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4-ALKYNOIC ACIDS IN THE SYNTHESIS OF BIOLOGICALLY IMPORTANT TETRAPYRROLES*

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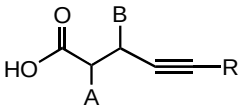
Abstract – In this review an account is given of the author's use of 4-alkynoic acid derivatives in the synthesis of members of the chlorin, bacteriochlorin and corrin classes of macrocyclic tetrapyrroles. In the case of chlorins, we employed a novel "2+2" condensation to prepare both C,D-symmetric and non-symmetric chlorins, made possible by the ready availability of semicorrins of type **25** derived from 4-alkynoic acids **1**. Alkyne acids **1** also played a prominent role in a new 16π-electrocyclization route to bacteriochlorins, and in iterative syntheses of semicorrins and secocorrins related to vitamin B_{12}. Mechanistic studies provided insight into the nature of these Pd(0)-catalyzed coupling/cyclization reactions. Finally, we describe enantioselective syntheses of ring-C and ring-D alkyne acids for an ongoing synthesis of cobyric acid.

CONTENTS

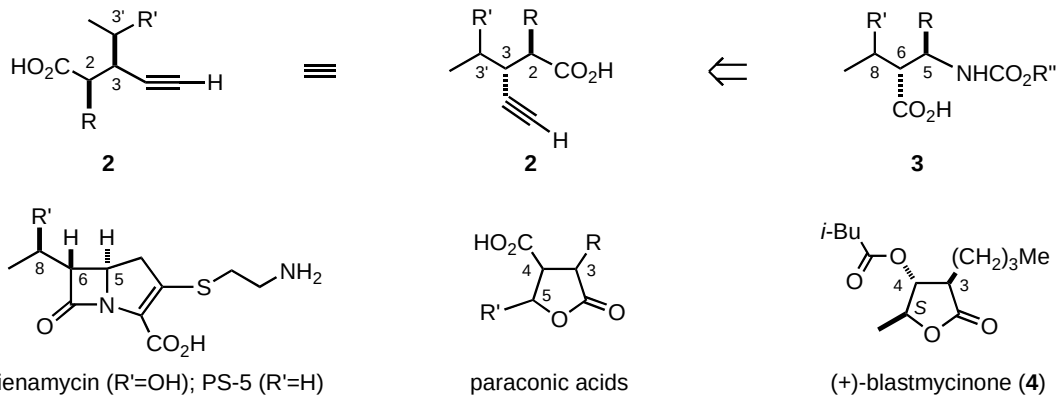
1. INTRODUCTION

For some time we have been exploring the synthetic utility of 4-alkynoic acid derivatives of general structure **1**, which are versatile intermediates for the synthesis of diverse naturally occurring heterocycles. Much of their versatility stems from their ready accessibility, as well as the breadth of reactivity exhibited by the carbon-carbon triple bond.



1 (R = H, alkyl, aryl)

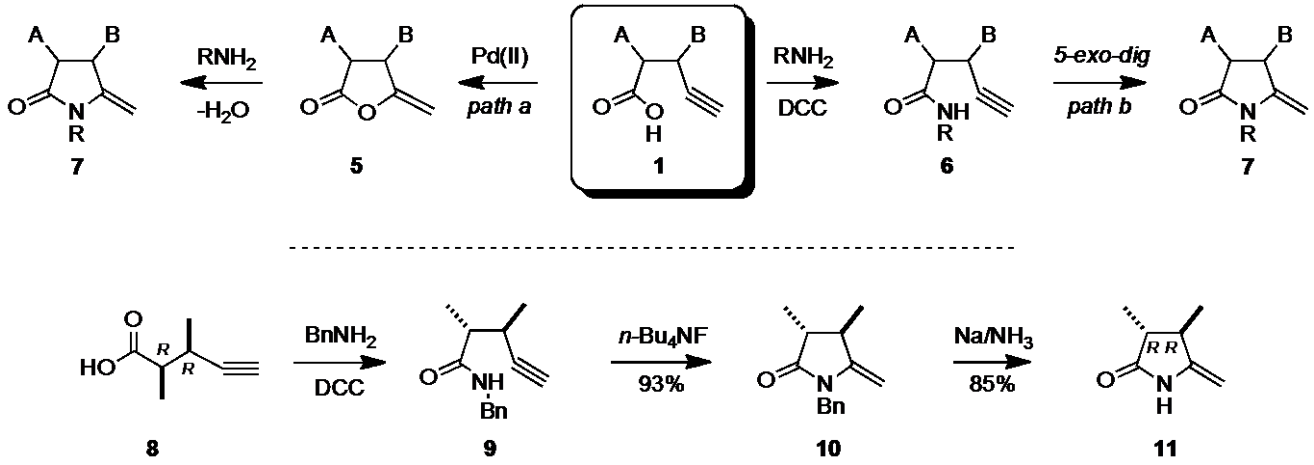
In one mode of reactivity the alkyne bond in **1** is an excellent surrogate for a strategically placed carboxyl or ketone functionality. For example, Curtius rearrangement of acids **2**, followed by oxidative cleavage, led smoothly to β-amino acid derivatives **3**,[1] which were employed in formal total syntheses of β-lactam antibiotics of the carbapenem class (Scheme 1). Similarly derived were members of the paraconic



Scheme 1

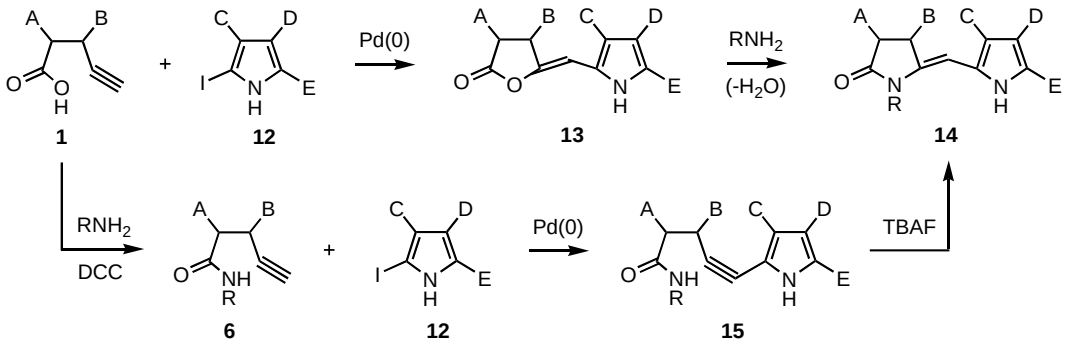
acid family of anti-fungal antibiotics,[2] as well as the novel hydroxylactone derivative (+)-blastmycinone (**4**).[3]

In a second mode, acids **1** are also efficient precursors to a wide range of monocyclic enelactams **7** of the type found in naturally occurring tetrapyrroles (Scheme 2).[4a] This transformation can be accomplished in either of two ways, involving (1) preliminary cyclization of **1** to the corresponding enelactone **5** followed by aminolysis (*path a*); or (2) amidation to **6** followed by 5-*exo-dig* ring closure (*path b*). This last pathway is exemplified by the high yield conversion of homochiral acid **8**, via amide **9**, to enantiomerically pure enelactam **10**, for which we found that *n*-Bu_4NF (TBAF) is a particularly effective catalyst.[4b]



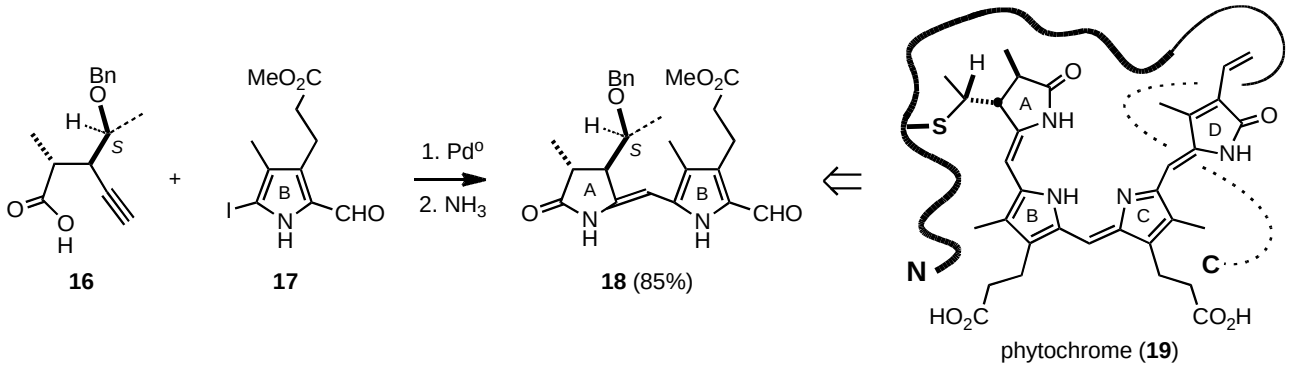
Scheme 2

Finally, and most pertinent to the current topic, both alkyne acids **1** and amides **6** are excellent substrates for Sonogashira coupling, undergoing clean reaction with a variety of iodopyrroles and imidoyl triflates/chlorides. In the case of **1**, Pd(0)-catalyzed coupling is invariably accompanied by enelactone cyclization, as illustrated for the general reaction of **1** with iodopyrrole **12** to yield **13** (Scheme 3). Aminolysis then provides the corresponding enelactams **14**. Alternatively, the same products are obtained on initial coupling of **12** with alkyne amides **6**, followed by TBAF-mediated cyclization.



Scheme 3

This last methodology was highlighted in a recent paper detailing the synthesis of the linear tetrapyrrole derivative phytochrome (**19**),[5] a key step of which involved Pd(0)-catalyzed coupling/cyclization of homochiral 4-pentynoic acid **16** with iodopyrrole **17**, followed by aminolysis (Scheme 4). After further elaboration, **18** was joined with a similarly derived C,D-ring pyrromethenone to complete the tetrapyrrole skeleton.



Scheme 4

In the present review we describe our efforts at extending this chemistry to the synthesis of macrocyclic tetrapyrroles of the chlorin, bacteriochlorin and corrin families (Figure 1), each of which presents their own set of challenges.

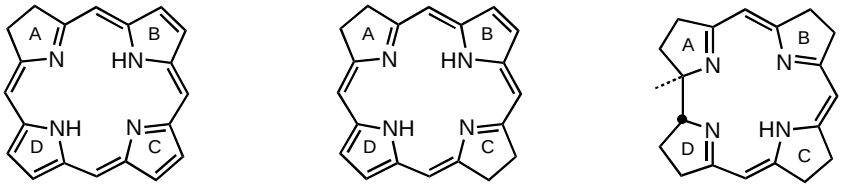


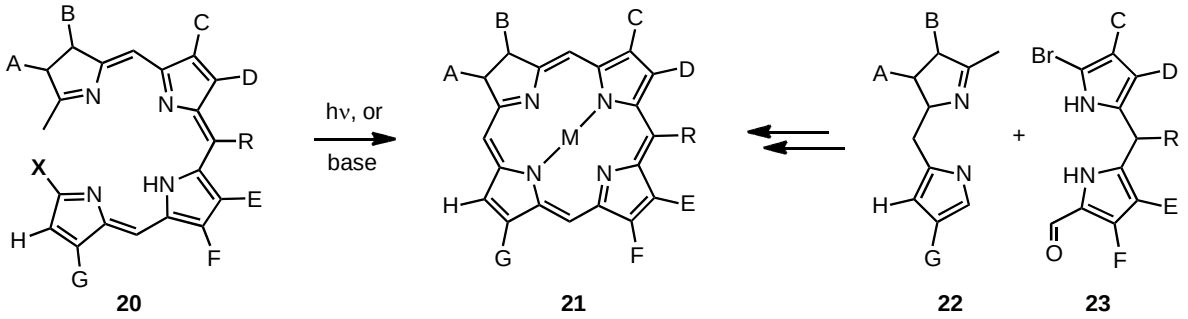
Figure 1

2. RESULTS AND DISCUSSION

I. Toward a General Synthesis of Chlorins.

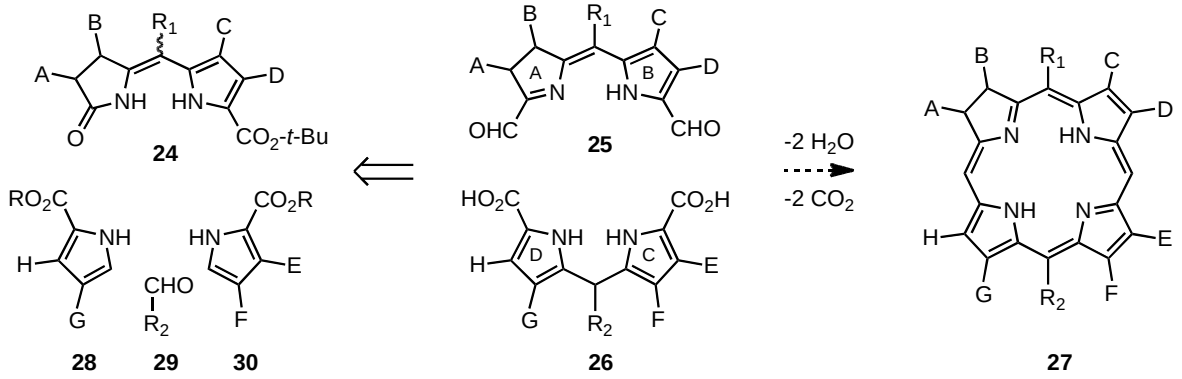
I. 1 Background. Most *de novo* syntheses of chlorins **21** are modeled on the methodology of Battersby[6a] and Montforts,[6b] involving either photochemical or alkali induced ring closure of properly substituted linear tetrapyrroles **20** (Scheme 5; X = OMe, Br, etc.).[7] Tetrapyrroles **20** are derived from simpler ring systems employing techniques such as sulfide contraction,[6b,8] thio-Wittig reaction,[9] and reductive cyclization of pyrrole-substituted nitroketones.[10] While elegant in concept, the cyclization of **20** to **21** can be problematic and is typically carried out on small scales, employing metal templates, and affording **21** in modest-good yields.[6,8] In a noteworthy variant of this approach, Lindsey *et al.* have shown that condensation of fragments **22** and **23**, followed by oxidative cyclization employing Zn as a

template, provides Zn-chlorins **21** in up to 45% yields.[11] As in the Battersby/Montforts strategies, though, a limiting factor in this approach is the availability of precursors of type **22** and **23**, in particular with respect to synthesizing more highly substituted derivatives. Finally, while numerous other strategies for synthesizing chlorins have been devised, a general approach remains elusive.[7]



Scheme 5

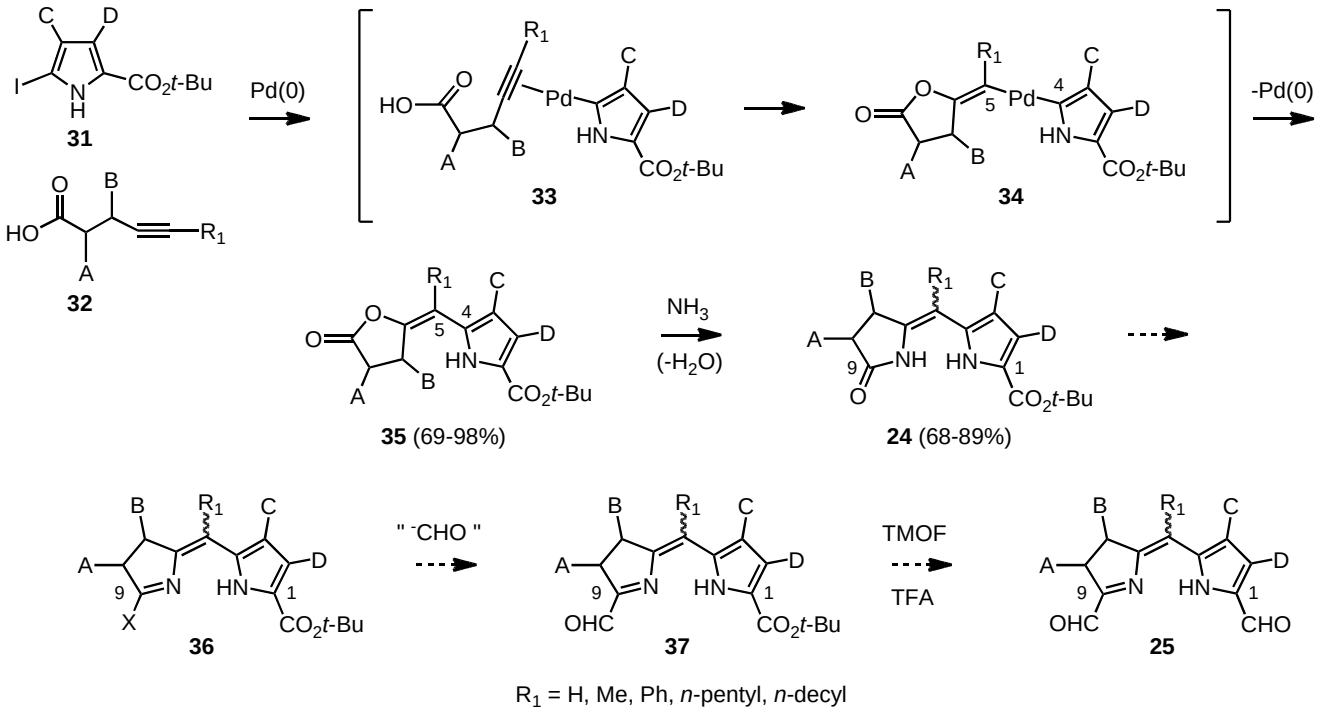
One means of addressing these issues would employ a "2+2" condensation of dihydrodipyrrins **25** with dipyrromethanes **26** (Scheme 6).[12] The precursors **25** and **26** are in the proper oxidation state for direct condensation to afford chlorins **27**, and macrocycle formation should be facile. Surprisingly however, this approach to chlorins had not been previously described, most likely due to difficulties in preparing A,B-ring diformyl derivatives of type **25**. We set out to synthesize **25** from enelactams **24**, themselves derived by aminolysis of the corresponding enelactones. The preparation of dipyrromethanes of type **26** was known to be straightforward (at least for the symmetrical case).[11d,13]



Scheme 6

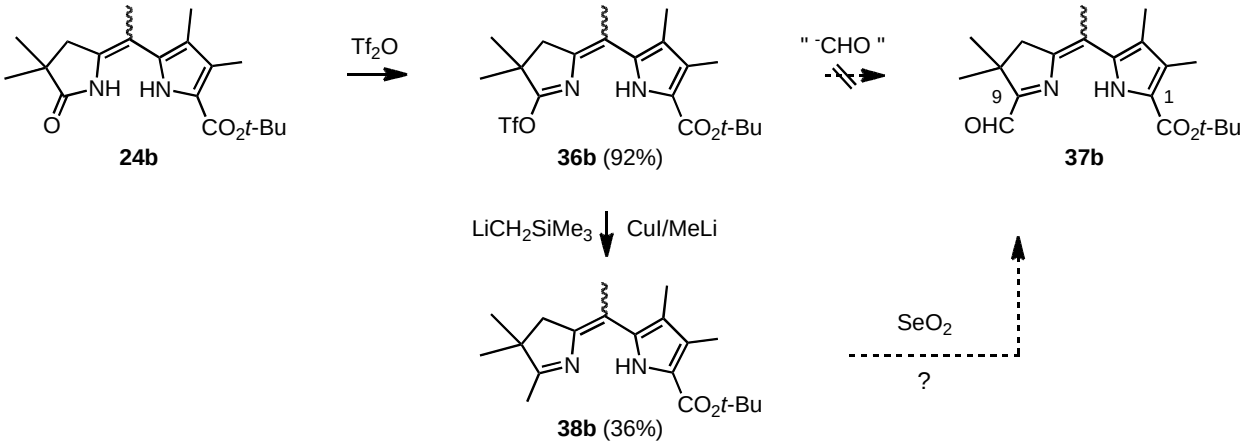
I. 2 Synthesis of the Key Dihydrodipyrrins 25. ***Method A.*** The requisite enelactones **35** were synthesized in good-excellent yield by Pd(0)-catalyzed coupling/cyclization between iodopyrroles **31** and alkyne acids **32**, the latter either known from the literature or prepared in straightforward fashion (Scheme 7).[14] The mechanism for this reaction, which is distinct from the Sonogashira protocol, presumably

involves oxidative addition of Pd(0) to **31**, followed by π-complexation and nucleophilic capture to give the vinyl Pd(II) species **34**. Reductive elimination then provides the thermodynamic driving force for bonding the sterically crowded C4 and C5 positions. As required by this mechanism, enelactones **35** are obtained exclusively as the *E*-isomers under kinetic control. Once in hand, aminolysis of **35** gave high yields of the corresponding enelactams **24** as mixtures of *E*- and *Z*-isomers, dependent on the size of R_1. We planned to build on **24** by substituting CHO groups at C1 and C9 (dihydrodipyrrin numbering). In principle the C9 formyl group could be introduced by initial conversion to activated imidoyl derivatives of type **36**, followed by displacement with a "formyl anion" equivalent. Decarboxylative formylation at C1 in **37** would then give the desired **25** (TMOF = trimethyl orthoformate).



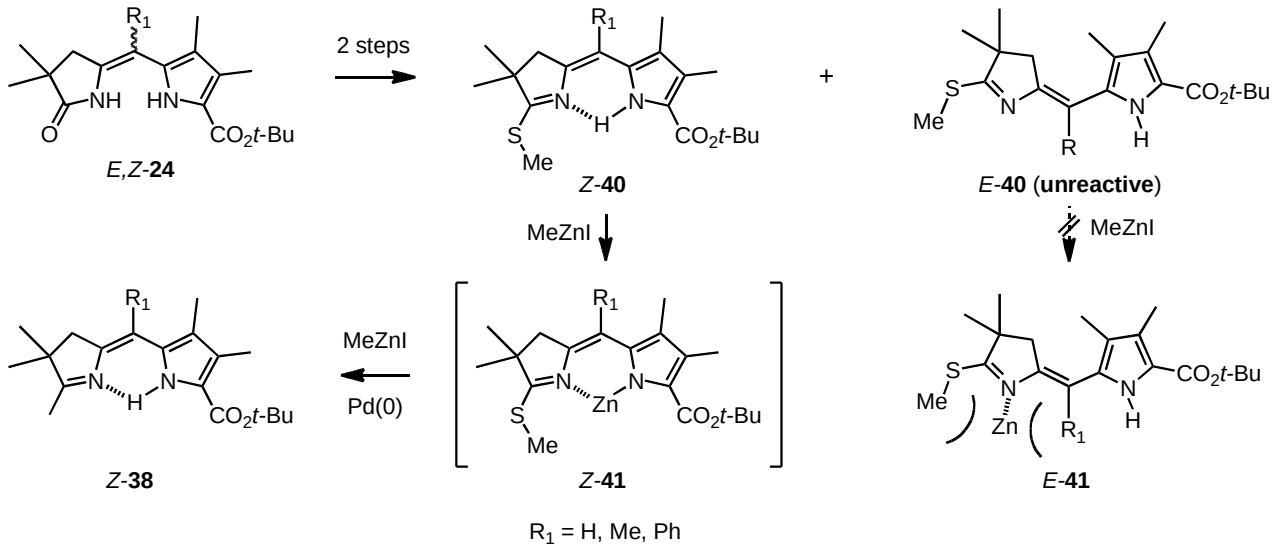
Scheme 7

To evaluate this route, our initial studies were carried out with enelactam **24b**, which gave a 92% yield of imidoyl triflate **36b** with Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine (Scheme 8).[14d] Surprisingly, though, triflate **36b** was relatively unreactive toward nucleophilic displacement, returning mainly starting material with various "formyl anion" equivalents. We also investigated several Pd(0)-catalyzed formylations, all without success. Ultimately, only the Bertz reagent gave even modest yields of displacement products, affording 36% of the methyl substitution product **38b**.[15] We believed that **38b** might be converted to the desired **37b** by SeO_2 oxidation. However, we were unable to isolate sufficient quantities of **38b** by this route to test this idea.



Scheme 8

Better results were obtained with the thioimidate derivatives **40** (*E,Z*-mixtures), which were obtained in 70-75% overall yield from lactams **24** by sulfonation with Lawesson's reagent followed by S-methylation (Scheme 9). We intended to convert both isomers of **40** to the corresponding dihydro- dipyrrins **38** by transition metal-catalyzed methylation, modeled on the elegant methodology of Liebeskind[16b,c] and Fukuyama.[16a] In practice this transformation worked well with *Z*-thioimidates *Z*-**40** employing the reagent system Pd(0)/MeZnI.[16d] Surprisingly, however, the corresponding *E*-thioimidates *E*-**40** were unreactive toward methylation using Pd(0)/MeZnI and most other commonly employed cross-coupling techniques (trace quantities of *E*-**38** were produced with Ni(II) catalysts).

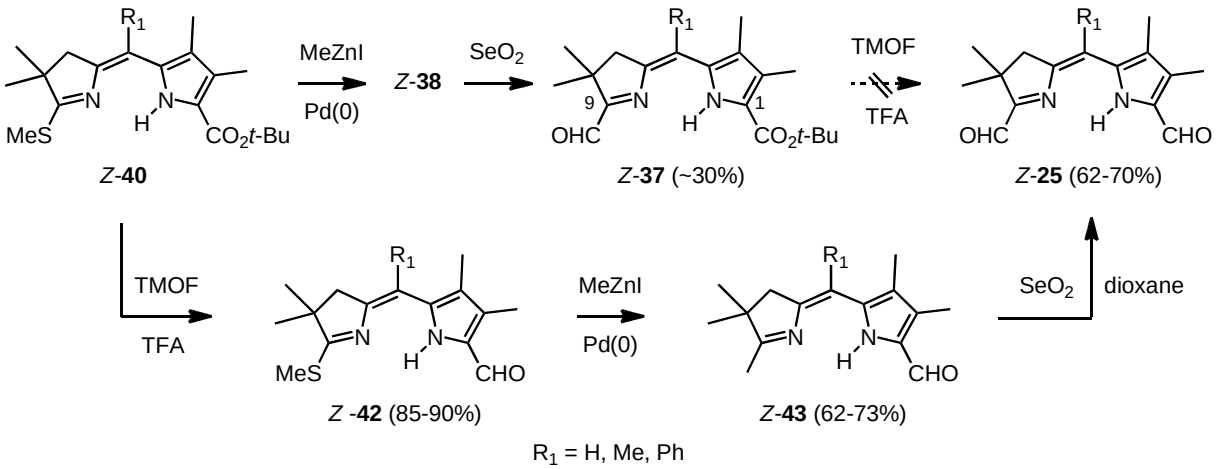


Scheme 9

Eventually this difference was traced to a selective activating effect of Zn, which serves to polarize the thioimidate C-S bond in *Z*-**40** by chelation (*cf.* *Z*-**41** in Scheme 9).[17] Control experiments showed that such activation is necessary for oxidative insertion of Pd(0). Chelation of this type is not possible for

E-**40**, which is also sterically prohibited from simple complexation (*cf*. *E*-**41**; for a detailed discussion of this mechanism see Ref. 17). Consequently the desired cross-coupling reaction fails. Compounding this problem, the ratio of *Z*-**40** : *E*-**40** decreases with increasing size of the *meso*-substituent R_1 (*i.e.* H > Me >> Ph), making it impractical to incorporate larger alkyl groups (for R_1 = Ph the *Z:E* ratio drops to 50:50). This follows from the fact that with small R-groups the planar *Z*-configuration is stabilized by hydrogen bonding, but as R_1 increases in size this effect becomes less important. Unfortunately, under the coupling conditions *Z*-**40** and *E*-**40** do not equilibrate.

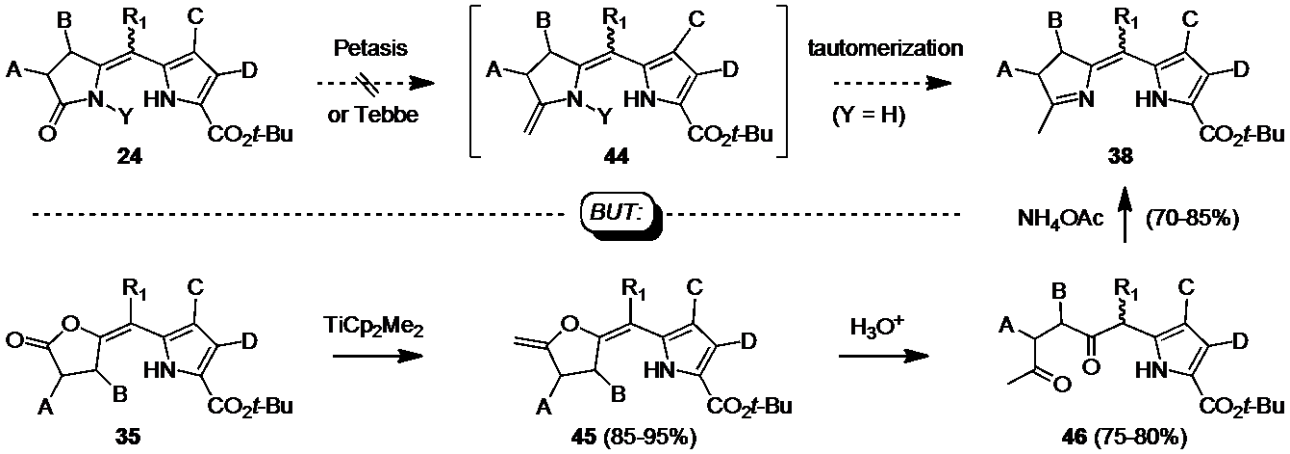
With workable quantities of dihydrodipyrrins *Z*-**38** in hand, we were next pleased to find that SeO_2 oxidation produced formyl derivatives *Z*-**37**, albeit in modest overall yield (Scheme 10).[18] Unexpectedly, however, we were unable to accomplish the decarboxylative formylation of *Z*-**37** leading to *Z*-**25**, presumably due to the inductive influence of the C9-formyl group. After considerable experimentation, this last hurdle was remedied by reversing the order of decarboxylation and methylation. Thus, dihydrodipyrrins *Z*-**40** were cleanly converted to the formyl compounds *Z*-**42** (TFA/TMOF), which gave moderate-good yields of the desired diformyl derivatives *Z*-**25** upon methylation followed by oxidation with SeO_2 in dioxane. As will be seen later, we were also able at this point to validate the basic concept of our chlorin synthesis. However, with an unavoidable loss of material at such a late stage we set out to develop a more efficient synthesis of diformyl dihydrodipyrrins **25**.



Scheme 10

Method B - The Petasis/Tebbe Route to Dihydrodipyrrins 25. We briefly explored the possibility that enelactams **24** might be directly converted to dihydrodipyrrins **38** by methylenation followed by tautomerization (Scheme 11). A number of closely related transformations have been reported with both amides and lactams, although activation by N-substitution is usually required.[19] However, in the present case both unsubstituted (Y = H) and substituted lactams **24** (Y = CO_2Me, CO_2t-Bu, TMS) were either unreactive or suffered slow decomposition employing either the Petasis reagent ($TiCp_2Me_2$),[20] or the

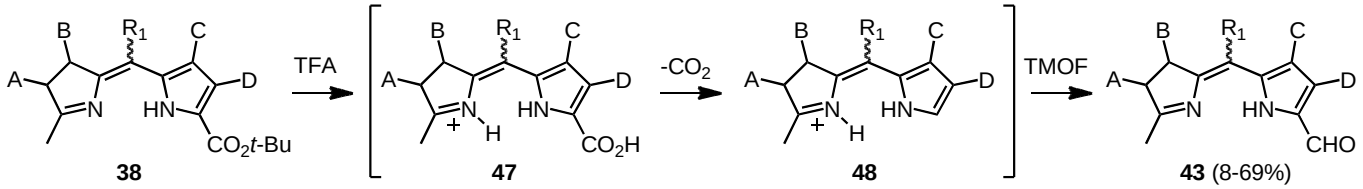
generally more reactive Tebbe reagent [$Cp_2TiCH_2ClAl(CH_3)$].[21]



Scheme 11

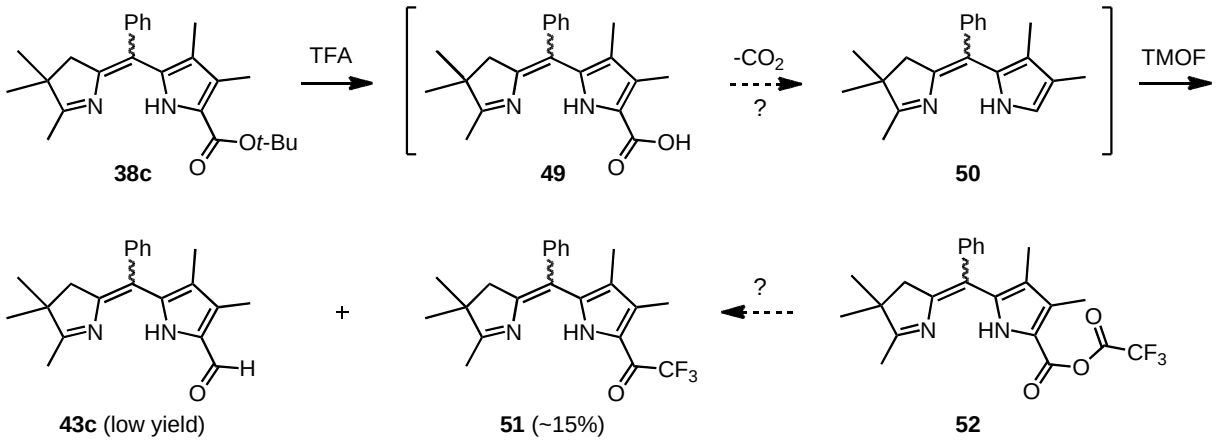
In contrast, ene*lactones* **35** underwent clean condensation with $TiCp_2Me_2$, affording high yields of enol ethers **45** incorporating a range of *meso*-substituents R_1 (Scheme 11).[22] This discovery provided the basis for a very streamlined synthesis of dihydrodipyrrins **38**, which were formed in "one pot" by hydrolysis of **45** to the corresponding diketones **46**, followed by condensation with an appropriate ammonia source. Importantly, the Petasis reagent was compatible with commonly occurring functional groups such as propionate esters (D = $CH_2CH_2CO_2Me$), as well as regioisomeric substitution patterns in ring-A (A, B = Me_2, H_2).

It remained now only to effect the decarboxylative formylation of dihydrodipyrrins **38** to formyl derivatives **43** to intersect with our previously established route to diformyl dihydrodipyrrins **25** (Scheme 12, cf. also Scheme 10). As in the conversion of *Z*-**40** to *Z*-**42** we expected this transformation to be straightforward, involving pre-treatment of **38** with TFA followed shortly thereafter with TMOF (*conditions i*). Again though, this seemingly well-precedented step proved to be highly capricious, affording **43** in yields ranging from 8% to 69% depending partly upon the nature of *meso*-substituents R_1. Only with R_1 = H were we able to obtain reproducible yields in the range of ~70%. In part this behavior might be due to competitive protonation at the basic pyrroline ring nitrogen in **38** to give **47**, thereby inhibiting decarboxylation and/or formylation. Battersby *et al.* experienced similar difficulties with a closely related ring system during the course of a synthesis of bonellin.[23]



Scheme 12

We explored many approaches for improving the conversion of **38** to **43**, initially employing *meso*-phenyl substrate **38c** in combination with variants of the standard protocol (TFA/TMOF, Scheme 13).[24] As above, these experiments gave erratic yields of the desired formylated compound **43c** accompanied by significant decomposition. In most cases the only identifiable by-product was the trifluoromethyl ketone **51** (~15%). Interestingly, we could find no trace of the presumed intermediates **49** and **50** in the crude reaction mixtures, and it is an open question whether formylation precedes or follows decarboxylation.



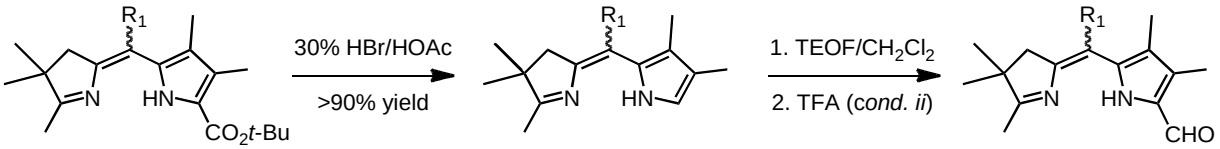
Scheme 13

Battersby *et al.* also observed trifluoromethyl ketone formation in their studies cited above, but the origin of this compound was not investigated.[23] In the case of ketone **51** two observations provided insight into this question. First, **38c** gave essentially identical yields of **51** upon treatment with TFA alone, seemingly eliminating any mechanistic role for TMOF in the formation of this compound. Second, **50** prepared independently (*vide infra*) reacted only very slowly with TFA under conditions that led to rapid conversion of **38c** to **51**. Together these results suggest that a likely intermediate in the conversion of **38c** to **51** is the mixed anhydride **52**, which might be transformed to **51** in either inter- or intramolecular fashion. It thus seemed clear that decarboxylation of dihydrodipyrrins **38** with TFA would inevitably lead to substantial loss of starting material to this side reaction.

Eventually we found that methylpyrroline **38c** underwent clean decarboxylation with HBr/HOAc, affording a 96% yield of the α-free pyrrole **50c** as a mixture of *Z*- and *E*-isomers (Table 1). With decarboxylation no longer an issue we examined a number of milder conditions for effecting the desired formylation of **50c** to **43c**. Of these, the Vilsmeier reagent $POCl_3$/DMF exhibited moderate promise, affording a 43% yield of **43c** as the *Z*-isomer only.[25] However, these conditions did not prove to be general. Interestingly, employing TMOF/TFA (*conditions i*) the yields of **43c** were actually lower than those obtained by direct decarboxylative formylation of **38c** to **43c** (*cf.* Scheme 13). Mainly this was because **50c** was unstable to prolonged exposure to TFA. In experiments to minimize this problem we

found that **43c** was obtained in 73% overall yield when a solution of crude **50c** in CH_2Cl_2/triethyl orthoformate (TEOF) was added to pre-cooled TFA (*conditions ii*). These conditions provided reproducible results and were also satisfactory for preparing formyl derivatives **43d** (R = C_5H_{11}, 57%) and **43e** (R = $C_{10}H_{21}$, 61%). However, for substrates bearing small *meso*-substituents (i.e. **43a,b**) even these conditions proved to be too harsh.

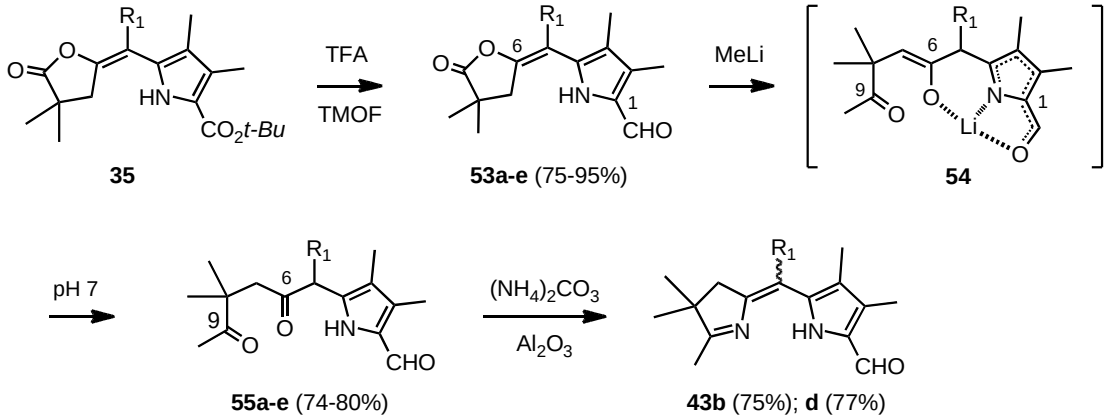
Table 1. Synthesis of Formyl Pyrrolines **43**



38 **50** **43**

38	R_1	Overall yield **43**-*Z,E*
a	H	<15% combined
b	Me	25% combined
c	Ph	*Z* (64%) *E* (9%)
d	C_5H_{11}	*Z* only (57%)
e	$C_{10}H_{21}$	*Z* only (61%)

Method C. In parallel studies we developed a third strategy for synthesizing **43** that provided additional flexibility. Based on mechanistic considerations we expected that enelactones **35** would be good substrates for decarboxylative formylation, since in these compounds there is no pyrroline ring to compete for protonation (*Method C*, Scheme 14). In agreement, **35a**-**e** routinely afforded 75-95% yields of formyl derivatives **53** with TEOF/TFA (*E*-isomers only). We further hoped that **53** might undergo a selective Petasis reaction at the lactone carbonyl group, as previously observed with ester-lactones **35** (cf. Scheme 11). However, all attempts at effecting this conversion produced complex mixtures. In contrast, ring opening with MeLi exhibited remarkable selectivity, affording 74-80% yields of **55a-e** upon slow addition at –78 ^{o}C. At present we have no rigorous explanation for this selectivity, although it is likely that the acidic pyrrole N-H group plays a role in both protecting the formyl group and in preventing multiple addition (two equivalents of MeLi are required for complete reaction). As a working hypothesis we suggest that the C6 ketone deriving from **53** is stabilized in a chelated structure of type **54**, maintaining the enolate tautomer until workup.



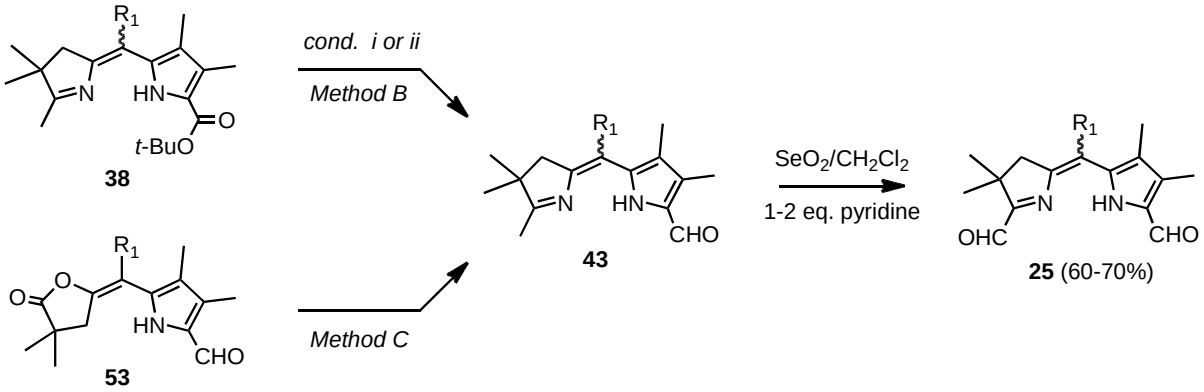
35 **53a-e** (75-95%) **54**

55a-e (74-80%) **43b** (75%); **d** (77%)

a: R' = H. **b**: R' = Me. **c**: R' = Ph. **d**: R' = C_5H_{11}. **e**: R' = $C_{10}H_{21}$

Scheme 14

Diketones **55** presented a number of hurdles to cyclization, partly because of the presence of the very sensitive formyl group (Scheme 14). Formylpyrroles as a class are generally unstable to acids,[26] a property that was especially pronounced with **55**. These substances underwent rapid decomposition with even weakly acidic ammonium salts. In contrast, working with substrate **55b** (R_1 = Me) we eventually found that the combination of $(NH_4)_2CO_3$/basic Al_2O_3 in MeCN at 75 °C gave ~75% yields of the corresponding dihydrodipyrrin **43b**, a significant improvement over *Method B* (*cf.* Table 1). In analogous fashion diketone **55d** (R_1 = *n*-pentyl) afforded **43d** in much improved yield (77%). Dihydrodipyrrin **43a** (R_1 = H), though, was still best prepared using *Method B*, *conditions I* (*cf.* Scheme 12), and dihydrodipyrrins **43c** (R_1 = Ph) and **43e** (R_1 = *n*-decyl) were best prepared using *conditions ii*. In *Methods B* and *C*, we thus established two complementary routes to key intermediates **43** that together are far more efficient than *Method A*. All of these results are summarized in Scheme 15 below.



43a (R = H, 71%).[a] **43b** (R = Me, 75%).[c] **43c** (R = Ph, 73%).[b] **43d** (R = C_5H_{11}, 77%).[c] **43e** (R = $C_{10}H_{21}$, 61%).[b]

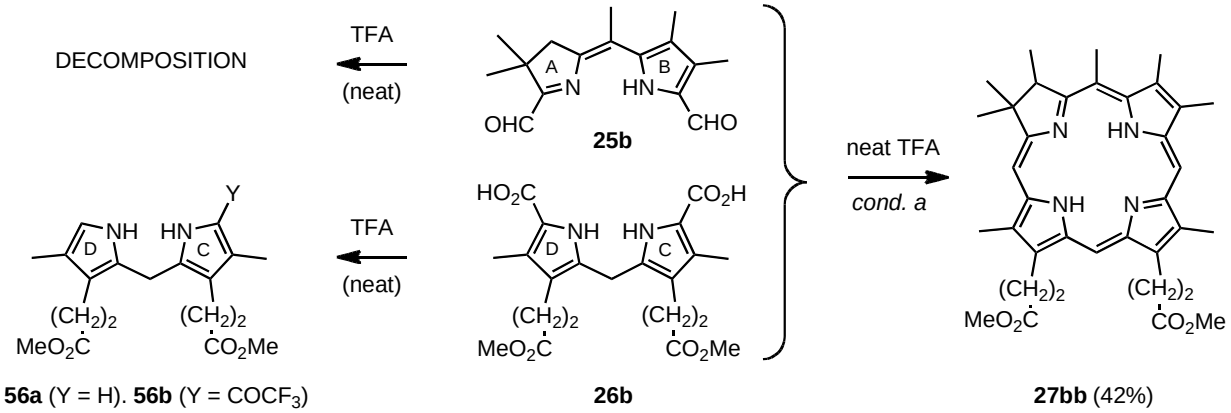
[a]*conditions i:* 1. TFA. 2. TMOF, 25 °C. [b]*conditions ii:* 1. HBr / HOAc. 2. TEOF / CH_2Cl_2. 3. TFA, 0 °C.
[c]*Method C:* 1.2 eq MeLi. 2. $(NH_4)_2CO_3$ / CH_3CN, 75 °C.

Scheme 15

In our initial studies we carried out the conversion of formyl dihydrodipyrrins **43a-c** to diformyl derivatives **25a-c** by oxidation with selenium dioxide in dioxane (*cf.* Scheme 10).[14d] While this procedure generally afforded satisfactory yields of **25a-c**, the oxidation products were invariably contaminated with selenium metal that was very difficult to separate. Among other consequences this made obtaining accurate analytical data difficult. Because of this, we spent considerable time exploring other means for accomplishing the desired oxidation. Generally speaking these fell into three categories: *(1)* direct oxidation using powerful reagents of the Cr(VI), Co(II), Cu(II), and Pb(IV) families;[27] *(2)* oxidation initiated by *bis*-halogenation (NCS, NBS, $SOCl_2$, etc.) followed by hydrolysis;[28] and (*3*) methyl anion generation followed by *in situ* capture with oxidants including diselenides, disulfides, NBS, etc.[28b] The results were uniformly discouraging, with some reagents exhibiting little reactivity while others caused rapid decomposition. Ultimately we returned to the SeO_2 procedure, exploring the effect of reagent purity, additives, and co-oxidants. To briefly summarize, freshly sublimed SeO_2 provided no apparent advantage,[29] nor did so-called "wet" solvents described in the literature as having beneficial effects (in our case even trace amounts of water accelerated decomposition).[30] We did, however, observe very clean reactions using dry CH_2Cl_2 as solvent with 1-2 equivalents of pyridine as additive (Scheme 15).[30] Employing **43b** (R = Me) as a substrate we consistently obtained yields of **25b** in the range of 65-70% following this protocol. The one issue remaining was that ICP-MS analysis indicated that the product was still contaminated with up to 0.61% by weight (2 mol%) selenium. This last problem was solved by briefly heating the crude **25b** in DMF, which produces a black metallic allotrope that can be easily removed by filtration.[31] In analogous fashion diformyl derivatives **25a-e** were prepared in 60-70% yield without further optimization.

I.3 The AB + CD Route to Chlorins. 1. C,D-Symmetric Chlorins.

In our first experiments the condensation of **25** and **26** was carried out in neat TFA, which was deemed necessary to effect decarboxylation of **26** to the presumably more reactive α-unsubstituted dipyrromethanes (*conditions a*).[14d] This protocol afforded 35-45% yields of a limited number of chlorins **27**, illustrated below for the specific case of **27bb** (Scheme 16). However, with greater quantities of **25** available, we carried out more detailed studies that revealed that our assumptions pertaining to decarboxylation were invalid.

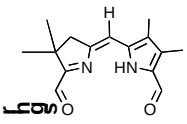
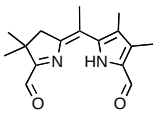
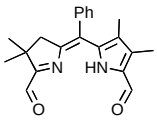
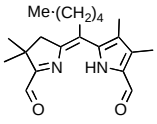
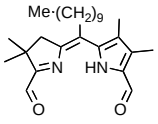
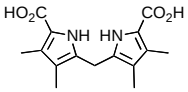
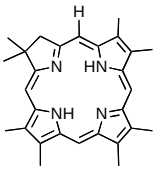
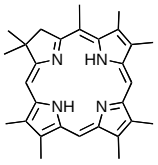
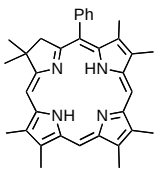
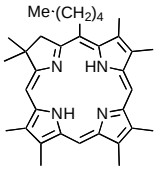
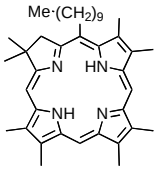
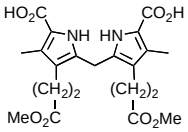
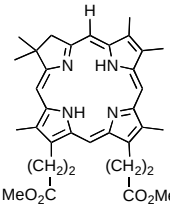
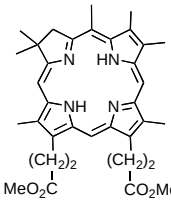
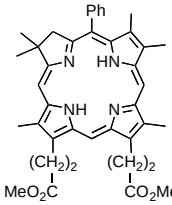
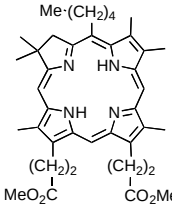
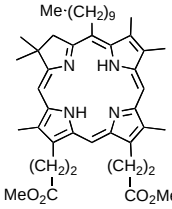
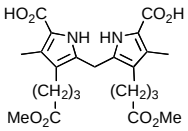
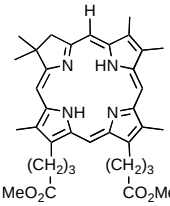
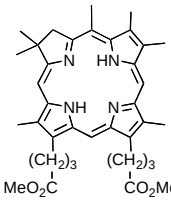
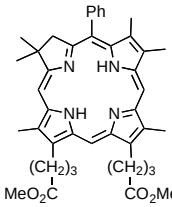
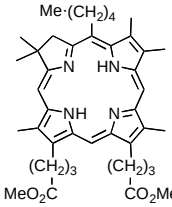
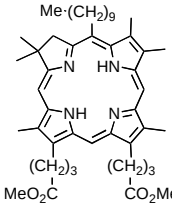
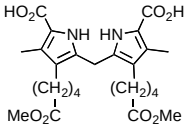
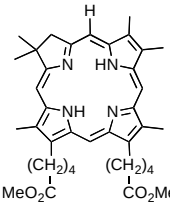
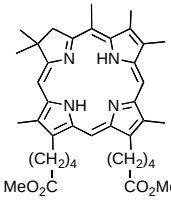
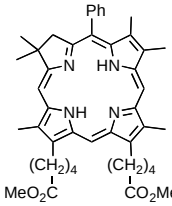
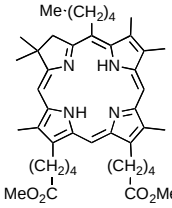
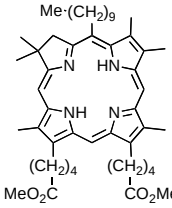
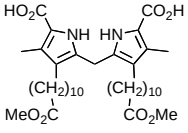
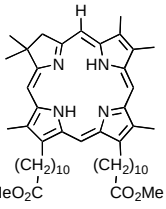
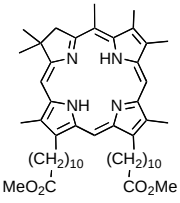
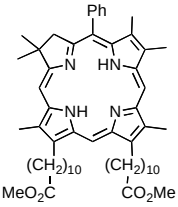
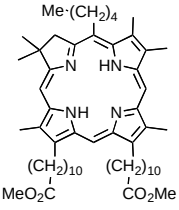
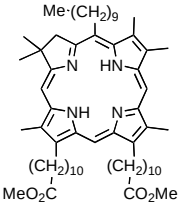


Scheme 16

We began our optimization studies by examining the stability of dihydrodipyrrin **25b** and dipyrromethane **26b** in neat TFA, now cognizant of the potential side reactions that this solvent might induce (Scheme 16). Under these conditions **25b** decomposed within minutes at ambient temperature. Dipyrromethane **26b** afforded moderate yields of the *bis*-decarboxylated product **56a** along with significant quantities of trifluoroacylated derivative **56b**,[32] mirroring our experience with dihydrodipyrrins **38** outlined in Scheme 13. Interestingly, isolated and purified dipyrromethane **56a**, for which we expected trifluoroacylation to be minimized (*vide supra*), gave *lower* yields of chlorin **27bb** than dicarboxylic acid **26b** under otherwise identical conditions (33% vs 42%). To explore this result further we screened numerous solvent and acid combinations with **25b** and **56a**, including such Lewis acids as $TiCl_4$, BF_3, and $Sc(Otf)_3$ that have been successfully employed in similar condensations.[33] In the present case these catalysts caused significant decomposition and little or no chlorin **27bb** could be detected by TLC and/or UV analysis. More promising results were obtained with Brönsted acids, in particular TsOH in $MeOH/CH_2Cl_2$ (*conditions b*),[34] although these conditions proved unreliable for larger scale syntheses of **27bb**.

Based on these experiments it was clear that decarboxylation was not a prerequisite to chlorin formation, raising the possibility that dicarboxylic acid **26b** might be a superior condensation partner under more refined conditions. Working from this premise we eventually identified the combination of 5% TFA in CH_2Cl_2 as a particularly effective medium for condensation,[35] affording chlorin **27bb** in a remarkably high state of purity following washing with either 3M NH_4OH or saturated $KHCO_3$ (conditions c). Final purification was by silica gel chromatography, which consistently afforded 65-75% yields of **27bb** on scales up to several hundred milligrams (however, reactions were typically run on 25-50 mg scale for convenience). In analogous fashion we prepared chlorin derivatives **27aa** - **27ee** bearing lipophilic substituents ranging up to *n*-decyl at C5, along with aliphatic esters of chain length 2-10 at C13 and C17 (Table 2). Yields employing *conditions c* ranged from 47-85% and are shown in bold. Where applicable yields employing *conditions a* and *b* are also included.

Table 2. Chlorins Synthesized Employing Conditions C.

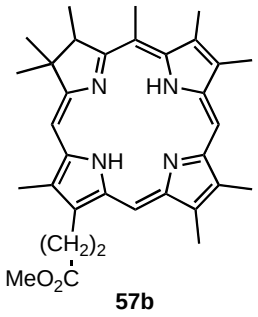
C-D rings \ A-B rings	 **25a**	 **25b**	 **25c**	 **25d**	 **25e**
 **26a**	 **27aa** (38%,[a] **58%**[c])	 **27ba** (44%,[a] **72%**[c])	 **27ca** (40%,[a] **74%**[c])	 **27da** (39%[b])	 **27ea** (38%[b])
 **26b**	 **27ab** (39%,[a] **63%**[c])	 **27bb** (42%,[a] **73%**[c])	 **27cb** (39%,[a] **60%**[c])	 **27db** (51%[b])	 **27eb** (42%[b])
 **26c**	 **27ac (57%[c])**	 **27bc (74%[c])**	 **27cc (75%[c])**	 **27dc (49%[c])**	 **27ec (72%[c])**
 **26d**	 **27ad (51%[c])**	 **27bd (64%[c])**	 **27cd (68%[c])**	 **27dd (49%[c])**	 **27ed (85%[c])**
 **26e**	 **27ae (55%[c])**	 **27be (68%[c])**	 **27ce (54%[c])**	 **27de (47%[c])**	 **27ee (77%[c])**

Conditions: **a**: neat TFA. **b**: TsOH/MeOH/CH_2Cl_2. **c**: 5% TFA in CH_2Cl_2.

2. Non-Symmetric Chlorins.

To this point our synthetic objectives were simplified by the fact that it was unnecessary to differentiate either the formyl groups in **25** or the α-pyrrole positions in dipyrromethanes **26** (cf. Table 2). However, while versatile in many aspects, the methodology summarized above is unsuited to the broader goal of synthesizing non-symmetric chlorins. This requires regioselective control over the four reacting carbon

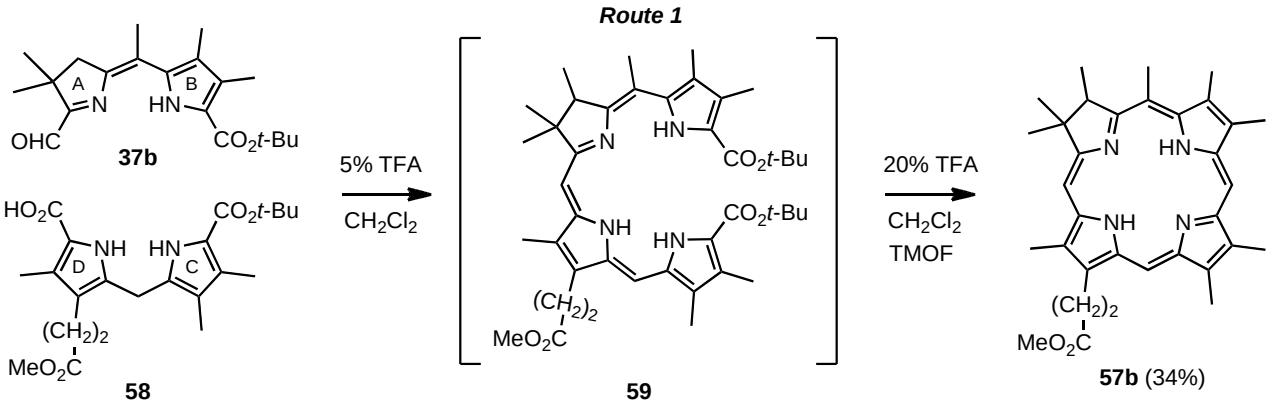
centers in **25** and **26**. To address this issue we explored a number of variations of our "2+2" condensation strategy that incorporate the desired level of selectivity, three of which are described below (*Routes 1-3*). For ease of comparison, each route is illustrated by the synthesis of the same chlorin **57b**.



57b

a. ***Route 1*** **to Non-Symmetric Chlorins.**

In Route 1, the regio-differentiating step involves mild acid-catalyzed condensation of A,B-ring precursor **37b** with the readily available C,D-ring precursor **58** (Scheme 17). Our plan was that *seco*-chlorins **59** would afford chlorin **57b** upon decarboxylative formylation, with the stipulation that *mono*-formylation is followed rapidly by cyclodehydration as opposed to oligomerization. As precedent for this approach, porphyrins have been prepared by a similar method in fair yields,[36] although in these examples post-cyclization oxidation was required to give the aromatic macrocycles. In the analogous cyclization of **59**, the aromatic chlorin would be obtained directly upon cyclodehydration, with the same advantages as described above for our syntheses of C,D-symmetric chlorins. In practice this approach worked moderately well, and could be carried out in a single flask without isolation of intermediate **59** or its *mono*-formylation product (not shown). Thus, a solution of **37b** and **58** in 5%TFA/CH_2Cl_2 was stirred

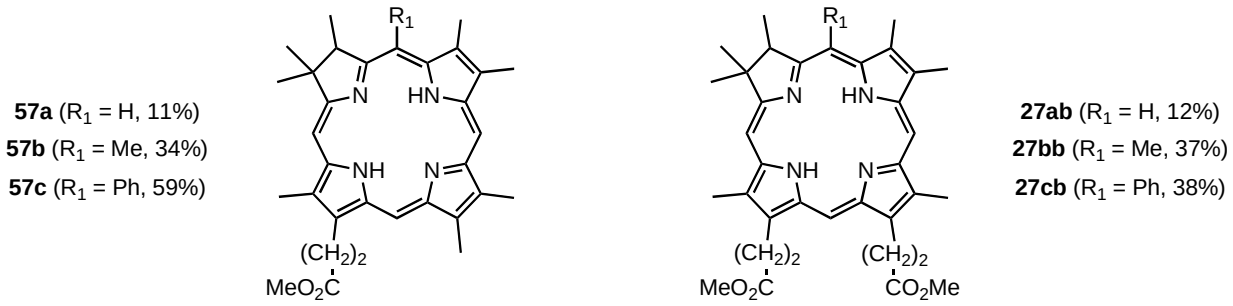


Scheme 17

at ambient temperature under Ar for a period of 5 h, when TLC analysis indicated that formation of **59** was complete (in separate experiments **59** was isolated and characterized in 68% yield). The resulting deep purple reaction was then adjusted to a concentration of 20% TFA/CH_2Cl_2 by addition of neat TFA,

followed by treatment with excess trimethyl orthoformate (TMOF). After stirring an additional 16 h at rt, chlorin **57b** was isolated in 34% overall yield by straightforward concentration and chromatography. The substitution pattern of **57b** was unequivocally established by NOE studies, as well as by direct comparison with its subsequently prepared regioisomer (*vide infra*).

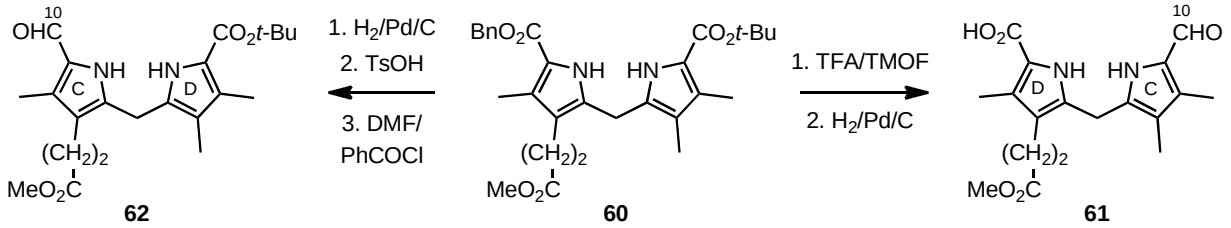
To test the generality and effectiveness of *Route 1* we synthesized two additional unsymmetrical chlorins **57a** and **57c**, together with three C,D-ring symmetric chlorins **27ab**, **27bb** and **27cb** previously prepared as described above (*cf.* also Table 2). As can be seen, there was little effect of non-*meso*-



substituents on the course of these syntheses. However, the nature of the A,B-ring *meso*-substituents R_1 had a strong influence on reaction efficiency, with chlorins **27ab** and **57a** (R_1 = H) being formed in considerably lower yield than the corresponding *meso*-substituted derivatives (R_1 = Me, Ph). These results are consistent with a reaction mechanism in which carbocation character at C5 is stabilized by electron donating groups. Interestingly, *Route 1* proved to be less efficient than our original methodology for synthesizing C,D-ring symmetric chlorins of type **27**, yields in each case being significantly lower (*cf.* Table 2 for comparison).

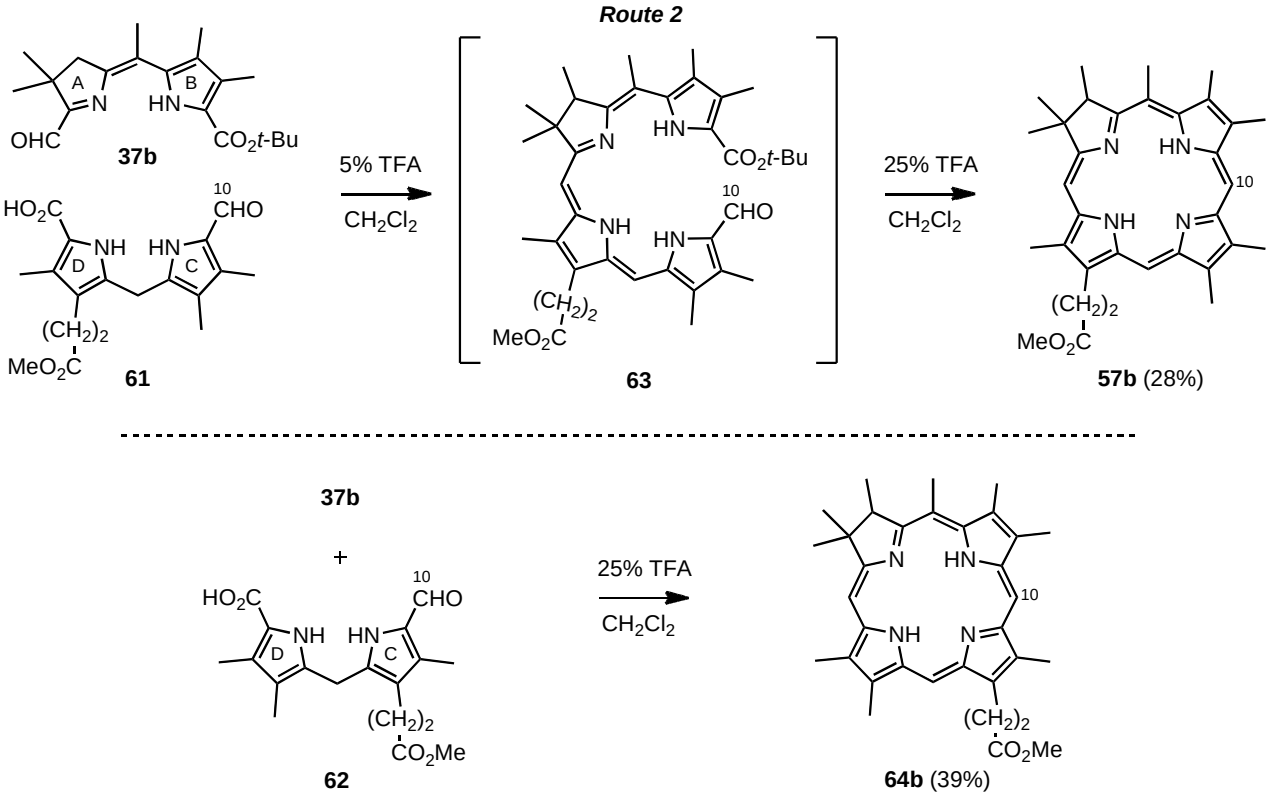
b. *Route 2* to Non-Symmetric Chlorins.

Our synthetic design for *Route 2* is similar in concept to *Route 1* except the aldehyde destined to become C-10 is incorporated early on. To test this approach the aldehyde-acid **61** was synthesized from the known dipyrromethane **60**,[37] by a two step sequence consisting of decarboxylative formylation followed by benzyl ester hydrogenolysis (Scheme 18). Also prepared from **60** was the regioisomeric C,D-ring precursor **62**, by the straightforward three step sequence indicated.[38]



Scheme 18

The next step called for mild acid-catalyzed condensation of **61** with the A,B-ring precursor **37b**, followed by *t*-butyl ester hydrolysis and cyclodehydration (Scheme 19). Each of these steps had close precedent in our previous work, although self-condensation of **61** was a potential complication. Blank experiments, however, indicated that side reactions of this nature could be controlled. In practice, condensation of **37b** and **61** in 5% TFA/CH_2Cl_2, followed by adjustment to 25% TFA/CH_2Cl_2, afforded chlorin **57b** in 28% yield, with no evidence for by-products arising from self-condensation. In analogous fashion, condensation of **37b** with dipyrromethane **62** in 25% TFA/CH_2Cl_2 gave a 39% yield of the regioisomeric chlorin **64b** (Scheme 19). Direct comparison of chlorins **57b** and **64b**, along with detailed NMR analysis, then demonstrated conclusively that there had been no crossover in regiochemical control.

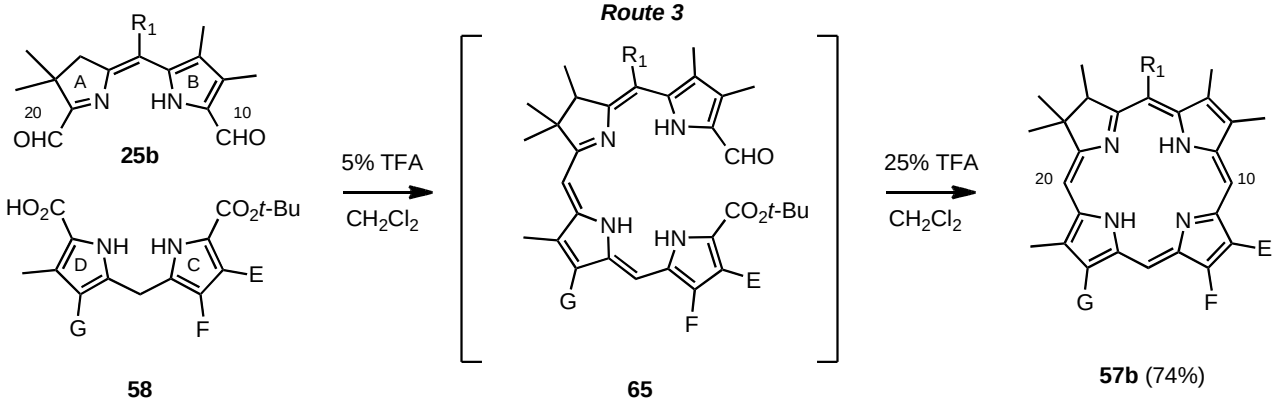


Scheme 19

During the condensation of **37b** and **61** a polar intermediate was observable by TLC, whose crude NMR spectrum was consistent with the anticipated tetrapyrrole condensation product **63**. However, several attempts at isolating and fully characterizing this compound were unsuccessful, making further optimization difficult. Thus, while clearly a viable means of synthesizing unsymmetrical chlorins, *Route 2* had no advantages over *Route 1* in terms of simplicity or effectiveness. In addition, evidence was accumulating that an even more straightforward approach to unsymmetrical chlorins was feasible employing diformyl ring-A,B precursors **25** (*Route 3*).

c. *Route 3* to Non-Symmetric Chlorins.

In our previous chlorin studies we demonstrated that diformyl derivatives **25** are excellent A,B-ring precursors for synthesizing C,D-symmetric chlorins **27** (*cf.* Table 2). We had assumed, though, that these materials lacked the unambiguous differentiation at C10 and C20 (chlorin numbering) necessary to impart regioisomeric selectivity. The validity of this assumption was now called into question, based upon the substantial reactivity differences we had uncovered between pyrrole- and pyrroline-type formyl groups (*vide supra*). Thus, it now seemed clear that electron rich pyrroles would undergo selective condensation with the more reactive pyrroline aldehyde found on ring A in **25**, as opposed to the vinylogous amide-like formyl group present in ring B. This approach was first tested with dialdehyde **25b** and dipyrromethane **58**, which were stirred together for 5 h at RT in 5% TFA/CH_2Cl_2 to effect decarboxylation at C19 and initial condensation to give **65** (Scheme 20). After stirring an additional 16 h in 25% TFA/CH_2Cl_2, chlorin **57b** was isolated in 74% yield without any effort at optimization. Furthermore, this methodology proved to be quite general. Both C,D-ring symmetric and non-symmetric chlorins were accessible by this route, with yields ranging from 22-87% (cf. Table).



Cmpd #	Substituents (P^{Me} = $CH_2CH_2CO_2Me$)	Yield (%)
27ab	E = Me; F,G = P^{Me}; R_1 = H	38
27bb	E = Me; F,G = P^{Me}; R_1 = Me	78
27cb	E = Me; F,G = P^{Me}; R_1 = Ph	73
57a	E,F = Me; G = P^{Me}; R_1 = H	39
57b	E,F = Me; G = P^{Me}; R_1 = Me	74
57c	E,F = Me; G = P^{Me}; R_1 = Ph	87
57d	E = P^{Me}; F,G = Me; R_1 = H	22
57e	E = P^{Me}; F,G = Me; R_1 = Me	38
57f	E = P^{Me}; F,G = Me; R_1 = Ph	77

Scheme 20

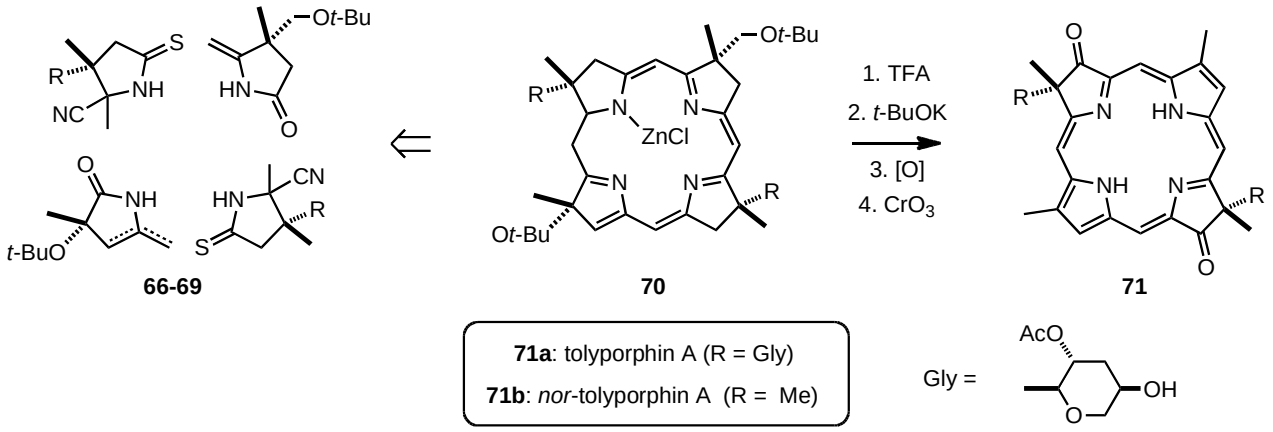
As can be seen, the C5 *meso*-substituent still exerted some influence on the reaction efficiency, with the trend mirroring that previously noted above. That is, *meso*-H derivatives **27ab**, **57a**, and **57d** were consistently formed in lower yields than the corresponding *meso*-Me or *meso*-Ph chlorins, again suggesting the likelihood of carbocation intermediates. Importantly, the yields of *all* chlorins were significantly improved over those obtained by *Routes 1* or *2*, including the *meso*-H series which were brought into a preparatively useful range. Even the C,D-symmetric chlorins **27bb** and **27cb** were obtained in higher yield than previously (*cf*. Table 2), presumably due to better control over competing oligomerization.

Conclusion

In summary, we have built on our "2+2" synthesis of C,D-ring symmetric chlorins to develop three new strategies for the preparation of chlorins that are fully asymmetric in their substitution pattern. *Route 3*, which combines operational simplicity with moderate to high product yields, proved to be the most effective route, with reactivity differences between the two formyl groups of A,B-rings **25** imparting excellent regioselectivity. *Routes 1* and *2* are also useful alternatives to *Route 3* if the appropriately functionalized precursors are readily available. All three strategies generate single regioisomers of diversely substituted chlorins, and in every case the "2+2" condensation is accomplished in a simple, one-flask procedure without need for additives such as oxidizing agents or metals.[14a] Taken together, these methodologies provide expanded access to an array of chlorins for structure activity studies that may advance the effectiveness of photodynamic therapy and other applications.

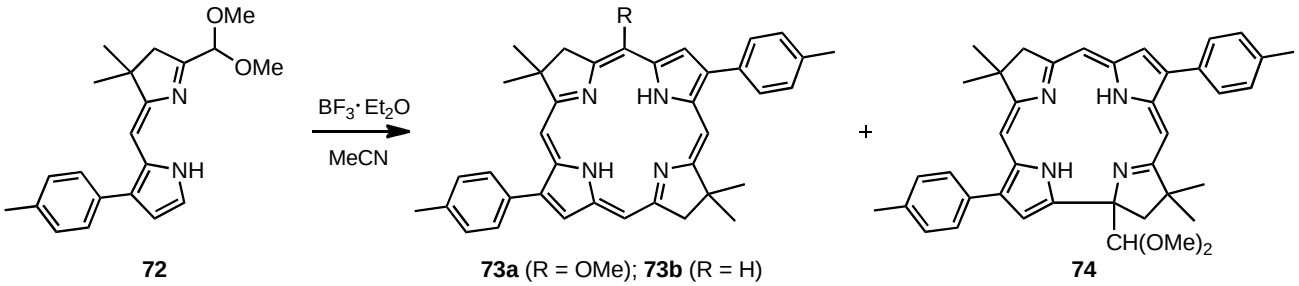
II. A New Synthesis of Bacteriochlorins.

II. 1 Background. Compared to chlorins, the lower oxidation state of bacteriochlorins makes it difficult to design a system that can undergo cyclization directly to the aromatic tetrapyrrole. This is reflected in the fact that only a very limited number of *de novo* syntheses of bacteriochlorins has appeared. In 1997 Kishi *et al*. described the first total syntheses of members of the tolyporphin (**71**) class of dioxo-bacteriochlorins, a novel group of tetrapyrroles that has been shown to reverse tumor multi-drug resistance (MDR) (Scheme 21).[39] The Harvard group employed an ingenious strategy for preparing **71a**,**b**, in which the pyrrocorphin derivatives **70** were synthesized from monocyclic precursors **66-69** using Eschenmoser's sulfide-contraction methodology.[40] The bacteriochlorin oxidation state was then attained by a multi-step sequence including *t*-butyl ether hydrolysis, *bis-retro*-aldol cleavage (-2 H_2C=O), and auto-oxidation. Further oxidation with CrO_3 gave the target compounds **71** in good yield.



Scheme 21

A second bacteriochlorin synthesis was developed by Lindsey *et al.*, who in 2005 described the formation of three tetrapyrrole products on self-condensation of dihydrodipyrrin **72** with $BF_3 \cdot Et_2O$ in MeCN (Scheme 22).[41a] Careful analysis showed that two of these products were the bacteriochlorins **73a** and **73b**, while the third corresponded to the ring-contracted bacteriochlorin **74** (a tetradehydrocorrin). The formation of **73b** was a matter of some mechanistic interest, since it requires an *in situ* reduction starting from dihydrodipyrrin **72**. While the authors noted that "Neither the source of the reductant nor the nature of the intermediate that undergoes reduction is known," careful optimization produced yields of **73-74** in the range of 30-66% on small scales (49% for **73b**). The strength of this approach is that it utilizes simple starting materials and proceeds under mild conditions. However, it is unclear whether this methodology can be extended to the synthesis of unsymmetrical bacteriochlorins.

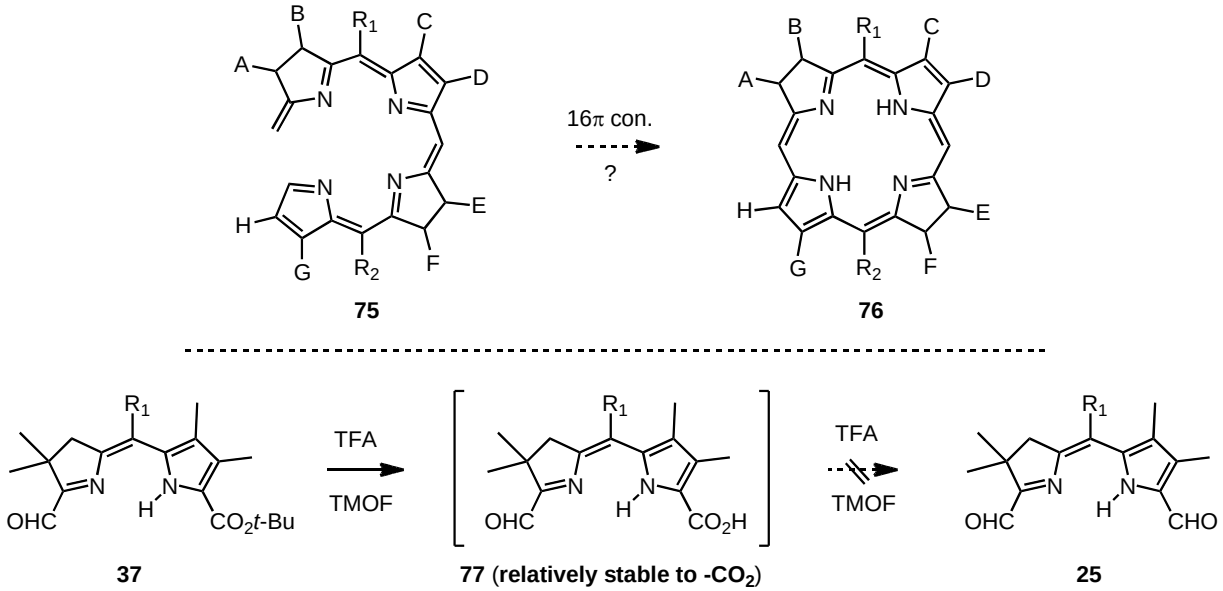


Scheme 22

II. 2 A 16π-Electrocyclization Route to Bacteriochlorins.

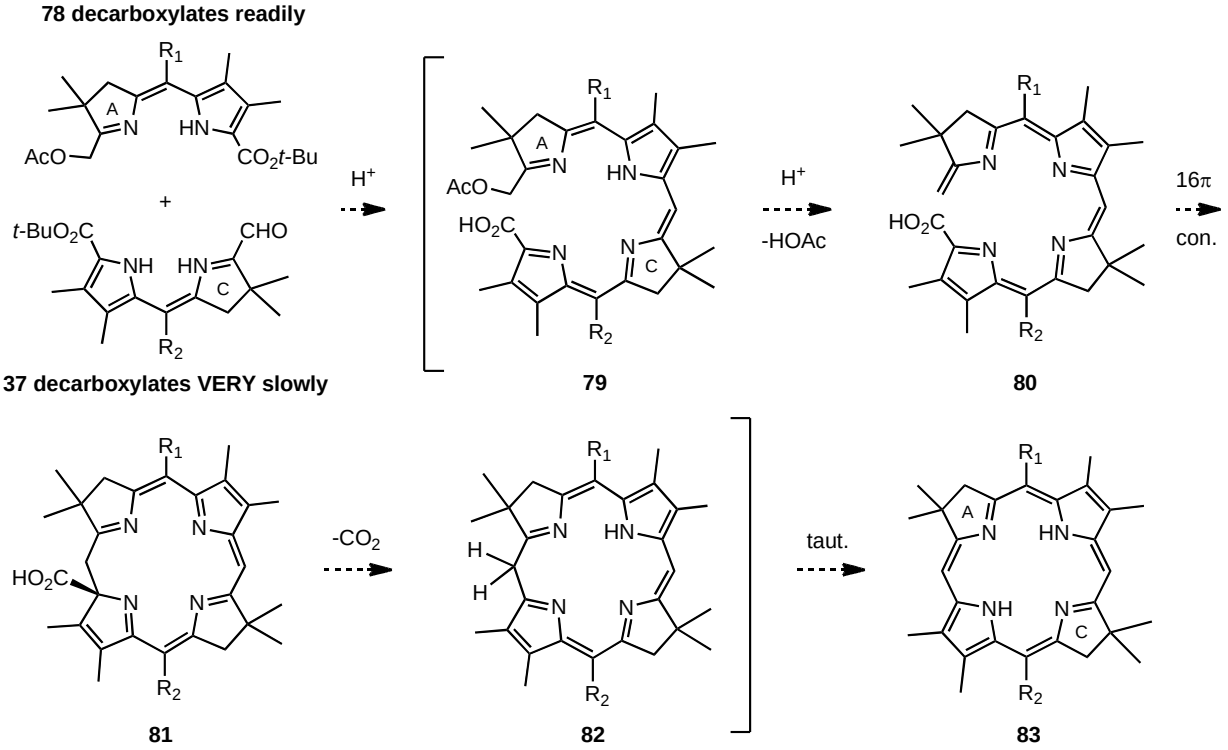
We were intrigued with the possibility that 16π-electron tetrapyrroles of type **75** might undergo a symmetry-allowed ring closure to afford bacteriochlorins **76** (Scheme 23, following page). However, it seemed unlikely that reactive species of type **75** would be stable enough to permit isolation, but rather

would have to be generated *in situ*. One solution came in the form of an observation made during our early efforts to synthesize diformyl dihydrodipyrrin derivatives of type **25**. Thus, we initially planned to prepare **25** by decarboxylative formylation of *t*-butyl esters **37**, but were surprised to find that the intermediate carboxylic acids **77** were relatively stable (bottom, Scheme 23).



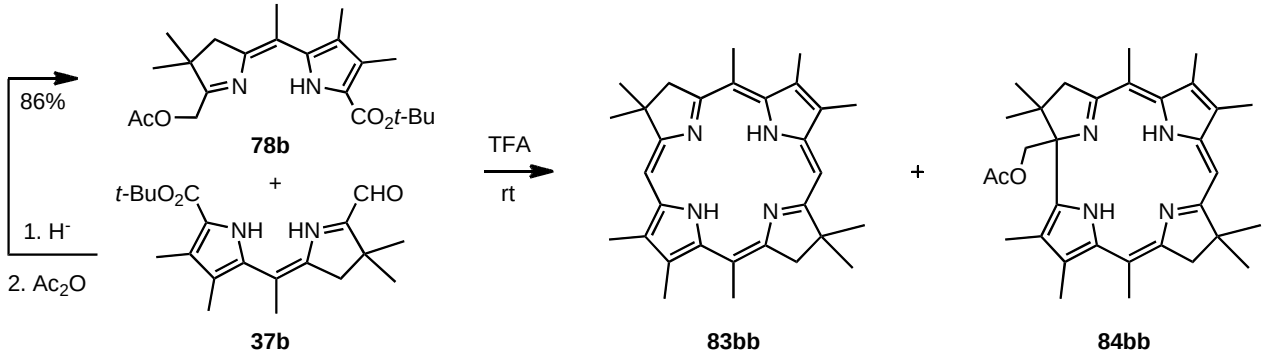
Scheme 23

With hindsight this result is understandable, since electron deficient pyrroles undergo decarboxylation only with great difficulty. Consequently, the possibility existed that precursors to a 16π-electron system might be generated concomitantly in solution, each in a form that limits self-condensation. A plausible mechanistic pathway is illustrated in Scheme 24, where chemoselective condensation of **37** and **78** generates the intermediate tetrapyrrole **79**. Acid-catalyzed elimination of HOAc would then generate the 16π-electron intermediate **80**, which on electrocyclization, followed by loss of CO_2 and tautomerization, would afford the bacteriochlorin **83**.



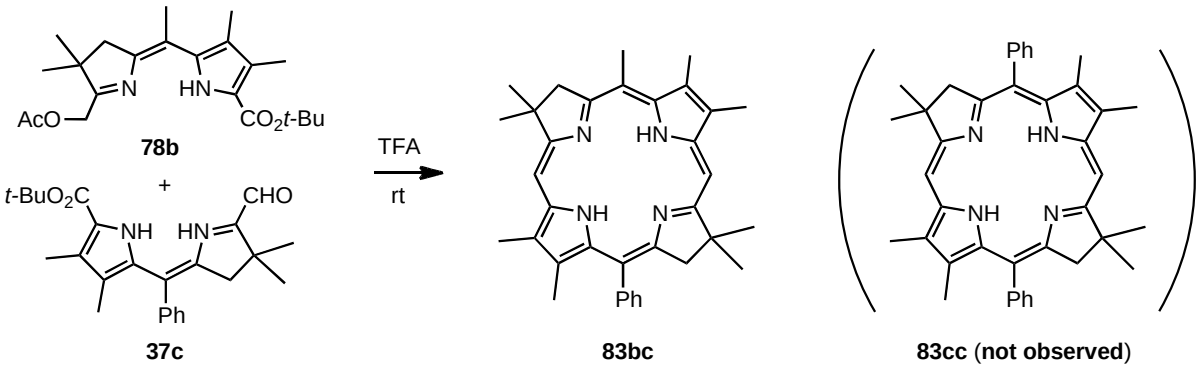
Scheme 24

This concept was first tested employing the formyl-dihydrodipyrrin **37b** and acetate derivative **78b**, the latter prepared in good yield by low temperature reduction of **37b** with Super-Hydride followed by quenching with acetic anhydride (Scheme 25). Screening of reaction conditions by UV spectroscopy was carried out employing a variety of solvents and acid catalysts. Of these, either neat TFA or the combination of TFA/CH_2Cl_2 appeared to be most effective, with the reaction exhibiting a characteristic bacteriochlorin spectrum almost immediately upon mixing at RT. On closer examination, though, it was clear that at least two pigments had been formed. One of these had NMR and UV data fully consistent with the anticipated bacteriochlorin **83bb**. The other (minor) product, while not fully characterized, displayed a UV spectrum that was remarkably similar to that of Lindsey's tetradehydrocorrin **74** (*cf.* Scheme 22). On this basis, and also NMR data, we have tentatively assigned structure **84bb** to this compound, which would be a reasonable by-product from cyclization of intermediate **79** in Scheme 24.



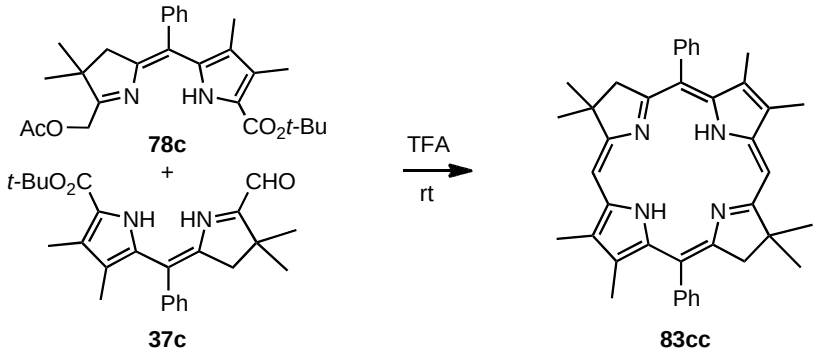
Scheme 25

While this result was gratifying, the possibility existed that bacteriochlorin **83bb** was forming via a reaction pathway involving self condensation of **37b**, which would correspond to the Lindsey methodology outlined in Scheme 22.[41] However, two experiments ruled out this possibility. In the first of these, self-condensation of **37b** was attempted under identical conditions to those employed in Scheme 25. While trace amounts of bacteriochlorin **83bb** could be detected by TLC, the amounts formed were far too small for this to be a major reaction pathway. Secondly, we carried out the mixed condensation of dihydrodipyrrin **37c** and acetate derivative **78b** (Scheme 26). Only a single bacteriochlorin product was



Scheme 26

observed, whose ^{1}H NMR and UV spectra allowed us to unambiguously assign the structure **83bc**. In particular we could find no trace of the **37c** self-condensation product **83cc**, which for comparison was prepared on small scale by condensation of dihydrodipyrrins **78c** and **37c** in neat TFA (Scheme 27).



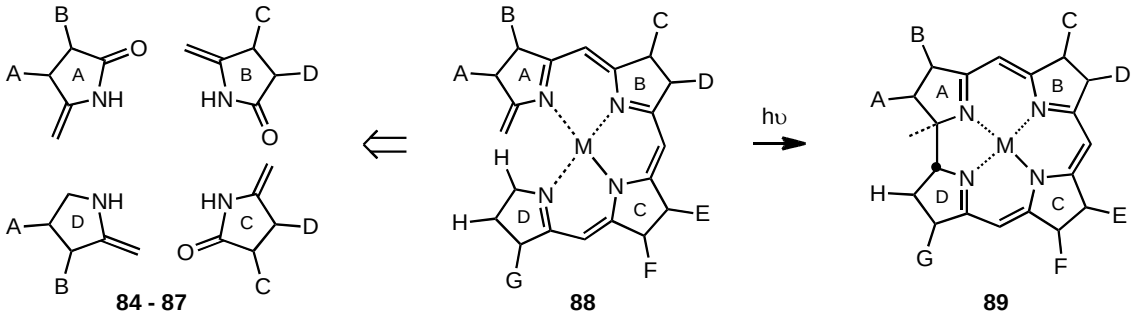
Scheme 27

Finally, on preparative scales the condensation of dihydrodipyrrins **78b**,**c** and **37b**,**c** was best carried out in 25% TFA/CH_2Cl_2, which appeared to minimize the formation of by-products **84**. Typical yields ranged from 20-40%, which will undoubtedly improve with further optimization. As a caveat, we should note that we have thus far been unsuccessful at effecting this condensation with the *meso*-H substituted dihydrodipyrrins **37a** and **78a** (R_1, R_2 = H in Scheme 24). This reactivity pattern follows the same general trend observed in our chlorin syntheses (*vide supra*) and is consistent with a carbocation

reaction pathway leading to intermediate **80** (cf. Scheme 24). As a strong point, the described methodology proceeds in a single flask under straightforward conditions, and does not involve redox chemistry or the use of a metal template. Also, to the best of our knowledge it is the only bacteriochlorin synthesis in which the starting materials are in the proper oxidation state to lead directly to the aromatic macrocycle.[41b] As such it should provide access to a variety of synthetic bacteriochlorins, including derivatives that are unsymmetrically substituted at C5 and C15.

III. An Iterative Synthesis of Semicorrins, Tripyrrolines and Higher Homologues.

III. 1 Background. The most complex of the naturally occurring tetrapyrroles are members of the corrin class, which incorporate up to ten chiral centers within the macrocycle (*cf.* **89** in Scheme 28).[42] Not surprisingly, these compounds also present the greatest synthetic challenge. In 1969 Eschenmoser



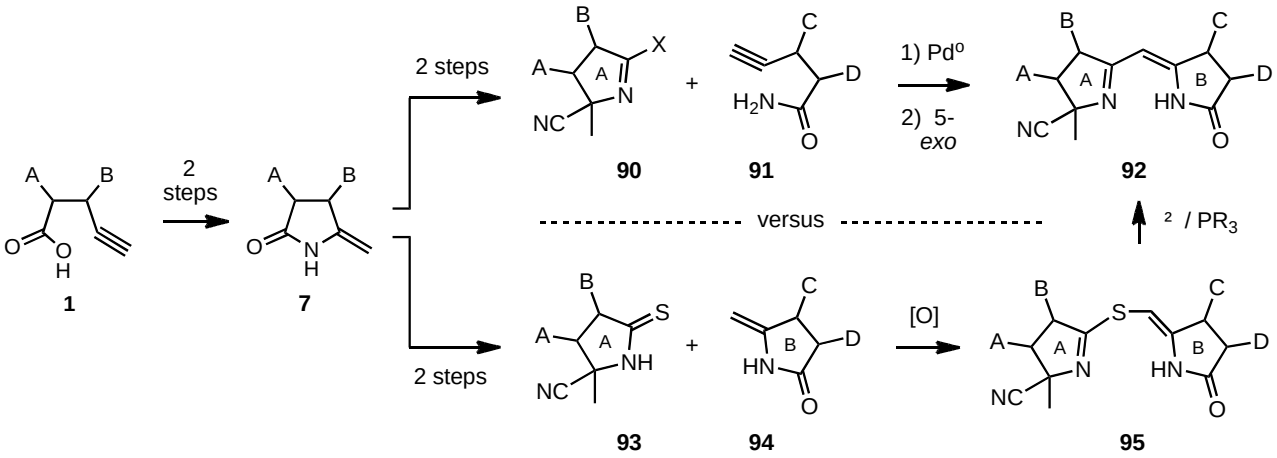
Scheme 28

et al. published an entirely new synthesis of corrins,[43] providing in the process a dramatic illustration of the power of the recently discovered Woodward-Hoffmann rules.[44] This strategy is outlined in Scheme 28 for the general case of corrin **89**. Thus, rings A-D (**84**-**87**) were assembled mainly employing sulfide contraction methodology[40] to afford the secocorrin derivative **88**, which was maintained in the all *Z*-geometry by complexation with an appropriate metal M. Secocorrin **88** then underwent a symmetry-allowed, antarafacial 1,16-hydrogen transfer upon exposure to visible light, and the resultant intermediate, upon cycloisomerization, afforded corrin **89** in excellent yield and with over 95% stereo-selectivity. This strategy remains the "gold standard" to the present day and its implementation was an extraordinary achievement.

The versatility of this strategy is limited only by the availability of the corresponding monocyclic intermediates **84**-**87**, and the fact that the sulfide contraction procedure is not well suited for introducing *meso*-substituents. In the following sections we describe our efforts at developing new methodology to supplement the sulfide contraction procedure, and its utility in synthesizing semicorrins, tripyrrolines and higher homologues.

III. 2 Non-*meso*-Substituted Semicorrins and Higher Homologues.

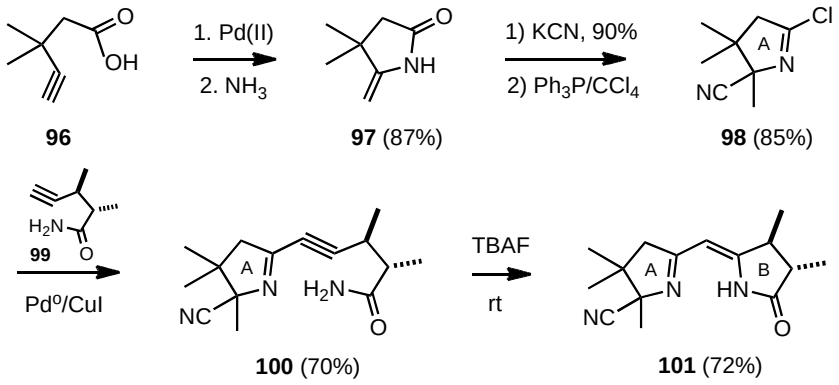
In Scheme 2 we described the facile conversion of alkyne acids **1** to enelactams **7**, employing either of two efficient pathways (*vide supra*). We hoped that cyclizations of this type might be employed in an iterative fashion to prepare semicorrins of general structure **92** (Scheme 29). To accomplish this goal, alkyne acids **1** would first be converted to imidoyl chlorides or triflates **90** by a four step sequence consisting of *(1)* Pd(II)-catalyzed cyclization; *(2)* aminolysis of the resultant enelactone to give lactam **7**; *(3)* enamide protection (KCN);[45] and *(4)* lactam activation employing either CCl_4/PPh_3 (X = Cl) or Tf_2O/imidazole (X = OTf). Imidoyl derivatives **90** would then be transformed to semicorrins **92** by Pd(0)-catalyzed coupling with alkyne amides **91**, followed by 5-*exo*-*dig* ring closure. For comparison, we also outline in Scheme 29 the sulfide contraction methodology leading to the same target. In many



Scheme 29

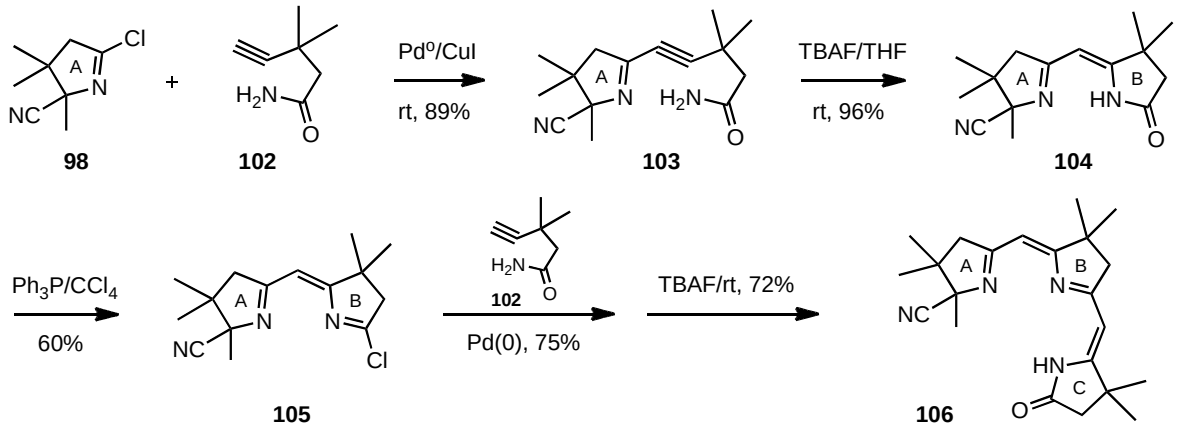
instances these two approaches will likely complement each other. However, a potential advantage of the proposed route is the ready accessibility of alkyne amides of type **91**. In addition, the Pd(0)-catalyzed coupling of alkynes to imidoyl halides is relatively insensitive to steric hindrance (*vide infra*).

This concept was first tested with the enelactam derivative **97**, itself derived by 5-*exo*-*dig* cyclization of the alkyne acid **96**,[46] followed by aminolysis (87%).[47] Enamide **97** was then readily converted to the imidoyl chloride **98** by initial protection with KCN (90%),[45] followed by chlorination using Ph_3P/CCl_4 (85%).[48] Finally, we were pleased to find that Sonogashira coupling of **98** with the homochiral alkyne amide **99** afforded a 70% yield of the pyrrolinoalkyne **100**,[49,4] which underwent clean cyclization with TBAF to afford the semicorrin **101** (72%; epimers at C2).



Scheme 30

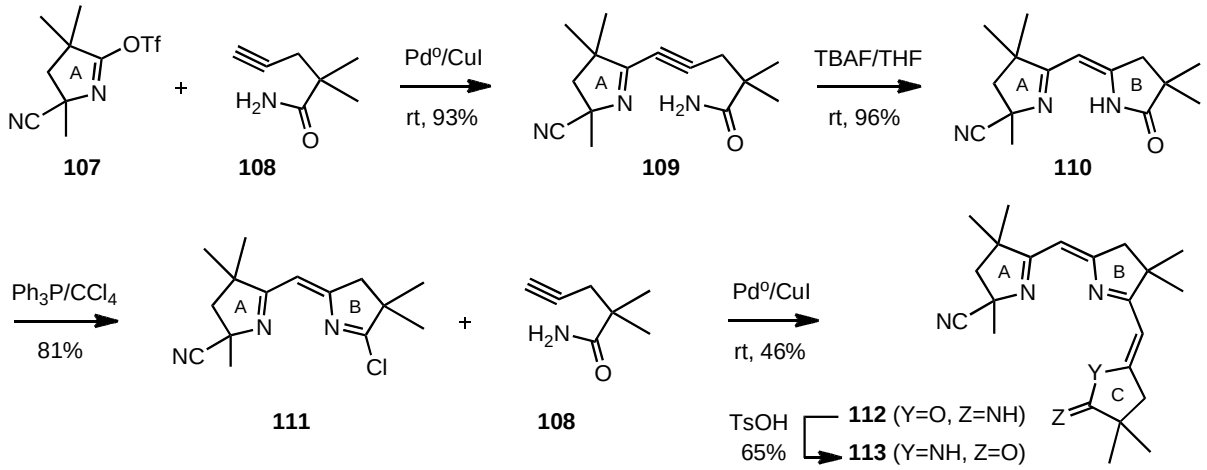
We next studied the coupling of the imidoyl chloride **98** with the alkyne amide **102**, which was accomplished in 89% yield using the reagent system Pd(0)/CuI. The resultant pyrrolinoalkyne **103** was then cleanly converted to the *Z*-semicorrin **104** upon treatment with TBAF in THF (96% yield). Both of these transformations were effected at rt and under essentially neutral conditions. Furthermore, repetition of this sequence of enamide activation, alkyne coupling, and cyclization led directly to the *Z,Z*-tripyrroline **106**,[50a] which had identical physical and spectral properties as the material previously reported by Eschenmoser in his model studies for the synthesis of cobyric acid.[43,50b]



Scheme 31

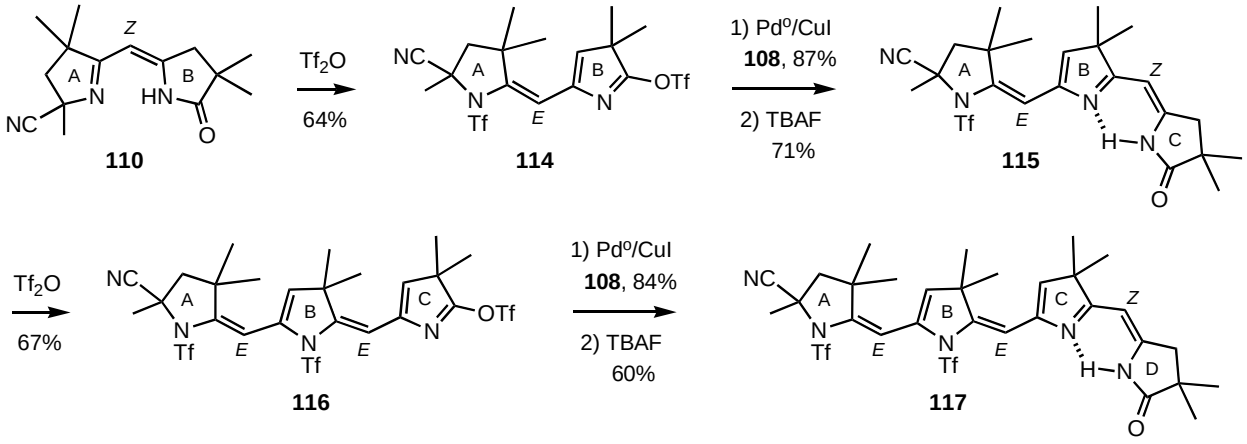
It was important to explore the effect of adjacent substituents on both the coupling and cyclization steps. Steric crowding turned out not to be a problem, as demonstrated for the case of imidoyl triflate **107** and alkyne amide **108** (Scheme 32). Once again, Sonogashira coupling of **107** with **108** afforded an excellent yield of the corresponding pyrrolinoalkyne **109**, which underwent cyclization at rt with TBAF to give a 96% yield of the *Z*-semicorrin **110**. Chlorination of **110** with Ph_3P/CCl_4 then gave an 81% yield of the imidoyl chloride **111**. Interestingly, Sonogashira coupling of **111** with **108** led directly to the iminolactone **112** (Y = O, Z = NH), which was isolated in 46% yield as the *Z,Z*-isomer. This

divergence in reaction pathway might be due to complexation of Cu with the A,B-rings of **111**, since concomitant coupling and cyclization of terminal alkynes is not observed with non-chelating substrates. In the event, acid catalyzed Dimroth rearrangement of **112** with $TsOH/H_2O/CHCl_3$ then gave a 65% yield of the desired tripyrroline **113** (Y = NH, Z = O) as an inseparable mixture of *E*- and *Z*-isomers.



Scheme 32

Finally, we have evaluated both imidoyl chlorides and triflates as substrates for Pd(0)-catalyzed coupling. Once in hand these species generally serve equally well for *terminal* alkyne acids and amides (*cf.* **107**, above). However, triflate formation is occasionally complicated by competing reaction at nitrogen. For example, treatment of *Z*-semicorrin **110** with Tf_2O/2,6-di-*t*-butyl-4-methylpyridine led directly to the N,O-ditriflate derivative **114**, obtained exclusively as the *E*-isomer due to steric repulsion (Scheme 33). Diversions of this type are not observed in imidoyl chloride formation, since the reagent system Ph_3P/CCl_4 reacts exclusively at the enamide carbonyl (*cf.* **110** → **111**, above). Interestingly, *bis*-triflation did not forestall subsequent elaboration. Thus, Sonogashira coupling of **114** with the acetylenic amide **108**, followed by 5-*exo*-*dig* cyclization, gave an excellent yield of the corresponding tripyrroline **115**, whose *E,Z*-geometry was confirmed by X-ray analysis (hydrogen bond between rings B and C).[52] Repetition of this sequence of activation, coupling, and cyclization then afforded the secocorphin derivative **117**. In **117**, the *E*,*E*,*Z*-geometry derives from hydrogen bonding between rings C and D, and steric repulsion between rings A-C.

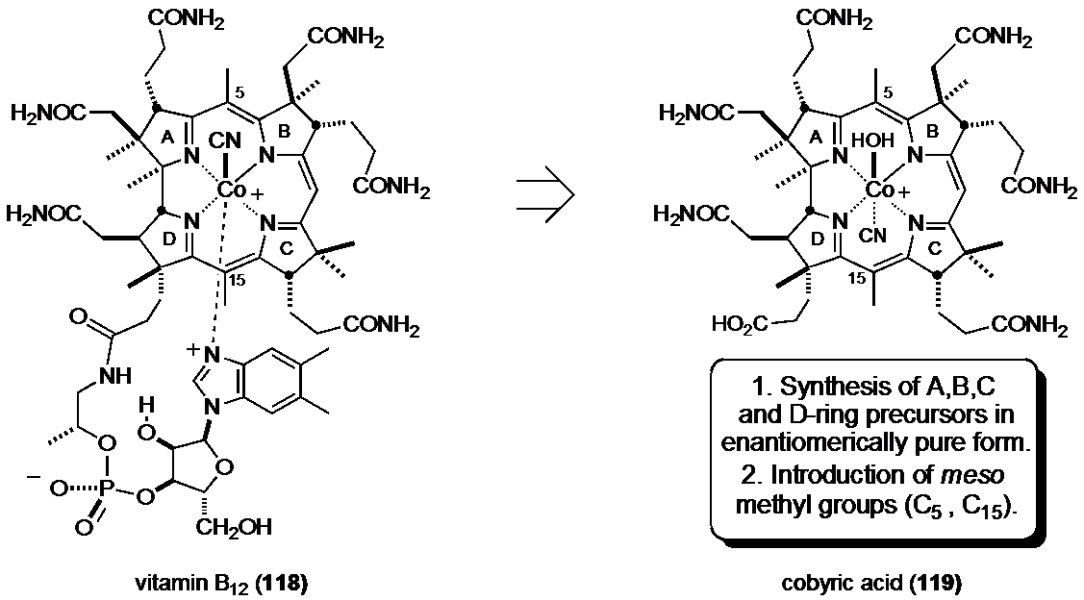


Scheme 33

In conclusion, we have described an iterative process for the synthesis of semicorrins and higher analogs that complements the sulfide contraction methodology and in some cases might prove advantageous. In the next section we describe the extension of this methodology to the incorporation of *meso*-substituents, which required only slight modification.

III. 3 *meso*-Substituted Semicorrins and Higher Homologues.

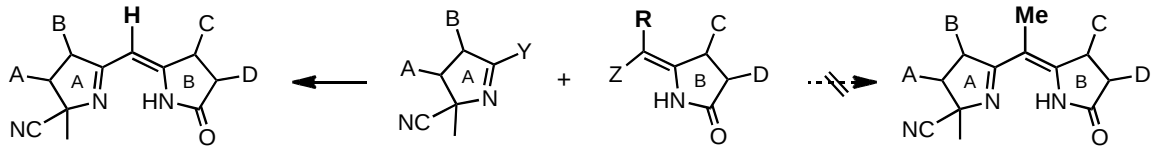
Vitamin B_{12} (**118**) is a member of the corrin class of hydroporphyrins,[42] which incorporate a vinylogous amidine chromophore within a tetrapyrroline skeleton (Figure 2). Members of this class have been the subject of extensive studies, not only because of their biological importance, but also due to their intriguing biosynthetic pathway.[9b,53] Recently this area has seen a resurgence of interest from synthetic chemists, mostly directed toward the degradation product cobyric acid (**119**).[4,54,67] This is because **119** is a known synthetic precursor to the more complex naturally occurring **118**.



vitamin B_{12} (**118**) cobyric acid (**119**)

Figure 2

Two of the greatest challenges in this area are the synthesis of the A, B, C and D-ring precursors in enantiomerically pure form, and the introduction of the *meso*-methyl groups at C5,15. In most cases, the amidine building blocks for corrins have been prepared by a combination of iminoether condensations and sulfide contraction steps, both of which were pioneered by Eschenmoser in his extraordinary synthesis of vitamin B_{12}.[55] This methodology can be very effective, as summarized for the hypothetical coupling of enamide derivatives **120** and lactam derivatives **121a** (R = H) to give semicorrins **122** (Scheme 34). However, the sulfide contraction procedure is highly sensitive to steric hindrance, and it is generally unsuited to synthesizing *meso*-substituted semicorrins of type **123** (*vide infra*).[56]



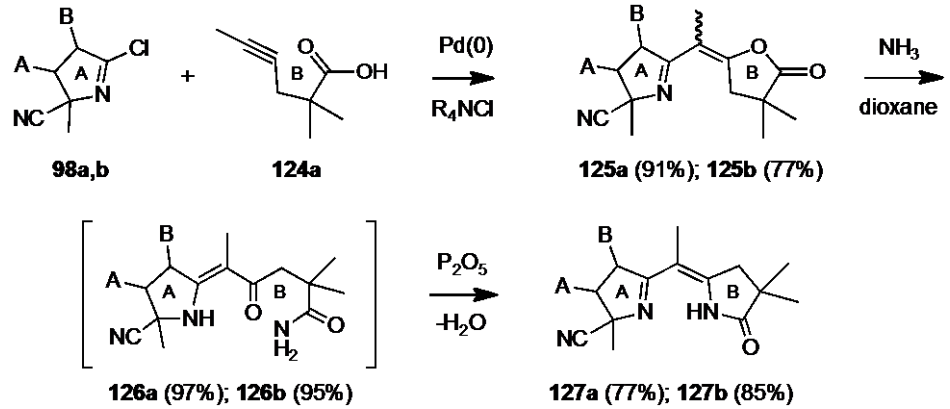
Sulfide Contraction: Y = SH; Z = H, I

Iminoether Condensation: Y = OEt; Z = H, CN

a: R = H; **b**: R = Me

Scheme 34

The cross-coupling methodology outlined in Scheme 7 was readily extended to the synthesis of *meso*-substituted semicorrins.[57] For example, Pd(0)-catalyzed coupling of imidoyl chloride **98a** with alkyne acid **124a** afforded a 91% yield of the enelactone **125a**, which was obtained as a 1:1 mixture of *E*- and *Z*-isomers (Scheme 35). In this case intramolecular hydrogen bonding is not possible, and the *E:Z*-ratio reflects steric interactions. Ring opening of **125a** with NH_3/dioxane then gave a 97% yield of the ketoamide **126a**, which upon dehydration was cleanly converted to the desired semicorrin **127a** (P_2O_5, 77%). Not surprisingly, **127a** was obtained exclusively as the *Z*-isomer due to internal hydrogen bonding. In identical fashion, imidoyl chloride **98b** underwent coupling with **124a** to afford a 77% yield

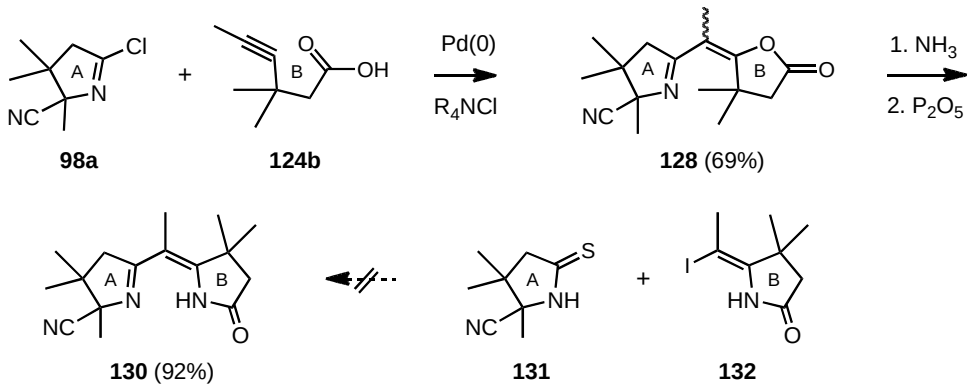


a: A = Me_2, B = H_2; **b**: A = H_2, B = Me_2

Scheme 35

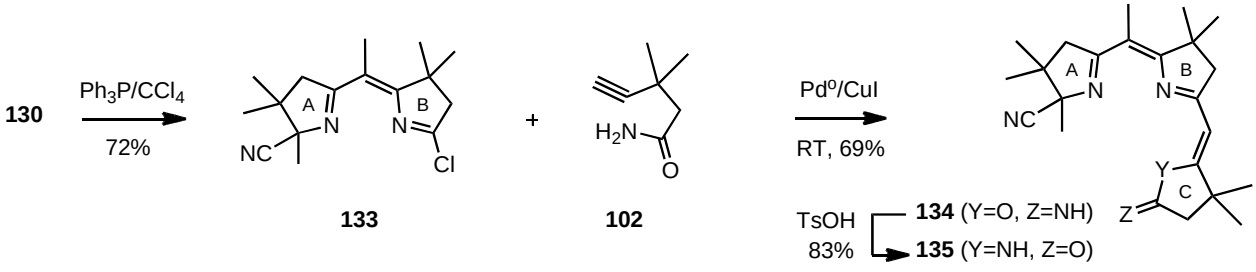
of the enelactone **125b**, which because of strong steric crowding exists predominantly in the *E*-configuration (*E:Z* = 10:1). Once again, however, aminolysis followed by dehydration provided only the *Z*-semicorrin **127b**, in 85% overall yield.

It was important to test the compatibility of this methodology with steric hindrance in ring-B, which is a critical issue in the synthesis of semicorrins related to cobyric acid (**119**). This question was explored using the alkyne acid **124b**, which gave a 69% yield of enelactone **128** on Pd(0)-catalyzed coupling/cyclization with **98a** (Scheme 36). Aminolysis and subsequent dehydration then afforded semicorrin **130** in 92% yield. In contrast, all attempts at preparing **130** employing the sulfide contraction procedure failed, returning only the starting materials **131** and **132**.



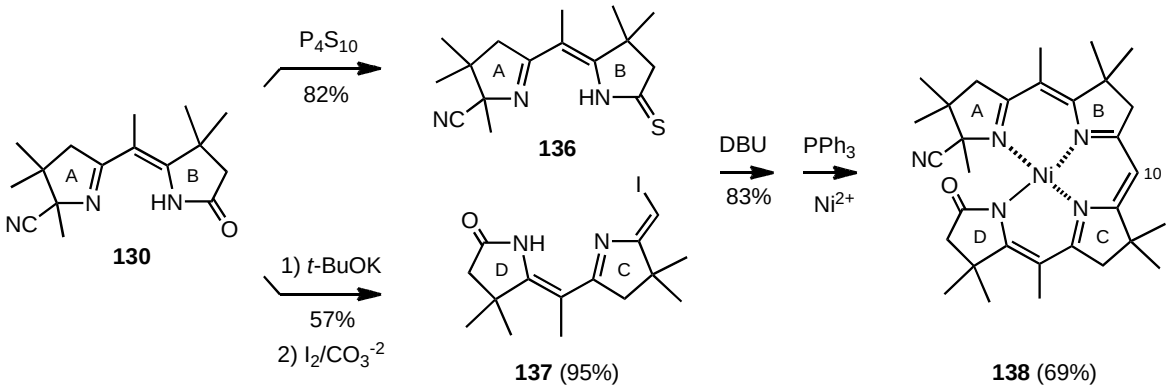
Scheme 36

Finally, the iterative capability of this strategy was demonstrated by converting **130** to the imidoyl chloride **133**, which was cleanly accomplished using CCl_4/Ph_3P (72%) (Scheme 37). Sonogashira coupling of **133** with the alkyne amide **102** then led directly to the iminolactone derivative **134** (69%), *via* a reaction pathway that most likely involves chelation of Cu (*vide supra*). As described previously (*cf.* Scheme 32), acid-catalyzed Dimroth rearrangement of **134** then gave an 83% yield of the *Z,Z*-tripyrroline **135**, which has a similar substitution pattern to that found in rings A-C in cobyric acid (**119**).[57]



Scheme 37

Further iterations of this process are possible, to produce tetrapyrroles and higher homologs. However, it is sometimes preferable to employ a more convergent approach. For example, for a synthesis of the di-*meso*-substituted secocorphin **138**, we envisioned linking semicorrins **136** and **137**, for which the sulfide contraction methodology is well suited (Scheme 38). Partly this is because the bridging *meso*-carbon (C10) is unsubstituted, and therefore steric hindrance is less pronounced. Of equal importance, metal chelation can be utilized to facilitate tetrapyrrole formation.



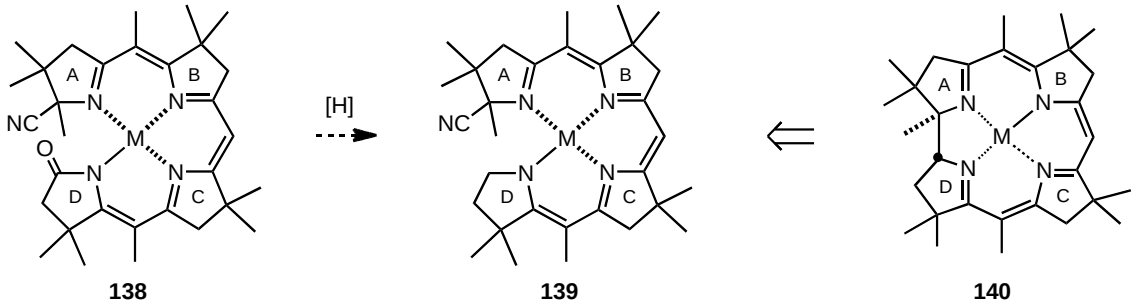
Scheme 38

The required coupling partners **136** and **137** were derived from enamide **130** following the routes indicated. For **136** this involved straightforward thiolactamization with P_4S_{10} (82%). Vinyl iodide **137** was obtained from **130** by initial base-induced elimination of HCN (57%), followed by iodination with I_2/K_2CO_3 (95%). Coupling of **136** and **137** was then effected using DBU, which gave an 83% yield of an intermediate vinyl sulfide after stirring 2 h in MeCN at rt. Finally, sulfide contraction to produce secocorphin **138** was accomplished in 69% yield,[57] using identical conditions to those employed by Eschenmoser *et al.* for synthesizing the non-*meso*-substituted analog of **138** ($Ni[ClO_4]_2/Ph_3P$).[58]

The ability to incorporate *meso*-substituents in secocorphins of type **138** provides a useful new tool in tetrapyrrole synthesis. In the section that follows we describe the application of similar methodology to the synthesis of hexahydrodipyrrins (*H6*-dipyrrins) and secocorrins, which are in the proper oxidation state for cyclization to corrins.

III. 4 Semicorrins and Secocorrins Related to Vitamin B_{12}

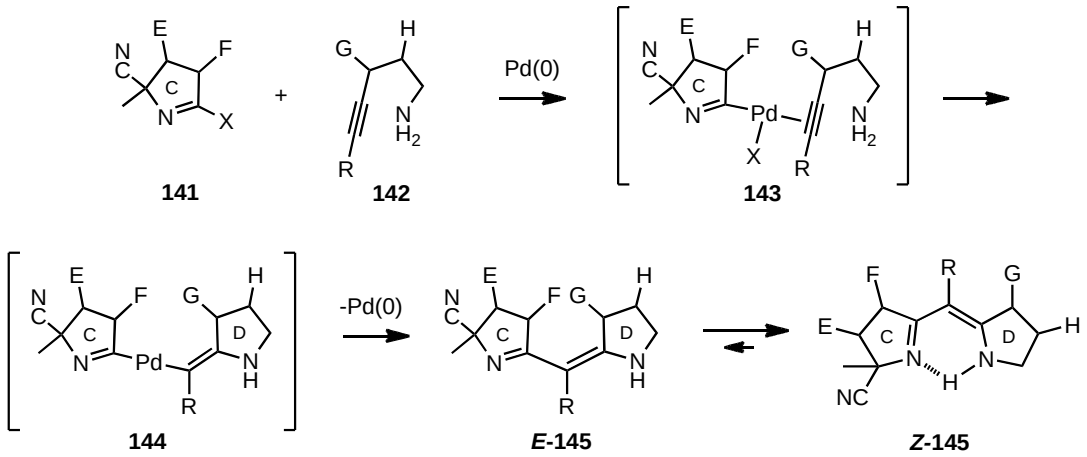
In Section III.3 we described a convergent synthesis of secocorphin **138** that took advantage of the ready availability of semicorrin **130** (*cf.* Scheme 38).[50a,57] In principle, reduction of ring D in **138** could provide secocorrin **139** having both the proper oxidation state and substitution pattern for cyclization to corrin **140** (Scheme 39). In practice, though, transformations of this type have proven difficult to achieve.



Scheme 39

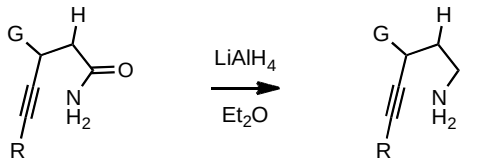
We therefore investigated two strategies for preparing CD-ring semicorrins where ring D is in the pyrroline oxidation state.

Our initial approach is outlined in Scheme 40 and takes advantage of the nucleophilic character of alkyne amines **142** in Pd(0)–catalyzed coupling/cyclization reactions.[59] Thus, oxidative addition of Pd(0) to imidoyl derivatives **141** would be followed by π-complexation, and then nucleophilic capture to generate vinyl–Pd(II) species of type **144** (Pd ligands have not been shown for clarity). Finally, reductive elimination would afford CD-ring hexahydrodipyrrins **145**, presumably as the *E*-isomers (retention of configuration).[60] However, *E*-**145** should undergo rapid equilibration to the more stable *Z*-**145**, which has an internal hydrogen bond. As previously noted, the thermodynamic driving force for expulsion of Pd(0) in **144** should overcome any steric crowding in the transition state leading to **145**.



Scheme 40

Alkyne amines **142a-e** were prepared by LAH reduction of the corresponding amides **146**, and were used to evaluate the effects of steric hindrance and alkyne substitution pattern on reactivity (Scheme 41).[61] Coupling experiments were then conducted with the imidoyl triflate **147**, which turned out to be far more

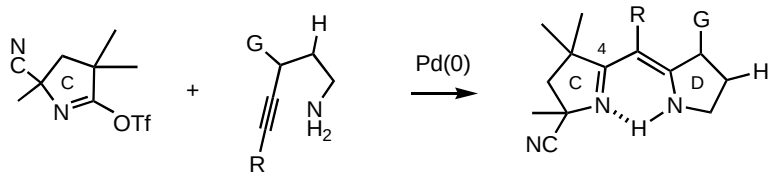


146 **142** (75-99%)

a: G = H_2, H = Me_2; R = Me. **b**: G = H_2, H = Me_2, R = H.
c: G = Me_2, H = H_2, R = H. **d**: G = Me_2, H = H_2, R = Me. **e**: G,H,R = H.

Scheme 41

reactive than the corresponding imidoyl chloride in couplings with alkyne amines (Scheme 42). The mechanistic rationale for this observation will be presented later. For the present, we were pleased to find that Pd(0)–catalyzed coupling/cyclization of **147** with alkyne amines **142** was readily effected, affording 70-85% yields of the corresponding (*H6*)-dipyrrins **148**. For example, **147** combined at RT with terminal alkynes **142b** and **142e** (R = H), using the reagent system $Pd(Ph_3P)_4/NEt_3$/THF (80% and 85% yields, respectively). Similarly, reaction of alkyne amine **142a** (R = Me) with **147** gave a 70% yield of the *meso*-substituted (*H6*)-dipyrrin **148a**. This last conversion required warming to 80 °C in MeCN and was accelerated by added $BnNEt_3Cl$.[60] Also, the most effective catalyst was the Pd_2dba_3/TFP system described by Farina.[62]



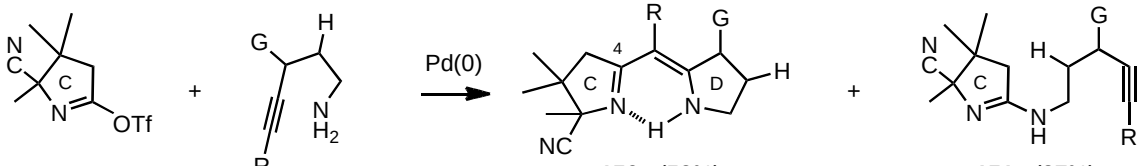
147 **142** **148** (70-85%)

a: G = H_2, H = Me_2; R = Me. **b**: G = H_2, H = Me_2, R = H. **e**: G,H,R = H.

Scheme 42

The results obtained with the isomeric imidoyl triflate **149** were less straightforward (Scheme 43). In **149** the geminal methyl groups at C2 are well removed from the reacting center at C4 and therefore provide little steric shielding. Consequently, direct nucleophilic displacement at C4 competes effectively with the Pd(0)-catalyzed process. In the best case, coupling of **149** with the alkyne amine **142a** gave a 52% yield of the *meso*-substituted (*H6*)-dipyrrin **150a**, accompanied by 37% of amidine **151a**, the product of amine displacement. In analogous fashion, the more sterically hindered alkyne **142c** afforded only 31% of the desired (*H6*)-dipyrrin **150c**, and 62% of amidine **151c**. Finally, alkyne amine **142d**, which contains the most shielded triple bond and the least hindered amine, gave amidine **151d** as the exclusive product (70% yield). To summarize this approach, steric crowding at C4 has little

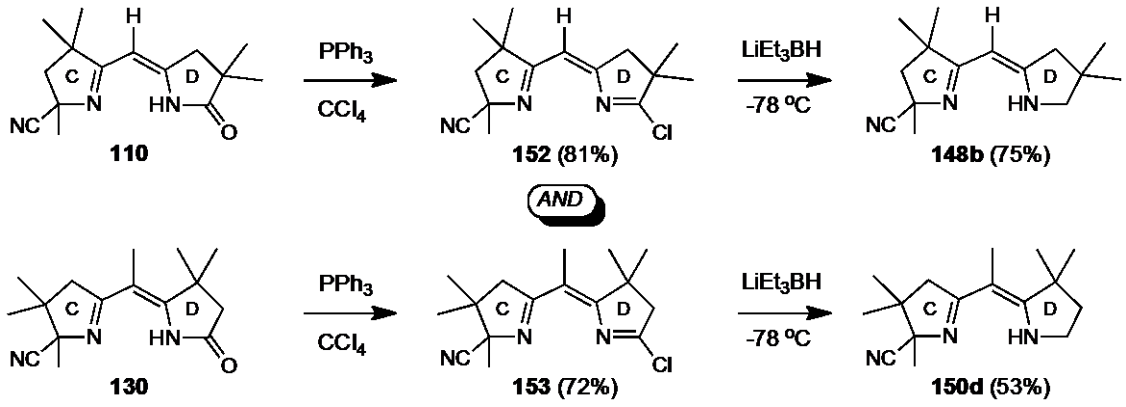
or no effect on the desired Pd(0)-catalyzed coupling/cyclization. In fact, it can be beneficial in retarding undesired side reactions (*cf.* Scheme 42). However, shielding of the alkyne bond by both terminal and adjacent methyl substituents has a pronounced effect on selectivity, and generally favors direct attack by the amine.



a: G = H_2, H = Me_2; R = Me. **c**: G = Me_2, H = H_2, R = H. **d**: G = Me_2, H = H_2, R = Me.

Scheme 43

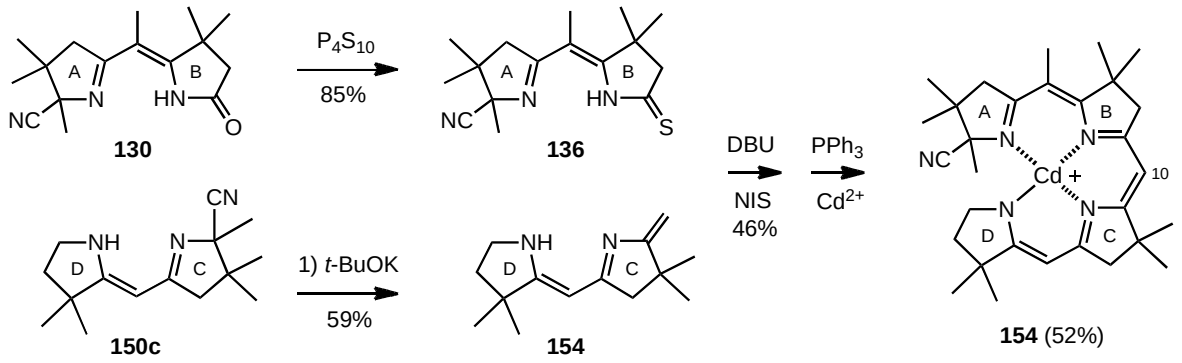
In principle, reduction of semicorrin **110** could provide an alternate route to the (*H6*)-dipyrrin **148b** previously synthesized as described in Scheme 41 (Scheme 44). If successful, this approach might then be applied to the synthesis of less accessible (*H6*)-dipyrrins of type **150**. Surprisingly, there appear to be no reports describing the reduction of semicorrins of type **110** to 1,2,3,7,8,9-hexahydrodipyrrins, and in fact this transformation proved to be very challenging. Eventually, though, we found that the desired reduction of imidoyl chloride **152** could be effected in 75% yield utilizing Super-Hydride ($LiEt_3BH$) in THF at –78 °C. In identical fashion, semicorrin **130** gave the corresponding imidoyl chloride **153** (72%), which on reduction afforded (*H6*)-dipyrrin **150d** in 53% yield.



Scheme 44

Having in hand both semicorrin **130** and (*H6*)-dipyrrin **150c**, we employed Eschenmoser's methodology to synthesize the *meso*-substituted secocorrin **154** (Scheme 45).[58] This required the initial preparation of thiolactam **136** and dipyrrin derivative **154**, both of which were readily obtained following literature

precedent.[58,61] Oxidative coupling of **136** with **154** was then accomplished in 46% yield using NIS in the presence of DBU. Finally, treatment of the resulting vinyl sulfide with PPh_3 and $CdCl_2$ led directly to the secocorrin **154** (52%), which is in the correct oxidation state for photochemical cycloisomerization.[61]

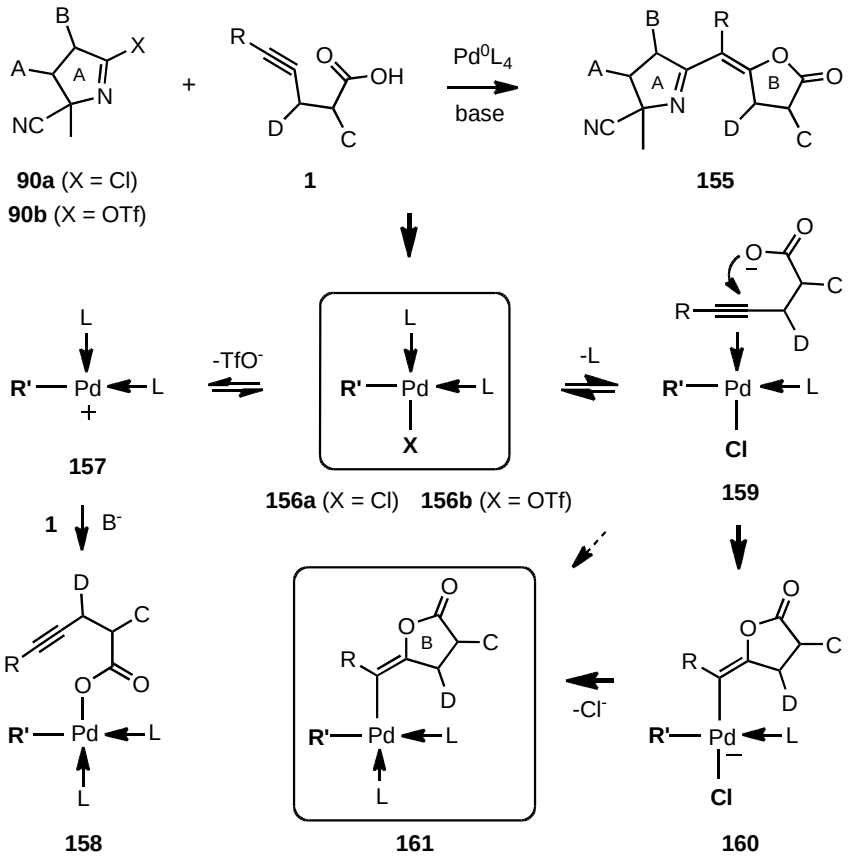


Scheme 45

III. 5 On the Mechanism of Pd(0)-Catalyzed Coupling/Cyclization Reactions[63]

In Section **III.2** we noted that *terminal* alkyne acids undergo Pd(0)-catalyzed coupling/cyclization with both imidoyl chlorides and triflates with little difference in rate. Moreover, the same is true for *terminal* alkyne amines. These reactions are carried out under Sonogashira conditions [Pd(0)/CuI], where the reactive species are alkynyl cuprates.[49] Accordingly, the most likely mechanistic pathway follows the sequence of oxidative addition, then transmetallation and reductive elimination. However, this pathway is not available for *internal* alkyne substrates, where substrate-dependent rate differences are common. For example, imidoyl chlorides **90a** are much more reactive than triflates **90b** in Pd(0)-catalyzed coupling/cyclizations with *internal* alkyne acids **1** (*cf.* Scheme 46, below). Conversely, imidoyl triflates **90b** are better substrates for coupling/cyclization with *internal* alkyne amines **142** (*vide infra*). Clearly different mechanisms operate in the Pd(0)-catalyzed coupling/cyclization of internal alkyne acids **1** and alkyne amines **142**.

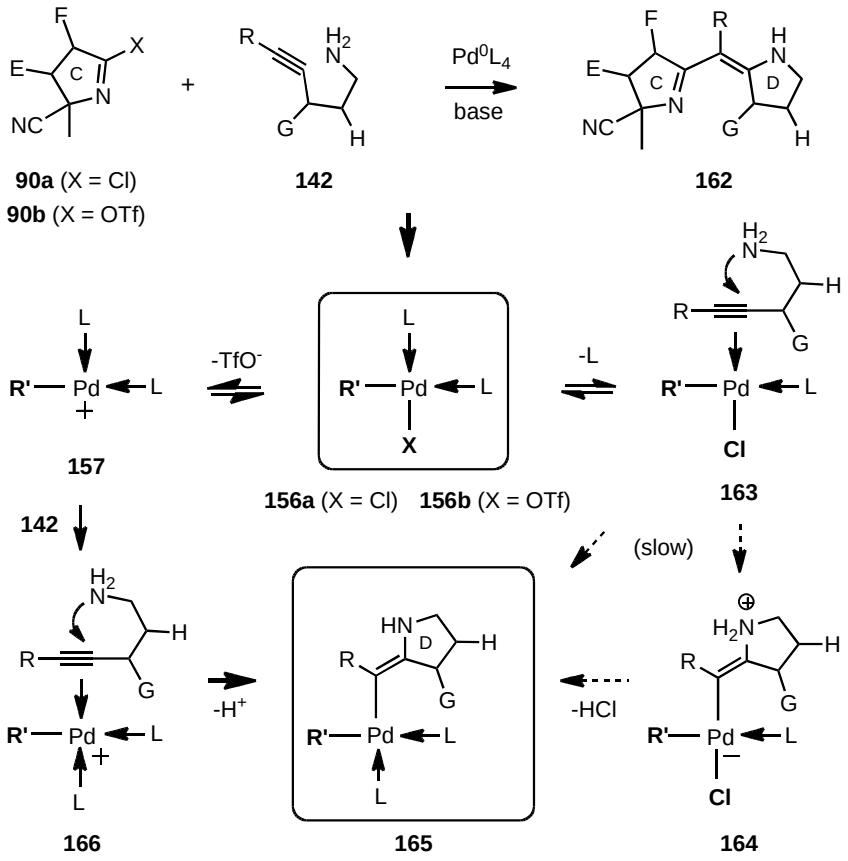
The reactivity pattern of acids **1** is best explained on the basis of the relative Pd(II)-ligand bond strengths of $RCO_2^- > Cl^- > TfO^-$. This is illustrated in Scheme 46, employing imidoyl chloride **90a** (X = Cl) and imidoyl triflate **90b** (X = OTf) as substrates. In both cases, Pd(0)-catalyzed coupling/cyclization reactions were carried out under weakly alkaline conditions (base = NEt_3), in which the alkyne acid **1** is substantially ionized. Starting with **90b**, *syn*-oxidative addition leads initially to the square planar Pd(II) complex **156b**, which is likely in equilibrium with the cationic species **157**.[64] However, a dissociative mechanism is not required. As pointed out by Arcadi *et al.*,[60] carboxylate anions readily displace the labile triflate ligand from Pd(II) complexes. The resultant σ-Pd(II)-carboxylate complex **158** is then effectively removed from the catalytic cycle, due to the strength of the Pd(II)-O(C=O)R bond. Consequently little or no enelactone **155** is formed.



Scheme 46

In contrast, under identical conditions the imidoyl chloride **90a** rapidly affords the desired lactones **155**. This change in reaction pathway is most likely due to the greater stability of the Pd-Cl bond in **156a**,[64a] which is inert to both heterolytic cleavage (**156a** → **157**) and direct anionic substitution (**156a** → **158**). Instead, π-complexation takes place by dissociation of a neutral ligand L to form the alkyne complex **159**.[60,64] Ligand substitution is then followed by nucleophilic capture, affording the vinylpalladium intermediate **161** either by direct displacement of Cl^- (**159** → **161**),[64] or *via* an anionic, associative process (**159** → **160** → **161**).[65] In either case σ-bond formation is facilitated by the high nucleophilicity of the participating carboxylate anion. Finally, *cis*-reductive elimination leads initially to the *E*-enelactone **155**,[64] which subsequently undergoes equilibration to the observed *E,Z*-mixture (bond isomerizations have been omitted for clarity).

A similar analysis applies to the Pd(0)-catalyzed coupling/cyclization of alkyne amines **142**, which is sluggish when effected with imidoyl chlorides **90a**, but rapid with triflates **90b** (Scheme 47). This is the opposite chemoselectivity to that exhibited with alkyne acids **1**, and presumably reflects the greatly reduced nucleophilicity of the alkyne amine π-complex **163**, as compared to the alkyne carboxylate π-complex **159** (*cf*. Scheme 46). Thus, the amino alkyne group in **163** is slow to substitute Cl^- by either direct displacement (**163** → **165**), or by an associative process (**163** → **164** → **165**).



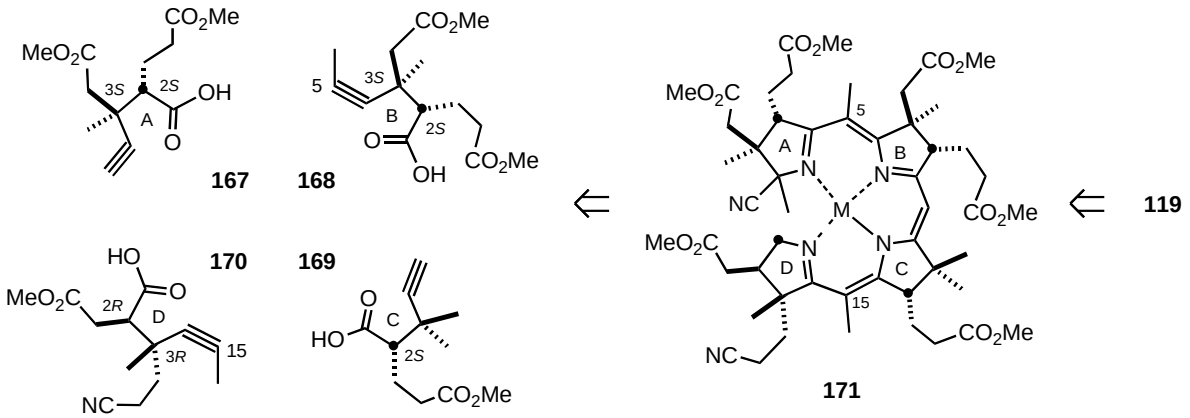
Scheme 47

Lastly we consider the coupling of imidoyl triflates **90b** and alkyne amines **142**, which is important for the synthesis of (*H6*)-dipyrrins **162** (Scheme 47). As described above, this transformation was much faster than that observed with chlorides **90a**, and afforded mixtures of dipyrrins **162** and the corresponding amidines obtained by direct displacement.[61] We considered the possibility that the displacement products were derived by a Pd(0)-catalyzed process.[66] However, control experiments demonstrated that TfO^- substitution occurred by direct nucleophilic displacement, and was not dependent on Pd(0). The more favorable Pd(0)-catalyzed coupling of triflates **90b** and alkyne amines **142** is consistent with a mechanism in which *syn*-oxidative addition of Pd(0) affords the square planar complex **156b**, followed by dissociation of the labile TfO^- ligand to give cation **157**. An identical sequence was postulated for steps 1-2 in the attempted coupling/cyclization of alkyne acids **1** and imidoyl triflates **90b** (*cf.* Scheme 46). At this point, however, the reaction pathways diverge. With carboxylate anions **1**, ion-pair bonding with cation **157** affords the neutral Pd(II)-σ-bond complex **158**, a favorable, albeit non-productive step (Scheme 46).[60] In contrast, primary alkyne amines **142** are much less likely to undergo Pd(II)-σ-bond formation under these conditions. This type of association typically requires concomitant deprotonation by strong base ($LiNR_2$, NaOR, etc.), or additional activating functionality ($SnNR_2$).[66] Therefore, in the present case π-complexation of **142** with **157** is more favorable (Scheme

47), and affords the cationic species **166** which is highly activated toward nucleophilic capture (**166** → **165**).[64] The resultant vinylpalladium species **165** then undergoes *cis*-reductive elimination to give the (*H6*)-dipyrrins **162**, which undergo facile equilibration to afford the observed thermodynamically more stable *Z*-isomers (For a more detailed discussion of these mechanisms, including solvent and ligand effects, see reference 65).

IV. The Alkyne Acids of Vitamin B_{12}.

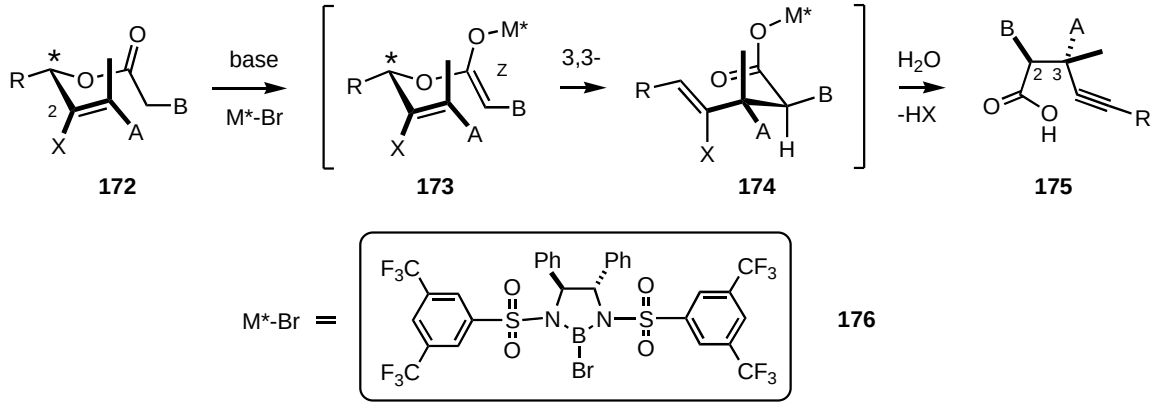
IV. 1 Background. In Section III we described iterative syntheses of semicorrins, tripyrrolines and higher homologues, in which the pyrroline and lactam rings are derived from suitably functionalized alkyne acids. For the purpose of synthesizing cobyric acid (**119**), and thence vitamin B_{12} (**118**), we require access to alkyne acids of type **167** - **170**, which would be employed in analogous fashion to construct the corrin nucleus (Scheme 48).[67] Simplifying this goal is the fact that **167** - **170** share a number of features that could facilitate their preparation from a common precursor. Thus, each has a C3 quaternary center and at least one of these substituents is methyl. Also, in **167**, **168**, and **170** the orientation of the acetate and propionate groups is *syn* (although in **170** the regio- and absolute stereochemistry are reversed). Finally, acids **167** and **168** are identical except for the C5 alkyne substituent (H vs Me). Assembly of these acids as described above would produce the secocorrin derivative **171**, which is properly functionalized for photochemical ring closure to produce a corrin precursor to **119**.



Scheme 48

IV. 2 Ring C

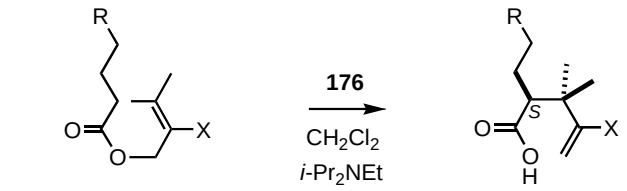
To accomplish these syntheses we are investigating variants of the Ireland–Claisen rearrangement, a powerful method for synthesizing 4-pentenoic acid derivatives.[68] In principle the alkyne oxidation level found in **167**-**169** can be attained by incorporating a leaving group "X" in allylic esters of general structure **172** (Scheme 49). Following 3,3-sigmatropic rearrangement to **174**, elimination of HX would provide the desired alkyne acid **175**.



Scheme 49

The stereochemical outcome depicted in **175** has strong precedent. Diastereoselectivity in this transformation is controlled by both enolate- and double-bond geometry, with the stipulation that reaction occurs through the most stable chair conformation. As indicated, the desired *syn*-selectivity would be obtained from the *Z*-enolate-*Z*-alkene configuration of **173**. Control of absolute stereochemistry is also precedented and might be accomplished in either of two ways. When R ≠ H, C3 is a chiral center (*) that can be introduced in enantioselective fashion (substrate control). Alternatively, with R = H facial selectivity might be achieved using a chiral Lewis acid (M*-Br; reagent control). Corey *et al.* have reported promising results in this area employing the boron reagent **176**.[69]

Our initial experiments were carried out employing reagent control and were targeted toward the ring-C precursor **169** (*cf.* Scheme 48).[67a] However, these studies were only partly successful (Scheme 50). Thus, a range of allylic esters **177** (X = H) and **178** (X = Br) were subjected to Ireland–Claisen rearrangement employing the Corey reagent **176**.[69] Of the eight substrates examined only **177a** (R = $CH_2OTPDPS$) and **177b** (R = CH_2OBn) gave useful quantities of 4-pentenoic acids, affording **179a,b** in 35-50% yields and ~85% *ee*. Unfortunately the bromo derivatives **178** were completely unreactive, thereby precluding their use in preparing alkyne acid **169**. This reactivity difference most likely derives from a combination of steric crowding and in some cases competing complexation with reagent **176** (i.e. when R = CO_2Me, CN).

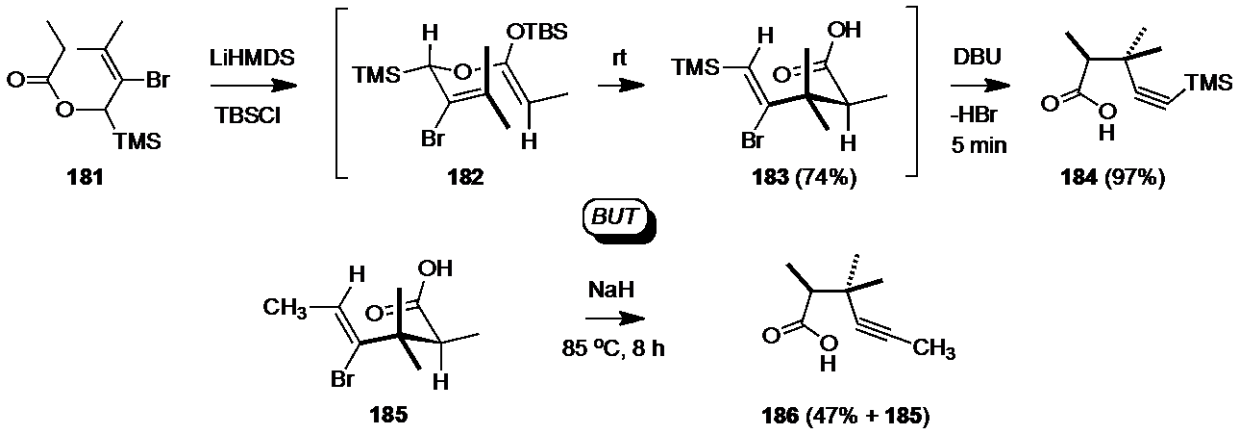


177 (X = H); **178** (X = Br) **179** (X = H); **180** (X = Br)

a: R = $CH_2OTPDPS$. **b:** R = CH_2OBn. **c:** R = CO_2Me. **d**: R = CN.

Scheme 50

In principle, substrate control offers a more practical means to control both enantio- and diastereoselectivity by avoiding the use of bulky and/or rigid chiral Lewis acids. Model studies showed this to be the case, working with the readily available racemic ester **181** (Scheme 51).[67b] Thus, following literature precedent,[68] **181** was treated with 1.1 equiv each of LiHMDS and TBSCl (*tert*-butyldimethyl-silyl chloride) in THF/HMPA at –78 °C. Upon warming to rt the resultant ketene silyl enolate **182** underwent smooth rearrangement, affording a 74% yield of alkene acid **183** after 1 h at 25 °C. Interestingly, **183** was accompanied by varying amounts of alkyne acid **184**, which increased to 71% after standing 96 h. Alternatively, **184** was obtained in 97% yield upon brief exposure of **183** to DBU (5 min). To better understand this remarkably facile elimination we prepared the alkene acid **185**, which differs



Scheme 51

from **183** only in the substitution of a CH_3 group for TMS. Compound **185** was inert to DBU at RT, and elimination of HBr was only partly complete after heating at 85 °C for 8 h with NaH/DME. Clearly the TMS group plays an important role in facilitating the conversion of **183** to **184**.

We believe the enhanced reactivity of **183** can be traced to two factors: The structural rigidity imposed by the vinyl bond and the ability of Si to stabilize *both* α-anions (the α-effect) and β-cations (the β-effect) (Figure 3).[70] For the general case of **187** → **189**, C-H bond cleavage is assisted by "negative hyperconjugation," utilizing the low-lying Si-alkyl σ*-orbitals to stabilize developing negative charge. Concomitantly, the vinyl-Si bond is held coplanar to the breaking C-Br bond, where the β-effect is most pronounced (hyperconjugation). These interactions should significantly stabilize the E2-like transition state **188** leading to *anti*-periplanar elimination of HBr. It is worth noting that simultaneous activation of this type is not feasible for silyl alkyl bromides **190**, since coplanarity of the Br, H, and Si-bonds is impossible (*cf.* conformer **190a**). These species normally react via desilylbromination, which occurs readily from conformation **190b**.

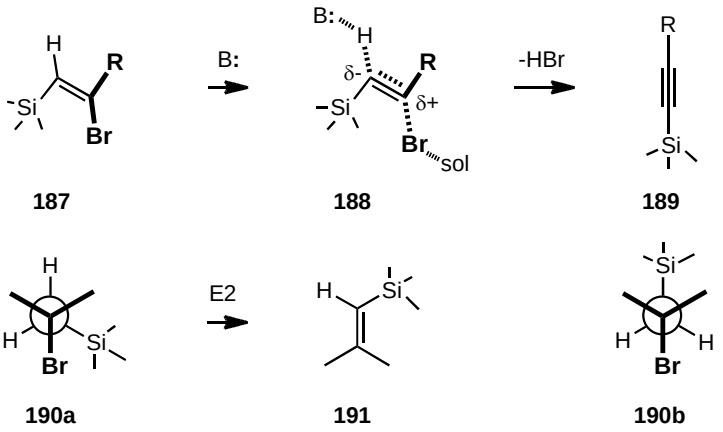
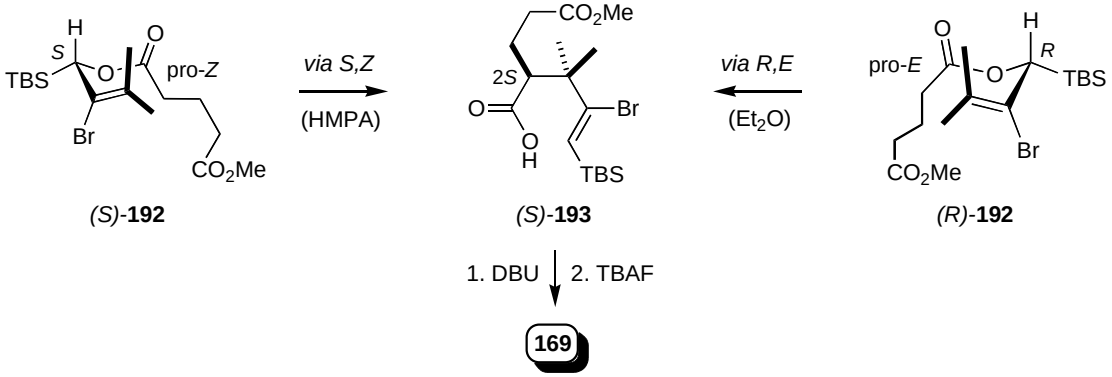


Figure 3

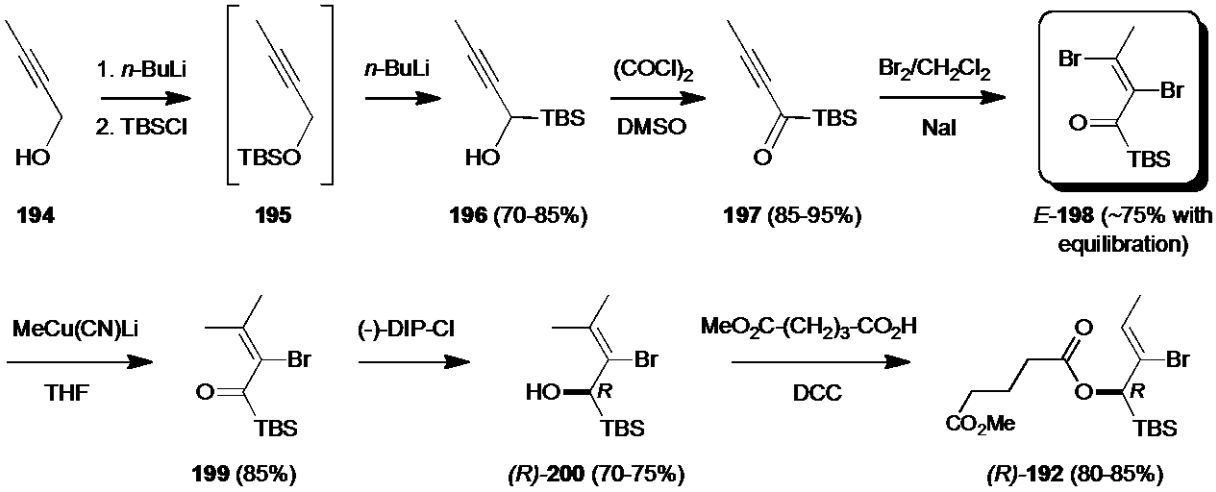
The model studies outlined in Scheme 51 were readily extended to the synthesis of **169**, which was accomplished following two independent routes (Scheme 52).[67a,d] The first of these involved the preparation and Ireland–Claisen rearrangement of the allylic ester *(S)*-**192**, which afforded the desired alkene acid *(S)*-**193** *via* the intermediacy of a *Z*-silylketene acetal (*cf.* also Scheme 49). Silicon-assisted elimination of HBr and de-silylation then afforded **169** in ~50% overall yield from *(S)*-**192**. While workable, though, the key Ireland-Claisen rearrangement leading from *(S)*-**192** to *(S)*-**193** was difficult to scale and required the use of carcinogenic HMPA as an additive. To address this issue, we also explored the possibility of effecting an *E*-selective ester-silylenolate rearrangement on the allylic ester *(R)*-**192** as an alternative means of establishing the 2*S*-configuration in (*S*)-**193** (Scheme 52). An important advantage to this route is that *E*-silylenolate formation is typically carried out in non- or weakly coordinating solvents such as Et_2O, eliminating the need for HMPA as an additive. In fact, this route turned out to be much preferred.[67d]



Scheme 52

It is worth considering the synthesis of *(R)*-**192** in some detail, since it proceeds through an intermediate dibromoenone *E*-**198** that could be common to each of our syntheses of the alkyne acids of vitamin B_{12}

(Scheme 53) Our synthesis began with commercially available 2-butyne-1-ol (**194**), which, following a literature procedure, was first silylated employing *n*-BuLi/TBSCl.[71] Without purification, the resulting silyl ether **195** was subjected to *in situ retro*-Brook rearrangement to produce TBS alcohol **196** in 70-85% yield.[71] Swern oxidation of **196** then gave an 85-95% yield of the corresponding alkynone **197**. Our plan was that **197** would undergo selective *anti*-bromination to afford the *E*-dibromoenone *E*-**198**, for which there was some precedent.[72] Initially, however, this reaction presented difficulties, in that under kinetic control the undesired *Z*-isomer predominated. For example, bromination of **197** at –78 °C (CH_2Cl_2/Br_2) gave a ~3:5 mixture of *E*-**198** and *Z*-**198**. In contrast, higher temperatures appeared to favor

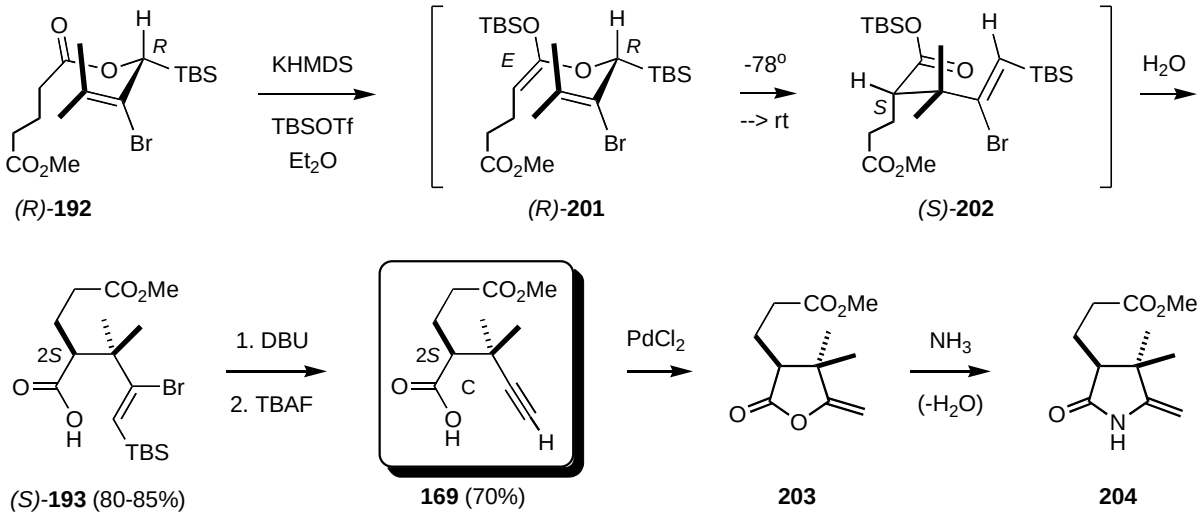


Scheme 53

thermodynamic control, with the best results obtained at RT and in the presence of catalytic NaI. Under these conditions the desired *E*-isomer predominated by >2:1, and isolated yields of *E*-**198** ranged from 60-65% (versus 25-30% for *Z*-**198**). Moreover, nearly the identical ratio of *E*-**198** : *Z*-**198** was obtained upon equilibration of isolated *Z*-**198** with $BF_3{\cdot}Et_2O$ at RT, raising the effective yield of *E*-**198** to ~75% after one recycle.[67c] In this way we were able to conveniently prepare multigram quantities of *E*-**198** for subsequent conversion to TBS-ketone **199**, which was accomplished in 85% yield upon treatment with MeCu(CN)Li/THF. With ample quantities of **199** now in hand, we devoted considerable effort to effecting the asymmetric reduction of **199** to give *(R)*-**200**. From among many reagent combinations screened, (–)-DIP-Cl provided the most satisfactory results,[73] affording 70-75% yields of alcohol *(R)*-**200** with *ee* ~95%. Finally, *(R)*-**200** underwent smooth coupling with *mono*-methylglutarate to afford the desired allylic ester *(R)*-**192** in 80-85% yield.

We had now reached the point of effecting the *E*-selective Ireland–Claisen rearrangement of *(R)*-**192**, for which the *t*-butyldimethylsilyl (TBS) group served two purposes: *(1)* as a proton surrogate providing the chirality necessary for inducing the 2*S*-configuration in **169**; and *(2),* as an anchor for stabilizing the

desired chair conformation leading from *(R)*-**192** to *(S)*-**193** (Scheme 54). After exploring many base/solvent combinations, excellent selectivity was achieved employing a slight modification of conditions recently reported by McIntosh *et al*.[74] Following this precedent, *E*-enolate formation was carried out with freshly prepared KHMDS and TBSOTf in Et_2O at –78 °C. After warming to RT, and aqueous hydrolysis, alkene acid *(S)*-**193** was obtained in 80-85% yields. The material thus obtained was identical in all respects to *(S)*-**193** prepared from *(S)*-**192** (*cf.* Scheme 52), and was produced in ~25% overall yield from 2-butyne-1-ol (**194**). Finally, as described previously, *(S)*-**193** was readily converted to the ring-C alkyne acid **169** by DBU-mediated dehydrobromination followed by de-silylation. The structure of **169** was confirmed by its two-step conversion to the known cyclic enamide **204**, previously employed by Eschenmoser in his synthesis of cobyric acid (**169**).[55a]



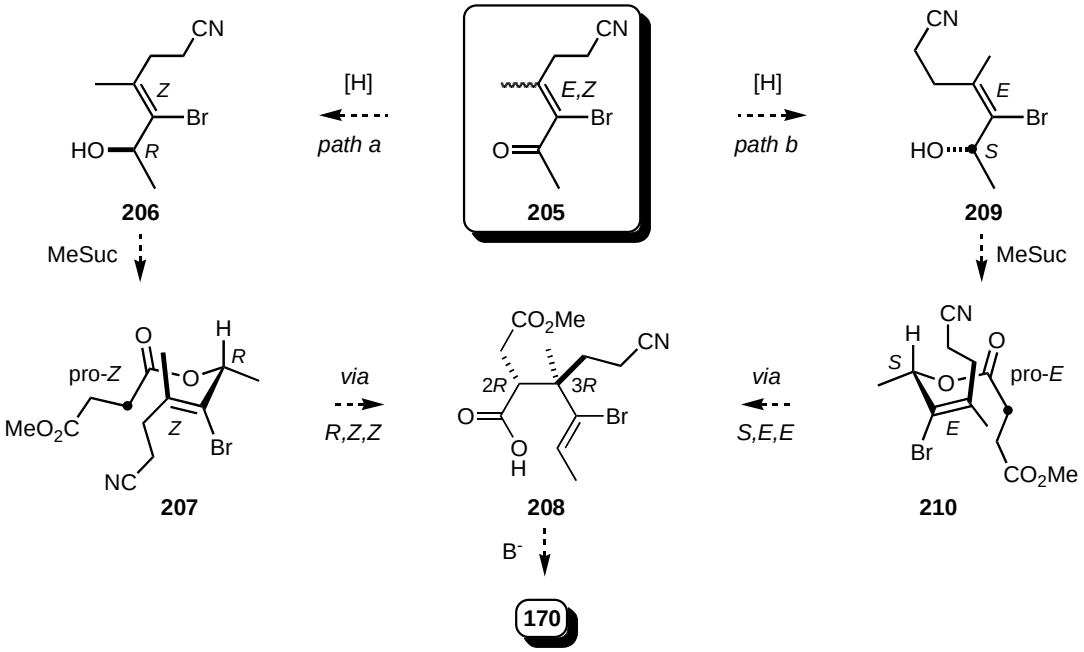
Scheme 54

IV. 3 Ring D

While the Ireland–Claisen (I–C) methodology was readily adapted to the synthesis of **169**, its application to alkyne acids of type **167**, **168** and **170** provides a more stringent test. This is especially the case with **170**, which in addition to containing a second, quaternary chiral center (C3), requires differentiation of the three carboxylate functionalities.

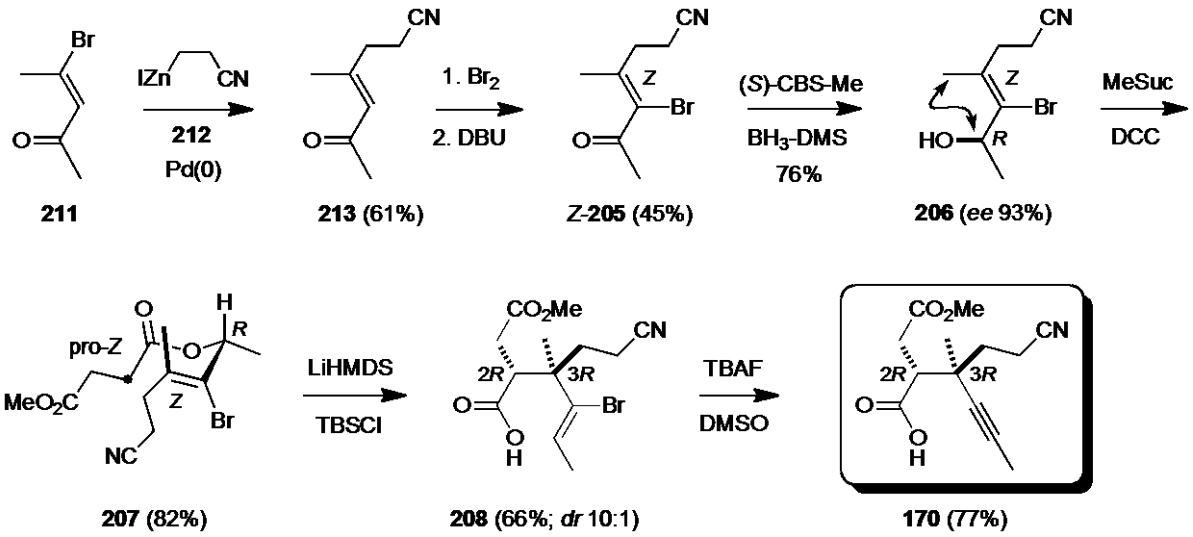
In principle, the desired stereo- and regiochemical features in **170** might be introduced employing either of the allylic ester derivatives **207** or **210**, themselves derived in enantioselective fashion from enones *E*- and *Z*-**205** (Scheme 55). Thus, following *path a*, reduction of *Z*-**205** from the *Si* face would afford the homochiral allylic alcohol **206**, which on coupling with *mono*-methyl succinate (MeSuc) would give **207**. Stereoselective *Z*-silylenolate formation, with *in situ* Ireland–Claisen rearrangement, would then produce the bromoalkene acid **208** having the 2*R*,3*R*-configuration found in **170**. Alternatively, the identical

intermediate **208** could be derived by *Re* face reduction of *E*-**205** (*path b*), esterification with MeSuc, and stereoselective *E*-silylenolate formation. Elimination of HBr would then give **170** in four steps starting with **205**.



Scheme 55

To evaluate *path a*, enone *Z*-**205** was synthesized by the route outlined in Scheme 56, which provided ample material to test the crucial Ireland–Claisen rearrangement.[67c] This synthesis began with the readily available β-bromoenone **211**,[75] which on Pd-catalyzed coupling with iodozinc reagent **212** afforded a 61% yield of the corresponding *E*-enone **213**.[76] Enone **213** was then converted in 92% yield to a mixture of α-bromoenones *E*- and *Z*-**205** by a one pot sequence consisting of bromination followed by dehydrobromination (DBU). Not surprisingly, this procedure gave essentially 1:1 *E,Z*-mixtures of **205**, which, however, were readily separated by chromatography. We were then pleased to find that *Z*-**205** underwent efficient enantioselective reduction with the reagent system (*S*)-CBS-Me/BH_3-DMS,[77a] giving a 76% yield of the chiral alcohol **206** (*ee* 93%), whose double bond geometry was established by NOE studies. With a ready supply of **206** now in hand, the remaining steps leading to the target ring-D precursor **170** followed as planned. These involved acylation with MeSuc to give ester **207** (82%), followed by stereoselective *Z*-silylenolate formation. We thus obtained a 66% yield of the alkene acid **208** with *dr* 10:1. Finally, HBr elimination using TBAF/DMSO produced **170** in 77% yield, completing a six step synthesis from enone **211**. The *syn*-stereochemistry of **170** was corroborated by conversion to the corresponding enelactone (not shown), in this case prepared by CuI catalyzed ring closure of bromoalkene acid **208** to avoid competitive 6-membered ring lactone formation.[77b] NOE studies then permitted unambiguous assignment of the relative stereochemistry as shown.



Scheme 56

Following *path a* we were routinely able to prepare alkyne acid **170** with high enantio- and diastereoselectivity, and it is likely that further improvements can be made. However, we were also interested in synthesizing the desmethyl analog **214** (Figure 4), in which case the C15 *meso*-methyl substituent would be added at a later stage. This approach was particularly attractive given the ease of synthesizing the starting dibromoenone *E*-**198** (cf. Scheme 53).

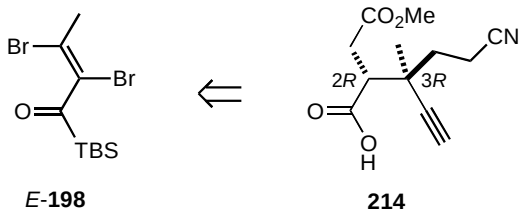
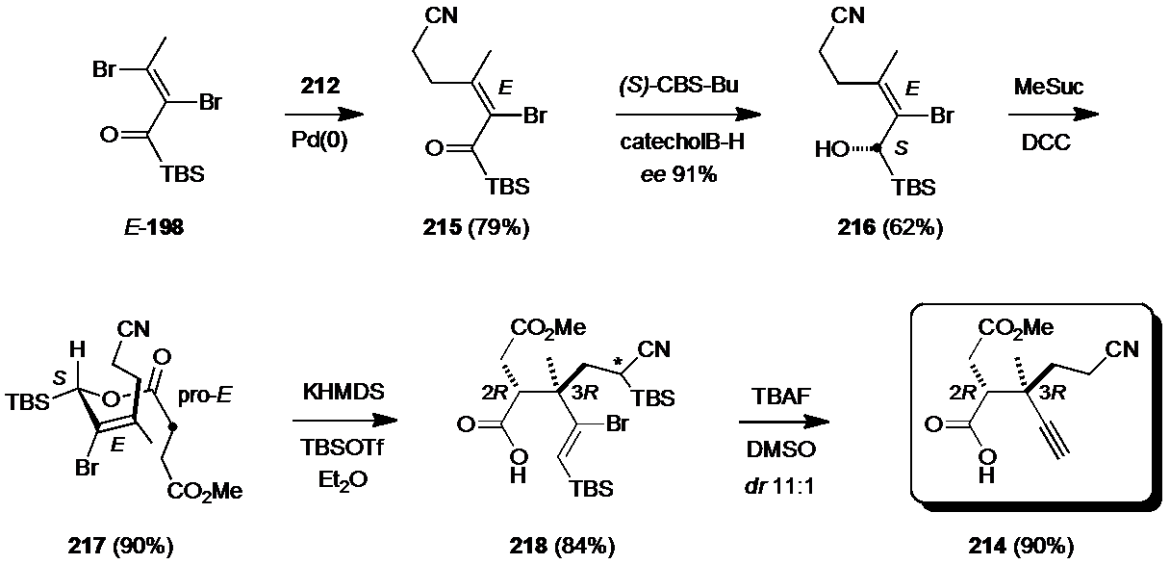


Figure 4

Our synthesis of **214** began with the Pd-catalyzed cross-coupling of *E*-**198** with the alkylzinc reagent **212**, which afforded a 79% yield of the desired *E*-bromoenone **215** (Scheme 57). The next step called for the asymmetric reduction of **215** to the (*S*)-allylic alcohol **216**, which proved to be a greater challenge than with the related methyl derivative *Z*-**205** (*cf.* Scheme 56). Most likely this was because of a less definitive "size" difference in the substituents attached to the ketone, and also the bromoalkene in TBS-ketone *E*-**198** is probably the "smaller" of the two ketone substituents. This represents a reversal of the ordering found in the methyl ketone *Z*-**205**. Working from this premise, our initial reduction studies on **215** were carried out with the same (*S*)-CBS-Me/BH_3-DMS combination employed in the reduction of *Z*-**205** to *R*-**206**, with the expectation that the *S*-enantiomer **216** would be favored. This turned out to be the case, as verified by careful inspection of the corresponding Mosher esters.[78] However, the *ee* for this

transformation was only 27%. Ultimately, the combination of (*S*)-CBS-Bu and catechol borane was found to give much better results,[79] affording **216** in 62% yield and *ee* 91%. Alcohol **216** then gave a 90% yield of the allylic ester **217** on coupling with MeSuc.



Scheme 57

The remaining hurdle was in developing reliable conditions for effecting the *E*-silylenolate Ireland–Claisen rearrangement of **217**. Once again, these were modeled on the conditions of McIntosh *et al*., employing KHMDS/TBSOTf in Et_2O (–78 °C → rt). We thus obtained an 84% yield of the rearrangement product **218**, incorporating an additional TBS group alpha to the nitrile (structure proof by X-ray analysis).[80] This was of little consequence, however, since both silyl groups were cleanly removed on treatment with TBAF in DMSO, giving a 90% yield of ring-D precursor **214** with *dr* 11:1. As with alkyne acids **169** and **170** above, the structure of **214** was confirmed by cyclization to the corresponding enelactone (not shown), which was subjected to detailed NOE analysis.

The described six step route leading from enone *E*-**198** to alkyne acid **214** proceeds with excellent enantio- and diastereoselectivity, and provides efficient access to this important ring-D precursor for cobyric acid (**119**). Moreover, we believe that *E*-**198** could serve as a common precursor to each of the pyrroline rings of **119**, and thence vitamin B_{12}.

3. CONCLUSIONS

We hope to have made the case that alkyne acids **1** are versatile intermediates for the synthesis of a variety of biologically important tetrapyrroles, including hydroporphyrins of the chlorin, bacteriochlorin and corrin families. In particular the chlorin methodology is quite robust and has formed the basis of numerous undergraduate and Ph. D. theses. The bacteriochlorin syntheses, while less developed, offer a

fresh approach and the promise of further improvement. Finally, in the corrin area, much work remains before these studies will achieve their goal of a total synthesis of vitamin B_{12}. However, we are encouraged by the results thus far and look forward to making additional contributions.

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**Dedicated to Professor Doctor Albert Eschenmoser on the occasion of his 85th birthday.*

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80. The structure of the predominate (*S*)-relative epimer was confirmed by X-ray analysis of a racemic sample. We thank the University of Massachusetts Amherst X-ray Structural Characterization Facility (NSF CHE 9974648) for providing diffractometer access and Mr. Travis Benanti of that facility for data collection and refinement.

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