Chapter II:
Synthesis of starting material

1 Introduction

This chapter will be devoted to the synthesis of the starting material that will be used in the first part of our work. This includes the synthesis of the chiral inductor, (2*S*)-(1-methoxy-1-methylethyl)pyrrolidine **27**, various sulfonamides and Michael acceptors that were not commercially available.

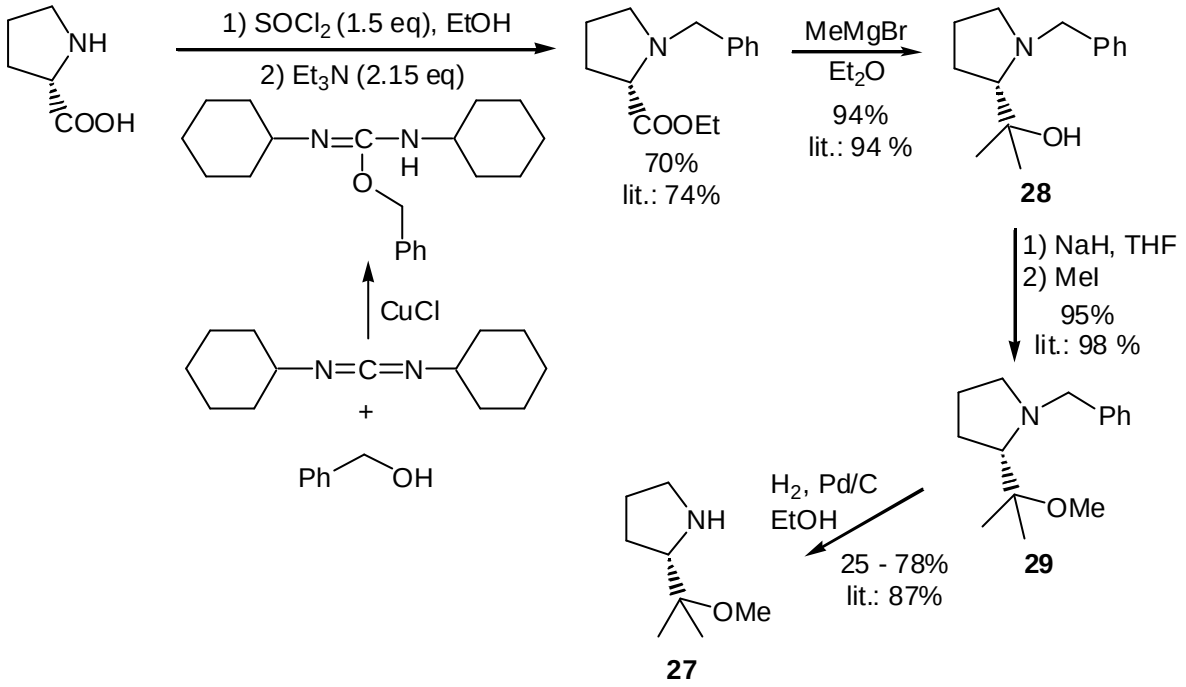
2 Synthesis of (2*S*)-(1-methoxy-1-methylethyl)pyrrolidine 27

C. Huart had shown that the proline-derived amine **27** was the best chiral inductor for the cyclopentannulation of enones.[67] We have therefore decided to use **27** in our studies. Two different syntheses towards **27** have been described. The major difference lies in the protecting groups used.

2.1 First method

Enders was the first to develop this amine as a chiral inductor (scheme 56).[109] His method used a benzyl protection for the amine. The key-step of the synthesis was the introduction of a tertiary alcohol by addition of a Grignard reagent to the ester. The chemistry was straightforward and **27** could be obtained in 60% overall yield.

[109] Enders, D.; Kipphardt, H.; Gerdes, P.; Brena-Valle, L. J.; Bhushan, V. *Bull. Soc. Chim. Belg.*, **1988**, *97*, 691-704.



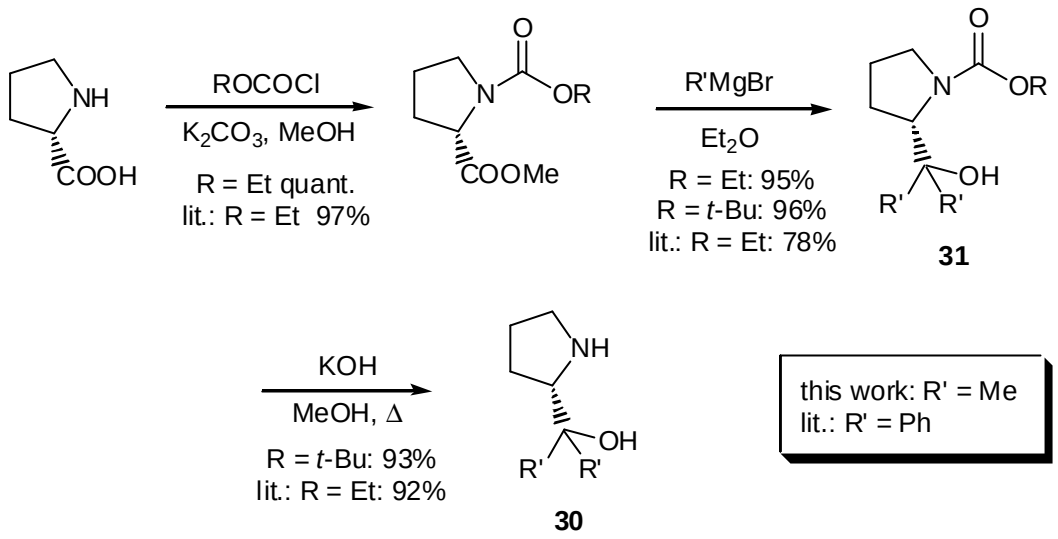
Scheme 56

We could easily repeat the first three steps of the sequence. However we observed some difficulties in reproducing the last reaction of Enders' sequence. Both the reaction rates and yields depended a lot on parameters difficult to control: purity and age of the catalyst, temperature, quantity of moisture in the reaction mixture. Moreover conversion was bad most of the times and good yields were an exception.

2.2 Second method

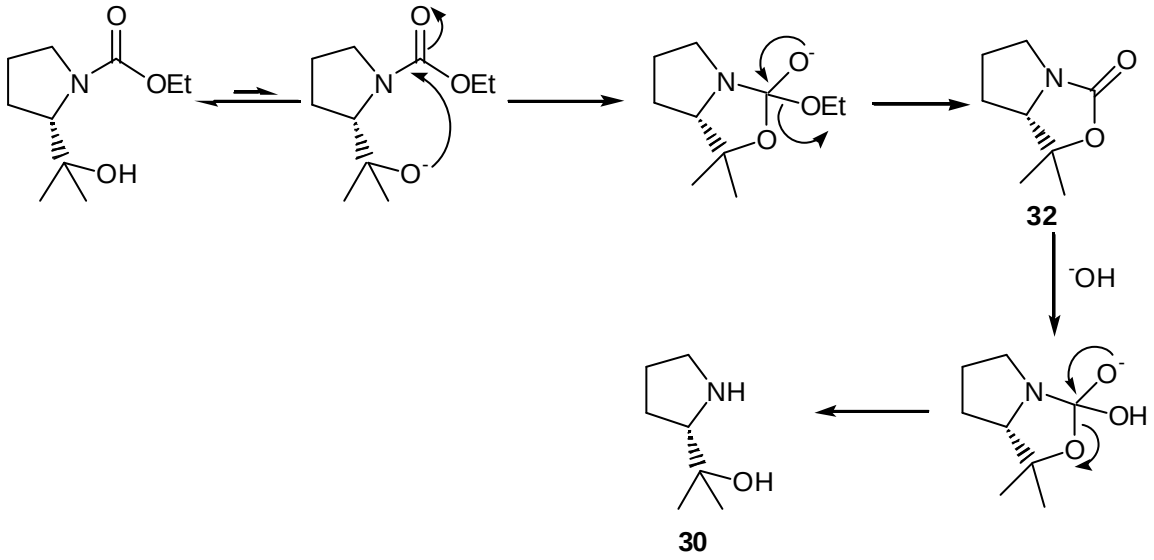
An interesting intermediate for the synthesis of **27** is aminoalcohol **30**. With R' = Ph it has been synthesized by Periasamy[110] using a similar approach as Enders (scheme 57). However his group chose a carbamate as protecting group for the amine.

[110] Kanth, J. V. B.; Periasamy, M. *Tetrahedron*, **1993**, *49*, 5127-5132.



Scheme 57

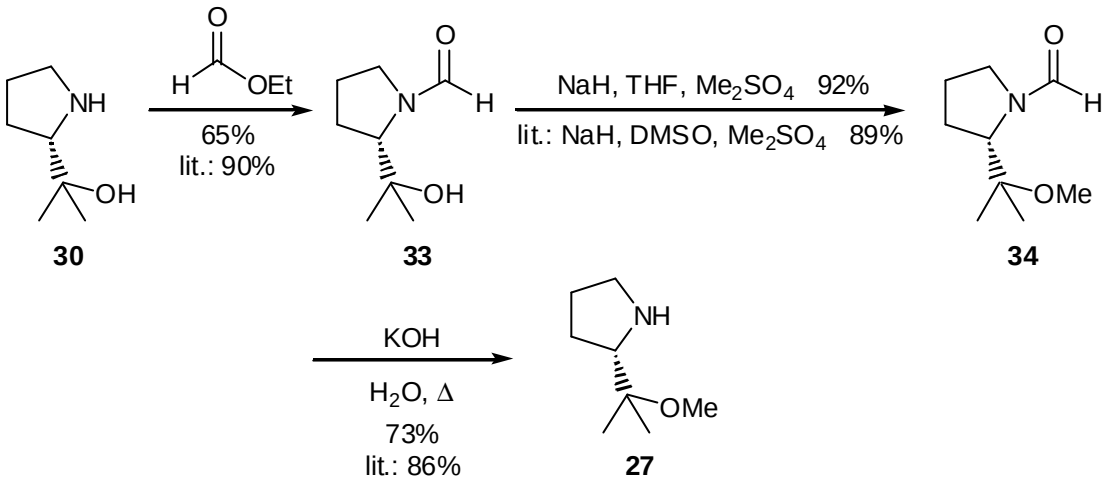
We could repeat this sequence with both ethyl and *tert*-butyl carbamate as protecting group. Yields were excellent and alcohol **31** was obtained nearly quantitatively. The authors showed that the carbamate was not stable under basic conditions. They explained this unusual behavior by an internal attack of the alkoxide onto the carbonyl. Thus before methylating the tertiary alcohol the carbamate has to be removed to yield aminoalcohol **30**. When a *tert*-butyl carbamate was used as protecting group we had no problems; with an ethyl carbamate however the reaction proceeded not as smoothly as described and the major compound that we obtained was the bicyclic carbamate **32** which was rather stable towards hydrolysis (scheme 58).



Scheme 58

We therefore used only the *tert*-butyl carbamate as protecting group.

Nakayama synthesized **27** starting from **30** by using a formyl protected amine (scheme 59).[111] We could repeat this sequence without any problem and obtained the chiral amine **27** in good yield.



Scheme 59

The overall yield of our synthesis was 41% and the sequence could easily be realized on a multi-gram scale (starting with 100 g of proline).

2.3 Conclusion

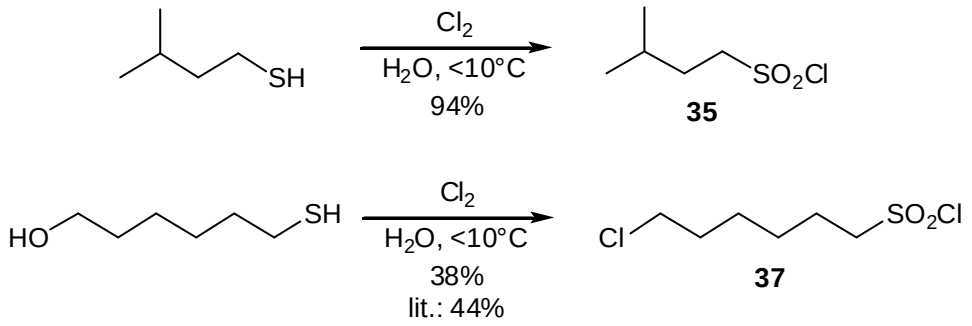
From our experience the most practical synthesis was that of scheme 57 and 59. The reproducibility of the yields outweighs the need of an additional protection-deprotection step. Moreover all the steps could be realized on a multigram scale which was not possible for the hydrogenolysis in Enders' method.

3 Synthesis of the sulfonamides

3.1 Synthesis of sulfonyl chlorides

All sulfonyl chlorides were commercially available or could be synthesized directly from the corresponding thiol. Bubbling chlorine through an aqueous emulsion of a thiol readily yields the sulfonyl chloride.[112] When an alcohol function is present an exchange occurs giving the corresponding chloride.[113] By this method we synthesized 3-methylbutane-1-sulfonyl chloride **35** and 6-chlorohexane-1-sulfonyl chloride[113] **36** (scheme 60).

[111] Nakayama, K.; Thompson, W. J. *J. Am. Chem. Soc.*, **1990**, *112*, 6936-6942.
[112] Douglass, I. B.; Johnson, T. B. *J. Am. Chem. Soc.*, **1938**, *60*, 1486-1489.
[113] Goethals, E. J.; Verzele, M. *Bull. Soc. Chim. Belg.*, **1965**, *74*, 21.

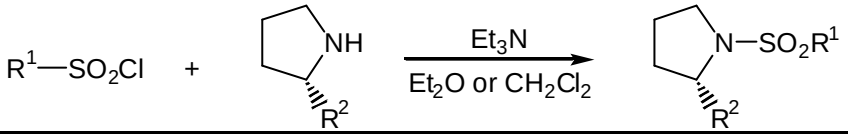


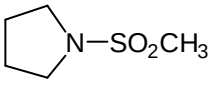
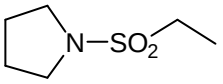
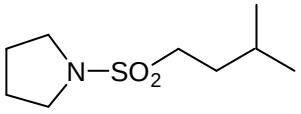
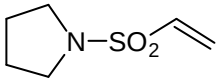
Scheme 60

3.2 Synthesis of the sulfonamides

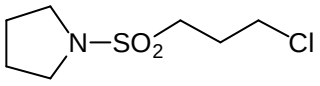
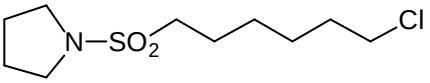
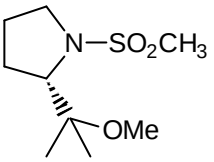
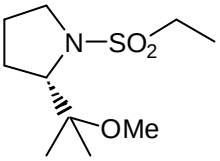
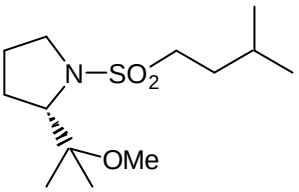
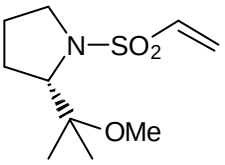
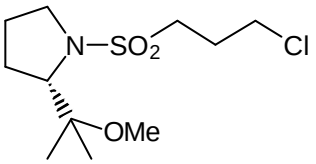
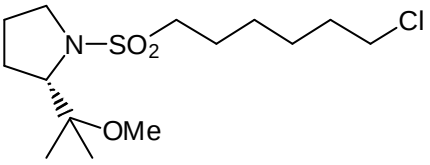
The sulfonamides were synthesized starting from pyrrolidine or the chiral amine **27** in the presence of triethylamine. It has been proven that the reaction proceeds *via* an intermediate sulphene.[70] The various sulfonamides that we have synthesized are shown in table 12.

Table 12: *Synthesis of the sulfonamides*



Entry	R^1	R^2	Product	Yield
1	CH_3	H	 **11**[114]	44%
2	CH_2CH_3		 **38**[115]	91%
3	$CH_2CH_2CH(CH_3)_2$		 **39**	89%
4	CH_2CH_2Cl		 **40**[116]	61%

[114] Sheehan, J. C.; Tulis, R. W. *J. Org. Chem.*, **1974**, *39*, 2264-2267.
[115] Atlani, M.; Corso, V.; Wakselman, C.; Loutaty, R.; Yacono, C. (Compagnie Française de Raffinage S. A., France), US 4170547, 1979
[116] Aumaitre, G.; Chanet-Ray, J.; Durand, J.; Vessières, R.; Lonchambon, G. *Synthesis*, **1983**, 816-821.

5	$CH_2CH_2CH_2Cl$	 **41**[117]	quant.
6	$(CH_2)_6Cl$	 **42**	70%
7	CH_3	 **14**	88%
8	CH_2CH_3	 **43**	95%
9	$CH_2CH_2CH(CH_3)_2$	 **44**	78%
10	CH_2CH_2Cl	 **45**	65%
11	$CH_2CH_2CH_2Cl$	 **46**	88%
12	$(CH_2)_6Cl$	 **47**	51%

The reaction with 2-chloroethanesulfonyl chloride was run with 2 equivalents of base (entries 4 and 10). Under these conditions elimination of the chloride occurred *in situ* and the corresponding vinylsulfonamides **40** and **45** were obtained.

[117] King, J. F.; Lam, J. Y. L.; Ferrazzi, G. *J. Org. Chem.*, **1993**, *58*, 1128-1135.

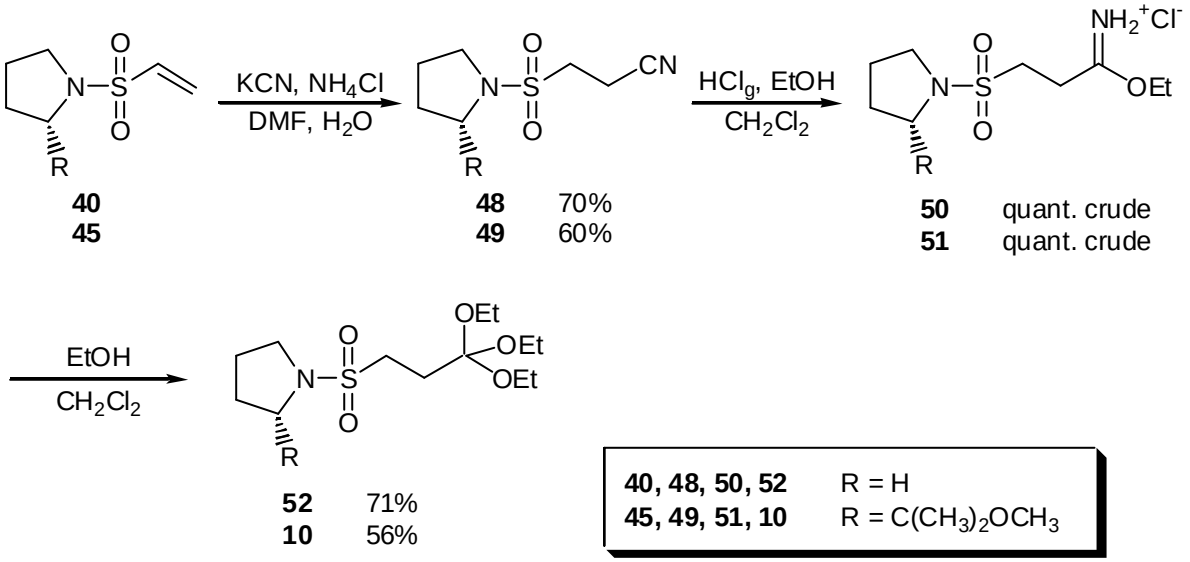
3.3 Functionalization of the sulfonamides

3.3.1 Introduction of the orthoester function

The sulfonamides containing an orthoester function were synthesized by the method developed in our laboratory by C. Huart (scheme 61).[67]

Vinylsulfonamides **40** and **45** were reacted with potassium cyanide in the presence of ammonium chloride to yield the corresponding nitriles **48** and **49**.

48 and **49** were submitted to the conditions of a Pinner reaction.[118] Nitriles were dissolved in dichloromethane in the presence of dry ethanol. Dry HCl was bubbled through this solution until saturation. After stirring overnight, solvents were evaporated and the residue was triturated with dry ether to remove residual HCl. The imidates **50** and **51** were obtained quantitatively. When stirred in the presence of ethanol they were transformed into the corresponding orthoester **52** and **10**. Ester that could have formed during the reaction was selectively hydrolyzed by a two-phase-system aqueous potassium hydroxide / dichloromethane.

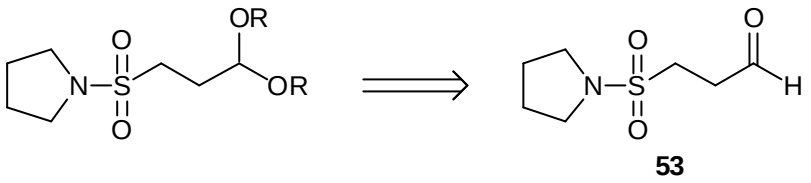


Scheme 61

3.3.2 Introduction of a ketal function

A ketal function could most easily be introduced *via* an aldehyde (scheme 62). The key compound to synthesize was therefore aldehyde **53**.

[118] Pinner, A. *Ber.*, **1883**, *16*, 325.

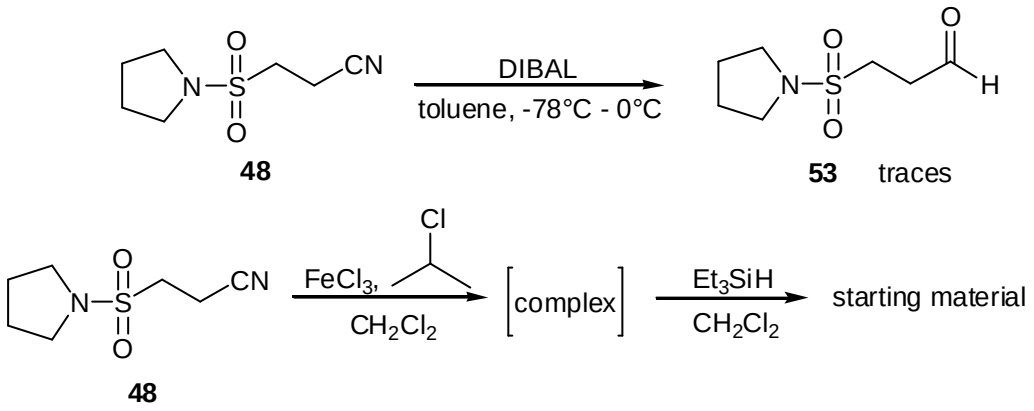


53

Scheme 62

3.3.2.a Reduction of **48**

Aldehydes can be obtained by reduction of nitriles. We tried two metal-based methods, but none gave the desired product (scheme 63).



48 **53** traces

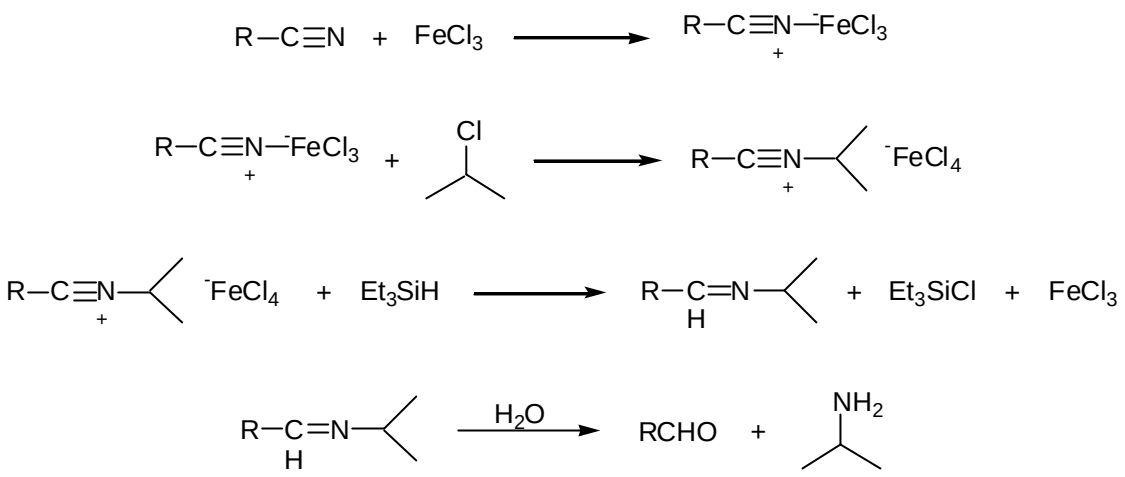
48

Scheme 63

When we treated nitrile **48** with DIBAL[119] we obtained only traces of aldehyde **53** which we were not able to purify.

Another possibility to reduce a nitrile into an aldehyde was described by Fry.[120] The reduction was realized by using triethylsilane in the presence of iron(III) chloride and isopropyl chloride. The reaction mechanism is given in scheme 64. Iron(III) chloride complexes the nitrile which is then alkylated by isopropyl chloride. Treatment of the resulting complex with triethylsilane leads to an imine which is hydrolyzed to an aldehyde by the addition of water.

[119] Mendez, J. M.; Flores, B.; Leon, F.; Martinez, M. E.; Vazquez, A.; Garcia, G. A.; Salmon, M. *Tetrahedron Lett.*, **1996**, *37*, 4099-4102.
[120] Fry, J. L.; Ott, R. A. *J. Org. Chem.*, **1981**, *46*, 602-607.



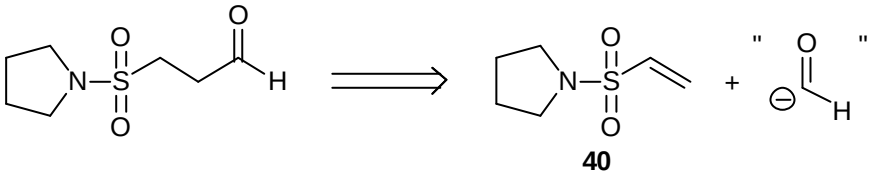
Scheme 64

When applied to nitrile **48** however this method did not afford the desired aldehyde. Treatment of nitrile **48** with iron(III) chloride gave indeed a complex, but only starting materiel was recovered upon treatment of this complex with triethylsilane (scheme 63).

The strong complexing ability of a sulfonamide could explain the lack of reactivity of this metal-based reductors. One could indeed imagine that the metal was complexed by the sulfonamide and not by the nitrile. Recovery of the starting materiel would be the result.

3.3.2.b Addition of an acyl anion analogue to **40**

Addition of an acyl anion analogue could be an interesting method to introduce the aldehyde (scheme 65).

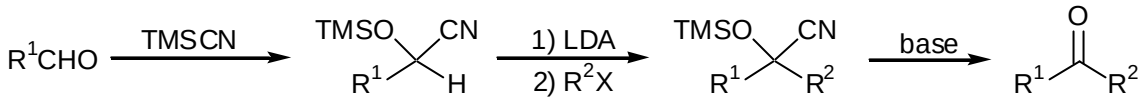


40

Scheme 65

Acyl anion analogues can be formed by cyanosilylation of aldehydes.[121] This is an example of an "Umpolung", where the initial electrophilic carbon of the carbonyl can be transformed into a nucleophilic carbon (scheme 66).

[121] Cunico, R. F.; Kuan, C. P. *J. Org. Chem.*, **1992**, *57*, 1202-1205.

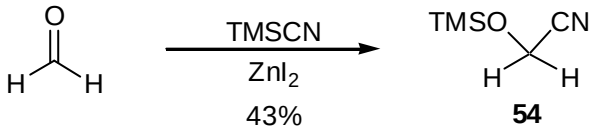


Scheme 66

α-aminonitriles can also be used as acyl anion analogues.[122] Hydrolysis of the α-aminonitrile can be achieved in either acidic or basic conditions; a procedure for sensitive compounds using copper sulfate has also been described.[123]

We thought it could be possible to add an acyl anion equivalent of formaldehyde to vinylsulfonamide **40** to introduce the desired carbonyl function. We chose [(trimethylsilyl)oxy]acetonitrile **54** and commercially available diethylaminoacetonitrile as acyl anion analogues.

For the cyanosilylation of formaldehyde we used the method described by Evans.[124] The aldehyde was reacted with trimethylsilyl cyanide in the presence of a catalytic amount of zinc iodide (scheme 67). The final product could be purified by bulb-to-bulb distillation.

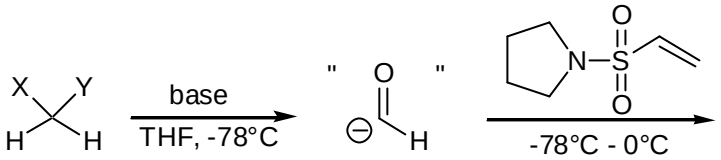


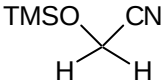
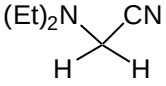
Scheme 67

The anion was then formed and added to vinylsulfonamide **40** under different conditions as described in table 13.

[122] Sanders, E. B.; Secor, H. V.; Seeman, J. I. *J. Org. Chem.*, **1978**, *43*, 324-330.
[123] Büchi, G.; Liang, P. H.; Wüest, H. *Tetrahedron Lett.*, **1978**, *31*, 2763-2764.
[124] Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.*, **1974**, *39*, 914-917.

Table 13: *Attempted addition of acyl anion analogues to **40**.*

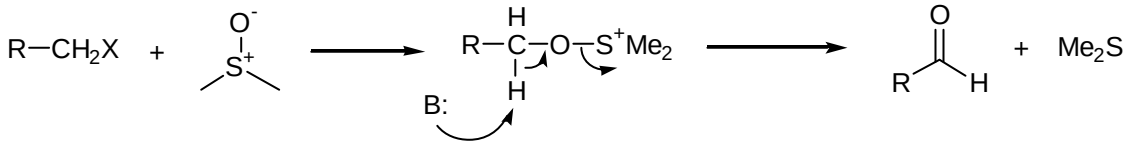


Entry		Base	Remarks	Yield
1		LDA	-	Complex mixture
2		*n*-BuLi	-	Complex mixture
3		LDA	-	Complex mixture
4		*n*-BuLi	-	Complex mixture
5		LDA	DMPU	Complex mixture
6		LDA	HMPA[125]	Complex mixture

Whatever the conditions used we always observed degradation of the reaction mixture. There was no difference between the two acyl anion analogues. The nature of the base did not seem to influence the outcome of the reaction. Even in the presence of a cosolvent, such as HMPA[125] or DMPU, no trace of the desired adduct could be obtained.

3.3.2.c Oxidation of **55**

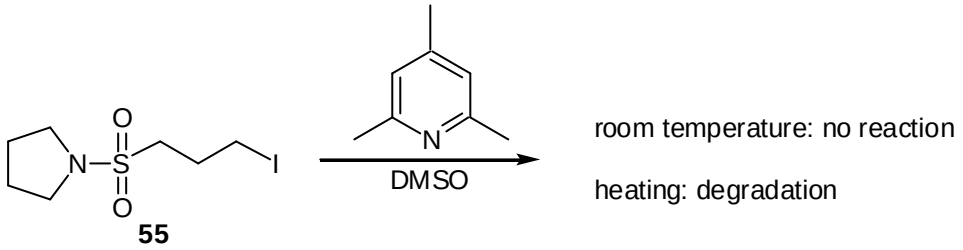
Oxidation of halides with DMSO constitutes another possibility to synthesize aldehydes.[126] The mechanism is displayed in scheme 68: the halide is displaced by DMSO, elimination under basic conditions yields the desired aldehyde.



Scheme 68

We will see in section 3.3.3 that 1-[(3-iodopropyl)sulfonyl]pyrrolidine **55** is an intermediate in the synthesis of the sulfonamide containing an ether function. **55** was reacted with collidine, which has been described as a good base for the oxidation reaction[127], in DMSO (scheme 69). However when working at low temperature no reaction occurred; when heated the reaction mixture decomposed into a complex mixture where no trace of the desired aldehyde could be found.

[125] Wakamatsu, T.; Hobara, S.; Ban, Y. *Heterocycles*, **1982**, *19*, 1395-1398.
[126] Johnson, A. P.; Pelter, A. *J. Chem. Soc.*, **1964**, 520-522.
[127] Jones, D. N.; Saeed, M. A. *J. Chem. Soc.*, **1963**, 4657-4663.



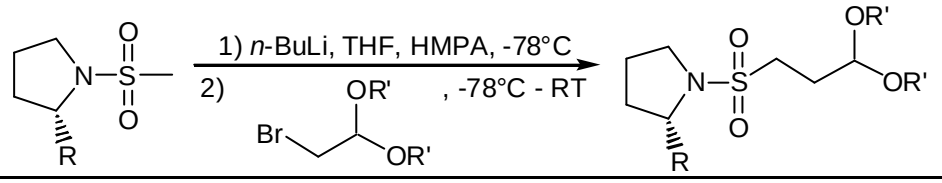
55

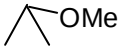
Scheme 69

3.3.2.d Reaction of **11** and **14** with a ketal of bromoacetaldehyde

We finally decided to use an existing ketal and to react it with a sulfonamide. We chose the commercially available bromoacetaldehyde diethylacetal and 2-bromomethyl-1,3-dioxolane. They could be reacted with sulfonamides **11** and **14** to yield the desired sulfonamides bearing a ketal function (table 14). Due to the rather low reactivity of the bromide reactions were allowed to come to room temperature to go to completion. Despite these precautions yields were only modest.

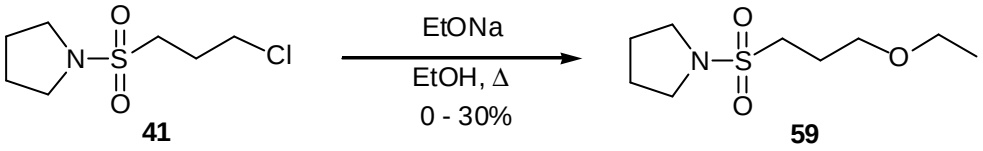
Table 14: *Synthesis of the sulfonamides bearing a ketal function.*



R	R'	Product	Yield
H	CH_2CH_3	**56**	56%
	CH_2CH_3	**57**	32%
	$-CH_2-$	**58**	49%

3.3.3 Introduction of an ether or thioether function

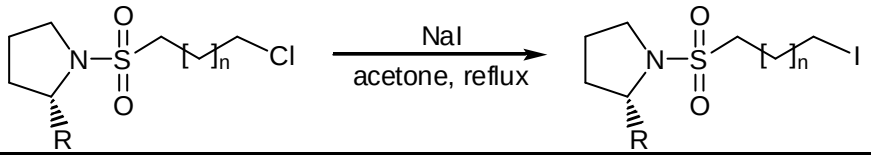
Williamson etherification is the method of choice for the synthesis of mixed ethers.[128] We reacted chloride **41** with sodium ethoxide formed by reaction of sodium with dry ethanol. However yields remained low or starting materiel was recovered (scheme 70).

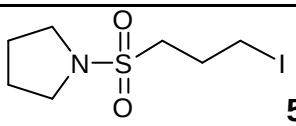
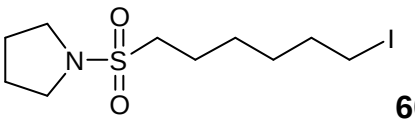
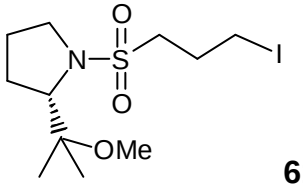
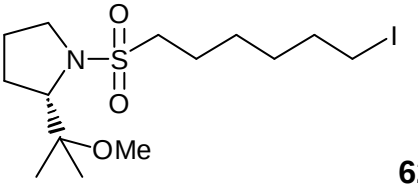


Scheme 70

To improve the reactivity we replaced the chloride by an iodide in a Finkelstein reaction. The chloride was refluxed overnight in the presence of sodium iodide in acetone. By this way, iodides **55**, **60**, **61** and **62** were obtained in good yield (table 15).

Table 15: *Transhalogention of chlorides.*

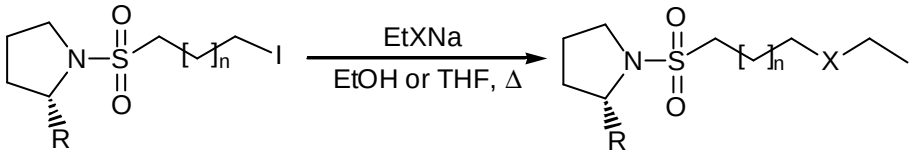


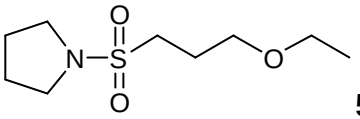
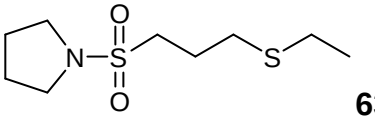
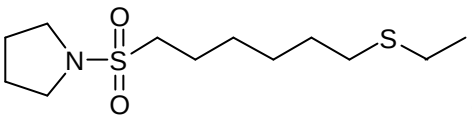
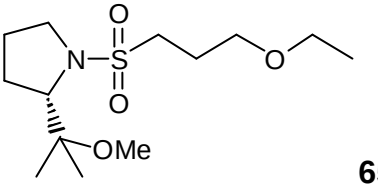
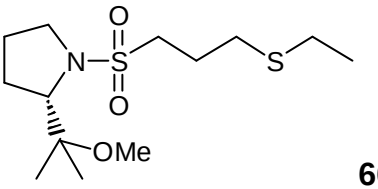
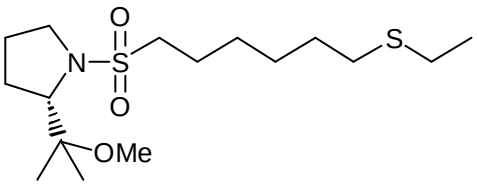
R	n	Product	Yield
H	1	 **55**	82%
	4	 **60**	70%
	1	 **61**	96%
	4	 **62**	79%

[128] Williamson, A. *J. Chem. Soc.*, **1852**, *4*, 229.

The different iodides were reacted with sodium ethoxide or sodium ethanethiolate (table 16).

Table 16: *Synthesis of ethers and thioethers.*

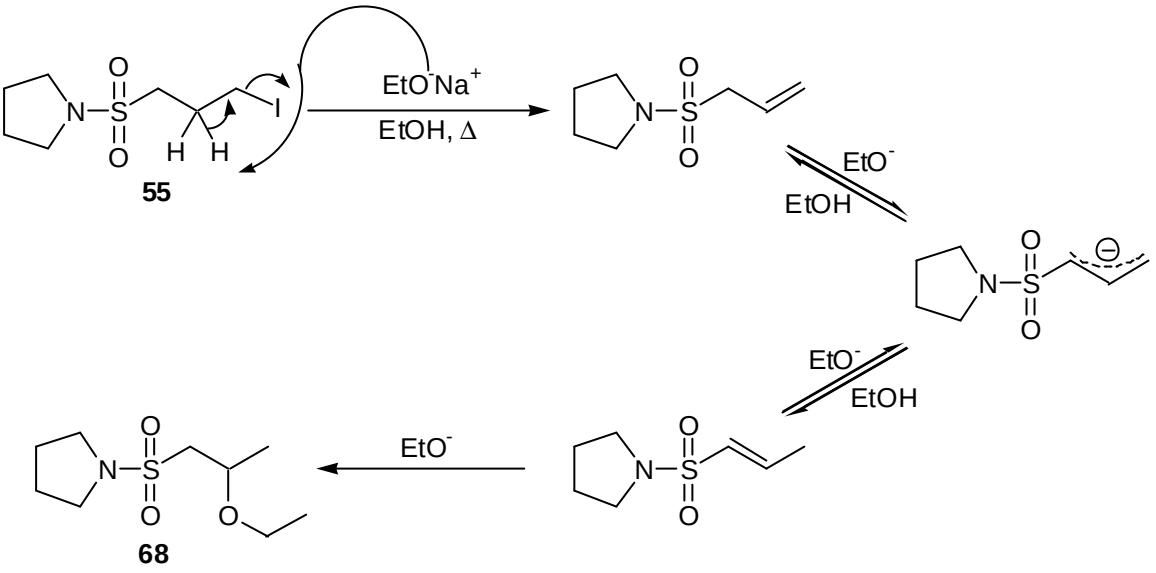


Entry	R	n	EtXNa	Product	Yield
1		1	EtONa	 **59**	49%
2	H	1	EtSNa	 **63**	72%
3		4	EtSNa	 **64**	74%
4		1	EtONa	 **65**	49%
5		1	EtSNa	 **66**	93%
6		4	EtSNa	 **67**	88%

Reaction with sodium ethanethiolate proceeded smoothly at room temperature and the corresponding thioethers were obtained in good yields (entries 2, 3, 5 and 6). When reacted at reflux with sodium ethoxide however only modest yield of the desired ether was obtained (entries 1 and 4). It appeared that an equimolar amount of a second product was formed.

NMR analysis suggested that the by-product had the same molecular formula than ether **59**. A detailed analysis by COSY allowed us to propose compound **68** with the ether function in the 2-position instead of the 3-position as structure. The

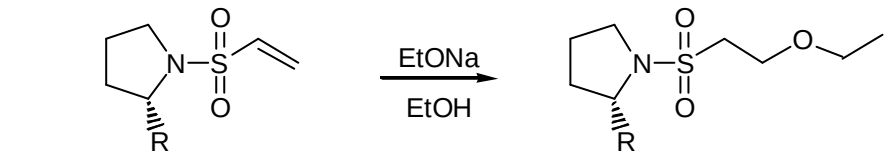
mechanism that could explain the formation of this compound is shown in scheme 71. In a first step the ethoxide acted as a base resulting in elimination of the iodide. Under basic conditions the double bond formed could isomerize to give the conjugated double bond which underwent Michael addition with ethoxide.



Scheme 71

We were not able to get better results by changing the reaction conditions.

Finally we also synthesized two sulfonamides having the ether function on carbon atom C-2. They were formed by the Michael addition of sodium ethoxide to a vinylsulfonamide (scheme 72).



R = H	**40**	**69**	92%
R = 	**45**	**70**	81%

Scheme 72

4 Synthesis of Michael acceptors

Other Michael acceptors than cyclic enones were used in this work. They are shown in figure 18. Furan-2(5*H*)-one **71** and 5,6-dihydro-2*H*-pyran-2-one **72** are commercially available; 1-methyl-1,5-dihydro-2*H*-pyrrol-2-one **73**, 1-methyl-5,6-

dihydropyridin-2(1*H*)-one **74** and the acyclic enone 2,2-dimethylhex-4-en-3-one **75** had to be synthesized.

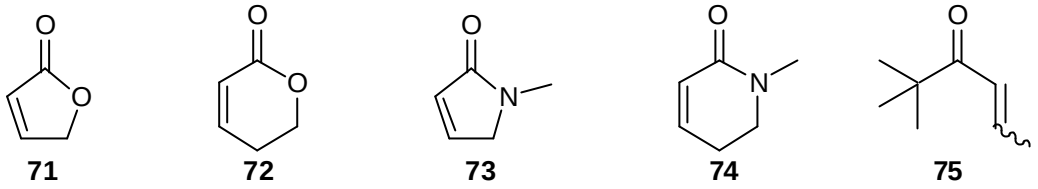
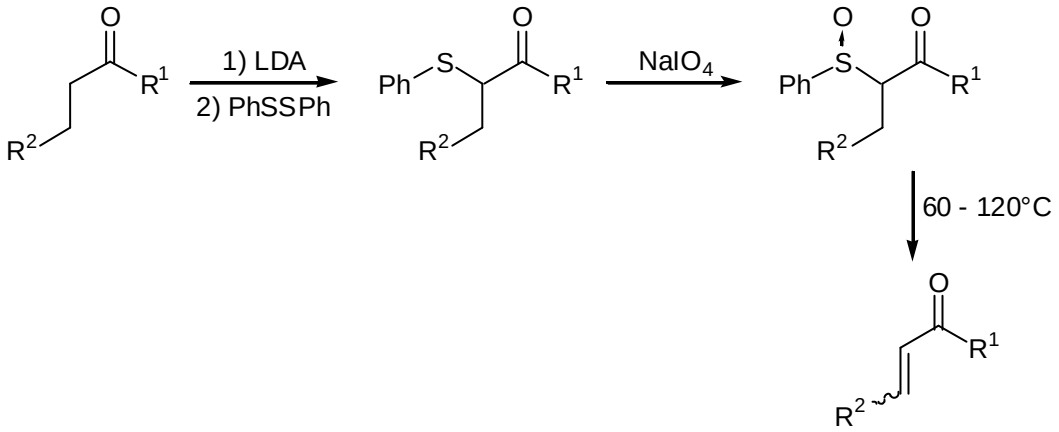


Figure 18

4.1 Synthesis of unsaturated lactams

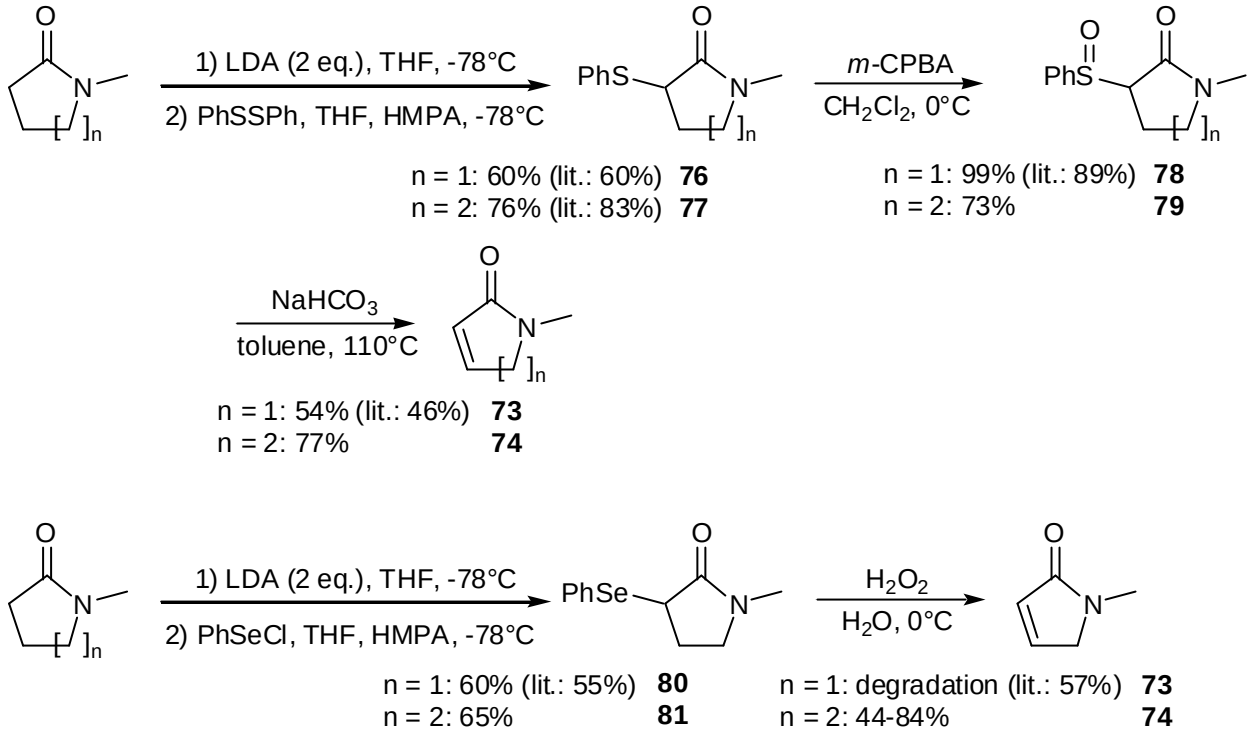
At first sight the most straightforward method to synthesize the unsaturated lactams would be by introduction of the unsaturation on the commercially available saturated compounds by the method described by Trost (scheme 73).[129] The procedure consists in the α-sulfanylation of a carbonyl compound. The resulting thioether is oxidized into a sulfoxide which undergoes elimination upon heating. A wide variety of unsaturated ketones and esters have been prepared by the authors.



Scheme 73

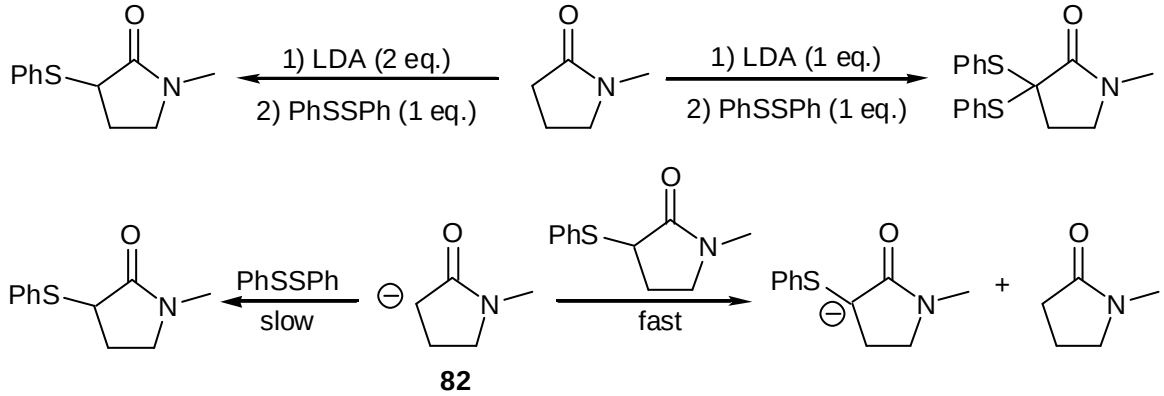
Zoretic applied the method to the synthesis of 1-methyl-1,5-dihydro-2*H*-pyrrol-2-one **73** (scheme 74).[130] A one-pot oxidation via a phenylselenenyl derivative was also applied. It has indeed been shown that selenoxides undergo elimination even at 0°C.[131,132] We thus applied these two methods to the synthesis of 1-methyl-1,5-dihydro-2*H*-pyrrol-2-one **73** and 1-methyl-5,6-dihydropyridin-2(1*H*)-one **74**

[129] Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.*, **1976**, *98*, 4887-4902.
[130] Zoretic, P. A.; Soja, P. *J. Heterocyclic Chem.*, **1977**, *14*, 681-682.
[131] Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.*, **1973**, 1979-1982.
[132] Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.*, **1973**, *95*, 6137-6139.



Scheme 74

In the first step two equivalents of base had to be used.[133] Zoretic had indeed observed that lactams, when treated with 1 equivalent of base, undergo bis-sulfanylation (scheme 75). According to the author proton transfer from monophenylthiolactam **76** occurred faster than the sulfanylation of the α-lithiated lactam **82**. The problem could be circumvented when 2 equivalents of base were used. In this case only the mono-sulfanylated lactam was isolated.



Scheme 75

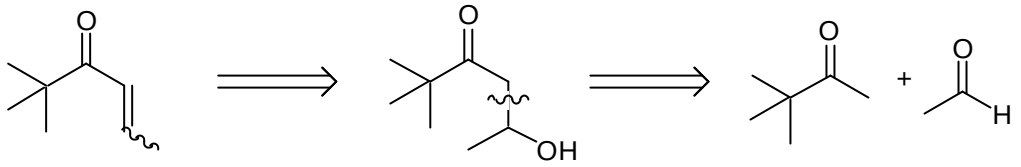
We obtained the desired unsaturated lactams with acceptable total yields comparable to the one described. However, in our hands, the selenenylated γ-lactam **80** led only to complete degradation in contrast to the described procedure.

[133] Zoretic, P. A.; Soja, P. *J. Org. Chem.*, **1976**, *41*, 3587-3589.

We did not observe higher yields when using selenenylated compounds. As the price for starting material is higher in this case (58.25 € for 10 g of phenylselenenyl chloride compared to 47.09 € for 250 g of diphenyldisulfide), the method using sulfanylated derivatives seemed the most interesting despite an additional step.

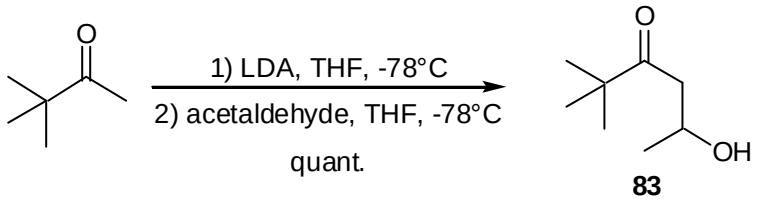
4.2 Synthesis of 2,2-dimethylhex-4-en-3-one 75

The application of the above described methodology was not possible in this case: the corresponding saturated ketone is not commercially available. However one can easily assume that the enone motive can be introduced by an aldol / dehydration reaction (scheme 76).



Scheme 76

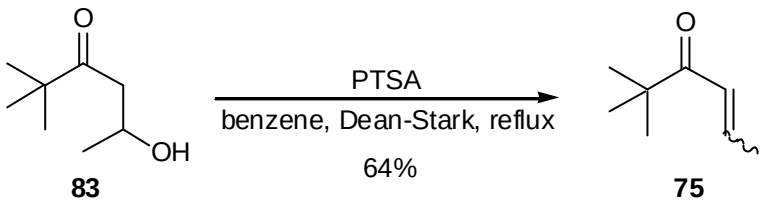
The synthesis was thus straightforward. Pinacolone was deprotonated by LDA; to the anion was added acetaldehyde (scheme 77).[134] This method allowed to isolate the aldol product 5-hydroxy-2,2-dimethylhexan-3-one **83** in quantitative crude yield.



Scheme 77

Dehydration was realized by refluxing hydroxyketone **83** in a Dean-Stark apparatus in the presence of a trace of *para*-toluenesulfonic acid (scheme 78).[134] The desired enone **75** was obtained in 64% yield.

[134] Stork, G.; Kraus, G. A.; Garcia, G. A. *J. Org. Chem.*, **1974**, *39*, 3459-3460.



83 **75**

Scheme 78

According to the proton NMR spectrum only one isomer of the double bond was formed. The coupling constant of the two olefinic protons was about 21 Hz. This means that the double bond formed had a *trans* geometry. So the compound we have synthesized was the (4*E*)-2,2-dimethylhex-4-en-3-one.