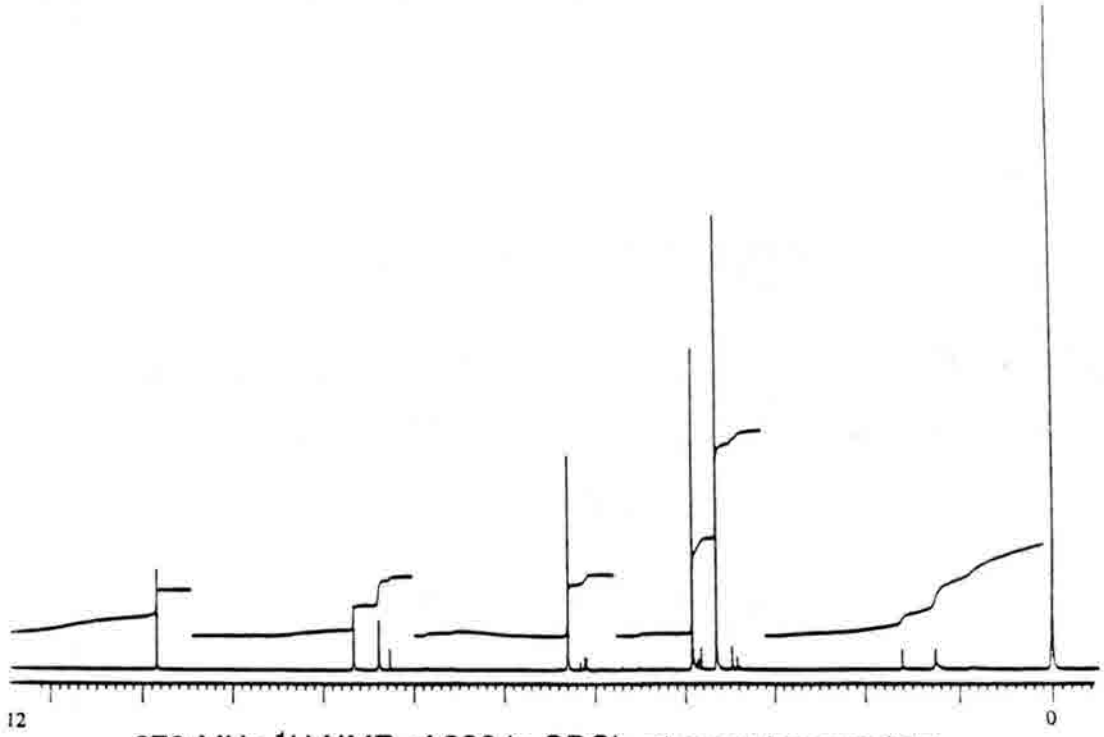


270 MHz ^1H NMR of **223** in $CDCl_3$ at room temperature.

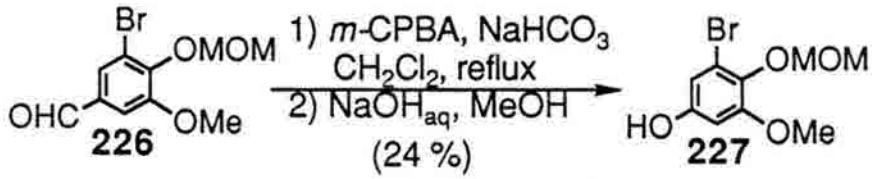


3-Bromo-4-(methoxy)methoxy-5-methoxybenzaldehyde (226). To a stirred solution of 5-bromovanillin (**220**) (10.00 g, 43.28 mmoles, 1.00 equiv.) and triethylamine (12.06 mL, 86.56 mmoles, 2.00 equiv.) in dry CH_2Cl_2 (300 mL) at room temp. was added chloromethylmethylether (3.29 mL, 43.28 mmoles, 1.00 equiv.). The resulting solution was stirred at room temp. for 2 h when the green solution was washed with water (2 x 200 mL) and brine (200

mL) and dried ($MgSO_4$), filtered, and evaporated. The residue was separated via column chromatography (3:2; Hex/EtOAc) yielding 8.338 g (70 %) of the desired product (**226**) as a pale yellow oil. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.63 (s, 3 H), 3.91 (s, 3 H), 5.27 (s, 2 H), 7.36 (d, J=1.0 Hz, 1 H), 7.64 (d, J=1.4 Hz, 1 H), 9.81 (s, 1 H). IR: (NaCl) 2941, 2830, 1694, 1588, 1568, 1484, 1463, 1417, 1386, 1274, 1207, 1138, 1080, 1043, 929, 854, 735 cm^{-1}.

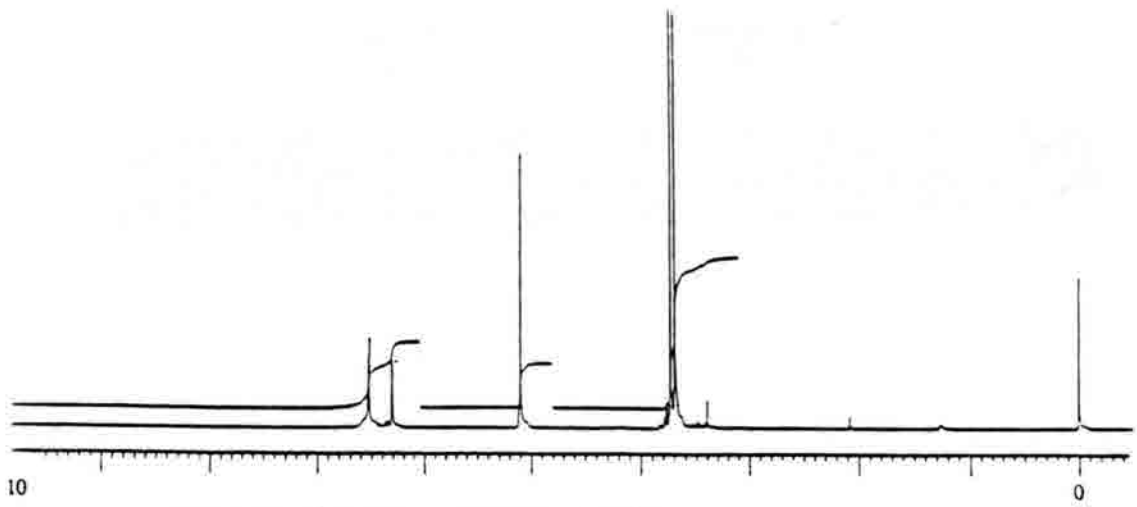


270 MHz ^1H NMR of **226** in $CDCl_3$ at room temperature.

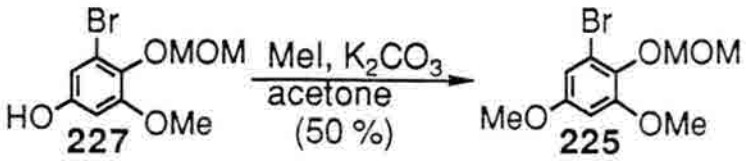


3-Bromo-4-(methoxy)methoxy-5-methoxyphenol (227).[78] To a stirred suspension of *m*-CPBA (339 mg, 1.964 mmoles, 1.08 equiv.) and $NaHCO_3$ (165 mg, 1.964 mmoles, 1.08 equiv.) in dry CH_2Cl_2 (5.00 mL) cooled to 0° C was added a solution of **226** (0.32 mL, 1.818 mmoles, 1.00 equiv.). The

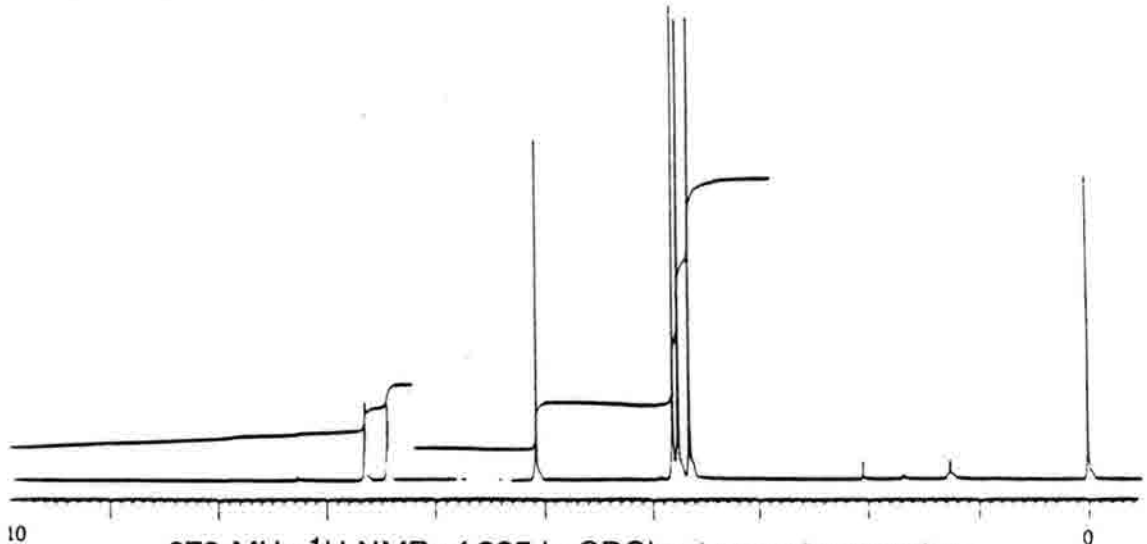
resulting mixture was allowed to warm to room temp. and then heated at reflux for 26 h. Upon cooling to room temp., the mixture was washed with sat. $NaHCO_3$ (8 x 3 mL) and 1 M $Na_2S_2O_3$ (4 mL). The organic layer was evaporated and the yellow, oily residue was taken up in MeOH (4 mL) and stirred at room temp. with 1.0 M $NaOH_{(aq)}$ (4 mL) for 1.5 h. The pH of the resulting solution was adjusted to 5 with the dropwise addition of 10 % $HCl_{(aq)}$ and extracted with CH_2Cl_2 (5 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was separated via column chromatography (3:2; Hex/EtOAc) yielding 117 mg (24 % and 44 % based on unreacted S.M.) of the desired product (**227**) as a yellow solid and 221 mg of starting material (**226**). ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.69 (s, 3 H), 3.73 (s, 3 H), 5.10 (s, 2 H), 6.31 (d, J=2.8 Hz, 1 H), 6.53 (d, J=2.8 Hz, 1 H), 6.57 (br. s, 1 H). IR: (NaCl) 3378, 2941, 2840, 1606, 1490, 1470, 1431, 1336, 1296, 1195, 1154, 1078, 1043, 976, 827, 765 cm^{-1}.



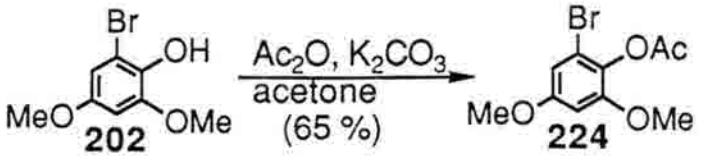
270 MHz ^1H NMR of **227** in $CDCl_3$ at room temperature.



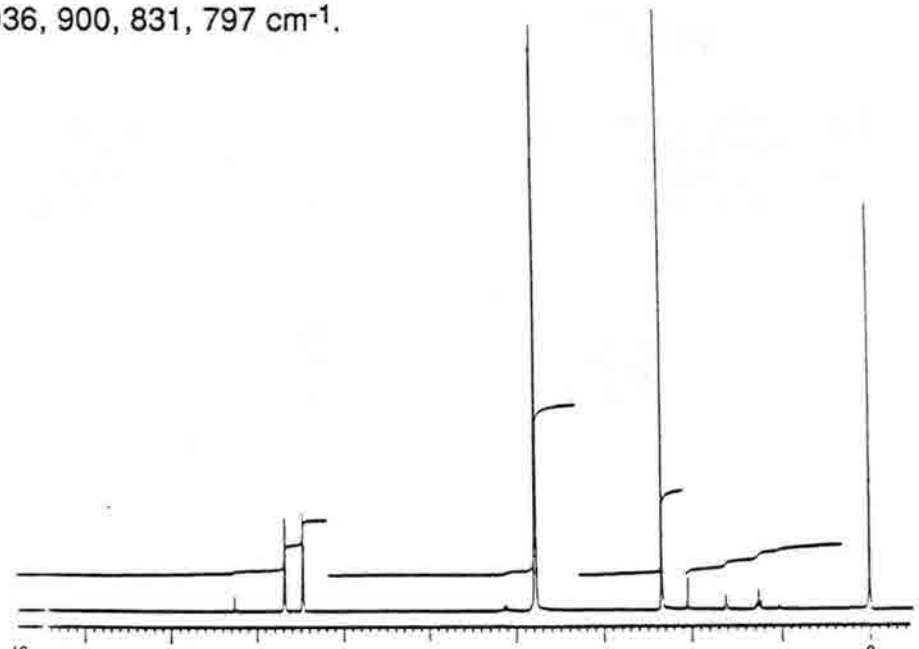
3,5-Dimethoxy-2-(methoxy)methoxybromobenzene (225).[102] To a stirred solution of **227** (117 mg, 0.445 mmoles, 1.00 equiv.) in dry acetone (1.00 mL) was added potassium carbonate (63 mg, 0.454 mmoles, 1.02 equiv.) and methyl iodide (0.28 mL, 4.448 mmoles, 10.00 equiv.). The resulting mixture was stirred at reflux for 12 h when the resulting mixture was cooled to room temp., acidified with the addition of 10 % $H_2SO_{4\ aq}$ and partitioned between water (2 mL) and CH_2Cl_2 (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated. The residue was separated via PTLC (4:1; Hex/EtOAc) yielding 62 mg (50 %) of the desired product (**225**) as a orange oil and 2 mg of starting material (**227**). ^{1}H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.65 (s, 3 H), 3.75 (s, 3 H), 3.81 (s, 3 H), 5.08 (s, 2 H), 6.44 (d, J=2.8 Hz, 1 H), 6.65 (d, J=2.9 Hz, 1 H). IR: (NaCl) 2940, 2838, 1738, 1600, 1574, 1488, 1435, 1415, 1321, 1269, 1215, 1157, 1080, 1051, 959, 822, 760 cm^{-1}.



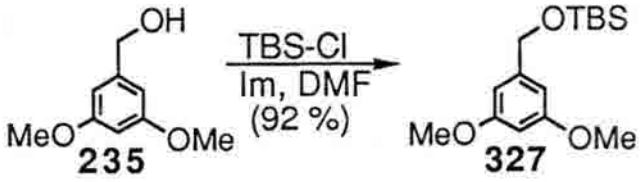
270 MHz ^{1}H NMR of **225** in $CDCl_3$ at room temperature.



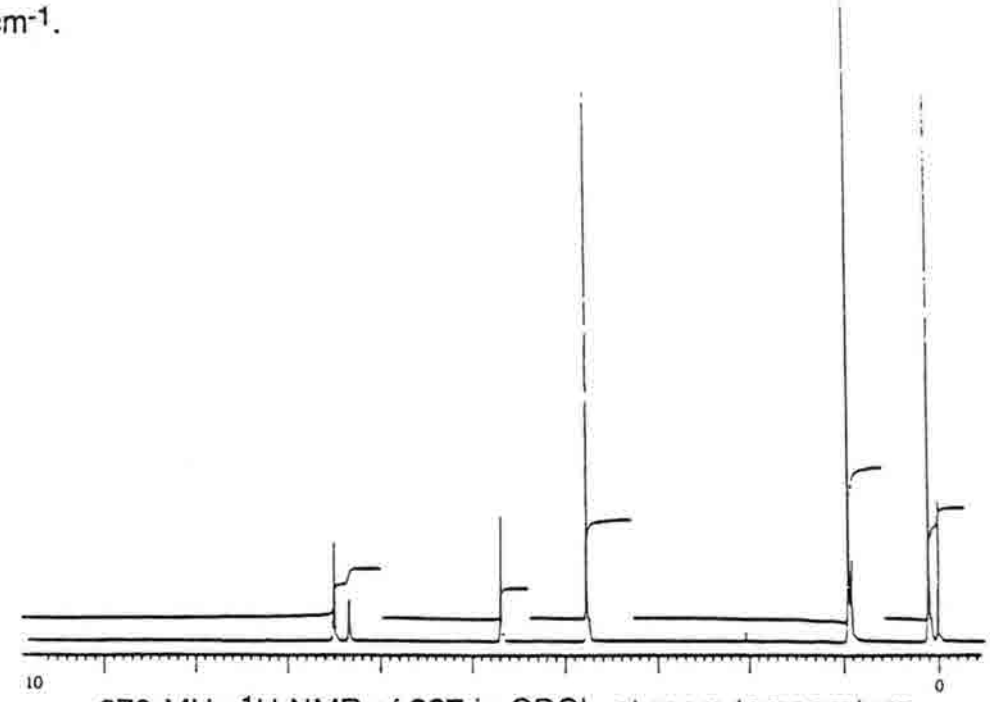
2-Bromo-4,6-dimethoxyacetoxybenzene (224). To a stirred suspension of 2-bromo-4,6-dimethoxyphenol (**202**) (1.00 g, 4.29 mmoles, 1.00 equiv.) and K_2CO_3 (2.97 g, 21.46 mmoles, 5.00 equiv.) in dry acetone (21.50 mL) at room temp. was added acetic anhydride (0.43 mL, 4.51 mmoles, 1.05 equiv.). The resulting mixture was stirred at room temp. for 2 h when the mixture was filtered, with CH_2Cl_2, and partitioned between water (75 mL) and CH_2Cl_2 (75 mL) and separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 75 mL) and the combined extracts were dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (7:3, Hex/EtOAc) yielding 770 mg (65 %) of the desired product (**224**) as a white solid and 47 mg of starting material (**202**). ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 2.33 (s, 3 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 6.47 (d, J=2.6 Hz, 1 H), 6.68 (d, J=2.4 Hz, 1 H). IR: (NaCl, $CHCl_3$) 3007, 2942, 2840, 1767, 1601, 1488, 1437, 1369, 1279, 1195, 1150, 1036, 900, 831, 797 cm^{-1}.



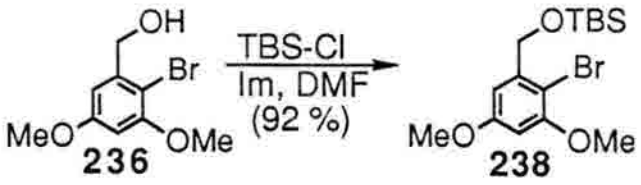
10 270 MHz ^1H NMR of **224** in $CDCl_3$ at room temperature. 0



3,5-Dimethoxy *tert*-butyldimethylsiloxymethylbenzene (327).[101] To a stirred solution of 3,5-dimethoxybenzyl alcohol (**235**) (5.00 g, 29.73 mmoles, 1.00 equiv.) in dry DMF (25.70 mL) was added *tert*-butyldimethylsilyl chloride (4.93 g, 32.70 mmoles, 1.10 equiv.) and imidazole (7.09 g, 104.05 mmoles, 3.50 equiv.). The resulting solution was stirred at room temp. overnight when the solution was partitioned between Et_2O (675 mL) and water (200 mL) and separated. The organic layer was washed with water (3 x 175 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (3:2; Hex/EtOAc) yielding 7.75 g (92 %) of the desired product (**327**) as a pale yellow oil. ^{1}H NMR: (270 MHz) ($CDCl_3$) δ TMS: 0.10 (s, 6 H), 0.95 (s, 9 H), 3.77 (s, 6 H), 4.69 (s, 2 H), 6.34 (d, J=2.2 Hz, 1 H), 6.50 (m, 2 H). IR: (NaCl, $CHCl_3$) 2954, 2930, 2856, 1599, 1462, 1205, 1155, 1103, 1066, 837, 777 cm^{-1}.

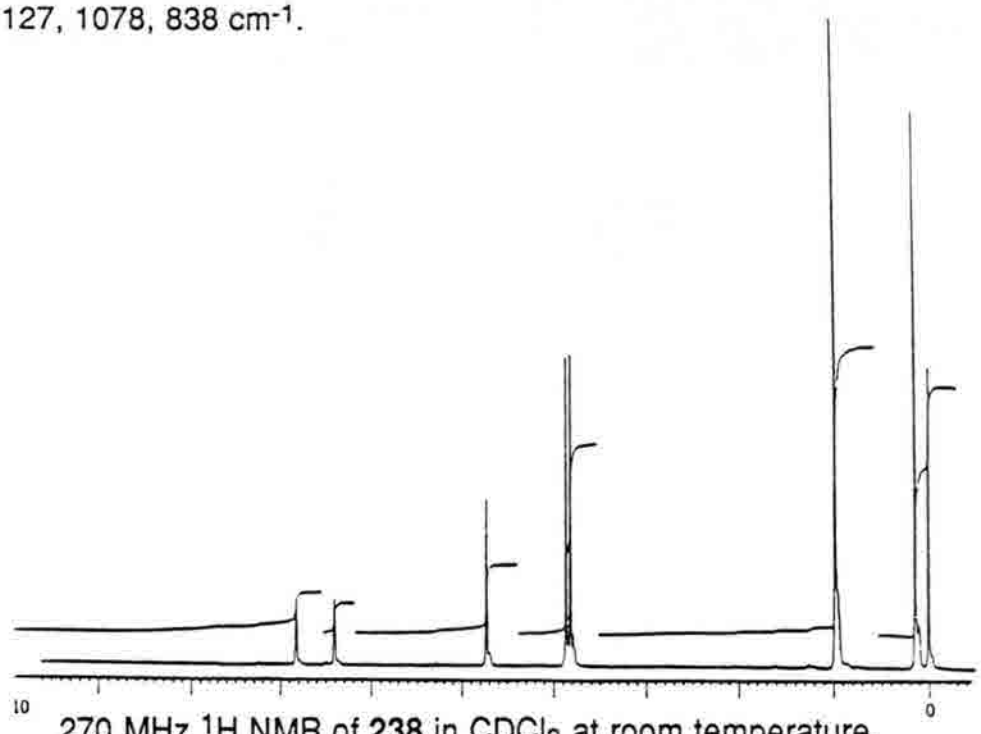


270 MHz ^{1}H NMR of **327** in $CDCl_3$ at room temperature.

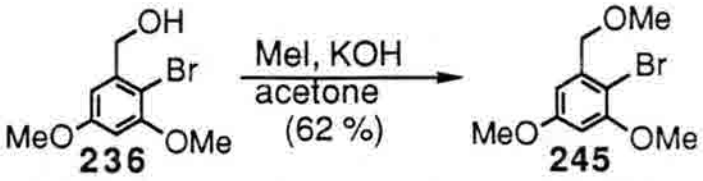


236 **238**

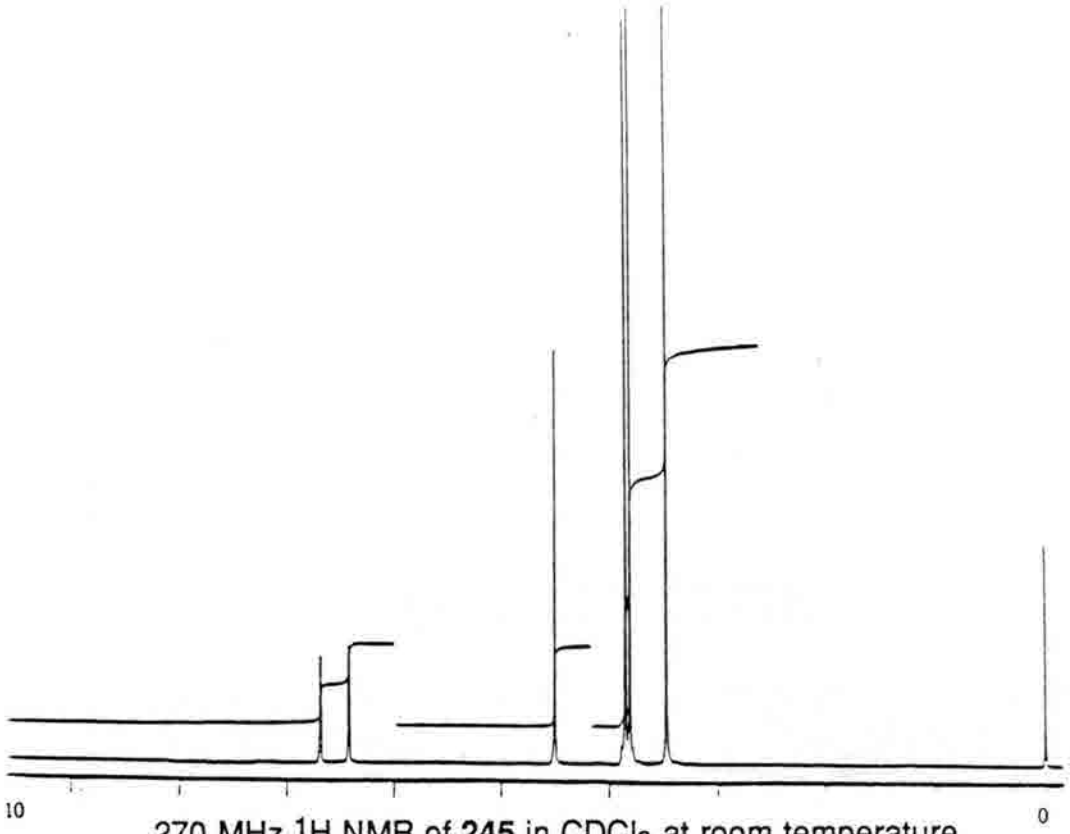
4,6-Dimethoxy-2-*tert*-butyldimethylsiloxymethylbromobenzene (238).[101] To a stirred solution of 2-bromo-3,5-dimethoxybenzyl alcohol (**236**)[80] (1.60 g, 6.49 mmoles, 1.00 equiv.) in dry DMF (10.00 mL) was added *tert*-butyldimethylsilyl chloride (1.08 g, 7.14 mmoles, 1.10 equiv.) and imidazole (1.55 g, 22.73 mmoles, 3.50 equiv.). The resulting solution was stirred at room temp. overnight when the solution was partitioned between Et_2O (150 mL) and water (45 mL) and separated. The organic layer was washed with water (3 x 40 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (20:1; Hex/EtOAc) yielding 2.05 g (88 %) of the desired product (**238**) as a clear, colorless oil. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 0.14 (s, 6 H), 0.98 (s, 9 H), 3.82 (s, 3 H), 3.86 (s, 3 H), 4.73 (s, 2 H), 6.41 (m, 1 H), 6.70 (m, 1 H). IR: (NaCl, $CHCl_3$) 2954, 2856, 1590, 1459, 1459, 1329, 1200, 1159, 1127, 1078, 838 cm^{-1}.



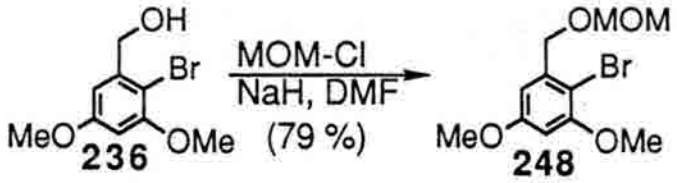
270 MHz ^1H NMR of **238** in $CDCl_3$ at room temperature.



4,6-Dimethoxy-2-methoxymethylbromobenzene (245).[102] To a stirred suspension of 2-bromo-3,5-dimethoxybenzyl alcohol (**236**)[80] (1.00 g, 4.05 mmoles, 1.00 equiv.) and solid, powdered potassium hydroxide (250 mg, 4.45 mmoles, 1.10 equiv.) in dry acetone (8.10 mL) was added methyl iodide (2.52 mL, 40.49 mmoles, 10.00 equiv.). The resulting mixture was stirred at room temp. overnight when the suspension was acidified with 10 % H_2SO_{4aq}. The resulting mixture was partitioned between water (20 mL) and CH_2Cl_2 (20 mL), separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with 1 M $Na_2S_2O_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (3:2; Hex/EtOAc) yielding 654 mg (62 %) of the desired product (**245**) as a pale, yellow oil and 270 mg of starting material. ^1H NMR: (200 MHz) ($CDCl_3$) δ TMS: 3.47 (s, 3 H), 3.81 (s, 3 H), 3.85 (s, 3 H), 4.50 (s, 2 H), 6.41 (d, J=2.4 Hz, 1 H), 6.68 (d, J=2.4 Hz, 1 H). IR: (NaCl) 2937, 2840, 1589, 1454, 1419, 1377, 1329, 1224, 1201, 1161, 1081, 1024, 951, 835 cm^{-1}.

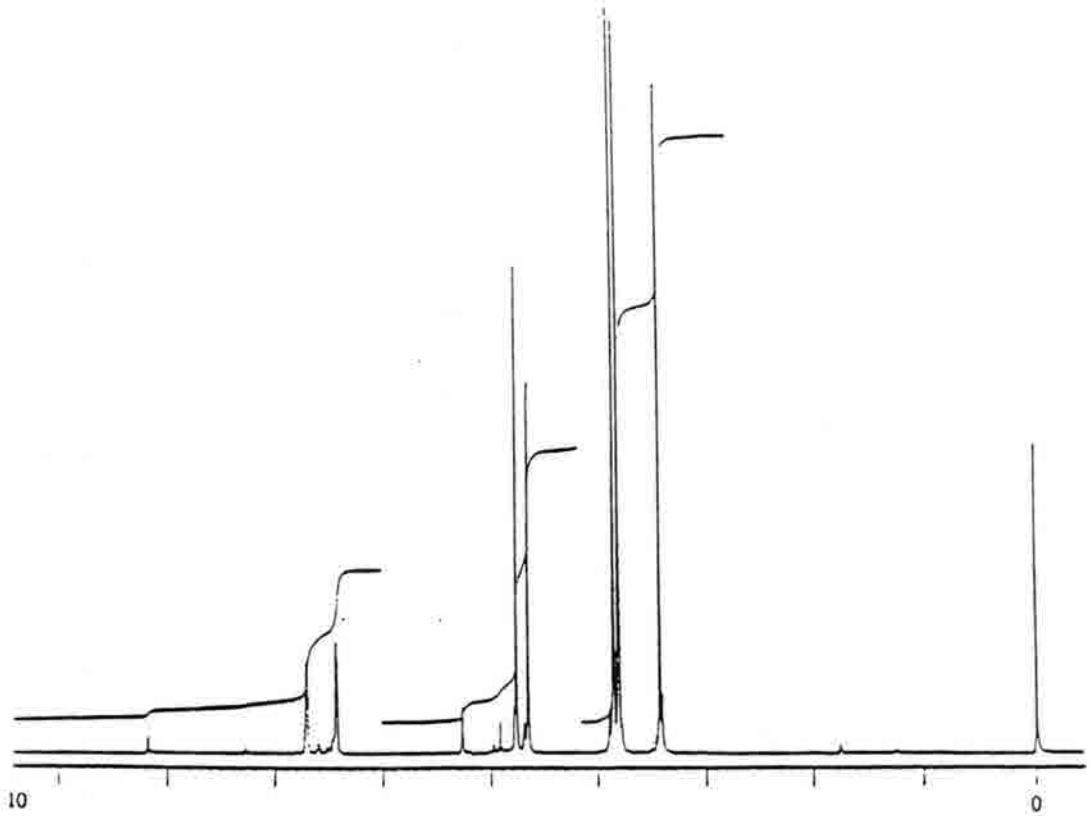


270 MHz ^{1}H NMR of **245** in $CDCl_3$ at room temperature.

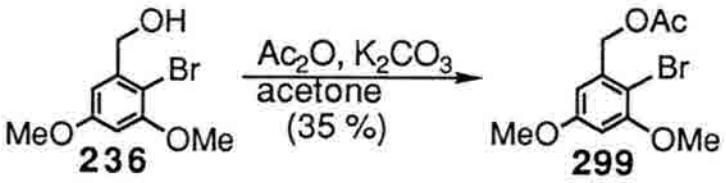


4,6-Dimethoxy-2-(methoxy)methoxymethylbromobenzene (248). To a stirred solution of 2-bromo-3,5-dimethoxybenzyl alcohol (**236**)[80] (500 mg, 2.02 mmoles, 1.00 equiv.) in dry DMF (5.00 mL) was added sodium hydride (146 mg, 3.04 mmoles, 1.50 equiv., 50 % oil dispersion). The resulting suspension was stirred at room temp. for 5 min when chloromethylmethylether (0.34 mL, 4.53 mmoles, 2.20 equiv.) was added. The resulting mixture was stirred at room temp. for 3 h when the mixture was partitioned between Et_2O (5 mL) and water (5 mL) and separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organic layers were washed with water (20

mL) and brine (20 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (3:2; Hex/EtOAc) yielding 463 mg (79 %) of the desired product (**248**) as a clear, colorless oil and 55 mg of starting material. ^1H NMR: (200 MHz) ($CDCl_3$) δ TMS: 3.42 (s, 3 H), 3.80 (s, 3 H), 3.85 (s, 3 H), 4.64 (s, 2 H), 4.76 (s, 2 H), 6.42 (d, J=2.7 Hz, 1 H), 6.70 (d, J=2.7 Hz, 1 H). IR: (NaCl) 2939, 2841, 1727, 1589, 1454, 1376, 1329, 1287, 1201, 1161, 1045, 923, 835 cm^{-1}.

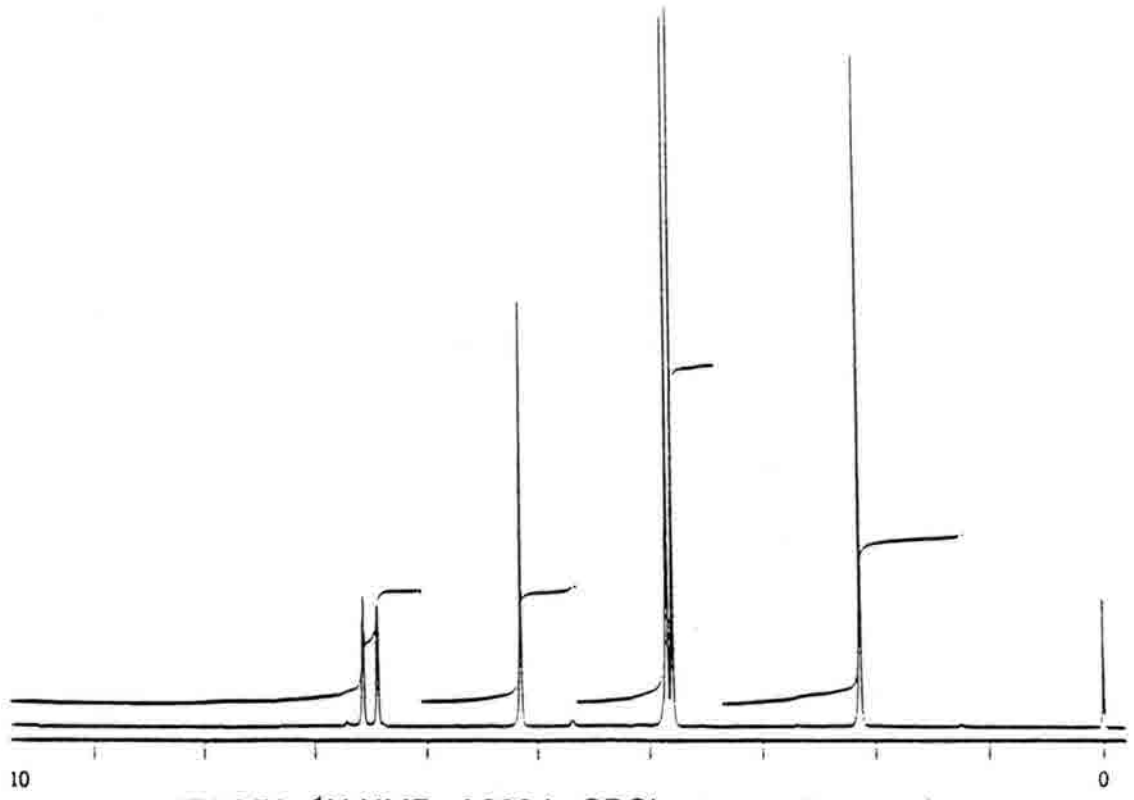


200 MHz ^1H NMR of **248** in $CDCl_3$ at room temperature.

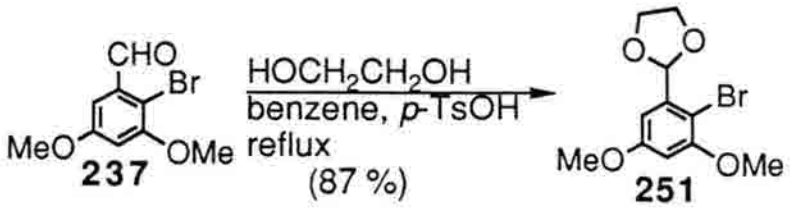


2-Bromo-3,5-dimethoxybenzyl acetate (299). To a stirred suspension of 2-bromo-3,5-dimethoxybenzyl alcohol (**236**)[80] (1.00 g, 4.049

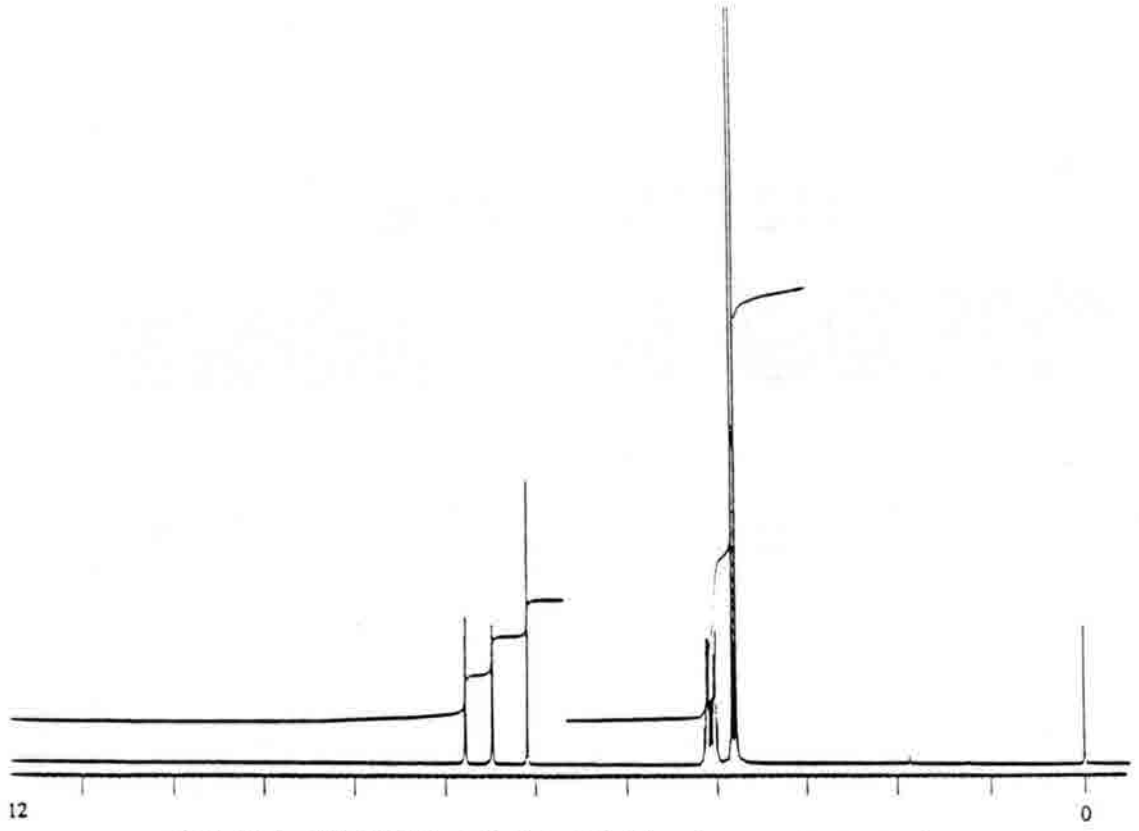
mmoles, 1.00 equiv.) and potassium carbonate (2.80 g, 20.24 mmoles, 5.00 equiv.) in dry acetone (16.25 mL) was added acetic anhydride (0.42 mL, 4.453 mmoles, 1.10 equiv.). The resulting mixture was stirred at room temp. for 18 h when the mixture was filtered, acidified with 10 % HCl_{aq}, partitioned between Et_2O (20 mL) and water (20 mL) and separated. The aqueous layer was extracted with Et_2O (4 x 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated. The residue was purified via recrystallization from Et_2O yielding 405 mg (35 %) of the desired product (**299**) as a white, crystalline solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 2.14 (s, 3 H), 3.80 (s, 3 H), 3.85 (s, 3 H), 5.15 (s, 2 H), 6.44 (d, J=2.6 Hz, 1 H), 6.57 (d, J=2.5 Hz, 1 H). IR: (NaCl, $CHCl_3$) 3019, 2966, 2942, 1736, 1591, 1458, 1422, 1363, 1330, 1216, 1164, 1095, 1028, 928, 836 cm^{-1}.



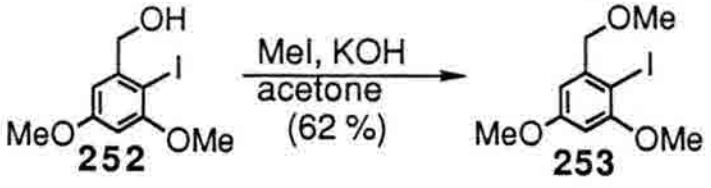
270 MHz ^1H NMR of **299** in $CDCl_3$ at room temperature.



2-(2'-Bromo-3',5'-dimethoxy)phenyl-1,3-dioxolane (251). To a stirred solution of 2-bromo-3,5-dimethoxybenzaldehyde (**237**)[81] (500 mg, 1.84 mmoles, 1.00 equiv.) in dry benzene (5.00 mL) was added ethylene glycol (0.15 mL, 2.76 mmoles, 1.50 equiv.) and p-toluene sulfonic acid monohydrate (35 mg, 0.18 mmoles, 0.10 equiv.). The resulting solution was stirred at reflux with a Dean-Stark trap for 2 h when, upon cooling to room temp., the mixture was washed with sat. $NaHCO_{3(aq)}$ (2 x 5 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (3:2; Hex/EtOAc) yielding 464 mg (87 %) of the desired product (**251**) as a pale, yellow solid and 79 mg of starting material. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.79 (s, 3 H), 3.83 (s, 3 H), 4.04 (m, 2 H), 4.12 (m, 2 H), 6.09 (s, 1 H), 6.48 (d, J=2.8 Hz, 1 H), 6.78 (d, J=2.8 Hz, 1 H). IR: (NaCl, $CHCl_3$) 3016, 2942, 2890, 1592, 1458, 1329, 1216, 1203, 1163, 1059, 1025, 970, 842, 755, 668 cm^{-1}.



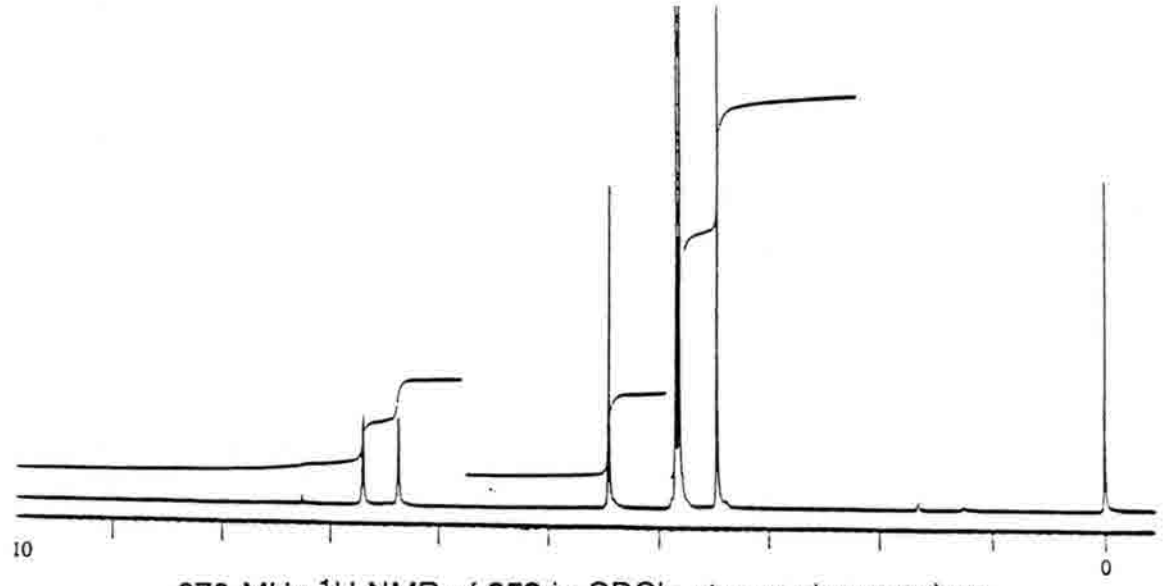
270 MHz ^1H NMR of **251** in $CDCl_3$ at room temperature.



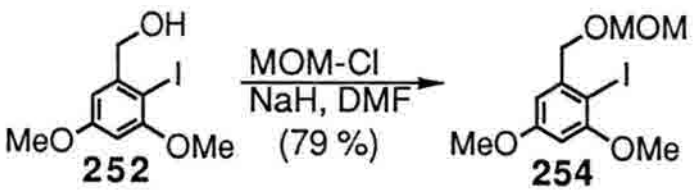
252 **253**

4,6-Dimethoxy-2-methoxymethyl iodobenzene (253).[102] To a stirred suspension of 3,5-dimethoxy-2-iodobenzyl alcohol (**252**)[103] (294 mg, 1.00 mmoles, 1.00 equiv.) and solid, powdered potassium hydroxide (62 mg, 1.10 mmoles, 1.10 equiv.) in dry acetone (2.00 mL) was added methyl iodide (0.62 mL, 10.00 mmoles, 10.00 equiv.). The resulting mixture was stirred at room temp. for 12 h when the suspension was acidified with 10 % $H_2SO_{4(aq)}$. The resulting mixture was partitioned between water (5 mL) and CH_2Cl_2 (5 mL), separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The

combined organic layers were dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (3:2; Hex/EtOAc) yielding 238 mg (72 %) of (**253**) as a clear, colorless oil and 61 mg of starting material (**252**). ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.48 (s, 3 H), 3.82 (s, 3 H), 3.86 (s, 3 H), 4.46 (s, 2 H), 6.38 (d, J=2.5 Hz, 1 H), 6.70 (d, J=2.4 Hz, 1 H). IR: (NaCl) 2936, 2838, 1585, 1455, 1416, 1376, 1323, 1222, 1199, 1160, 1078, 1012, 950, 836 cm^{-1}.

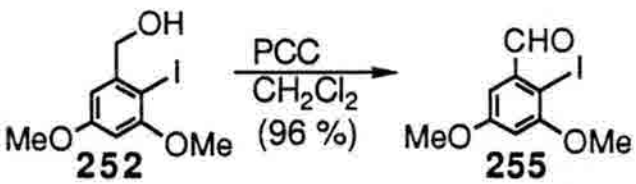


270 MHz ^1H NMR of **253** in $CDCl_3$ at room temperature.



4,6-Dimethoxy-2-(methoxy)methoxymethyl iodobenzene (254). To a stirred solution of 2-iodo-3,5-dimethoxybenzyl alcohol (**252**)[103] (1.00 g, 3.401 mmoles, 1.00 equiv.) in dry DMF (8.40 mL) was added sodium hydride (327 mg, 6.803 mmoles, 2.00 equiv., 50 % oil dispersion). The resulting suspension was stirred at room temp. for 5 min when chloromethyl methylether

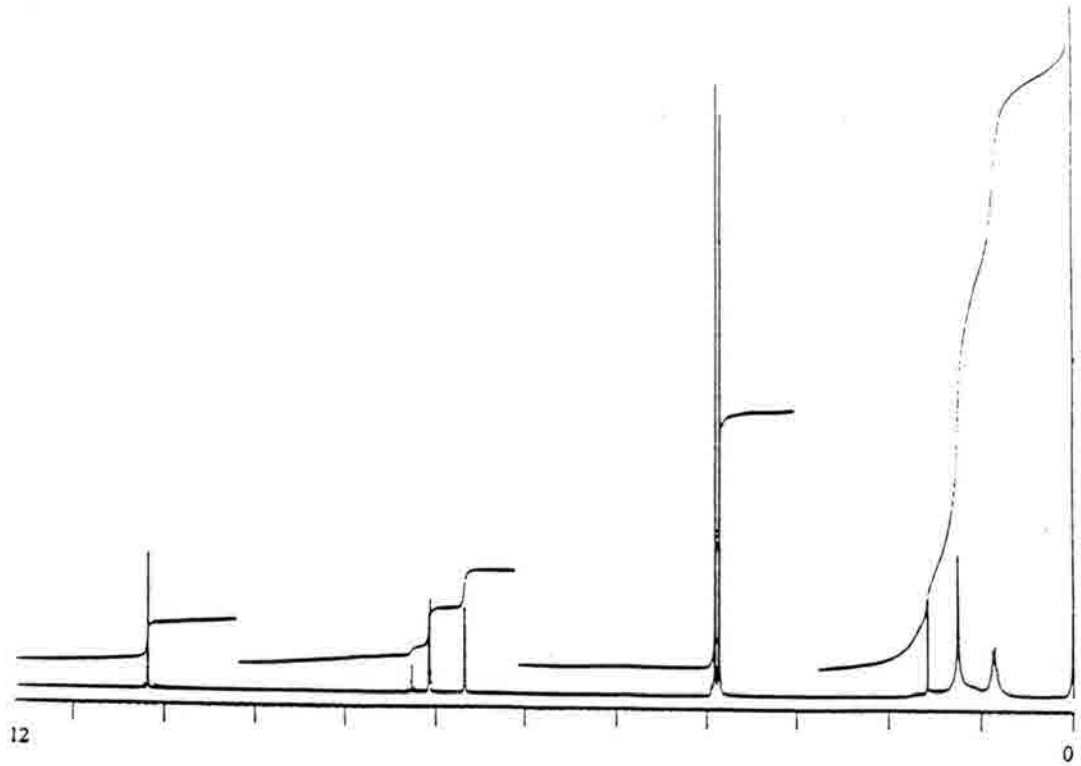
(0.65 mL, 8.503 mmoles, 2.50 equiv.) was added. The resulting mixture was stirred at room temp. for 2 h when the mixture was partitioned between Et_2O (10 mL) and water (10 mL) and separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers were washed with water (40 mL) and brine (40 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (3:2; Hex/EtOAc) yielding 383 mg (33 %) of the desired product (**254**) as a clear, colorless oil / white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.44 (s, 3 H), 3.81 (s, 3 H), 3.84 (s, 3 H), 4.59 (s, 2 H), 4.77 (s, 2 H), 6.36 (d, J=2.7 Hz, 1 H), 6.73 (d, J=2.6 Hz, 1 H). IR: (NaCl) 2999, 2940, 2839, 1585, 1453, 1431, 1335, 1201, 1160, 1078, 1045, 1012, 923, 836 cm^{-1}.



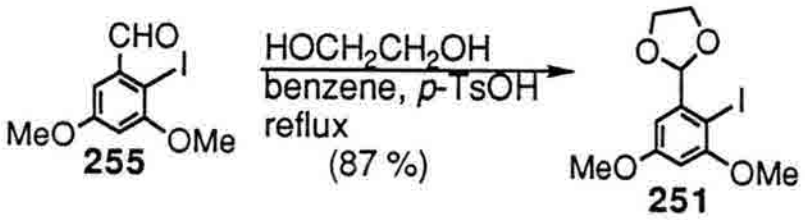
252 **255**

3,5-Dimethoxy-2-iodobenzaldehyde (255).[81] To a mechanically stirred suspension of PCC (2.93 g, 13.61 mmoles, 2.00 equiv.) in dry CH_2Cl_2 (6.80 mL) was added a solution of 3,5-dimethoxy-2-iodobenzyl alcohol (**252**)[103] (2.00 g, 6.80 mmoles, 1.00 equiv.) in dry CH_2Cl_2 (14.20 mL) via cannula. The mixture was stirred at room temp. for 2.5 h when the supernatant was decanted and the residue was thoroughly washed with CH_2Cl_2 (3 x 20 mL). The combined organic layers were diluted with Et_2O (10 - 15 % of the total volume of the CH_2Cl_2) and then passed through a column of silica gel (20 g) in 9:1 CH_2Cl_2/Et_2O. Further elution with 15 % Et_2O in CH_2Cl_2 and evaporated. The residue was separated via column chromatography (3:2; Hex/EtOAc) yielding 1.91 g (96 %) of 3,5-dimethoxy-2-iodo-benzaldehyde (**255**) as a light yellow crystalline solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.86 (s, 3H), 3.91

(s, 3 H), 6.67 (d, J=2.8 Hz, 1 H), 7.07 (d, J=2.8 Hz, 1 H), 10.18 (s, 1 H). IR: (NaCl, $CHCl_3$) 3022, 2961, 2931, 2869, 1732, 1681, 1585, 1456, 1384, 1330, 1287, 1217, 1161, 1073, 1011, 918, 841, 757, 667 cm^{-1}.

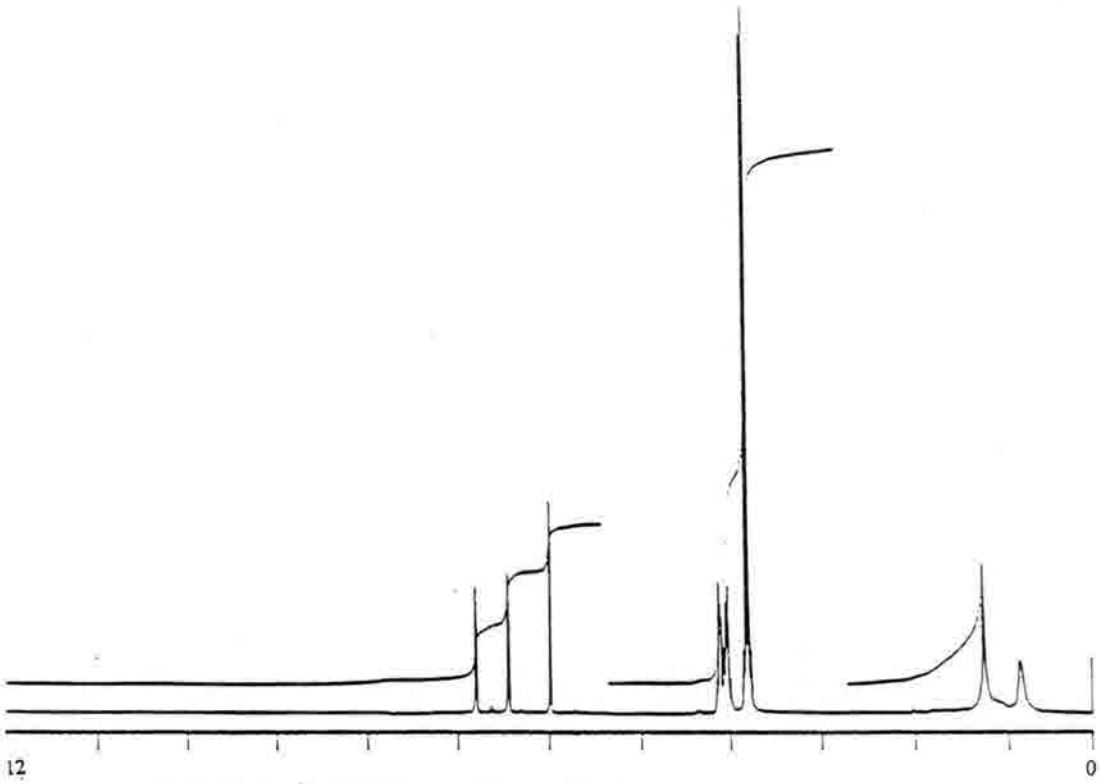


270 MHz ^1H NMR of **255** in $CDCl_3$ at room temperature.

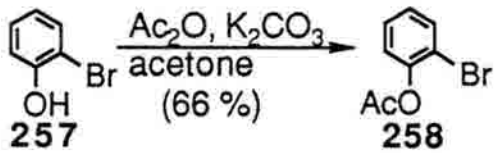


2-(3',5'-Dimethoxy-2'-iodo)phenyl-1,3-dioxolane (251). To a stirred solution of 3,5-dimethoxy-2-iodobenzaldehyde (**255**) (685 mg, 2.35 mmoles, 1.00 equiv.) in dry benzene (6.40 mL) was added ethylene glycol (0.20 mL, 3.52 mmoles, 1.50 equiv.) and p-toluene sulfonic acid monohydrate (45 mg, 0.24 mmoles, 0.10 equiv.). The resulting solution was stirred at reflux with a Dean-Stark trap for 2 h when, upon cooling to room temp., the mixture was

washed with sat. $NaHCO_{3(aq)}$ (2 x 5 mL), 1 M $Na_2S_2O_3$ (2 x 5 mL), and brine (5 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (4:1; Hex/EtOAc) yielding 590 mg (75 %) of the desired product (**251**) as a white solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 3.79 (s, 3 H), 3.82 (s, 3 H), 4.05 (m, 2 H), 4.13 (m, 2 H), 5.98 (s, 1 H), 6.43 (d, J=2.5 Hz, 1 H), 6.79 (d, J=2.7 Hz, 1 H). IR: (NaCl, $CHCl_3$) 3011, 2938, 2891, 1588, 1455, 1383, 1324, 1202, 1163, 1058, 1072, 971, 843, 762, 668 cm^{-1}.



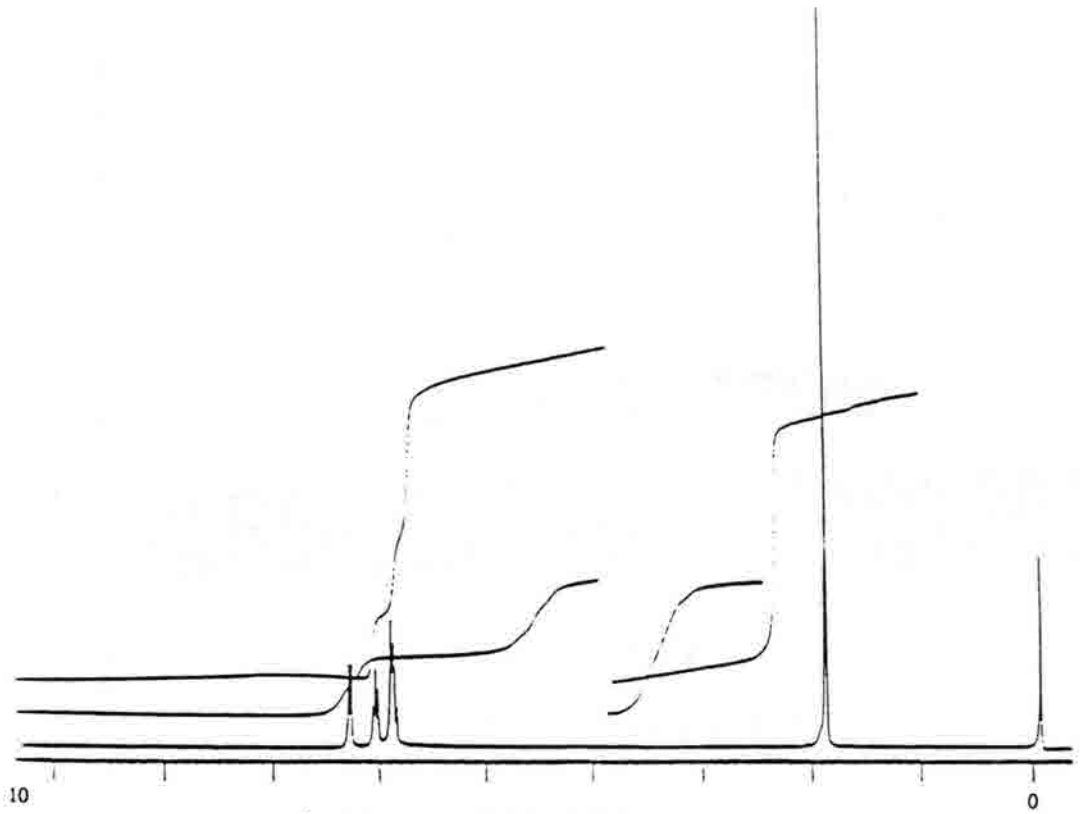
270 MHz ^1H NMR of **251** in $CDCl_3$ at room temperature.



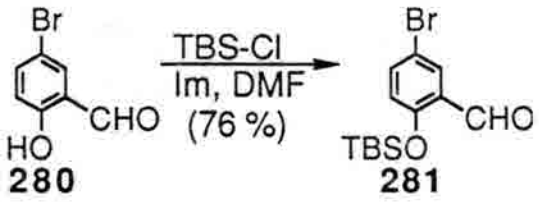
257 **258**

2-Acetoxybromobenzene (258).[104] To a stirred suspension of 2-bromophenol (0.34 mL, 2.890 mmoles, 1.00 equiv.) and potassium carbonate

(1.997 g, 14.450 mmoles, 5.00 equiv.) in dry acetone (11.60 mL) was added acetic anhydride (0.30 mL, 3.179 mmoles, 1.10 equiv.). The resulting mixture was stirred at room temp. for 24 h when the mixture was filtered, acidified with 10 % HCl_{aq}, partitioned between Et_2O (15 mL) and water (15 mL) and separated. The aqueous layer was extracted with Et_2O (4 x 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (3:2; Hex/EtOAc) yielding 411 mg (66 %) of the desired product (**258**) as a clear, colorless oil. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 2.31 (s, 3 H), 7.11 (m, 2 H), 7.28 (m, 1 H), 7.57 (d, J=6.5 Hz, 1 H). IR: (NaCl) 3068, 1770, 1583, 1471, 1444, 1369, 1194, 1047, 1010, 906, 821, 751, 713, 670, 593 cm^{-1}.

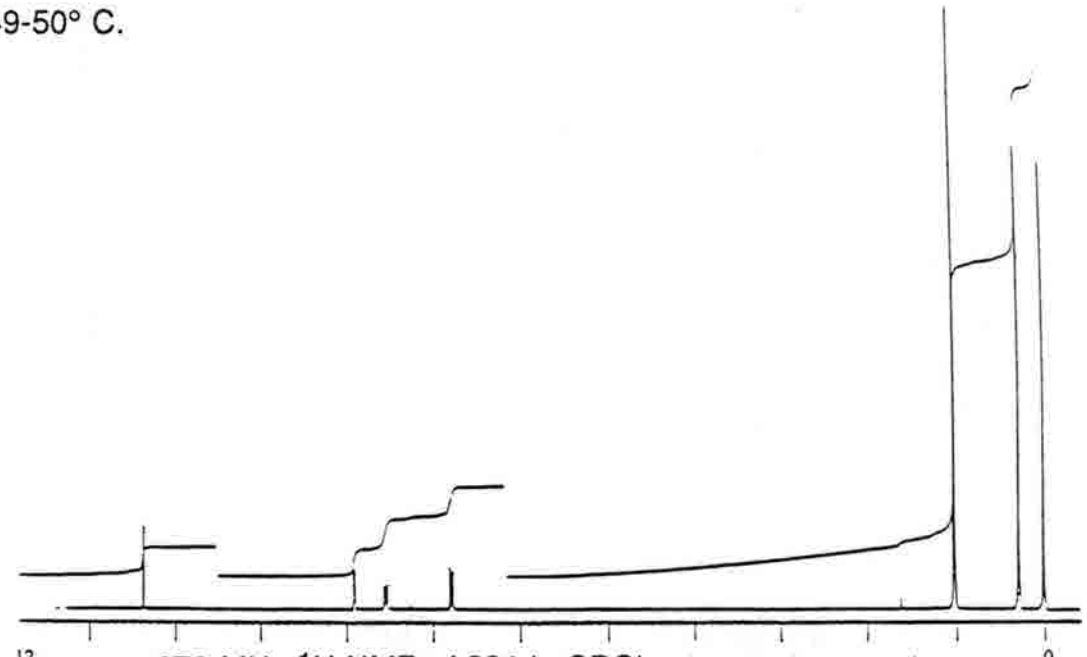


270 MHz ^1H NMR of **258** in $CDCl_3$ at room temperature.

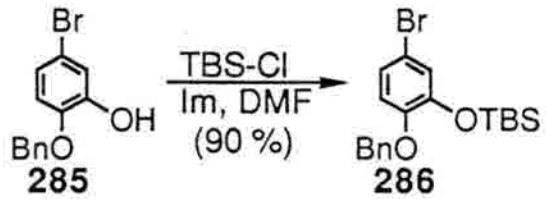


280 **281**

5-Bromo-2-*tert*-butyldimethylsiloxybenzaldehyde (281).[101] To a stirred solution of 5-bromosalicylaldehyde (**280**) (5.00 g, 24.87 mmoles, 1.00 equiv.) in dry DMF (21.50 mL) was added *tert*-butyldimethylsilyl chloride (4.12 g, 27.36 mmoles, 1.10 equiv.) and imidazole (5.93 g, 87.06 mmoles, 3.50 equiv.). The resulting solution was stirred at room temp. overnight when the solution was partitioned between Et_2O (400 mL) and water (135 mL). The ether layer was washed with water (3 x 135 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (4:1; Hex/EtOAc) yielding 5.93 g (76 %) of the desired product (**281**) as a white solid and 226 mg of starting material. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 0.28 (s, 6 H), 1.02 (s, 9 H), 6.79 (d, J=8.7 Hz, 1 H), 7.54 (dd, J=5.8 Hz, 1 H), 7.91 (d, J=2.6 Hz, 1 H), 10.37 (s, 1 H). IR: (NaCl, $CHCl_3$) 3020, 2957, 2932, 2861, 1686, 1591, 1472, 1388, 1291, 1260, 1216, 1176, 1117, 1006, 916, 865, 843, 769, 669 cm^{-1}. Mp: 49-50° C.

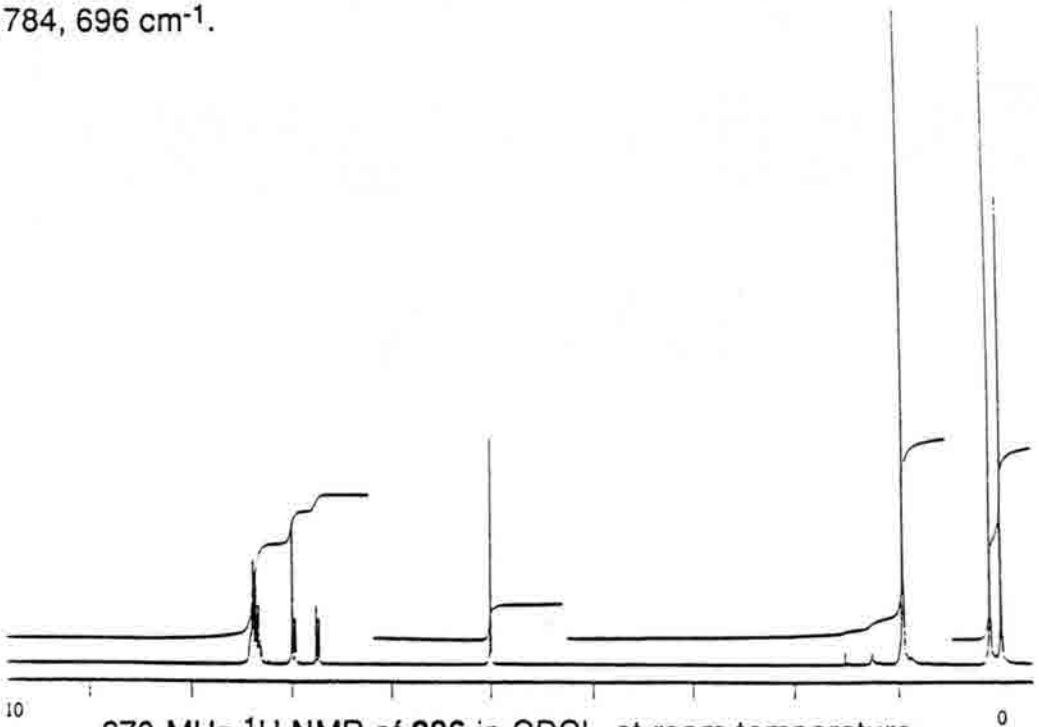


270 MHz ^1H NMR of **281** in $CDCl_3$ at room temperature.

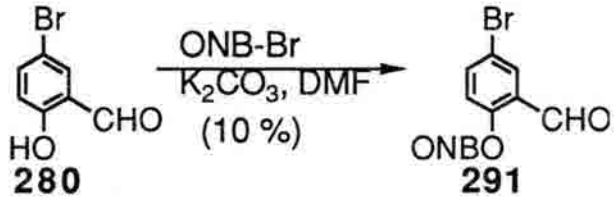


285 **286**

4-Benzyloxy-3-*tert*-butyldimethylsiloxybromobenzene (286).[101] To a stirred solution of 5-bromo-2-benzyloxyphenol (**285**) (4.60 g, 16.50 mmoles, 1.00 equiv.) in dry DMF (14.25 mL) was added *tert*-butyldimethylsilyl chloride (2.73 g, 18.15 mmoles, 1.10 equiv.) and imidazole (3.93 g, 57.75 mmoles, 3.50 equiv.). The resulting solution was stirred at room temp. overnight when the solution was partitioned between Et_2O (265 mL) and water (90 mL). The ether layer was washed with water (3 x 90 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (20:1; Hex/EtOAc) yielding 5.84 g (90 %) of the desired product (**286**) as a pale, yellow oil. ^{1}H NMR: (270 MHz) ($CDCl_3$) δ TMS: 0.11 (s, 6 H), 0.95 (s, 9 H), 5.00 (s, 2 H), 6.75 (d, J=8.2 Hz, 1 H), 6.96 (dd, J=1.7 Hz, 1 H), 7.00 (s, 1 H), 7.39 (m, 5 H). IR: (NaCl) 2929, 2858, 1584, 1494, 1402, 1299, 1214, 1133, 1009, 934, 830, 784, 696 cm^{-1}.

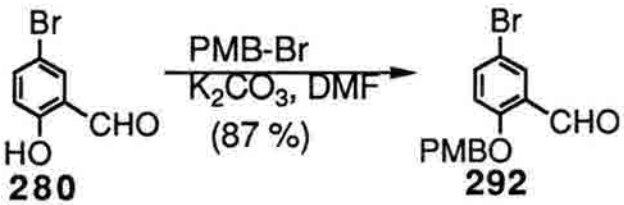


270 MHz ^{1}H NMR of **286** in $CDCl_3$ at room temperature.



280 **291**

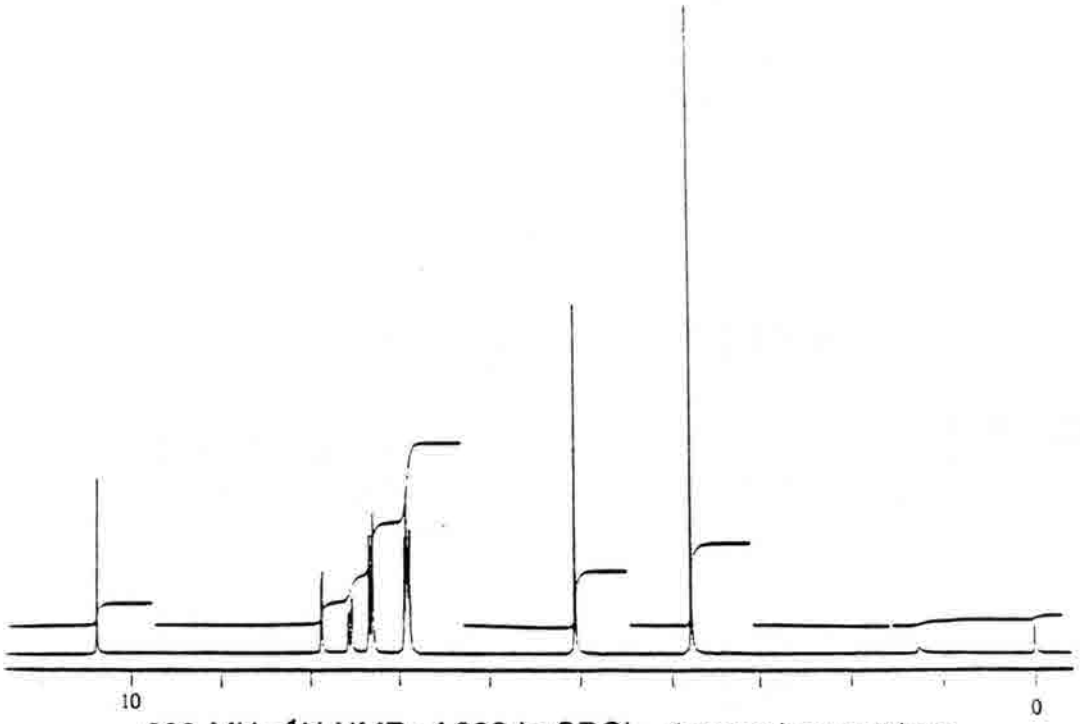
5-Bromo-2-(2'-nitrobenzyloxy)benzaldehyde (291). To a stirred suspension of 5-bromosalicylaldehyde (**280**) (500 mg, 2.487 mmoles, 1.00 equiv.) and potassium carbonate (1.719 g, 12.437 mmoles, 5.00 equiv.) in dry DMF (4.15 mL) was added *o*-nitrobenzylbromide (645 mg, 2.985 mmoles, 1.20 equiv.). The resulting mixture was stirred at room temp. for 18 h when the mixture was filtered, partitioned between Et_2O (10 mL) and water (10 mL) and separated. The aqueous layer was extracted with Et_2O (4 x 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated yielding 76 mg (10 %) of the desired product (**291**) as a white / yellow solid. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 5.60 (s, 2 H), 6.99 (d, J=8.9 Hz, 1 H), 7.46-8.22 (m, 6 H), 10.49 (s, 1 H).



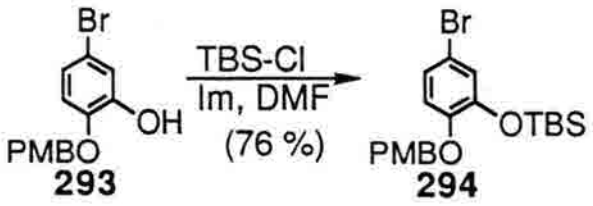
280 **292**

5-Bromo-2-(4'-methoxybenzyloxy)benzaldehyde (292). To a stirred suspension of 5-bromosalicylaldehyde (**280**) (500 mg, 2.487 mmoles, 1.00 equiv.) and potassium carbonate (1.719 g, 12.437 mmoles, 5.00 equiv.) in dry DMF (4.15 mL) was added *p*-methoxybenzyl bromide (0.56 mL, 2.985 mmoles, 1.20 equiv.). The resulting mixture was stirred at room temp. overnight when the mixture was filtered into water (4 mL) and acidified with 10 % HCl_{aq}. The resulting mixture was extracted with Et_2O (4 x 5 mL) and the combined organic

layers were dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (4:1; Hex/EtOAc) yielding 696 mg (87 %) of the desired product (**292**) as a white solid. ^1H NMR: (200 MHz) ($CDCl_3$) δ TMS: 3.78 (s, 3 H), 5.05 (s, 2 H), 6.92 (m, 3 H), 7.32 (d, J=8.6 Hz, 2 H), 7.55 dd, J=6.2 Hz, 1 H), 7.87 (d, J=2.5 Hz, 1 H), 10.38 (s, 1 H). IR: (NaCl, $CHCl_3$) 3019, 2937, 2876, 1682, 1614, 1591, 1516, 1481, 1464, 1393, 1378, 1251, 1216, 1176, 1123, 1035, 995, 778, 669 cm^{-1}. Mp: 98-100° C.



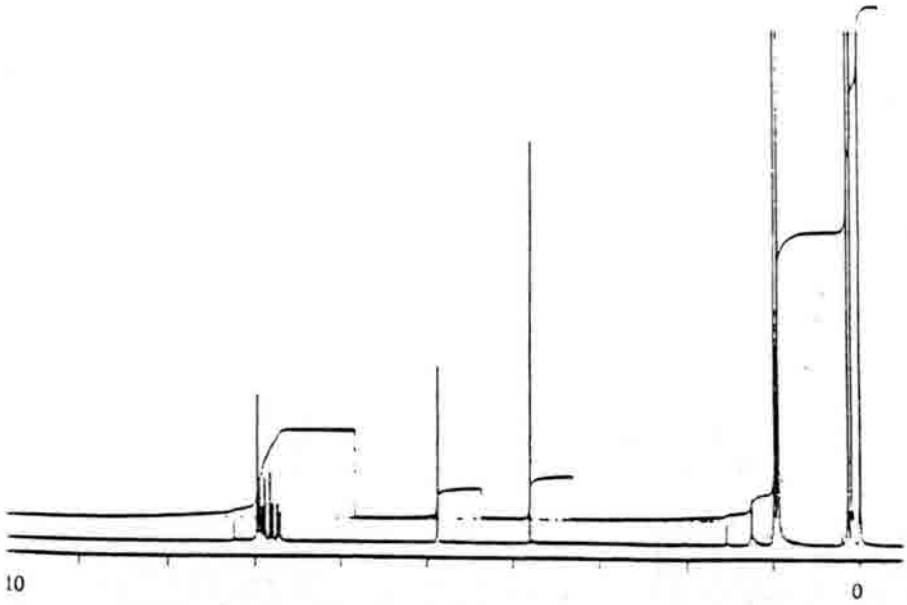
200 MHz ^1H NMR of **292** in $CDCl_3$ at room temperature.



293 **294**

3-*tert*-butyldimethylsiloxy-4-(4'-methoxybenzyloxy) bromobenzene (294).[101] To a stirred solution of 5-bromo-2-(4'-methoxybenzyloxy)phenol (**293**) (1.60 g, 5.176 mmoles, 1.00 equiv.) in dry

DMF (4.10 mL) was added *tert*-butyldimethylsilyl chloride (858 mg, 5.649 mmoles, 1.10 equiv.) and imidazole (1.23 g, 18.12 mmoles, 3.50 equiv.). The resulting solution was stirred at room temp. overnight when the solution was partitioned between Et_2O (75 mL) and water (25 mL). The ether layer was washed with water (3 x 25 mL), dried ($MgSO_4$), filtered and evaporated. The residue was separated via column chromatography (20:1; Hex/EtOAc) yielding 1.66 g (76 %) of the desired product (**294**) as a pale, yellow oil. ^1H NMR: (270 MHz) ($CDCl_3$) δ TMS: 0.14 (s, 6 H), 0.94 (s, 9 H), 3.80 (s, 3 H), 4.88 (s, 2 H), 6.72 (dd, J=7.9 Hz, 1 H), 6.81 (d, J=8.2 Hz, 1 H), 6.98 (m, 5 H). IR: (NaCl) 2929, 2896, 2858, 1586, 1514, 1495, 1471, 1443, 1429, 1403, 1270, 1212, 1165, 1135, 1036, 1006, 976, 935, 839, 735, 649 cm^{-1}.



270 MHz ^1H NMR of **294** in $CDCl_3$ at room temperature.

Chapter V

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APPENDIX

REPRINTS

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Asymmetric Synthesis of Arylglycines

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The asymmetric synthesis of several arylglycines are reported. The methodology deployed involves either cuprate or Friedel–Crafts couplings to chiral bromoglycinates. The % ee's range from 82 to 94%. Both an oxidative and reductive protocol are employed to unmask the oxazinone chiral auxilliary providing the free α-amino acids.

The arylglycines constitute an important class of nonproteinogenic α-amino acids.[1] For example, *p*-hydroxyphenylglycine is a side-chain constituent of the β-lactam antibiotic amoxicillin.[2] Numerous other, highly functionalized arylglycines are found in numerous peptide and glycopeptide antibiotics such as the vancomycins.[3] The apparent simplicity of the arylglycine structure is complicated by the ease of base-catalyzed racemization of the α-methine proton, rendering these substances challenging synthetic targets to obtain in optically pure form.

Numerous approaches to the synthesis of arylglycines have recently appeared, including: enzymatic resolution of racemic Strecker-derived amides and esters;[4] Friedel–Crafts additions to chiral cationic glycine equivalents;[5] asymmetric Strecker reactions;[6] electrophilic amination of chiral enolates;[7] and nucleophilic ring opening of aryl epoxy

Scheme I

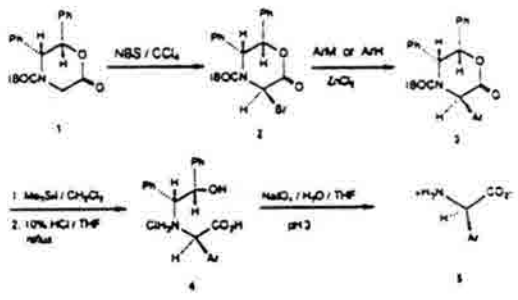

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Table I

	ArM/ArH	conditions	% yield (3)	% yield (5)*	% ee (5)
a		Et_2O/THF, −78 °C, 1 h	56	52	82
b		Et_2O/THF, −78 °C, 1.5 h	55	29	94
c		$ZnCl_2$/THF, 25 °C, 4.5 h	83[b]	62	91
d		$ZnCl_2$/THF, 25 °C, 5.5 h 4A molecular sieves	50	26	90
e		$ZnCl_2$/MeCN, 25 °C, 4 h 4A molecular sieves	39	73	93

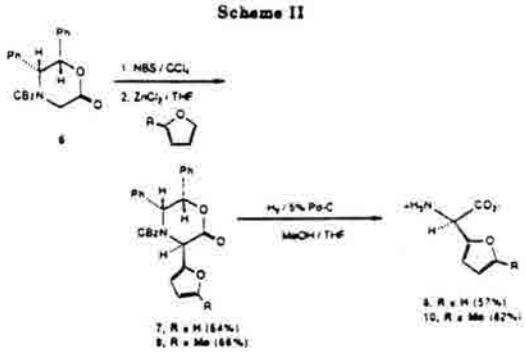
*Yield for three steps. [b]Two-step yield for the lactone after TMSI removal of the *t*-BOC group.

alcohols,[8] amongst others.[9] While all of these methods offer avenues to access this increasingly important and difficult functional array, much work in this area remains to be developed to broaden the functional diversity that this class of substances poses. In this paper, we report the further extension of our electrophilic glycinates[10] to the asymmetric synthesis of several arylglycines.

In applying the diphenyloxazinone templates[11] 1 and 6 to the problem of arylglycines, an alternate means of removing the chiral auxilliary needed to be devised that would selectively cleave the C–O and C–N benzylic residues of the auxilliary and not cleave the C–N benzylic bond of the arylglycine unit (3, 7, or 9) itself. The standard protocol we have developed for effecting destructive removal of the chiral auxilliary involves either a dissolving metal reduction or a catalytic hydrogenation. It was anticipated that neither reaction condition would achieve the desired chemoselectivity. The Strecker-based method of Weinges[6c,d] proceeds through a related 3-aryl-5-phenyl-6-(hydroxymethyl)oxazinone and is reported to be disassembled using either *oxidation* with periodate or reduction on a Raney nickel catalyst. It seemed reasonable that periodate should selectively remove 2 molar equiv of benzaldehyde from the hydroxy acids (4), providing the arylglycines in a similar fashion. In the event, we have found that application of the oxidative protocol employed by Weinges provides the desired selectivity on the present substrates.

As illustrated in Scheme I, glycinate 1 is brominated as previously described[10] to furnish the bromide 2. Reaction of this material with either an arylcuprate or electron-rich aromatic under Friedel–Crafts conditions provides the anti-arylated substances 3. Removal of the *t*-BOC group with trimethylsilyl iodide in methylene chloride proceeds cleanly and the lactones are then subjected to hot aqueous HCl to afford the hydroxy acids 4. Treatment of these crude substances with sodium periodate in (pH 3) aqueous THF, followed by ion-exchange purification, furnishes the free amino acids 5. The coupling conditions, yields and % ee's are presented in Table I. Varying amounts of partial racemization accompany the final deprotection as diastereochemically homogeneous materials (3) are obtained from the couplings to 2. These seemed to be quite substrate-dependent and consistent for each substance on repeated processing.

Scheme II



We have also found that the *N*-CBz substrate 7 (Scheme II) could be converted into 2-furylglycine (8) by a selective three-step method involving: (1) selective removal of the *N*-CBz group with 5% Pd–C/H_2 at atmospheric pressure; (2) ring opening of the lactone (4); and (3) periodate cleavage. It is noteworthy that the furan ring is not saturated in the first step, nor oxidized in the last step. In one remarkable instance, we found that the furan adducts 7 and 9 could be cleanly hydrogenated to the corresponding amino acids 8 and 10 in 57% and 82% yield, respectively. This reaction is noteworthy in that, the furan ring is not saturated nor is the "benzylic" C–N moiety of the amino acid cleaved under these conditions. Based on extensive experience hydrogenating these type of oxazinones to the amino acids, we know that the *N*-CBz group is cleaved first followed by the lactone C–O benzylic bond and lastly, the C–N residue. We have been able to isolate these stepwise reduction products by carefully varying the pressure and loading of the catalyst. It would seem reasonable that the anti stereochemistry of 7/9 and the relative sluggishness of reducing the furan C–N benzylic residue relative to that of the benzyl C–N bond contribute to the observed se-

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lectivity in these two cases. At higher pressure on a Pd^0 catalyst, substrates 7 and 9 suffer clean conversion to the corresponding 2-tetrahydrofuranylglycine derivatives.[10] We have examined the direct hydrogenation of other α-aryl-*N*-CBz substrates corresponding to 3 but with only limited success. In most cases, small amounts (~10%) of the arylglycine can be obtained under 1 atm of H_2/Pd–C conditions, but myriads of other products are produced. The furan substrates would seem to be an unusual (but reproducible) exception. The oxidative periodate protocol is consistantly successful for all of the aryl substitution we have examined. Further applications of oxazinones 1 and 6 to the synthesis of a variety of complex and sensitive amino acids are under investigation in these laboratories.

Experimental Section

(3*R*,5*R*,6*S*)-4-(*tert*-Butoxycarbonyl)-2,3,5,6-tetrahydro-3,5,6-triphenyl-1,4-oxazin-2-one (3a, Ar = Ph). To a stirred solution of bromobenzene (0.84 mL, 8.00 mmol, 4.00 equiv) in dry Et_2O (4.00 mL) cooled to −15 °C was added *n*-BuLi (4.20 mL, 8.40 mmol, 4.20 equiv, 2.0 M in hexanes) dropwise. The resulting solution was stirred at −15 °C for 30 min when additional dry Et_2O (5.00 mL) was added with copper bromide dimethyl sulfide (0.822 g, 4.00 mmol, 2.00 equiv). The resulting mixture was stirred at −78 °C for 3 h when a solution of the (3*R*,5*R*,6*S*)-3-bromo-4-(*tert*-butoxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (2) (0.864 g, 2.00 mmol, 1.00 equiv) in a 1:1 solution of dry Et_2O and dry THF (62.00 mL) was added via cannula. Compound 2 was synthesized from compound 1 by standard and previously reported methodology.[10] The resulting mixture was stirred at −78 °C for 1 h when a saturated solution of NH_4Cl (40 mL) was added at −78 °C. The resulting mixture was allowed to warm to room temperature and separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 40 mL). The combined organic layers were washed with 10% HCl (2 × 40 mL), dried ($NaSO_4$), filtered, and evaporated. The residue was separated via column chromatography (7:2:1 Hex/$CHCl_3$/EtOAc) and recrystallized from EtOAc/hexanes, yielding 484 mg (56%) of the desired product (3a) as a white solid. ^1H NMR (270 MHz, $CDCl_3$) δ TMS: 7.59–6.68 (m, 15 H), 6.42 (s) and 6.19 (s) (1 H), 5.85 (d) and 5.76 (d) (1 H), 5.45 (d) and 5.18 (d) (1 H), 1.33–1.13 (m, 9 H). ^1H NMR (200 MHz, DMSO-d_6 at 380 K) δ DMSO: 7.66–7.02 (m, 13 H), 6.72–6.68 (m, 2 H), 6.11 (s, 1 H), 5.95 (d, 1 H), 5.50 (d, 1 H), 1.11 (s, 9 H). IR (NaCl, $CHCl_3$): 3020, 1755, 1695, 1375, 1210, 1150, 1110, 735, 687, 650 cm^{-1}. MS: *m/e* (relative intensity) 428 (0.2), 390 (29.4), 329 (42.6), 284 (76.5), 196 (57.7), 106 (100.0). Mp: 227–228 °C (recrystallization, EtOAc/hexanes). Anal. Calcd for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.34; N, 3.26. Found: C, 75.52; H, 6.61; N, 2.99. $[\alpha]^{25}_D$: +78.2° (*c* 1.00, CH_2Cl_2).

(3*R*,5*R*,6*S*)-2,3,5,6-Tetrahydro-3,5,6-triphenyl-1,4-oxazin-2-one. To a stirred solution of 3a (250 mg, 0.58 mmol, 1.00 equiv) in dry CH_2Cl_2 (5.80 mL) was added trimethylsilyl iodide (0.20 mL, 1.40 mmol, 2.40 equiv). The resulting orange solution was stirred at room temperature for 10 min, when water (10 mL) was added. The resulting mixture was separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were washed with 1 M $Na_2S_2O_3$ (2 × 20 mL), dried (Na_2SO_4), filtered, and evaporated. The residue was separated via silica gel column chromatography (5:3:2 Hex/$CHCl_3$/EtOAc) yielding 139 mg (73%) of the desired product as a white foam. ^1H NMR (270 MHz, $CDCl_3$) δ TMS: 7.63–6.89 (m, 15 H), 5.70 (d, 1 H), 5.21 (s, 1 H), 4.72 (d, 1 H), 2.35 (br s, 1 H). IR (NaCl, $CHCl_3$): 3364, 3029, 2924, 2851, 2359, 1740, 1494, 1453, 1259, 1181, 1065, 757, 694, 689 cm^{-1}. MS: *m/e* (relative intensity) 330 (23.4), 329 (100.0), 327 (71.9), 283 (71.9), 251 (43.7), 196 (51.6), 106 (60.9), 71 (28), 35 (100.0), 31.9 (64.1).

D-Phenylglycine Hydrochloride (5a, Ar = Ph). A stirred solution of (3*R*,5*R*,6*S*)-2,3,5,6-tetrahydro-3,5,6-triphenyl-1,4-oxazin-2-one (93.8 mg, 0.285 mmol, 1.00 equiv) in THF (5.00 mL) and 10% HCl (20.00 mL) was heated at reflux for 15 min. Upon cooling, the solution was evaporated and taken up in distilled water (7.50 mL) and sodium periodate (134 mg, 0.627 mmol, 2.2 equiv), and pH was adjusted to 3.0, and the resulting solution was stirred at room temperature for 36 h. The pH of the resulting suspension was adjusted to approximately 5.5 with the dropwise addition of 0.1 N NaOH, 10 drops of ethylene glycol was added to destroy excess $NaIO_4$, and the mixture was stirred for 15 min. The resulting mixture was washed with EtOAc (3 × 25 mL) and evaporated. The resulting white solid was separated via anion exchange chromatography (Amberlite IRA-45) yielding 38 mg (71%) of D-phenylglycine hydrochloride (5a) as a white amorphous solid. Spectral data matches that of authentic material (Sigma).

(3*R*,5*R*,6*S*)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-3-(1′-naphthyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (3b, Ar = 1-Naphthyl). To a stirred solution of 1-bromonaphthalene (1.68 mL, 12.00 mmol, 4.00 equiv) in dry Et_2O (6.00 mL) cooled to −15 °C was added *n*-BuLi (7.88 mL, 12.60 mmol, 4.20 equiv, 1.60 M in hexanes) dropwise. The resulting white suspension was stirred at −15 °C for 30 min when additional dry Et_2O (7.50 mL) was added with copper bromide dimethyl sulfide (1.233 g, 6.00 mmol, 2.00 equiv). To the resulting thick, dark solution was added dry dimethyl sulfide (3.00 mL) to aid the solubility of the reactants. The resulting mixture was stirred at −78 °C for 3 h when a solution of 2 (1.296 g, 3.00 mmol, 1.00 equiv) in a 1:1 solution of dry Et_2O and dry THF (93.00 mL) was added via cannula. The resulting mixture was stirred at −78 °C for 1.5 h when a saturated solution of NH_4Cl (60 mL) was added at −78 °C. The resulting mixture was allowed to warm to room temperature and separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 60 mL). The combined organic layers were washed with 10% HCl (2 × 60 mL), dried ($NaSO_4$), filtered, and evaporated. The residue was separated via column chromatography (7:2:1 Hex/$CHCl_3$/EtOAc) and recrystallized from EtOAc/Hex, yielding 789 mg (55%) of the desired product as a white solid. ^1H NMR (270 MHz, $CDCl_3$) δ TMS: 7.24–7.04 (m, 14 H), 6.81 (d, 1 H), 6.64 (dd, 3 H), 5.53 (s, 1 H), 4.85 (d, 1 H), 1.15 (s, 9 H). IR (NaCl, neat): 2970, 1740, 1682, 1381, 1359, 1321, 1268, 1245, 1176, 1150, 1112, 1045, 687 cm^{-1}. MS: *m/e* (relative intensity) 440 (74.2), 380 (58.7), 334 (21.5), 232 (32.9), 215 (100.0), 196 (32.7), 180 (31.1), 156 (22.5), 106 (52.4), 100 (31.4), 58 (34.2). Anal. Calcd for $C_{37}H_{39}NO_4 \cdot 1.5H_2O$: C, 73.50; H, 6.37; N, 2.76. Found: C, 73.64; H, 6.31; N, 2.83. Mp: 214–215 °C (recrystallization, EtOAc/hexanes). $[\alpha]^{25}_D$ +33.9 (*c* 0.99, CH_2Cl_2).

(3*R*,5*R*,6*S*)-5,6-Diphenyl-3-(1′-naphthyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one. To a stirred solution of 3b (789 mg, 1.65 mmol, 1.00 equiv) in dry CH_2Cl_2 (16.50 mL) was added trimethylsilyl iodide (0.56 mL, 3.95 mmol, 2.40 equiv). The resulting orange solution was stirred at room temperature for 10 min, when the reaction was quenched with the addition of water (25 mL). The resulting mixture was separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 25 mL). The combined organic layers were washed with 1 M $Na_2S_2O_3$ (2 × 40 mL), dried (Na_2SO_4), filtered, and evaporated, yielding a crude yellow oil/foam. The resulting mixture was separated via column chromatography (2:2:1 Hex/$CHCl_3$/EtOAc), yielding 443 mg (71%) of the desired product as a white foam. ^1H NMR (270 MHz, $CDCl_3$) δ TMS: 7.28–7.16 (m, 10 H), 6.86–6.68 (m, 7 H), 5.83 (d, 1 H), 5.06 (d, 1 H), 4.95 (s, 1 H), 2.50 (br s, 1 H). IR (NaCl, neat): 3322, 2960, 2850, 1725, 1440, 1220, 1182, 1000, 740, 680 cm^{-1}. MS: *m/e* (relative intensity) 287 (0.2), 106 (5.8), 104 (19.1), 88 (83.2), 71 (58.6), 56 (3.6), 35 (100).

D-Naphthylglycine (5b, Ar = 1-Naphthyl). To a stirred solution of (3*R*,5*R*,6*S*)-5,6-diphenyl-3-(1′-naphthyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (152 mg, 0.401 mmol, 1.00 equiv) in THF (2.5 mL) was added 10% HCl (5.0 mL). The resulting solution was stirred at room temperature for 1 h and evaporated. The white residue was taken up in water (7.0 mL) and THF (5.0 mL). The pH of the resulting suspension was adjusted to 3 with the dropwise addition of 1 N NaOH. To this solution was added sodium periodate (189 mg, 0.882 mmol, 2.20 equiv), and the resulting mixture was stirred at room temperature for 2 days when the pH was adjusted to 5.5 with the dropwise addition of 1 N NaOH and several drops of propylene glycol were added (to destroy excess $NaIO_4$). The resulting solution was stirred at room temperature for 15 min, the resulting mixture was washed with EtOAc (3 × 5 mL), and the aqueous layer was evaporated, yielding a yellow/white solid mixture which was taken up in water/EtOH and filtered through a C_{18} silica plug and evaporated. This white solid mixture was separated via cation exchange chromatography

(eluted with 1 N NH_4OH, Dowex 50W-X8) yielding 33 mg (41%) of naphthylglycine (5b) as a white solid. ^1H NMR (270 MHz, DCl in D_2O) δ HOD: 7.53–7.22 (m, 7 H)8 4.83 (s, 1 H). ^1H NMR (270 MHz, DMSO-d_6) δ DMSO: 8.33 (br s, 1 H), 7.98–7.35 (m, 7 H), 5.01 (s, 1 H), 1.13 (m, 2 H). IR (NaCl, neat): 3380, 3050, 2956, 1594, 1369, 1167, 1047, 1026, 818 cm^{-1}. MS: *m/e* (relative intensity) 171 (20.6), 158 (63.9), 141 (28.8), 128 (3.0), 102 (25.6), 85 (100.0). $[\alpha]^{25}_D$: +8.0° (*c* 0.05, H_2O).[12]

(3*R*,5*R*,6*R*)-5,6-Dipbenyl-2,3,5,6-tetrahydro-3-(2′-(1′,3′,5′-trimethoxyphenyl))-1,4-oxazin-2-one (Ar = 1,3,5-Trimethoxyphenyl). To a stirred solution of 2 (0.432 g, 1.00 mmol, 1.00 equiv) in dry THF (7.00 mL) was added 1,3,5-trimethoxybenzene (1.958 g, 11.64 mmol, 11.64 equiv) and zinc chloride (1.33 mL, 2.00 mmol, 2.00 equiv, 1.50 M in THF). The resulting solution was stirred at room temperature for 4.5 h; the solution was then poured into water (10 mL). The resulting mixture was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. Since the residue contained both the *t*-BOC protected and unprotected coupled products it was found to be most efficient to carry the crude mixture on to the *t*-BOC deprotection reaction. Spectral data for the *t*-BOC-protected product (3c) is described below. To the yellow solid was added dry CH_2Cl_2 (10.00 mL) and trimethylsilyl iodide (0.28 mL, 2.00 mmol, 2.00 equiv). The resulting deep red solution was stirred at room temperature for 10 min, and water (15 mL) was added. The resulting mixture was separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were washed with 1 M $Na_2S_2O_3$ (2 × 10 mL), dried (Na_2SO_4), filtered, and evaporated. The oily residue was separated via silica gel column chromatography (6.5:2.5:1.0 Hex/$CHCl_3$/EtOAc), yielding 347 mg (83%) of the desired product as a white foam. ^1H NMR (270 MHz, $CDCl_3$) δ TMS: 7.21–7.06 (m, 12 H), 5.94 (d, 1 H), 5.41 (s, 1 H) 4.79 (d, 1 H), 3.80 (s, 6 H), 3.78 (s, 3 H), 2.22 (br s, 1 H). IR (NaCl, neat): 3315, 2950, 2850, 1734, 1600, 1488, 1456, 1409, 1330, 1220, 1193, 1140, 1110, 1050, 900, 795, 715, 680 cm^{-1}. MS: *m/e* (relative intensity) 420 (87.5), 375 (2.6), 285 (2.8), 252 (2.9), 210 (25.6), 196 (25.0), 169 (21.1), 104 (22.7), 88 (14.6), 71 (11.2)8 35 (100.0).

(3*R*,5*R*,6*S*)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-3-(2′-(1′,3′,5′-trimethoxyphenyl))-1,4-oxazin-2-one (3c). ^1H NMR (270 MHz, $CDCl_3$): δ TMS: 7.26–7.09 (m, 12 H), 6.88 (d, 1 H), 6.51 (d, 1 H), 6.18 (s, 1 H), 3.91 (s, 6 H), 3.83 (s, 3 H), 1.11 (s, 9 H). IR (NaCl, $CHCl_3$): 2968, 2860, 1745, 1695, 1608, 1460, 1448, 1360, 1345, 1225, 1198, 715, 695 cm^{-1}. MS: *m/e* (relative intensity) 520 (0.6), 388 (3.0), 331 (4.0), 306 (3.3), 252 (100.0), 250 (15.0), 196 (14.2), 162 (10.3), 122 (23.3), 106 (26.1), 105 (18.3), 88 (12.4), 58 (12.5), 35 (100.0). Anal. Calcd for $C_{30}H_{33}NO_7$: C, 69.35; H, 6.40; N, 2.70. Found: C, 69.11; H, 6.58; N, 2.48 (obtained as a sticky foam). $[\alpha]^{25}_D$: +61.3° (*c* 0.46, CH_2Cl_2).

D-α-Amino-2,4,6-trimethoxyphenylacetic Acid Hydrochloride (5c, Ar = 1,3,5-Trimethoxyphenyl). A stirred solution of (3*R*,5*R*,6*S*)-5,6-diphenyl-2,3,5,6-tetrahydro-3-(2′-(1′,3′,5′-trimethoxyphenyl))-1,4-oxazin-2-one obtained above (184 mg, 0.440 mmol, 1.00 equiv) in THF (2.90 mL) and 10% $HCl_{(aq)}$ (5.80 mL) was stirred at mild reflux for 30 min. Upon cooling to room temperature, the solution was thouroghly extracted with CH_2Cl_2 (5 × 10 mL), dried (Na_2SO_4), filtered, and evaporated. The resulting residue was taken up in a 1:1 solution of THF and water (9.2 mL) followed by the addition of sodium periodate (207 mg, 0.968 mmol, 2.20 equiv). The pH of the resulting mixture was adjusted to approximately 3 and was stirred at room temperature for 2 days. The pH of the resulting mixture was the adjusted to 7 with the dropwise addition of 1 N NaOH. A white precipitate gradually formed with increasing pH. The resulting neutral solution was allowed to precipitate in the refrigerator overnight. The white solid was collected by filtration, taken up in 10% $HCl_{(aq)}$ and evaporated. The residue was taken up in a minimum amount of 10% $HCl_{(aq)}$, precipitated with the addition of absolute EtOH, filtered, and dried, yielding 66 mg (62%) of the HCl salt of D-α-amino-2,4,6-trimethoxyphenylacetic acid (5c) as a yellow solid. ^1H NMR (270 MHz, D_2O) δ HOD: 7.36 (m, 1 H), 7.18 (m, 1 H), 6.11 (s, 1 H), 3.54 (s, 3 H), 3.38 (s, 6 H). IR (NaCl, neat): 3387, 2969, 2848, 1609, 1455, 1417, 1384, 1334, 1208, 1153, 1120, 1054, 949, 817, 700 cm^{-1}. MS: *m/e* (relative intensity) 276 (12.5), 242 (0.3), 210 (17.7), 181 (100.0), 169 (11.2), 106 (20.7), 85 (17.4), 35 (91.8). $[\alpha]^{25}_D$: −14.0° (*c* 0.05, H_2O).[12]

(3*R*,5*R*,6*S*)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-3-(2′-furyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (3d, Ar = 2-Furyl). To a solution of 2 (0.432 g, 1.00 mmol, 1.00 equiv) in THF (10.00 mL) stirred over powdered molecular sieves (0.5 g, 4 Å) was added furan (1.13 mL, 15.60 mmol, 15.60 equiv) and zinc chloride (2.00 mL, 2.00 mmol, 2.00 equiv, 1.0 M in THF). The resulting solution was stirred at room temperature for 5.5 h when the solution was filtered into water (10 mL). The resulting mixture was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The residue was separated via silica gel column chromatography (7:2:1 Hex/$CHCl_3$/EtOAc), yielding 211 mg (50%) of the desired product as a white solid. ^1H NMR (270 MHz, $CDCl_3$) δ TMS: 7.47–7.45 (m, 2 H), 7.26–6.97 (m, 6 H), 6.69–6.43 (m, 3 H), 6.31 (s, 1 H), 6.26–6.23 (m, 1 H), 6.09 (s, 1 H), 5.35 (d, 1 H), 5.09 (d, 1 H), 1.36 (s, 4 H), 1.10 (s, 5 H). IR (NaCl, $CHCl_3$): 3130, 2980, 2937, 2874, 1752, 1702, 1501, 1453, 1391, 1350, 1242, 1164, 1055, 952, 883, 757, 716, 701 cm^{-1}. MS: *m/e* (relative intensity) 419 (0.2), 381 (11.3), 320 (9.0), 316 (18.0), 274 (100.0), 244 (3.4), 196 (21.9), 106 (8.8), 96 (6.4), 35 (100.0), 32 (34.4). Anal. Calcd for $C_{26}H_{29}NO_5$: C, 71.58; H, 6.01; N, 3.34. Found: C, 71.79; H, 6.11; N, 3.20. Mp: 202–204 °C (recrystallization, EtOAc/hexanes). $[\alpha]^{25}_D$: −2.4° (*c* 1.00 CH_2Cl_2).

D-α-2-Furylglycine Hydrochloride (5d, Ar = 2-Furyl). To a stirred solution of 3d (271 mg, 0.646 mmol, 1.00 equiv) in dry $CHCl_2$ (6.50 mL) was added trimethylsilyl iodide (0.22 mL, 1.55 mmol, 2.40 equiv). The resulting red solution was stirred at room temperature for 10 min when the reaction was quenched with the addition of water (6.5 mL). The resulting mixture was separated, the aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL), and the combined organic layers were washed with $Na_2S_2O_3$ (2 × 20 mL) and evaporated. Since the product of this reaction rapidly decomposes, the residue was immediately taken up in THF (4.25 mL), and to this solution was added 10% HCl (8.50 mL). The resulting was stirred at reflux for 15 min, when, upon cooling to room temperature, the pH was adjusted to 3 with the dropwise addition of 1 N NaOH, and sodium periodate (0.304 g, 1.43 mmol, 2.20 equiv) was added. The resulting solution was stirred at room temperature for 2 days, and several drops of ethylene glycol was added to quench the excess sodium periodate. The resulting mixture was stirred at room temperature for 15 min when the mixture was washed with EtOAc (15 mL). The organic layer was washed with water (10 mL), and the pH of the combined aqueous layers was adjusted to 7 with the dropwise addition of 1 N NaOH. The resulting was evaporated to about one-fourth of the original volume and allowed to crystallize in the refrigerator overnight. The resulting mixture was filtered, and the solid material was further purified via anion exchange chromatography (eluted with 10% HCl, Amberlite IR-45), yielding 30 mg (26%) of D-α-2-furylglycine hydrochloride (5d) as a white amorphous solid (see data below).

D-α-2-Furylglycine (8). To a stirred suspension of 5% palladium on activated carbon (75 mg) in absolute MeOH (40.00 mL) charged with hydrogen was added a solution of (3*R*,5*R*,6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-3-(2′-furyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (7) (383 mg, 0.846 mmol, 1.00 equiv) in dry THF (11.50 mL) via syringe. Compound 7 was prepared via standard and previously reported conditions.[10] The resulting mixture was stirred at room temperature under hydrogen (1 atm) for 2 h, when the resulting mixture was purged with nitrogen, filtered through Celite, and evaporated to dryness. The predominately white solid was washed with THF and filtered, and the water-soluble white solid was collected and dried. This solid was further purified by filtering an aqueous solution through a C_{18} silica plug followed by cation exchange chromatography (eluted with 1 N NH_4OH, Dowex 50W-X8) and recrystallization from absolute EtOH, yielding 68 mg (57%) of D-furylglycine as a white solid. ^1H NMR

(12) New compounds that were recalcitrant to analytical purification for microanalyses were converted into their corresponding *N*-CBz amino acid derivatives and ester derivatives and compared to known, literature substances. 5b: Baumgarten, H. E.; Dirks, J. E.; Petersen, J. M.; Zey, R. L. *J. Org. Chem.* **1966**, *31*, 3708 (see also O'Donnel, M. J.; Falmagne, J.-B. *Tetrahedron Lett.* **1985**, *26*, 699). 5c: Reference 5a. 5d: Matsumoto, K.; Suzuki, M.; Miyoshi, M. *J. Org. Chem.* **1973**, *38*, 2094. 5e and 5d: Ben-Ishai, D.; Sataty, I.; Bernstein, Z. *Tetrahedron* **1976**, *32*, 1571.

(270 MHz, D_2O) δ HOD: 7.43 (d, 1 H), 6.45 (d, 1 H), 6.36 (q, 1 H), 4.84 (s, 1 H). ^1H NMR (DMSO-d_6): δ 7.72 (br, s, 1 H), 6.57 (d, 1 H), 6.49 (br d, 1 H), 5.05 (s, 1 H), 1.87 (m, 2 H). IR (NaCl, mineral oil): 3445, 3169, 3015, 2849, 1605, 1513, 1380, 1215, 1159, 759, 667 cm^{-1}. MS: *m/e* (relative intensity) 142 (17.2), 141 (0.5), 125 (1.5), 111 (3.2), 98 (42.3), 96 (100.0), 93 (30.2), 81 (10.9), 69 (2.9), 64 (3.0), 56 (1.3), 54 (1.6), 46 (1.4), 44 (1.6), 39 (4.9), 35 (100.0), 32 (20.2). Mp: 159–161 °C (recrystallization, absolute EtOH). $[\alpha]^{25}_D$: −32.0° (c 0.05, H_2O).[12]

(3*R*,5*R*,6*S*)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-3-(2′-(5′-methylfuryl))-2,3,5,6-tetrahydro-1,4-oxazin-2-one (3e, Ar = 5-Methyl-2-furyl). To a solution of 2 (0.432 g, 1.00 mmol, 1.00 equiv) in CH_3CN (7.00 mL) stirred over powdered molecular sieves (1 g, 4-Å) was added 2-methylfuran (1.35 mL, 15.00 mmol, 15.00 equiv), and zinc chloride (2.00 mL, 2.00 mmol, 2.00 equiv, 1.0 M in THF). The resulting solution was stirred at room temperature for 4 h, and the solution was filtered into water (20 mL). The resulting mixture was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The residue was separated via column chromatography (7:2:1 Hex/$CHCl_3$/EtOAc), yielding 170 mg (39%) of the desired product (3e) as a white solid. ^1H NMR (270 MHz, $CDCl_3$) δ TMS: 7.22–6.98 (m, 7 H), 6.69–6.63 (m, 2 H), 6.44 (d, 1 H), 6.38 (d, 1 H), 6.29–6.25 (m, 1 H), 6.05–6.01 (m, 1 H), 5.35 (d, 1 H), 5.11 (d, 1 H), 2.29 (s, 3 H), 1.38 (s, 4 H), 1.09 (s, 5 H). IR (NaCl, $CHCl_3$): 3058, 3021, 2970, 2909, 1758, 1742, 1685, 1591, 1572, 1489, 1445, 1365, 1268, 1211, 1195, 1170, 1160, 1010, 744, 688, 650, 579 cm^{-1}. MS: *m/e* (relative intensity) 434 (0.5), 430 (1.6), 429 (8.8), 428 (29.5), 395 (10.8), 378 (2.5), 334 (7.5), 289 (14.6), 252 (11.4), 214 (29.7), 197 (100), 105 (65.6), 95 (46.1). Anal. Calcd for $C_{28}H_{27}NO_5$: C, 72.04; H, 6.28; N, 3.23. Found: C, 72.02; H, 6.40; N, 3.13. Mp: 213–215 °C (recrystallization, EtOAc/hexanes). $[\alpha]^{25}_D$: −21.2° (c 1.00, CH_2Cl_2).

(3*R*,5*R*,6*S*)-5,6-Diphenyl-3-(2′-(5′-methylfuryl))-2,3,5,6-tetrahydro-1,4-oxazin-2-one. To a stirred solution of 3e (108 mg, 0.249 mmol, 1.00 equiv) in dry CH_2Cl_2 (2.50 mL) was added trimethylsilyl iodide (85 μL, 0.598 mmol, 2.40 equiv). The resulting orange solution was stirred at room temperature for 10 min, and the reaction was quenched with the addition of water (5 mL). The resulting mixture was separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were washed with 1 M $Na_2S_2O_3$ (2 × 5 mL), dried (Na_2SO_4), filtered, and evaporated. The resulting oil was separated via PTLC silica gel (7:2:1 Hex/$CHCl_3$/EtOAc) yielding 71 mg (86%) of the desired product as an amber oil. ^1H NMR (270 MHz, $CDCl_3$) δ TMS: 7.21–6.87 (m, 10 H), 6.30 (d, 1 H), 5.96 (d, 1 H), 5.69 (d, 1 H), 5.24 (s, 1 H), 4.85 (d, 1 H), 2.27 (s, 3 H), 2.15 (br s, 1 H). IR (NaCl, neat): 3330, 3030, 2920, 1750, 1734, 1491, 1448, 1210, 1200, 1195, 1012, 760, 692, 686 cm^{-1}. MS: *m/e* (relative intensity) 334 (2.5), 333 (0.5), 332 (2.6), 288 (2.9), 214 (47.5), 197 (100.0), 105 (51.9), 95 (2.6), 35 (97.3).

D-α-Amino-5-methyl-2-furanacetic Acid (5e, Ar = 5-Methyl-2-furyl). A stirred supension of (3*R*,5*R*,6*S*)-5,6-diphenyl-3-(2′-(5′-methylfuryl))-2,3,5,6-tetrahydro-1,4-oxazin-2-one obtained above (174 mg, 0.521 mmol, 1.00 equiv) in water (4.50 mL) and 10% hydrochloric acid (1.75 mL) was heated at reflux for 30 min. When most of the organic material went into solution, the mixture was cooled to room temperature and washed with CH_2Cl_2 (3 × 3 mL), and the aqueous layer was evaporated. The resulting white solid was taken up in water (10.60 mL), and sodium periodate (0.245 g, 1.15 mmol, 2.20 equiv) was then added. The pH of the resulting suspension was adjusted to 3 with the dropwise addition of 1 N NaOH. The resulting mixture was stirred at room temperature for 36 h when the pH was adjusted to 5.5 with the dropwise addition of 1 N NaOH and several drops of propylene glycol were added (to destroy excess $NaIO_4$). The resulting solution was stirred at room temperature for 15 min and washed with EtOAc (3 × 5 mL), and the aqueous layer was evaporated, yielding a pure white solid mixture. This white solid mixture was separated via cation exchange chromatography (eluted with 1 N NH_4OH, Dowex 50W-X8), yielding 68.6 mg (85%) of D-α-amino-5-methyl-2-furanacetic acid (5e) as a white solid. (Spectral data is given below.)

D-α-Amino-5-methyl-2-furanacetic Acid (10). To a stirred suspension of 5% palladium on activated cabon (177 mg) in absolute MeOH (75.00 mL) charged with hydrogen was added a solution of (3*R*,5*R*,6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-3-(2′-(5′-methylfuryl))-2,3,5,6-tetrahydro-1,4-oxazin-2-one (9) (798 mg, 1.71 mmol, 1.00 equiv) in dry THF (25.00 mL) via syringe. Compound 9 was prepared via standard and previously reported conditions.[10] The resulting mixture was stirred at room temperature under hydrogen (1 atm) for 5 h, and the resulting mixture was purged with nitrogen, filtered through Celite, and evaporated to dryness. The predominately white solid was washed with THF and filtered, and the water-soluble white solid was collected and dried, yielding 216 mg (82%) of D-α-amino-5-methyl-2-furanacetic acid (10) as a white solid. ^1H NMR (270 MHz, DMSO-d_6) δ DMSO: 7.87 (br s, 1 H), 6.19 (d, 1 H), 6.01 (d, 1 H), 4.20 (s, 1 H), 3.31 (br s, 2 H), 2.22 (s, 3 H). IR (NaCl, mineral oil): 3413, 3178, 2919, 2849, 2625, 2355, 1608, 1501, 1455, 1378, 1108, 1020, 785, 720 cm^{-1}. MS: *m/e* (relative intensity) 156 (2.3), 155 (0.3), 139 (4.8), 125 (15.7), 110 (52.3), 95 (5.5), 83 (1.1), 52 (7.3), 36 (13.7), 35 (100.0), 32 (20.3). Anal. Calcd for $C_7H_9NO_3$: C, 59.19; H, 5.85; N, 9.03. Found: C, 54.31; H, 6.05; N, 9.18. Mp: 161–163 °C (recrystallization, EtOH). $[\alpha]^{25}_D$: −22.3° (c 1.00, H_2O).

General Procedure for CBz Protection of Amino Acids.[12] To a stirred solution of the amino acid (0.100 mmol, 1.00 equiv) in saturated sodium carbonate (0.50 mL) was added benzyl chloroformate (16 μL, 0.110 mmol, 1.10 equiv). The resulting solution was vigorously stirred at room temperature for 30 min to 2 h, and the mixture was thoroughly extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The oily residue could be purified via PTLC or by precipitating with Et_2O followed by recrystallization from CH_2Cl_2.

***N*-(Benzyloxycarbonyl)naphthylglycine.** ^1H NMR (270 MHz, $CDCl_3$) δ TMS: 7.38–7.25 (m, 12 H), 5.26 (s, 2 H), 5.17 (s, 1 H), 1.56 (s, 1 H). IR (NaCl, $CHCl_3$): 3333, 2956, 2889, 1828, 1761, 1500, 1456, 1372, 1289, 1261, 1150, 1067, 928, 756, 700 cm^{-1}.

***N*-(Benzyloxycarbonyl)furylglycine.** ^1H NMR ($CDCl_3$): δ 11.53 (s, 1 H), 7.32 (s, 5 H), 6.33 (d, 2 H), 5.80 (br s, 1 H), 5.29 (d, 1 H), 5.12 (s, 2 H), 1.22 (s, 1 H). IR (NaCl, $CHCl_3$): 3400, 3067, 3033, 2956, 1744, 1700, 1622, 1494, 1456, 1261, 1217, 1167, 1017, 978, 739, 694 cm^{-1}. MS: *m/e* (relative intensity) 276 (21.6), 275 (16.2), 230 (8.3), 211 (2.4), 198 (25.7), 184 (6.1), 168 (10.8), 141 (1.1), 126 (10.4), 106 (100.0), 88 (30.7), 71 (17.8), 52 (13.3).

***N*-(Benzyloxycarbonyl)-5-methyl-2-furylglycine.** ^1H NMR (270 MHz, $CDCl_3$) δ TMS: 7.34 (s, 5 H), 6.20 (d, 1 H), 5.91 (d, 1 H), 5.45 (d, 1 H), 5.12 (s, 2 H), 2.23 (s, 3 H), 1.25 (br s, 1 H). IR (NaCl, neat): 3333, 2956, 2889, 1750, 1722, 1456, 1344, 1322, 1194, 1067, 967, 928, 733, 700 cm^{-1}. MS: *m/e* (relative intensity) 288 (0.3), 146 (5.7), 104 (0.5), 88 (17.2), 71 (22.8), 58 (14.3), 56 (13.1).

General Procedure for the Esterification of Amino Acids.[12] A stirred suspension of the amino acid (0.050 mmol, 1.00 equiv) in a dry MeOH/HCl solution (0.50 mL) was heated until the amino acid completely dissolved. The resulting solution was cooled to 0 °C, and thionyl chloride (11 μL, 0.155 mmol, 3.10 equiv) was added. The resulting solution was stirred at 0 °C for 1 h and then at room temperature overnight. The resulting solution was evaporated, and the residue was washed with THF. **Naphthylglycine methyl ester.** ^1H NMR (270 MHz, D_2O) δ HOD: 7.98 (m, 3 H), 7.50 (m, 4 H), 5.97 (s, 1 H), 3.68 (s, 3 H). IR (NaCl, $CHCl_3$): 3400, 2922, 2856, 1744, 1722, 1589, 1439, 1133, 1106, 1022, 778 cm^{-1}. MS: *m/e* (relative intensity) 216 (0.8), 215 (0.4), 214 (0.8), 200 (2.5), 171 (4.9), 157 (0.9), 153 (4.0), 141 (1.1), 128 (0.5), 102 (37.4), 88 (1.1), 85 (100.0), 74 (0.4), 71 (5.6), 58 (1.6). **Methyl (α-Amino-2,4,6-trimethoxyphenyl)acetate.** ^1H NMR (270 MHz, $CDCl_3$) δ TMS: 6.07 (m, 2 H), 5.05 (s, 1 H), 3.84 (br s, 9 H), 3.63 (s, 3 H), 1.89 (m, 2 H). IR (NaCl, (NaCl, neat): 3333, 2956, 2922, 2844, 1722, 1611, 1456, 1361, 1344, 1189, 1156, 1122, 1067, 1033, 956, 928, 850, 706 cm^{-1}. MS: *m/e* (relative intensity) 255 (1.9), 241 (1.1), 197 (2.1), 169 (2.3), 119 (2.1), 104 (26.1), 88 (98.4), 71 (100.0), 56 (15.1). **Furylglycine methyl ester.** ^1H NMR (270 MHz, D_2O) δ HOD: 7.50 (d, 1 H), 6.59 (d, 1 H), 6.43 (m, 1 H), 5.39 (s, 1 H), 3.74 (s, 3 H). IR (NaCl, $CHCl_3$): 3411, 2922, 2850, 1743, 1500, 1247, 1154, 926 cm^{-1}.

General Procedure for the Generation of a Mosher (MTPA) Amide.[13] To a stirred suspension of the amino acid

(13) The % ee's determined for each final amino acid was determined by examination of the ^{19}F NMR of the derived MTPA-amides. Authentic racemic amino acids were synthesized and derivatized in like manner to provide the diastereomeric reference signals of the CF_3 groups.

(0.13 mmol, 1.00 equiv) in dry THF (1.00 mL) was added Mosher's chloride (10 μL, 0.13 mmol, 1.00 equiv) and propylene oxide (31 μL, 0.52 mmol, 4.00 equiv). The resulting suspension was heated at reflux for 20 min, when the resulting solution was allowed to cool to room temperature. The solution was filtered and thoroughly evaporated yielding the desired Mosher's amide, usually as a white solid. The % ee's of each amino acid (5) were determined by an examination of the ^{19}F NMR spectra of their respective MTPA amides.

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A New Synthetic Approach to 1-(Hydroxymethyl)-8-methoxy-1,2,3,4-tetrahydroisoquinolin-4-one

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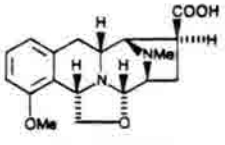
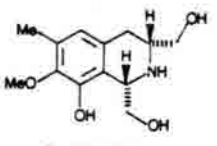
The tetrahydroisoquinoline moiety occurs as the structural nucleus of a wide variety of naturally occurring alkaloids.[1] As a result, numerous methods[2] have been developed and employed in the construction of natural alkaloids constituted of this ring system. Perhaps the most widely used synthetic construction is the classic Pictet–Spengler isoquinoline synthesis,[1] which involves the condensation of β-arylethylamines and carbonyl compounds. Cyclization occurs via the intermediacy of the putative Schiff base, furnishing the tetrahydroisoquinoline. The related Bischler–Napieralski reaction furnishes the corresponding 3,4-dihydroisoquinolines through an electronically similar electrophilic aromatic substitution. In both instances, rate-accelerating electron-releasing substituents generally induce cyclization to occur (ortho/para) at the less hindered (para) position to a significant extent. In the case of a *m*-methoxy-substituted β-arylamine, cyclization occurs to give the 6-methoxy regioisomer as the major and, often times, exclusive product.[1]

As part of a program to construct and study the rare tetrahydroisoquinoline antitumor alkaloid quinocarcin (DC-52, 1)[3] and the β-adrenergic receptor antagonist MY



1, quinocarcin



2, MY 336-a

336-a,[4] we needed a reliable and unambiguous synthetic protocol that would embrace the 8-oxygenated 1,2,3,4-tetrahydroisoquinoline nucleus.[5] Our approach is related to the classic Pomeranz–Fritsch reactions, wherein an appropriately substituted benzylic amine serves as the template for the penultimate C-4a/C-4 bond construction.[6]

2-Bromoanisole is lithiated (*n*-BuLi, THF) and condensed with the *N*-methoxy-*N*-methylamide[7] of (benzyloxy)acetic acid[8] (4) to furnish the ketone 5 in 90% yield (Scheme I). This coupling proved to be significantly superior to condensations of 3 with (benzyloxy)acetyl chloride,[8] the corresponding tertiary alcohol resulting from further reaction of 5 and 3 being the predominant product. However, preparatively useful quantities of 5 could also be obtained by coupling (benzyloxy)acetyl chloride and 3 in the presence of $CdCl_2$.[9]

Reductive amination of the ketone using the Borch[10] procedure (65%) followed by hydrogenolytic removal of the benzyl ether furnished the amino alcohol 7 (81%). Alkylation of the amine with ethyl bromoacetate (8; 95%) and formation of the cyclic urethane furnished the ethyl ester 9 (77%). Selective basic hydrolysis of the ethyl ester furnished the crystalline acid (75%; mp 165–166 °C), which was converted to the acid chloride with thionyl chloride. The crucial intramolecular Friedel–Crafts acylation proved to be extremely difficult and required extensive experimentation. Low yields (<10%) were obtained under classical conditions (hot CS_2, $AlCl_3$), but eventually the conditions reported by Uggeri[11] ($AlCl_3$, $Cl_2CH_2CH_2Cl_2$, 25

† Fellow of the Alfred P. Sloan Foundation 1986–1988. NIH Research Career Development Awardee 1984–1989. Eli Lilly Grantee 1986–1988.

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(2) Miscellaneous approaches: (a) Venkov, A. P.; Mollov, N. M. *Synthesis* 1982, 216. (b) Danishefsky, S.; Berman, E. *Tetrahedron Lett.* 1980, *21*, 4819. (c) Kano, S.; Yuasa, Y.; Shibuya, S. *Heterocycles* 1984, *22*, 2327. (d) Liu, J.-M.; Young, J.-J.; Li, Y.-J.; Sha, C.-K. *J. Org. Chem.* 1986, *51*, 1120. (e) Otomasu, H.; Higashiyama, K.; Honda, T.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* 1982, 2399. (f) Mendelson, W. L.; Spainhour, C. B.; Jones, S. S.; Lam, B. L.; Wert, K. L. *Tetrahedron Lett.* 1980, *21*, 1393. (g) Deady, L. W.; Pirzada, N.; Topsom, R. D. *J. Chem. Soc. D* 1971, 799. (h) Tamura, Y.; Uenishi, J.; Maeda, H.; Choi, H.; Iahibashi, H. *Synthesis* 1981, 534.

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(5) An approach from isoquinoline involving selective electrophilic aromatic substitution has been reported: Rey, M.; Vergnani, T.; Dreiding, A. S. *Helv. Chim. Acta* 1985, *68*, 1828.

(6) A completely different approach to this ring system that adequately (though not completely) addresses the 1,2,3-substitution pattern in this 8-methoxytetrahydroisoquinoline ring system has been reported: Danishefsky, S.; Harrison, P. J.; Webb, R. R.; O'Neill, B. T. *J. Am. Chem. Soc.* 1985, *107*, 1421 and references cited therein.

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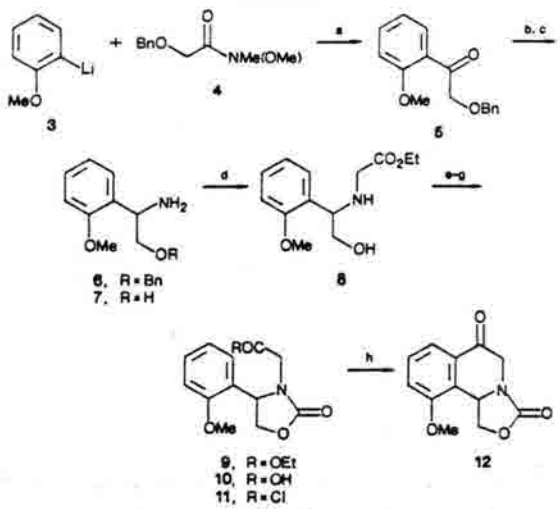
0022-3263/87/1952-2615$01.50/0

Scheme I[a]



[a] Reagents and conditions: (a) −15 °C, THF, 30 min, 5% HCl/EtOH, 90%; (b) $AcO^-N^+H_4$, $NaBH_3CN$, MeOH, 36 h, 65%; (c) 10% Pd/C, 0.5 M HCl/EtOH, 50 psi, 20 h, 81% (d) $BrCH_2CO_2Et$, Et_3N, THF, 20 h, 95%; (e) Im_2CO, THF, 2 h, 77%; (f) 1.0 M LiOH, EtOH, 1.5 h, 75%; (g) $SOCl_2$, C_6H_6, 80 °C, 3 h, 100%; (h) $AlCl_3$, $Cl_2HCCHCl_2$, 24 h, 65%.

°C; 65% yield) proved satisfactory to furnish the crystalline 1,2,3,4-tetrahydroisoquinoline **12**.

In a parallel series of experiments, the acid chloride corresponding to **11** prepared from phenylglycinol did *not* react intramolecularly to furnish the homologous tetrahydroisoquinoline. Instead, only *intermolecular* acylation products resulting from solvent incorporation or dimerization were obtained. Indeed, it seems that some electronic activation of the aromatic ring is required to effect closure in the modified Pomeranz–Fritsch approach.[12]

Experimental Section

(Benzyloxy)methyl 2-Methoxyphenyl Ketone (5). To a stirred solution of *o*-bromoanisole (1.28 mL, 10.0 mmol, 1.0 equiv) in dry pentane (15 mL) was added a 1.60 M solution of *n*-butyllithium in hexanes (6.25 mL, 10.0 mmol, 1.0 equiv) at room temperature in a nitrogen atmosphere. After 30 min, the solvent was removed in vacuo, and freshly distilled benzene (15 mL) was added immediately, followed by the addition of cadmium chloride (0.916 g, 5.0 mmol, 1.0 equiv) at room temperature. The resulting vigorously stirred suspension was heated to reflux in a nitrogen atmosphere for 6.5 h, at which time the mixture gave a negative Gilman's test. The mixture was allowed to cool to room temperature, (benzyloxy)acetyl chloride (1.845 g, 10.0 mmol, 1.0 equiv) was added, and the mixture was heated to reflux in a nitrogen atmosphere. After 2 h, the vigorously stirred mixture was cooled to room temperature, added to an equal volume of 10% HCl solution, and stirred for at least 30 min. The mixture was then separated, and the aqueous layer was washed with ether. The combined organic layers were then washed with 5% $NaHCO_3$ followed by saturated NaCl, dried over $MgSO_4$, concentrated, and separated by silica gel (eluted with 2.5% EtOAc/benzene) to afford 0.994 g (39%) of **5** as a yellow oil: ^1H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 3.87 (3 H, s), 4.68 (2 H, s), 4.72 (2 H, s), 6.93 (2 H, m), 7.39 (6 H, m), 7.89 (1 H, dd, J = 7.73 Hz); IR (NaCl, neat) 3024, 2938, 1685, 1240, 1104 cm^{-1}.

(Note: The same procedure carried out with CdI_2 gave a 25% yield, and the same procedure carried out with the aryl Grignard reagent with $CdCl_2$ gave a 20% yield.)

***N*-Methoxy-*N*-methyl-2-(benzyloxy)acetamide (4).** To a stirred solution of (benzyloxy)acetyl chloride (3.226 g, 17.54 mmol, 1.0 equiv) and methoxymethylamine hydrochloride (1.93 g, 19.29 mmol, 1.1 equiv) in dry $CHCl_3$ (175 mL) cooled to 0 °C was added pyridine (3.12 mL, 38.58 mmol, 2.2 equiv). The resulting solution was stirred at room temperature for 12 h, when the $CHCl_3$ was evaporated, yielding a white residue. The residue was partitioned between brine and a 1:1 mixture of CH_2Cl_2/Et_2O. The organic layer was separated, dried over Na_2SO_4, filtered, and evaporated, yielding **4** (3.64 g, 99.5%) as a colorless oil: bp 132 °C (0.2 mmHg); ^1H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 3.19 (3 H, s), 3.63 (3 H, s), 4.29 (2 H, s), 4.67 (2 H, s), 7.36 (5 H, m); IR (NaCl, neat) 3020, 3060, 2940, 1675, 1450, 1325, 1130, 1080, 980, 730, 690 cm^{-1}; mass spectrum, CI (NH_3) m/z 209.8 (M^+, 0.7%), 197 (3.1), 180 (9.0), 108 (5.8), 106 (10.4), 91 (2.4), 74 (5.9), 44 (4.5), 35 (100).

(Benzyloxy)methyl 2-Methoxyphenyl Ketone (5). To a stirred solution of *o*-bromoanisole (4.56 mL, 36.68 mmol, 3.0 equiv) in dry THF (12.5 mL) cooled to −15 °C was added *n*-BuLi (23.7 mL of a 1.54 M solution in hexanes, 3.0 equiv). The resulting solution was allowed to stir for 1 h at −15 °C, when it was added to a solution of **4** (2.55 g, 12.23 mmol, 1.0 equiv) in dry THF (125 mL), cooled to −15 °C, via cannula. The resulting solution was stirred for 30 min and poured into 50 mL of 5% HCl/EtOH at 0 °C. This solution was then partitioned between brine and a 1:1 mixture of CH_2Cl_2/Et_2O. The organic layer was separated, dried over Na_2SO_4, filtered, and evaporated, yielding **5** as a colorless oil (2.82 g, 90%): ^1H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 3.87 (3 H, s), 4.68 (2 H, s), 4.72 (2 H, s), 6.93 (2 H, m), 7.39 (6 H, m), 7.89 (1 H, dd, J = 7.73 Hz); IR (NaCl, neat) 3020, 3060, 2930, 1680, 1595, 1480, 1280, 1235, 1100, 1010, 940, 740, 685 cm^{-1}; mass spectrum, CI (NH_3) m/z 257 (M^+, 14.5%), 151 (100), 135 (6.6), 106 (6.0), 91 (2.4), 35 (100).

***O*-Benzyl(2-methoxyphenyl)glycinol (6).** To a stirred solution of **5** (2.82 g, 11.029 mmol, 1.0 equiv) and ammonium acetate (8.50 g, 110.3 mmol, 10 equiv) in absolute methanol (35 mL) was added sodium cyanoborohydride (0.485 g, 7.72 mmol, 0.70 equiv) in one portion. The resulting solution was stirred at room temperature for 36 h. Concentrated HCl was added until pH <2. The MeOH was then evaporated, and the resulting white residue was dissolved in H_2O (10 mL) and washed with Et_2O (2 × 10 mL). The aqueous phase was then basified with powdered KOH to pH >10, saturated with NaCl, and extracted with CH_2Cl_2 (4 × 10 mL). The combined CH_2Cl_2 extracts were dried over $MgSO_4$, filtered, and evaporated to a colorless oil (1.832 g, 65%): ^1H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 1.82 (2 H, br s), 3.45 (1 H, t, J = 8.52 Hz), 3.69 (1 H, dd, J = 9.24 Hz), 3.79 (3 H, s), 4.56 (3 H, m), 6.92 (2 H, m), 7.32 (7 H, m); IR (NaCl, neat) 3380, 3300, 3020, 3060, 2900, 2840, 1580, 1485, 1450, 1230, 1080, 1115, 850, 735, 680 cm^{-1}; mass spectrum, CI (NH_3) m/z 258 (M^+, 100), 256 (210), 241 (2.5), 228 (1.8), 150 (19.2), 136 (38.5), 106 (19.5), 91 (6.8), 35 (100).

(2-Methoxyphenyl)glycinol (7). To a solution of **6** (2.885 g, 11.21 mmol, 1.0 equiv) in 60 mL of 0.5 M HCl/EtOH contained in a Parr pressure vessel was added 10% Pd/C (2.98 g, 2.8 mmol, 0.25 equiv). The vessel was purged with hydrogen several times, charged to 50 psi, and hydrogenated for 20 h. The Pd/C was filtered off over Celite and the filtrate evaporated to a white solid. The solid was dissolved in water and washed once with Et_2O, basified to pH >10 with solid KOH, saturated with NaCl, and extracted with CH_2Cl_2 (4 × 20 mL). The organic phase was then dried over $MgSO_4$, filtered, and evaporated, yielding **7** (1.52 g, 81%) as a colorless oil: ^1H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 2.57 (3 H, br s), 3.59 (1 H, m), 3.73 (1 H, m), 3.81 (3 H, s), 4.27 (1 H, m), 6.68 (1 H, d, J = 8.24 Hz), 6.91 (1 H, m), 7.23 (2 H, m); IR (NaCl, neat) 3360, 3280, 2920, 2830, 1590, 1490, 1235, 1140, 1120, 740 cm^{-1}; mass spectrum, CI (NH_3) m/z 168 (M^+, 5.8%), 151 (10.9), 136 (23.6), 44 (6.0), 35 (100).

***N*-(Carboxymethyl)(2-methoxyphenyl)glycinol (8).** To a stirred solution of **7** (1.16 g, 6.935 mmol, 1.0 equiv) and triethylamine (1.45 mL, 10.437 mmol, 1.5 equiv) in dry THF (60 mL) was added ethyl bromoacetate (1.00 mL, 9.04 mmol, 1.3 equiv). The reaction solution was stirred at room temperature for 20 h. The Et_3N·HBr was filtered off and washed with THF. The filtrate was evaporated to a clear residue, which was taken up in 70 mL of CH_2Cl_2, washed with H_2O (3 × 20 mL) and brine (1 × 20 mL), dried over $MgSO_4$, filtered, and evaporated to yield

(11) Ugeri, F.; Giordano, C.; Brambilla, A. *J. Org. Chem.* **1986**, *51*, 97.
(12) Some notable exceptions are included in ref 2f–h; see also ref 6.

8 (1.665 g, 95%) as a colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 1.23 (3 H, t, J = 7.45 Hz), 2.50 (2 H, br s), 3.35 (2 H, d, J = 5.43 Hz), 3.70 (2 H, m), 3.82 (3 H, s), 4.13 (3 H, m), 6.92 (2 H, m), 7.28 (2 H, m); IR (NaCl, neat) 3310, 2910, 1735, 1595, 1485, 1455, 1230, 1180, 1020, 740 cm^{-1}; mass spectrum, CI (NH_3) m/z 254 (M^+, 1.9), 236 (1.8), 208 (18.9), 168 (2.5), 150 (6.7), 130 (61.1), 104 (11.3), 72 (7.2), 55 (100).

Cyclic Urethane 9. To a stirred solution of 8 (1.665 g, 6.59 mmol, 1.0 equiv) in dry THF (60 mL) was added *N,N'*-carbonyldiimidazole (1.60 g, 9.87 mmol, 1.5 equiv). The resulting solution was stirred at room temperature for 2 h and evaporated to a white residue. The residue was taken up in CH_2Cl_2 (100 mL), washed with 1 M HCl (3 × 25 mL), H_2O (2 × 25 mL), and brine (1 × 25 mL), dried over $MgSO_4$, filtered, and evaporated, yielding 9 as a colorless oil (1.41 g, 77%): ^{1}H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 1.25 (3 H, t, J = 7.03 Hz), 3.43 (1 H, d, J = 17.96 Hz), 3.82 (3 H, s), 4.16 (3 H, m), 4.34 (1 H, d, J = 17.98 Hz), 4.72 (1 H, t, J = 8.67 Hz), 5.35 (1 H, m), 6.97 (2 H, m), 7.27 (2 H, m); IR (NaCl, neat) 2960, 2920, 2820, 1750, 1600, 1580, 1485, 1460, 1415, 1240, 1195, 1080, 1115, 745 cm^{-1}. Mass spectrum, CI (NH_3) m/z 280 (M^+, 54.9%), 250 (3.1), 235 (1.2), 220 (1.4), 162 (1.8), 148 (1.7), 133 (2.0), 104 (1.7), 35 (100).

Carboxylic Acid 10. To a stirred solution of 9 (1.41 g, 5.059 mmol, 1.0 equiv) in 16 mL of absolute ethanol at −10 °C was added 6.7 mL of 1 M LiOH (6.7 mmol, 1.32 equiv). The reaction was allowed to stir for 1.5 h at −10 °C and was then neutralized with 6 M HCl (1.11 mL, 6.7 mmol, 1.32 equiv). The ethanol was evaporated, and the resulting residue was partitioned between 1 M HCl and CH_2Cl_2. The organic layer was separated, washed with H_2O (1 × 10 mL) and brine (1 × 10 mL), dried over $MgSO_4$, filtered, and evaporated to a white solid. Recrystallization from EtOAc/hexanes afforded 957 mg of pure 10 (75%): mp 165–166 °C; ^{1}H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 3.48 (1 H, d, J = 18.25 Hz), 3.83 (3 H, s), 4.19 (1 H, t, J = 8.02 Hz), 4.39 (1 H, d, J = 18.438 Hz), 4.73 (1 H, t, J = 9.174 Hz), 5.36 (1 H, m), 6.95 (2 H, m), 7.36 (2 H, m), 8.52 (1 H, br s); IR (NaCl, neat) 2900, 2810, 2700, 2585, 2500, 1750, 1675, 1595, 1580, 1450, 1240, 1200, 1190, 1110, 940, 850, 750, 735, 700, 630 cm^{-1}; mass spectrum, CI (NH_3) m/z 251 (M^+, 13.8%), 236 (3.5), 208 (7.9), 194 (6.6), 164 (2.5), 150 (5.5), 135 (4.1), 102 (3.7), 76 (3.2), 44 (8.1), 35 (100). Anal. ($C_{12}H_{13}NO_5$) C, H, N.

Acid Chloride 11. To a suspension of 10 (408 mg, 1.626 mmol, 1.0 equiv) in dry benzene (8 mL) was added $SOCl_2$ (0.36 mL, 4.91 mmol, 3.02 equiv). The suspension was then heated to mild reflux for 3 h, and the benzene and $SOCl_2$ were evaporated under reduced pressure. The resulting light amber residue (438 mg, 100%) was used directly for the next step without purification: ^{1}H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 3.78 ($^1/_2$ H, s), 3.84 (3.5 H, s), 4.25 (1 H, dd, J = 8.63 Hz), 4.73 (2 H, m), 5.32 (1 H, dd, J = 9.02 Hz), 6.97 (2 H, m), 7.27 (2 H, m); IR (NaCl, neat) 3060, 3020, 2940, 2830, 1800, 1760, 1600, 1590, 1490, 1460, 1420, 1250, 1180, 1110, 1090, 1020, 950, 920, 850, 750, 670 cm^{-1}.

Isoquinolone 12. To a stirred solution of 11 (438 mg, 1.626 mmol, 1.0 equiv) in 16 mL of dry 1,1,2,2-tetrachloroethane was added $AlCl_3$ (867 mg, 6.5 mmol, 4.0 equiv). The reaction was stirred at room temperature for 24 h, when it was poured into 40 mL of ice water and acidified to pH <2 with concentrated HCl. The resulting slurry was extracted with CH_2Cl_2 (4 × 20 mL), and the combined organic extracts were washed with 1 M NaOH (1 × 10 mL) and brine (1 × 10 mL), dried over $MgSO_4$, filtered, and evaporated to an oil, which was separated by column chromatography (silica gel, 3:2 hexanes/EtOAc), yielding 12: 246 mg, 65%; mp 157–159 °C dec (recrystallized from EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 3.83 ($^1/_2$ H, s), 3.91 (3.5 H, s), 4.25 (1 H, t, J = 8.54 Hz), 4.67 (1 H, d, J = 18.15 Hz), 5.03 (1 H, t, J = 8.94 Hz), 5.23 (1 H, t, J = 8.61 Hz), 7.16 (1 H, dd, J = 8.28 Hz), 7.46 (1 H, t, J = 8.41 Hz), 7.73 (1 H, dd, J = 8.14 Hz); IR (NaCl, neat) 3080, 3020, 2940, 2870, 1765, 1695, 1595, 1580, 1430, 1280, 1250, 1120, 1030, 785, 740, 670 cm^{-1}; mass spectrum, CI (NH_3) m/z 233 (M^+, 16.9%), 219 (7.9), 189 (2.1), 174 (7.4), 159 (2.8), 132 (1.3), 35 (100). Anal. ($C_{12}H_{11}NO_4$) C, H, N.

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