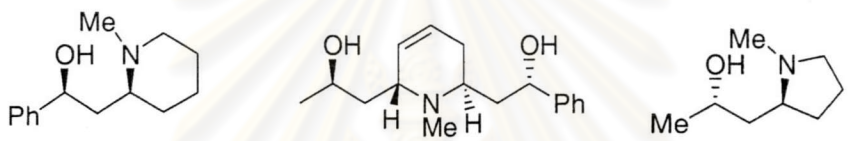
Chapter II

Results and discussion

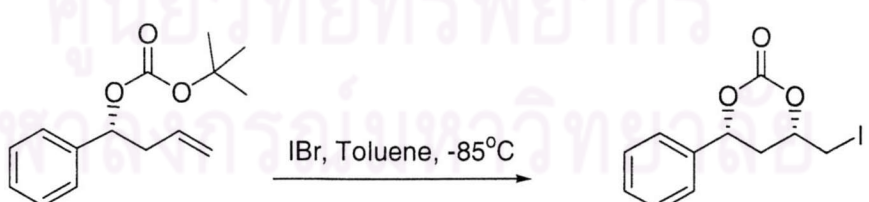
The aim of this work was to develop a new strategy for the synthesis of piperidine and pyrrolidine alkaloids. In particular, some piperidine alkaloids, known as sedum alkaloids from the species of plants from which they have often been isolated, have recently been reported to enhance cognition and to be potentially useful in Alzheimer's disease therapy.[28] Examples of sedum alkaloids are sedamine (**1**) and sedinine (**2**). Hygroline (**3**) is structurally related.



(1) (2) (3)

The key feature of these alkaloids is the 1,3-aminoalcohol moiety. This occurs in both the *syn* and *anti* forms. Numerous strategies have been reported for the synthesis of sedum alkaloids, although some of these rely on the separation of *syn/anti* isomeric mixtures. A reasonable strategy would be to use the chirality of a homoallylic alcohol to generate the amine chirality by tethered cyclofunctionalization.

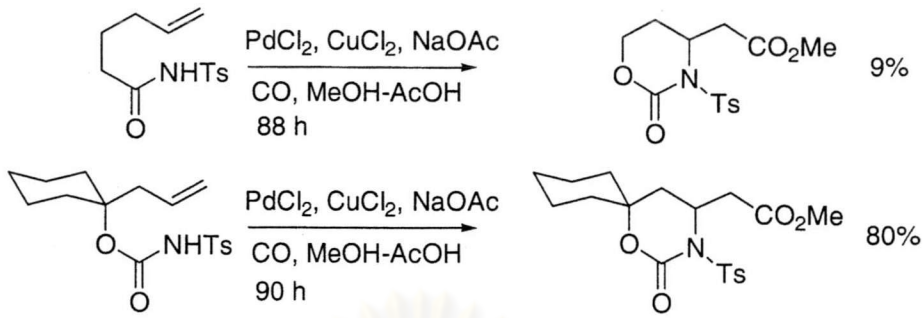
When this work commenced there were no reports of this to our knowledge and, during the course of this work, a single report, using a cyclofunctionalization, was made. (**Scheme 33**)[29]



(4) (5)

Scheme 33 Carbamate cyclofunctionalization

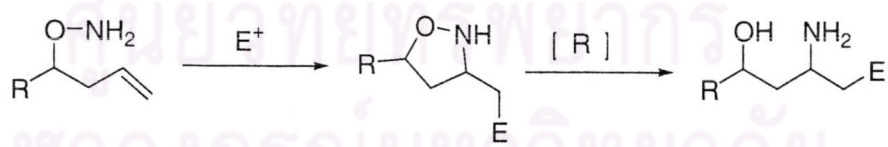
As discussed in chapter I, a palladium catalyzed tethered cyclofunctionalization would offer the advantage of concomitant C-N and C-C bond formation. Once again, there is to our, knowledge, only a single report of such a reaction. (**Scheme 34**)[27]



Scheme 34 Tamaru's cyclofunctionalization

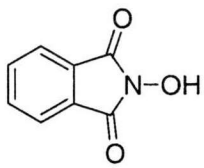
From the perspective of sedum alkaloid synthesis, this method is deficient in two aspects. Firstly, *cis/trans* mixtures were obtained and, secondly, 1,2-aminoalcohol derivatives were formed efficiently *via* a 5-membered ring transition state, but 1,3-aminoalcohol derivatives were only formed efficiently when the substrates had the full benefit of the Thorpe-Ingold effect. It can be suggested that the formation of a six-membered ring, to give a 1,3-aminoalcohol derivative, is too slow compared to catalyst degradation. The requirement for a six-membered ring is a direct consequence of the use of a one-atom tether: the carbonyl group. Efficient formation of a 1,3-aminoalcohol *via* a five membered ring transition state would, therefore, necessitate a zero-atom tether, i.e. a direct O-N bond. Hence the required substrates would be derivatives of hydroxylamines.

Removal of the tether would be by subsequent reduction of the O-N bond, using a dissolving metal, a hydride or catalytic hydrogenation. (**Scheme 35**)



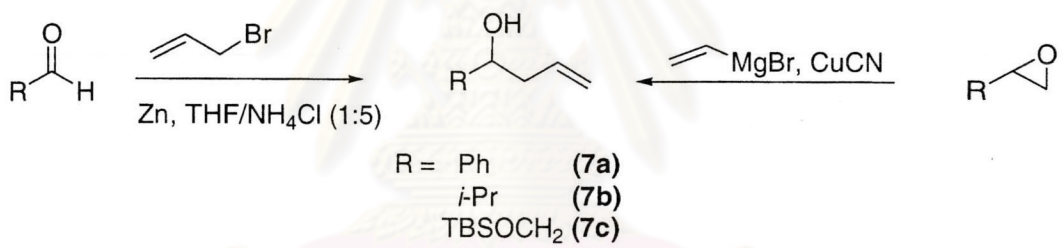
Scheme 35 Hydroxylamine cyclofunctionalization

N-hydroxyphthalimide **(6)** is a convenient and commercially available derivative of hydroxylamine. It is sufficiently acidic that it can be deprotonated with KOH and the resulting anion can participate in S_N2 alkylation reactions.[30] The acidity of N-hydroxyphthalimide is high enough that it can be coupled with alcohols using Mitsunobu chemistry.[31] The very mild conditions of this reaction make it highly suitable for the synthesis of complex natural products.



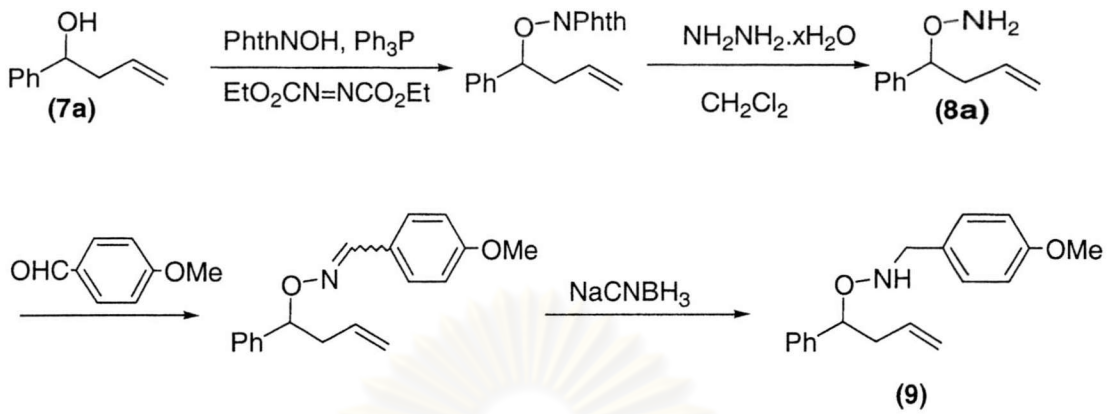
(6)

It was, therefore, planned that the desired substrates could be prepared using the Mitsunobu reaction of homoallylic alcohols. Two homoallylic alcohols (**7a**, **7b**) were prepared by Barbier reactions under the conditions reported by Luche.[32] While many metals, such as tin, aluminium, and indium, may be used,[33] this reaction is quick and clean, it uses economic reagents and the work up is simple. A third homoallylic alcohol (**7c**) was prepared by ring opening of a glycidol derivative with a higher order cuprate reagent derived from commercially vinyl magnesium bromide (**Scheme 36**) or by vinyl lithium in the presence of boron trifluoride etherate.[34]



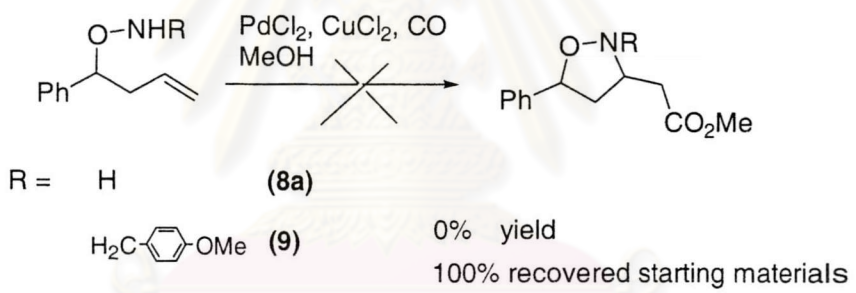
Scheme 36 Synthesis of homoallylic alcohols

Mitsunobu reaction of the homoallylic alcohols proceeded smoothly, however, it was generally found that separation of the products from the triphenylphosphine oxide by-product was difficult. The crude reaction mixtures were, therefore, subjected directly to hydrazinolysis. It was found that this proceeded under very mild conditions, in comparison with the Huang-Minlon modification of the classical Gabriel synthesis. Indeed, the reaction proceeded satisfactorily at room temperature, rather than reflux. The unblocked hydroxylamine (**8**) could then be isolated and purified by column chromatography. An N-alkyl derivative of one hydroxylamine (**9**) was formed by condensation with anisaldehyde followed by reduction with sodium cyanoborohydride. (**Scheme 37**)



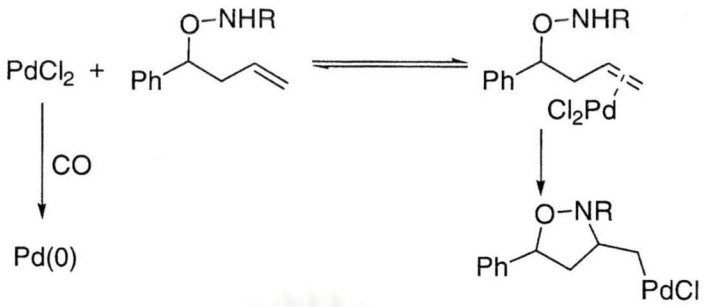
Scheme 37 Synthesis of hydroxylamines

When either hydroxylamine **(8a)** or **(9)** was subjected to cyclocarbonylation conditions, which are typical for alkenol cyclocarbonylation, the starting materials were recovered unchanged and the palladium was converted to a black metallic precipitate. (**Scheme 38**)



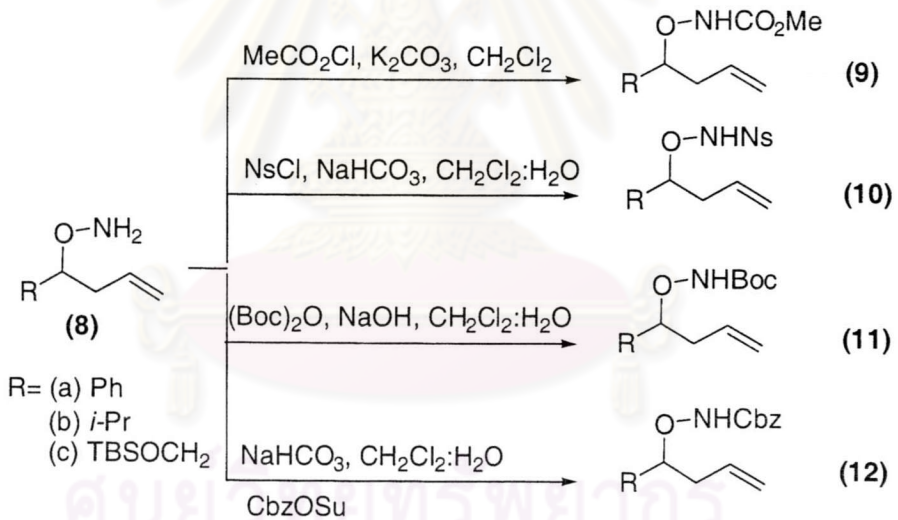
Scheme 38 Unsuccessful cyclization of hydroxylamines

A possible reason for the failure of the reaction is that the alkene may not coordinate effectively to the palladium(II) salt. This seems unlikely, however, as a wide range of alkenes is known to participate in such reactions. Another possibility is the reaction failed due to the inefficiency of the nucleophile. It may be suggested that the hydroxylamine nitrogen is not very nucleophilic due to the inductive effect of its σ-bonded oxygen. Thus cyclization is too slow to compete with direct reduction of palladium(II) to palladium(0) by carbon monoxide. (**Scheme 39**)[35]



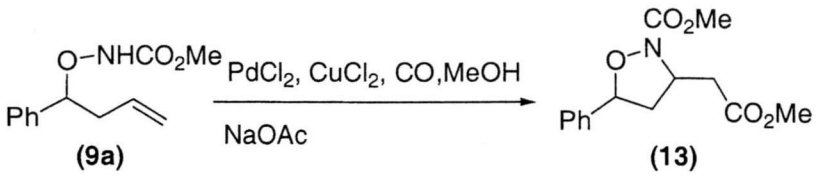
Scheme 39 Competing Palladium pathways

To make the nitrogen more nucleophilic, it would be necessary to generate a nitrogen based anion. This would be facilitated by the presence of an electron-withdrawing group on nitrogen. For this reason, a series of electron withdrawing group were employed. In each case standard N-protection conditions were used. (**Scheme 40**)[36]



Scheme 40 Hydroxylamine protection

The methyl carbamate **(9a)** was prepared first, and used to test the cyclofunctionalization. It was very pleasing to find that cyclization now proceeded, although the reaction terminated (precipitate of palladium black) before completion. (**Scheme 41**)



Scheme 41 Cyclofunctionalization of a protected hydroxylamine

It was further pleasing to find that the isoxazolidine product (**13**) was isolated as a single diastereomer (**Figure 1**). The stereochemistry was determined using nOe experiments.

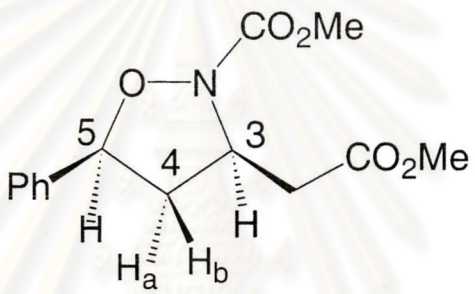


Figure 1 the isoxazolidine product (**13**)

When H5 was irradiated, the *ortho*-hydrogen atoms of the phenyl group were enhanced. Only one of the diastereotopic pair of H4 protons (H4a) was also enhanced. (**Figure 3**) It was found that the same H4 proton, which had enhancement with H5 irradiation, was also enhanced when H3 was irradiated. (**Figure 4**) This clearly indicated formation of the *cis*-isomer, as it shows that H3, H4a and H5 are on the same face.

When the same H4 proton (H4a), which had enhancement due to H3 and H5, was irradiated, H3 and H5 had enhancements. (**Figure 5**) In the same experiment, one side chain proton α to the ester with a chemical shift very close to H4a of the H4 pair was also irradiated giving enhancements of its geminal proton and of H3. Hence the H3 enhancement can not be quantified.

When the other side chain proton was irradiated, its geminal proton and H4b of the H4 pair were enhanced. (**Figure 6**)

Figure 7 shows the irradiation of the H4b of H4 protons, which results in no enhancement of H3 or H5 but enhancement of the side chain protons and its geminal proton (H4a).

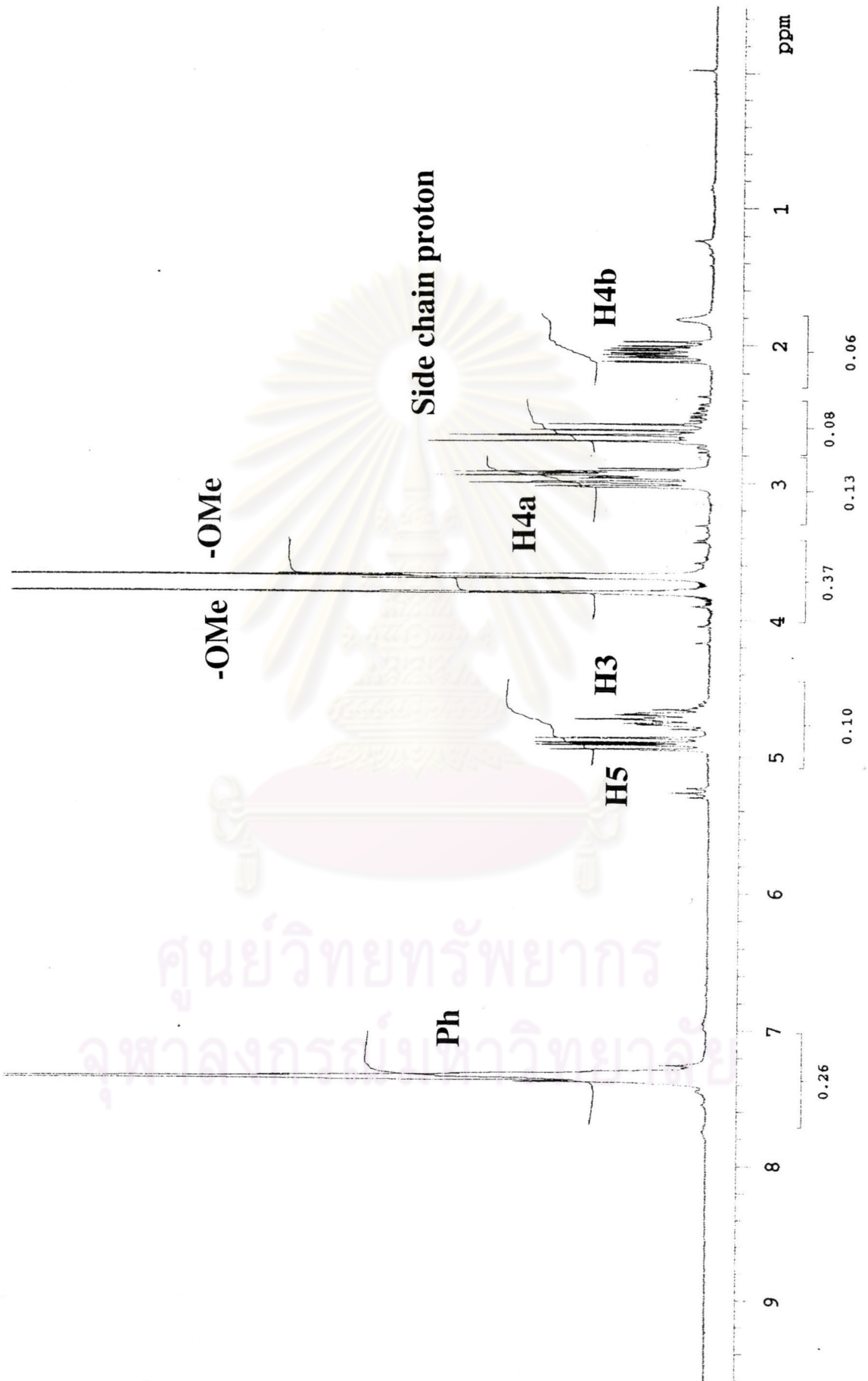


Figure 2 The isoxazolidine **(13)** spectra

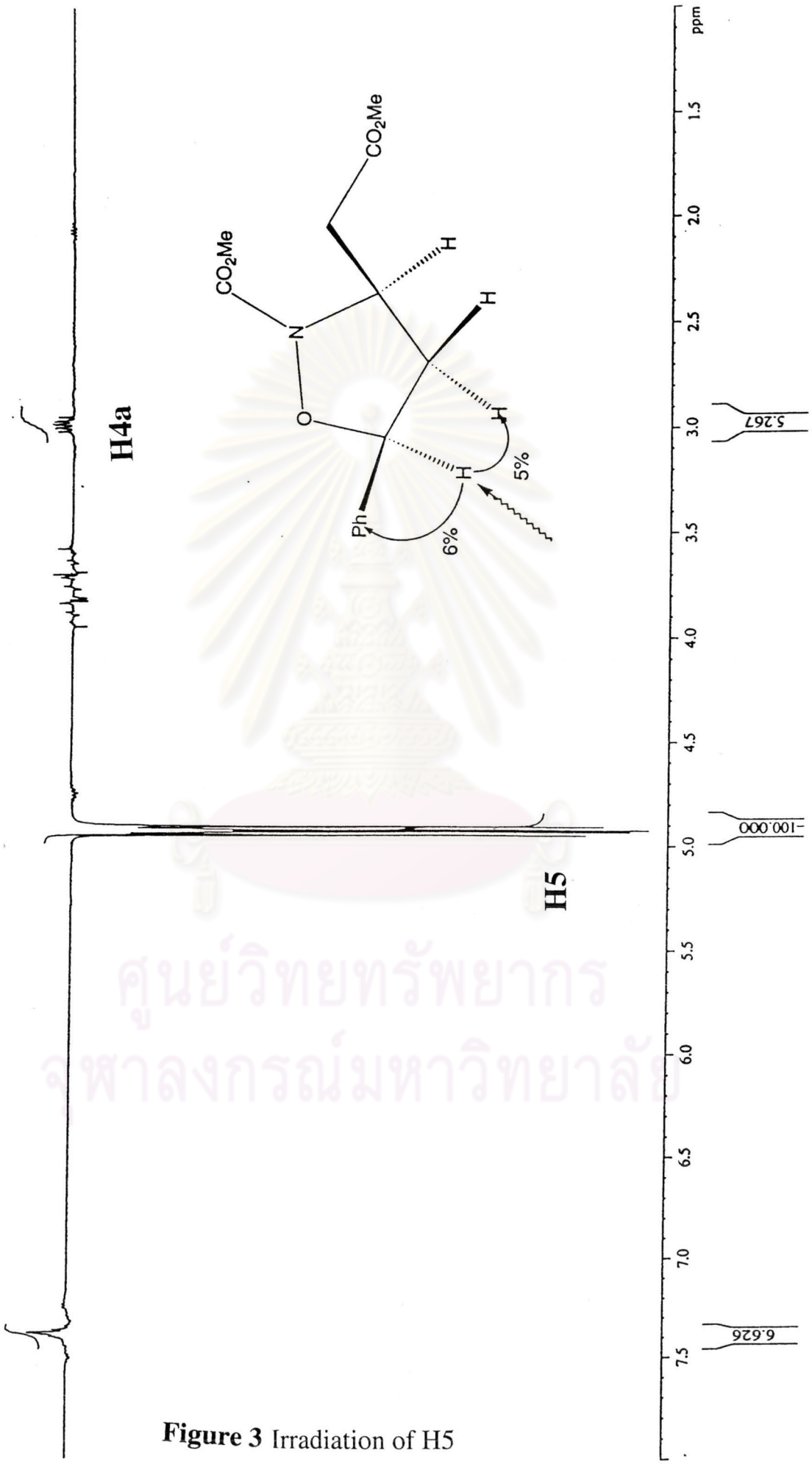


Figure 3 Irradiation of H5

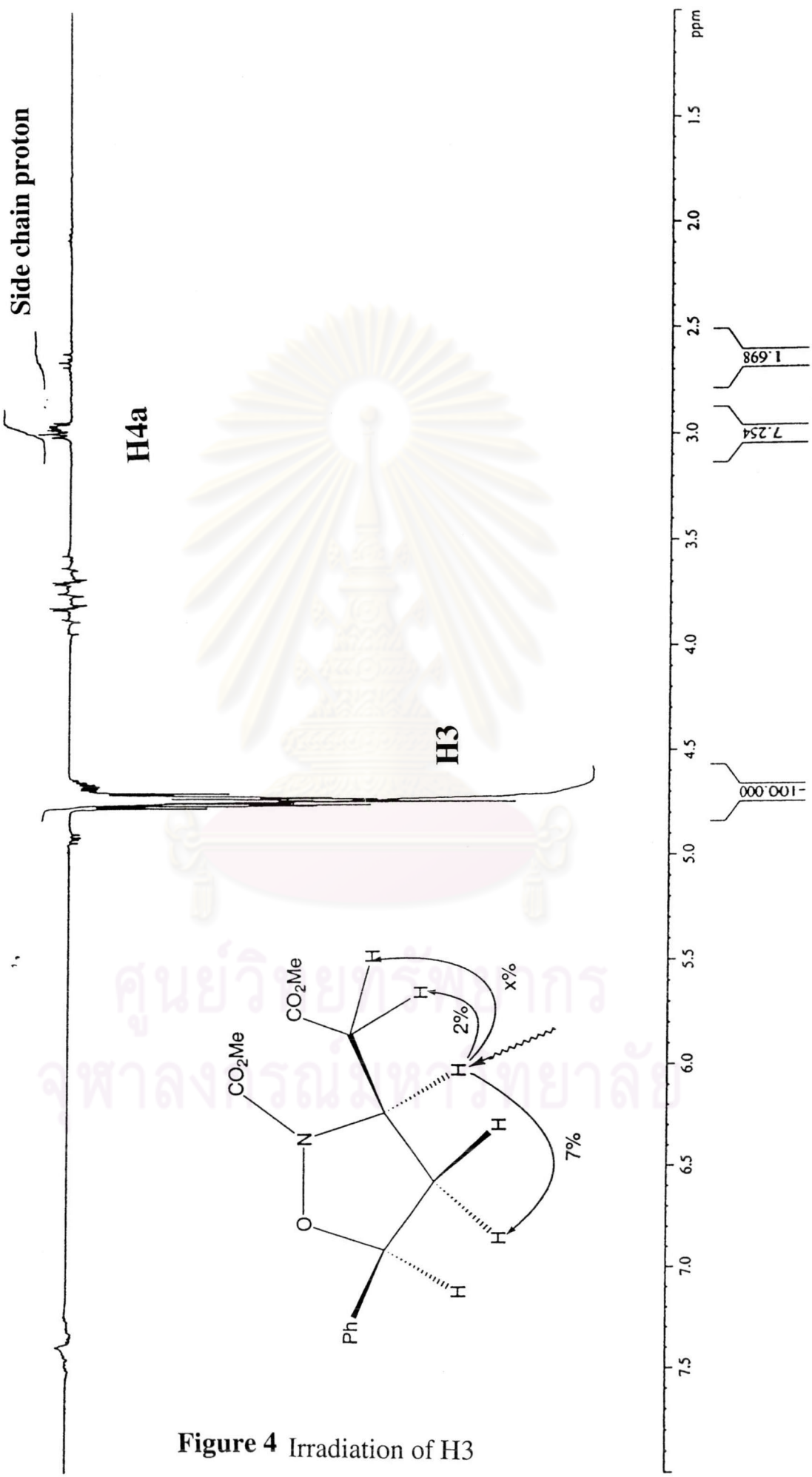


Figure 4 Irradiation of H3

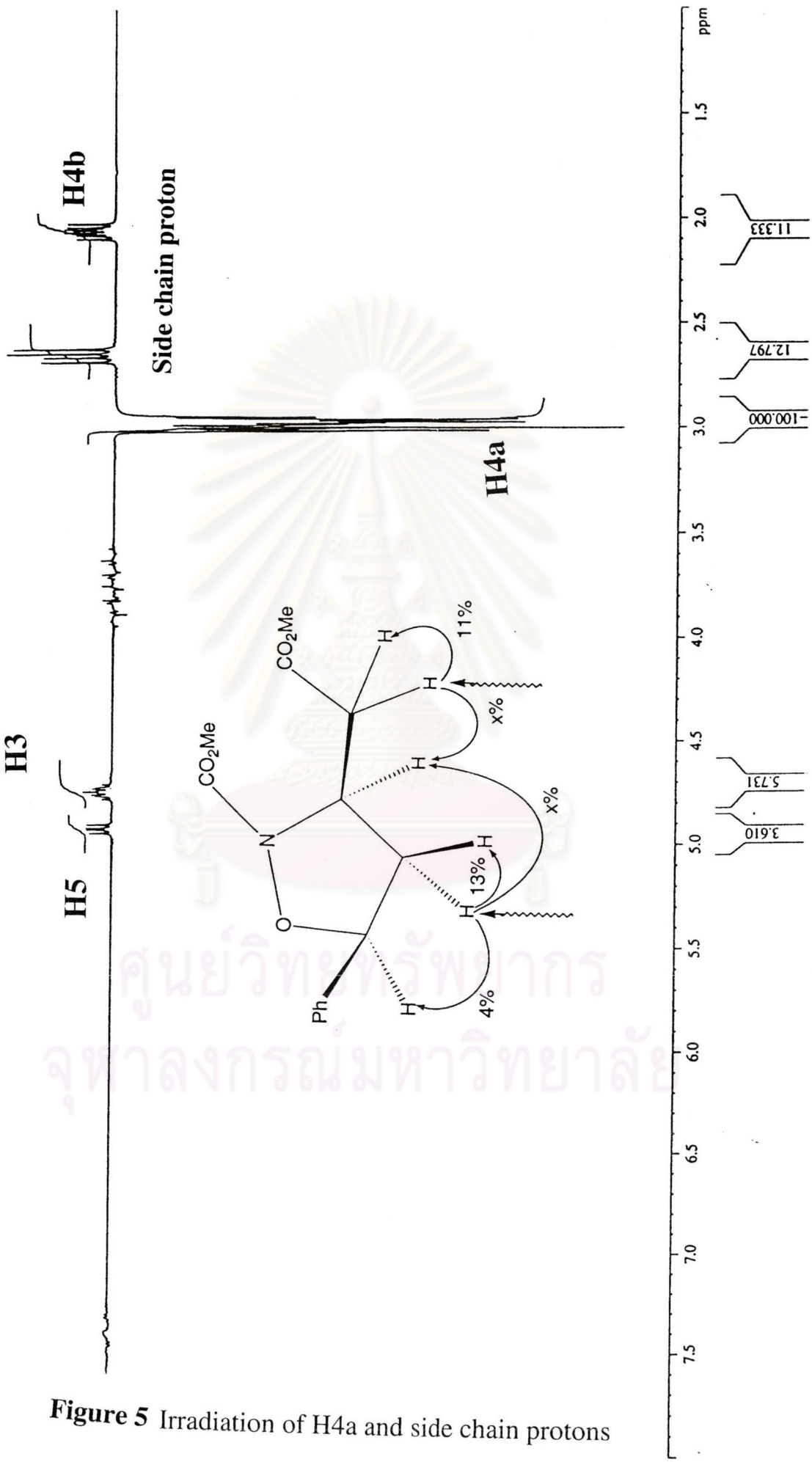


Figure 5 Irradiation of H4a and side chain protons

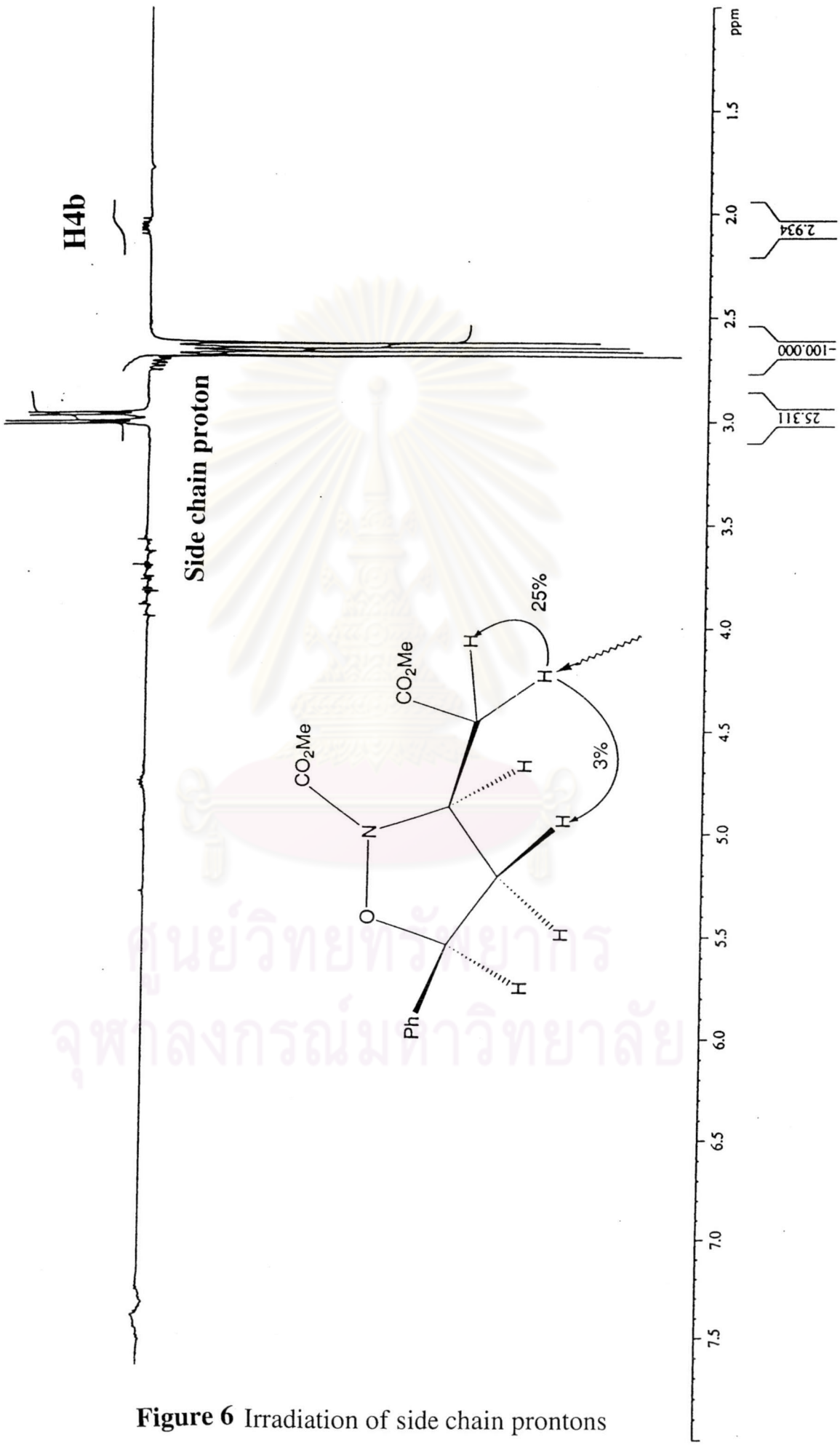


Figure 6 Irradiation of side chain prontons

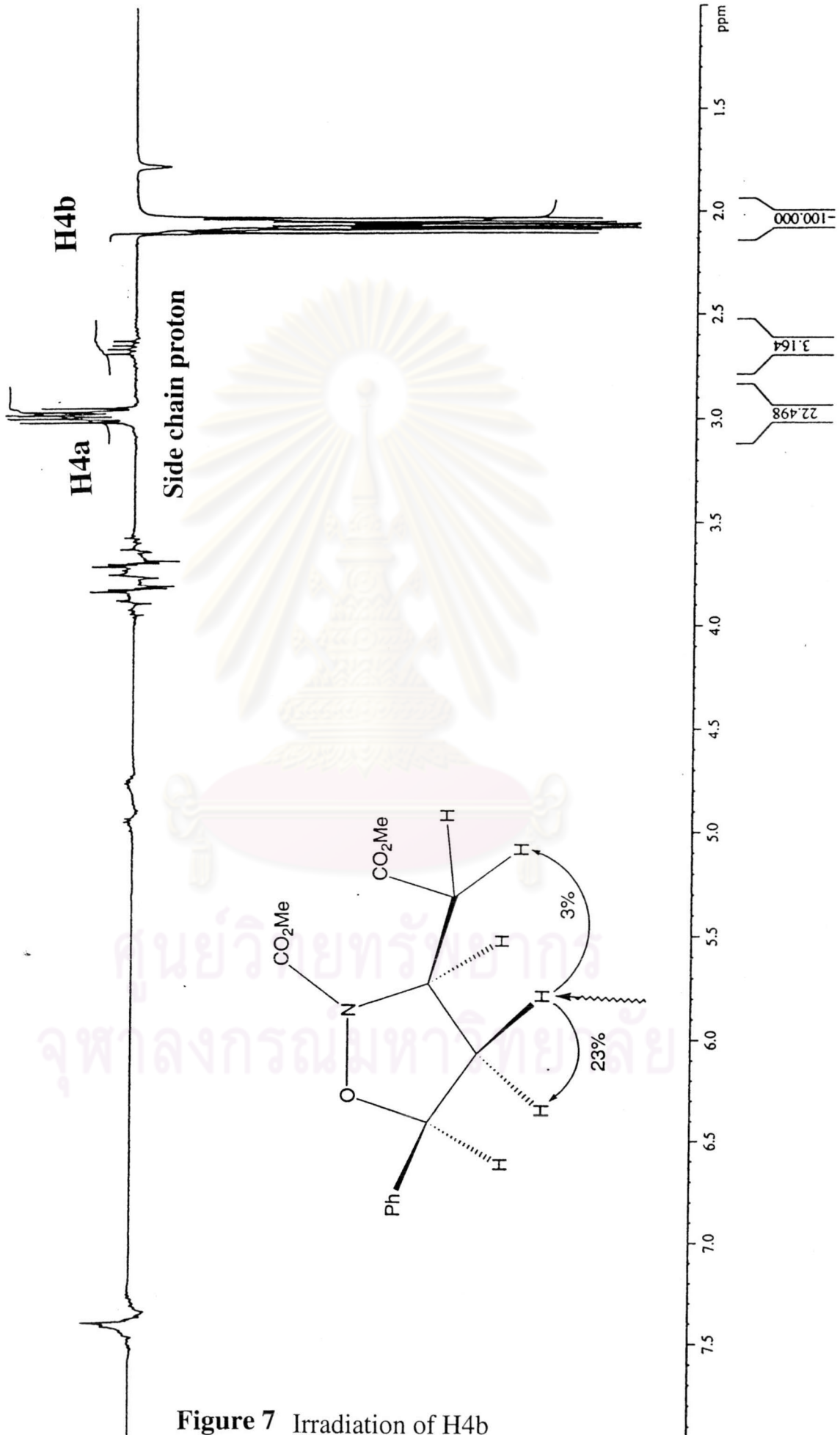
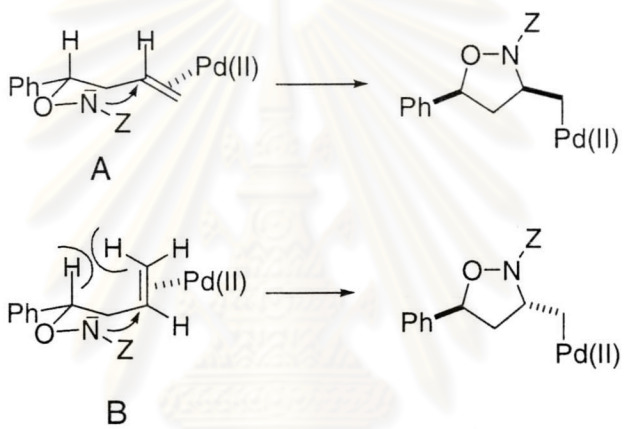


Figure 7 Irradiation of H4b

All of the irradiations are consistent only with the assertion that H3 and H5 are on the same face because irradiation of H3 and H5 cause enhancement of only one of the H4 pair.

From this result, it can be concluded that the product of the cyclofunctionalization of the carbamate hydroxylamine with palladium (II) chloride is the *cis*-diastereomer.

This stereochemical outcome can be explained by consideration of the conformation during cyclization. In the conformation A that leads to the cis-isomer, with the phenyl group pseudo-equatorial, there are no significant steric interactions. (**Scheme 42**)



Scheme 42 5-membered ring intermediate conformations

On the other hand, in the conformation B that would lead to the *trans* isomer, there is an unfavorable interaction between the alkene moiety and the benzylic hydrogen. The same result was found for each carbamate-protected hydroxylamine: only one isomer was isolated. On the other hand, the sulfonamide **(10a)** gave a 4:1 mixture of *cis*- and *trans*-isomers. This may be due to the larger size of the sulfonamide group and the smaller bond angles due to the sp^3 rather than sp^2 hybridization of nitrogen. These factors might lead to steric interactions between the sulfonamide and the alkene moieties in conformation A.

Despite there encouraging results, yields were modest and studies to optimize the reaction were required. A number of variables were considered. (**Table 5**)

Table 5 Cyclofunctionalization reactions

entry	R	Z	Substrate	conditions[a]	yield %	yield after RSM / %	RSM %
1	Ph	CO_2Me	**9a**	**A**	37	54	31
2				**D1**	43	63	32
3	Ph	Ns	**10a**	**A**	61 + 12[b]	-	1
4	Ph	Cbz	**12a**	**A**	49	75	35
5				**B**	28	68	59
6				**C**	48	59	19
7				**D1**	63	-	-
8	Ph	Boc	**11a**	**A**	0	-	-
9				**D1**	79	-	-
10				**D2**	42	58	28
11				**E1**	75	-	-
12				**E2**	0	-	-
13				**E3**	51	67	24
14	*i*-Pr	Boc	**11b**	**D1**	30	52	42
15	*i*-Pr	Cbz	**12b**	**D1**	41	49	16
16	$TBSOCH_2$	Cbz	**12c**	**D1**	38	41	8

[a]Conditions: **A**: $PdCl_2$, $CuCl_2.2H_2O$, NaOAc, MeOH, CO, RT;

[b] cis + trans isomers. Isolated yields of chromatographically separated compounds

B: $PdCl_2$, $CuCl_2.2H_2O$, K_2CO_3, CH_3CN/ MeOH (1:1), CO, RT;

C: $PdCl_2$, $Cu(OAc)_2.2H_2O$, K_2CO_3, CH_3CN/ MeOH (1:1), CO, RT;

D1: $PdCl_2$, $Cu(OAc)_2.2H_2O$, TMG, CH_3CN/ MeOH (1:1), CO, RT;

D2: as **D1**, but using 25% CO in N_2;

E1: addition of NaOMe to $PdCl_2$, $Cu(OAc)_2.2H_2O$, CH_3CN/ MeOH (1:1), CO, RT;

E2: as **E1**, but using $CuCl_2.2H_2O$;

E3: addition of $PdCl_2$, $Cu(OAc)_2.2H_2O$ to NaOMe, CH_3CN/ MeOH (1:1), CO, RT

It was found that copper(II) acetate was superior to copper(II) chloride as the oxidizing agent (Entries 5 and 6). It was also found that the nature of the base had a profound effect on the reaction. If the reaction does proceed *via* an equilibrium concentration of the N-anion, then a stronger base would be expected to enhance reactivity. A change to potassium carbonate was not, however, effective (Entries 4, 5, 6). This may be due to low solubility in the reaction medium. Triethylamine was not tested as an experiment involving mixing it with organic solutions of copper (II) salts resulted in the rapid formation of thick precipitates. DBU also resulted in precipitates. This was not observed with tetramethyl guanidine and this base, which is about 100 times stronger than triethylamine, was found to be quite effective (Entries 7, 9, 14, 15 16).[37] On the other hand, sodium methoxide gave highly variable results (Entry 11).

Another significant variable was the solvent. Acetonitrile is widely used as a solvent in reactions mediated by transition metals due to its capability as a ligand. It is known to be a particularly good ligand for copper (I), resulting in many quite stable complexes. As a consequence, the use of acetonitrile is known to enhance the oxidizing ability of copper (II).[38] Attempting to suppress the over reduction of the palladium by diluting the carbon monoxide with nitrogen was ineffective (Entry 10).

Hence, the final optimized conditions were the use of palladium chloride (10 mole %), copper acetate (3 eq.) in acetonitrile/methanol in the presence of TMG (3 eq.) at 0° C under 1 atm of CO.

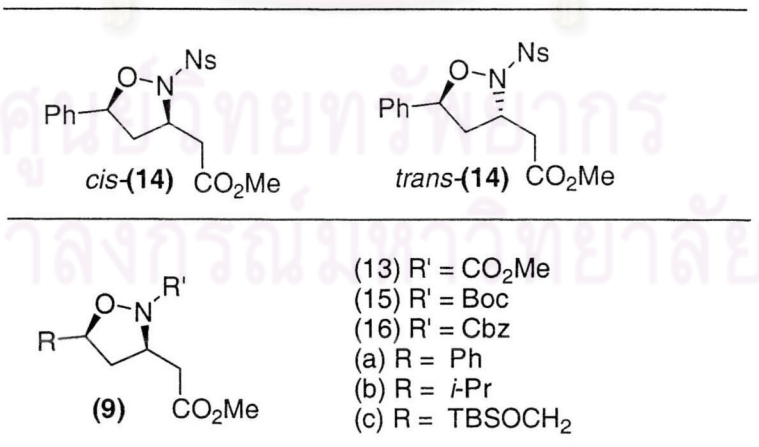
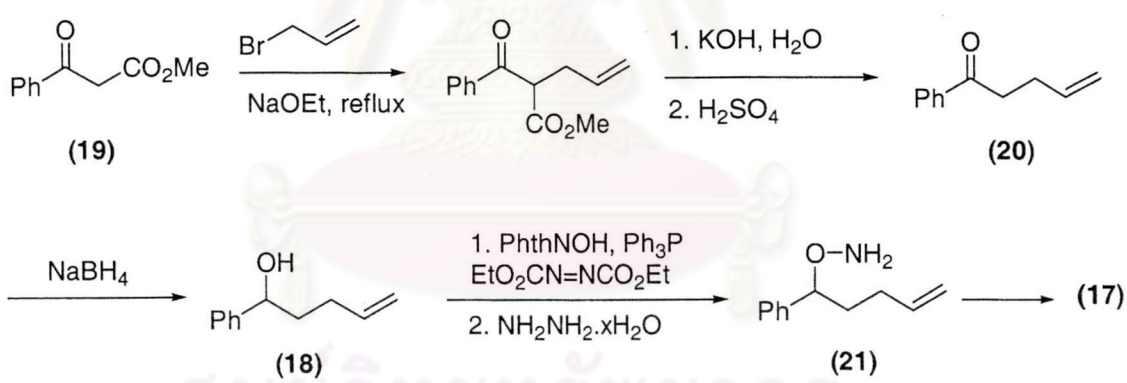


Table 6 List of cyclized products from the cyclofunctionalization reaction using Palladium (II)

The successful results of the cyclization reaction with the homoallylic hydroxylamine inspired us to think about the six-membered ring cyclization of the hydroxylamine alkene substrate (**17**). Successful cyclization would lead to 1, 4-amino alcohol derivatives.

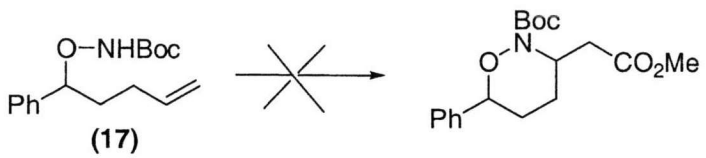
Scheme 43 6-membered ring cyclization

The alcohol (**18**) was made from ethyl benzoylacetate (**19**).[39] Allylation followed by saponification of the ester and decarboxylation gave a ketone (**20**). Reduction with sodium borohydride gave a secondary alcohol (**18**), which was converted to the hydroxylamine (**21**). (**Scheme 44**) The desired hydroxylamine (**17**) was then prepared by acylation of the free amino group.



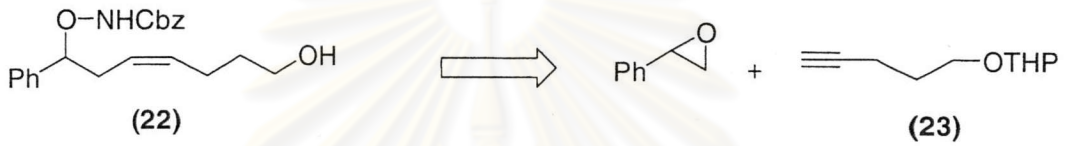
Scheme 44 Preparation of the hydroxylamine (**17**)

The hydroxylamine (**17**) was then submitted to the cyclization procedure with palladium(II) chloride, but the starting material was recovered and no product could be detected. The cyclization reaction failed, possibly due to the slower 6-membered ring formation (**Scheme 45**), allowing direct Palladium reduction to occur.



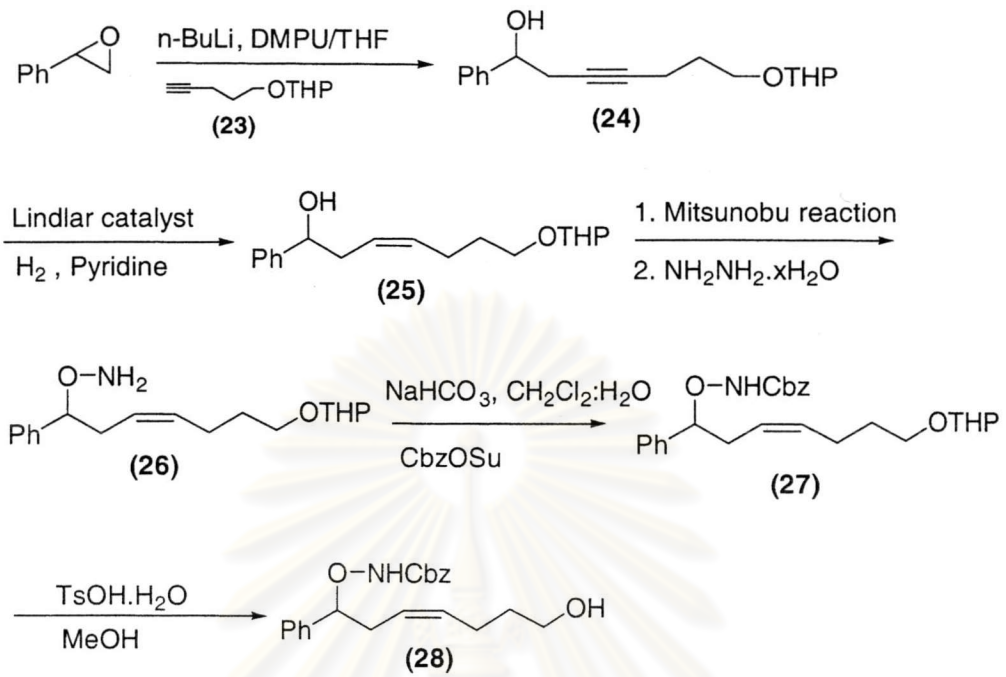
Scheme 45 6-membered ring attempting of cyclization

Another aspect that was explored was the use of an internal nucleophile. It was anticipated that a suitable test-substrate (**22**) might be prepared from styrene oxide and an acetylide ion.



Scheme 46 Synthesis strategy for the internal alkene hydroxylamine

The hydroxylamine (**22**) was made from styrene oxide and the alkyne (**23**). Addition of the lithium acetylide to styrene oxide using DMPU as a polar co-solvent[40] yielded the expected alcohol (**24**). The alkyne underwent semi-hydrogenation in the presence of Lindlar's catalyst to give exclusively the *cis*-alkene (**25**). This was confirmed by observation of a coupling constant between the two vinyl protons of 11 Hz. This coupling constant could be accurately measured on ^{1}H NMR spectra recorded using homonuclear decoupling. At this point, the secondary alcohol (**25**) was converted to the Cbz-protected hydroxylamine (**27**) in the usual way. Finally, the protecting group of the primary alcohol was removed to give the alcohol (**28**). (**Scheme 47**)

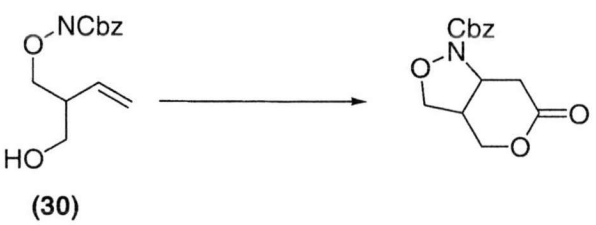


Scheme 47 Preparation of an internal alkene

However, once again, cyclization failed, perhaps due to the weaker coordination of the more substituted alkene to Pd(II). (**Scheme 47**)

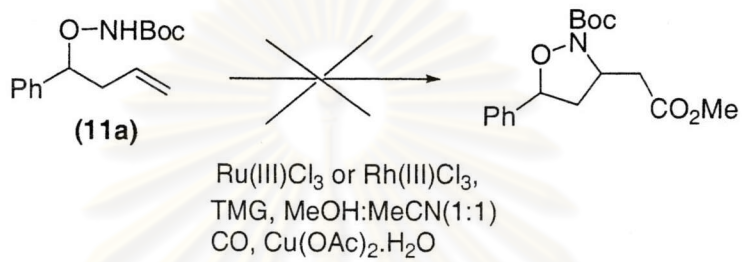
Scheme 48 Attempted cyclofunctionalization

A better substrate for testing the viability of an internal nucleophile might be the hydroxylamine **(30).** (**Scheme 49**)



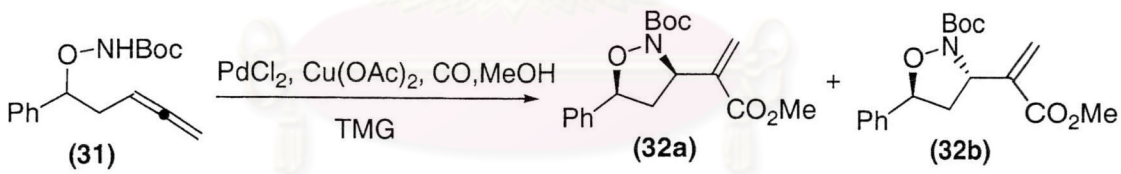
Scheme 49 Testing of cyclofunctionalization

Although palladium is very widely used to activate alkenes to nucleophilic attack, it has been reported that both rhodium and ruthenium can participate in the Wacker reaction.[41] However, when rhodium(III) chloride and ruthenium(III) chloride were employed as the electrophiles instead of palladium(II) chloride, the cyclization of the hydroxylamine **(18a)** was not observed. (**Scheme 50**) It is possible that their reduction to inactive complexes is too fast.



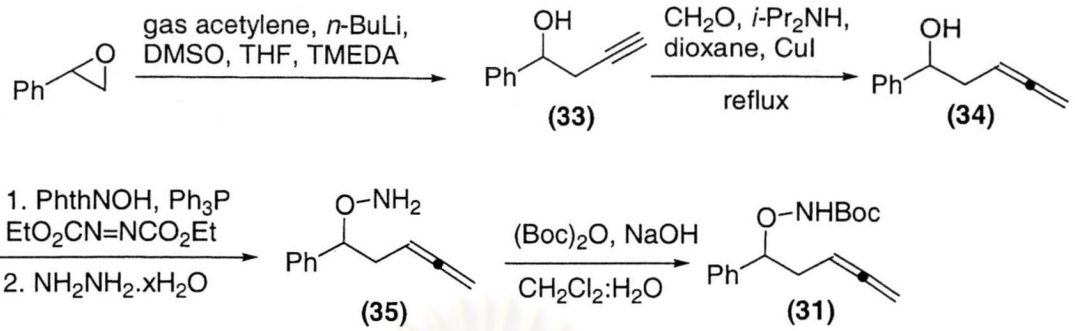
Scheme 50 The cyclofunctionalization reaction with Ru(III) and Rh(III)

Other unsaturated groups can also participate in cyclofunctionalization. Allenes have been widely used and, on cyclization, also generate a new chiral centre.[42] Therefore, the allene **(31)** was studied. (**Scheme 51**)



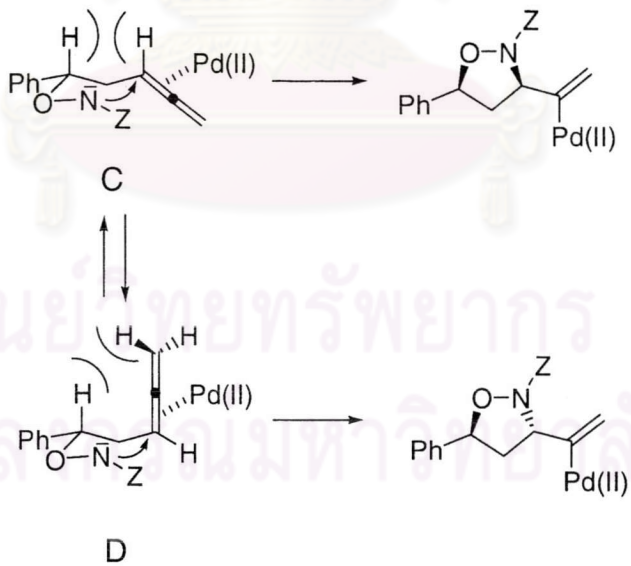
Scheme 51 The allene cyclofunctionalization

Styrene epoxide was used as a starting material for the allene **(34)**. Ring opening with lithium acetylide proceeded smoothly according to the procedure reported by Brandsma.[43] The terminal alkyne **(33)** was then homologated to the allene **(34)** using the Searles-Crabbe reaction.[44] The alcohol group was then converted to Boc protected hydroxylamine **(31)** in the usual way.



Scheme 52 The hydroxylamine allene synthesis

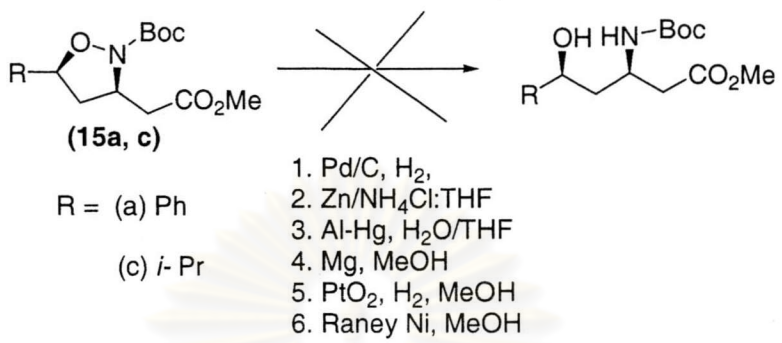
Cyclization of the allenic hydroxylamine (**31**) using the standard procedure yielded an 2:1 (*cis*:*trans*) mixture of stereoisomers in a combined yield of 36 % and recovered 36% of starting material. The reason for the lower stereoselectivity of the allene compared to the alkene substrates could be the lesser steric bulk of the allenic sp-carbon. This would result in a much weaker interaction with the benzylic proton in reactive conformation D in the allenic case. (**Scheme 53**) In addition, due to the 90° twist of the allenic axis, the protons on the terminal allene methylene are orthogonal to the benzylic C-H bond, thus minimizing H/H steric interaction.



Scheme 53 Allene intermediates

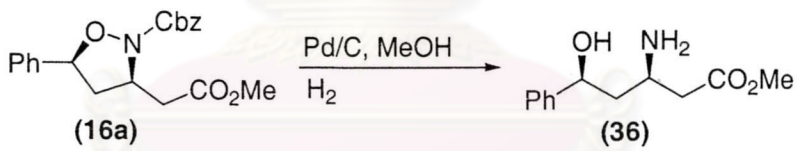
Cleavage of the O-N bond of the isoxazolidine (**37**) was attempted with many types of reducing reagents (**Scheme 54**) but the protecting group (Boc) and O-N bond survived. The reagents used included metals such as zinc, aluminium amalgam and magnesium and catalyst systems, including palladium, platinum and nickel. The lack of reactivity of this

molecule is in sharp contrast to other isoxazolidines in which the nitrogen is not acylated.[28]



Scheme 54 Attempted removal of the tether.

On the other hand, when the Cbz protected isoxazolidine **(16a)** was subjected to catalytic hydrogenation at ambient pressure using ordinary palladium on carbon, both the Cbz group and the O-N bond were removed. Given the stability of the Boc protected isoxazolidine, it can be suggested that, Cbz deprotection occurs first, rendering the isoxazolidine susceptible to further reduction. (**Scheme 56**)



Scheme 55 Removal of the tether

The successful cleavage of the tether using this reaction completes the development of the desired cyclofunctionalization reaction, as the product **(36)** was the desired 1,3-aminoalcohol exclusively as its syn isomer.