Chapter V: Cyclization

1 Cyclization starting from cyclohexenone

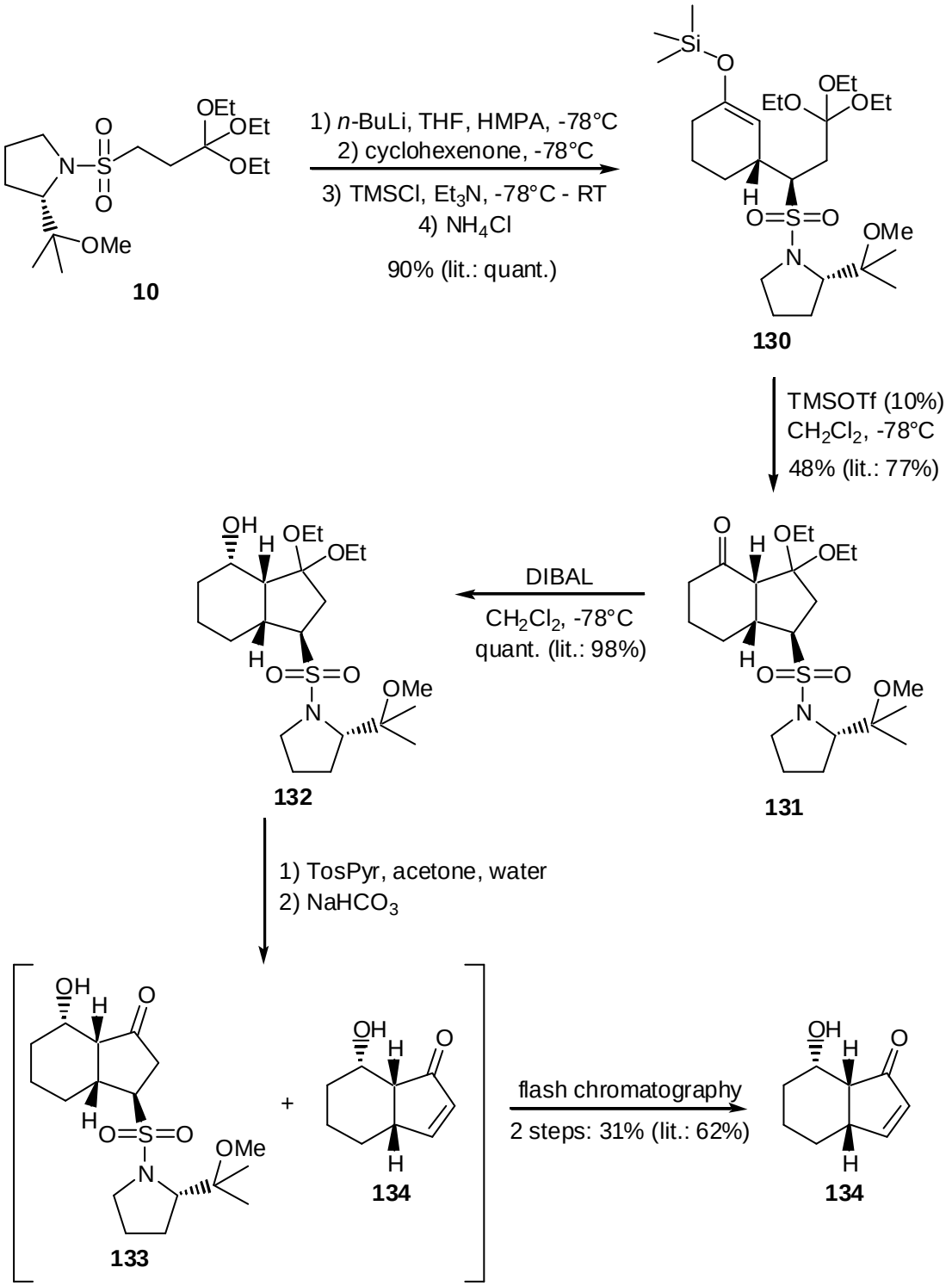
We first repeated the sequence developed by C. Huart[68] (scheme 92).

The addition reaction was realized in the standard conditions described before. A saturated ammonium chloride solution was used for the hydrolysis to preserve the silylated enol ether. The crude product was washed five times with a saturated NaCl solution in order to eliminate HMPA. Indeed no HMPA should be present in the cyclization step. The adduct **130** was obtained in good yield.

The cyclization of adduct **130** was induced by the use of a catalytic amount of trimethylsilyl trifluoromethanesulfonate. Cyclized product **131** was obtained in only modest yield. The low yield was probably due to some contamination of starting material by the ester resulting from uncontrolled hydrolysis of the orthoester.

The chiral inductor had to be released by β-elimination which should be easily done after hydrolysis of the ketal into the corresponding ketone. A risk of epimerization could not be excluded. Thus the carbonyl group of the cyclohexanone ring was first reduced by DIBAL. The reduction was stereoselective giving *endo* alcool.[67] Alcool **132** was obtained in quantitative yield.

Hydrolysis of ketal **132** was realized with a catalytic amount of pyridinium tosylate in a mixture of acetone and water. Ketone **133** was obtained together with a non-negligible amount of **134** (~15%). The elimination reaction was completed by passing through a column of silicagel.

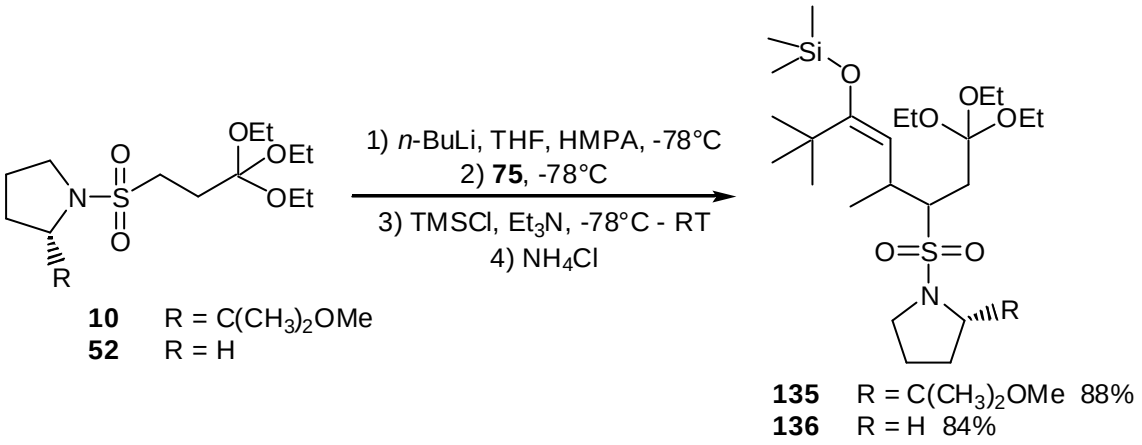

1) n-BuLi, THF, HMPA, -78°C
2) cyclohexenone, -78°C
3) TMSCl, Et3N, -78°C - RT
4) NH4Cl
90% (lit.: quant.)
10
130
TMSOTf (10%)
CH2Cl2, -78°C
48% (lit.: 77%)
DIBAL
CH2Cl2, -78°C
quant. (lit.: 98%)
131
132
1) TosPyr, acetone, water
2) NaHCO3
133
134
flash chromatography
2 steps: 31% (lit.: 62%)
134

Scheme 92

2 Cyclization starting from 2,2-dimethylhex-4-en-3-one 75

2.1 Addition to 2,2-dimethylhex-4-en-3-one 75

Addition to 2,2-dimethylhex-4-en-3-one **75** was realized with orthoesters **52** and **10** in the same conditions as before. Adducts **135** and **136** were obtained in good yields and were pure according to ^{1}H NMR (scheme 93).

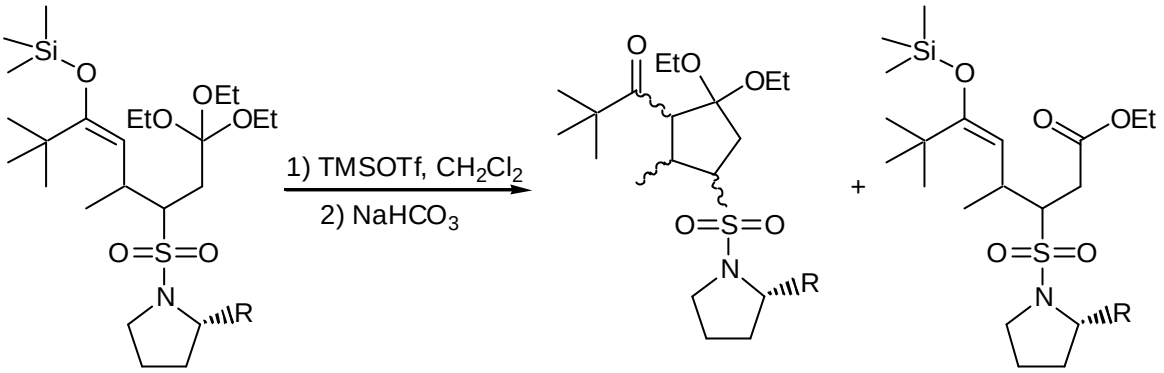


Scheme 93

We were not able to determine the stereochemistry of the products due to the complexity of the spectra.

2.2 Cyclization of adducts 135 and 136

When we applied the conditions used before (see section 109) no cyclization occurred. Ester **137** was the only isolable product. It resulted from the attack of the Lewis acid on the orthoester without concomitant reaction with the silylated enol ether and hydrolysis during work-up (scheme 94). A possible explanation could be the steric hindrance caused by the *tert*-butyl group.



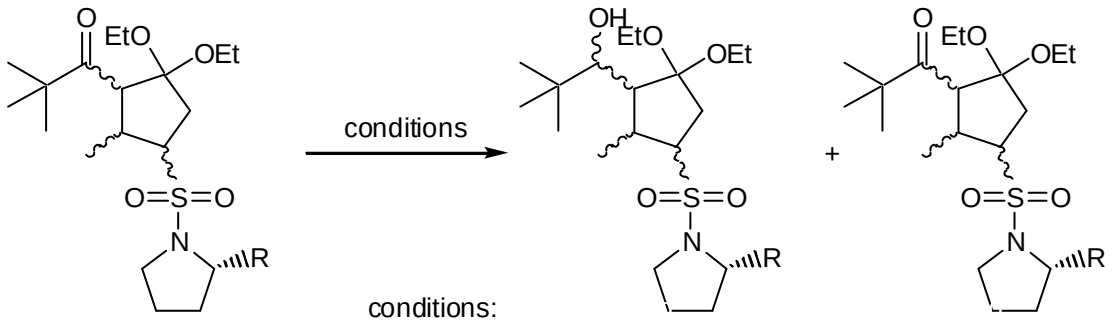
135	R = $C(CH_3)_2OMe$	-78°C -45°C	0% 55%	**138**		quant. 0%	**137**
136	R = H	-45°C	67%	**139**		0%	

Scheme 94

However when the reaction was conducted at -45°C, the cyclized product **138** was formed in good yield. Adduct **136** was cyclized in the same conditions.

2.3 Reduction of 138 and 139

The reaction with DIBAL did not occur; starting materiel was recovered (scheme 95). The lack of reaction could easily be explained by the bulkiness of both reactant and reagent.



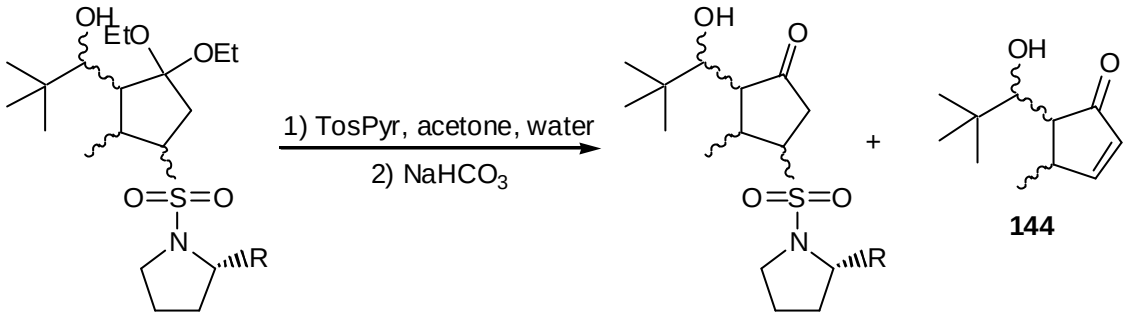
138	R = $C(CH_3)_2OMe$	DIBAL, CH_2Cl_2, -78°C $LiAlH_4$, Et_2O, 0°C	0% 79%	**140**		63% 0%	**138**
139	R = H	$LiAlH_4$, Et_2O, 0°C	86%	**141**			

Scheme 95

With a stronger and less hindered reducing agent, $LiAlH_4$, the reaction proceeded smoothly and the desired products **140** and **141** were obtained in good yield. Only one diastereomer was formed; we indeed observed only one clear signal (*dd*, *J* = 7.85, 3.9 Hz, see section 2.6 for a discussion) for the proton next to the hydroxyl group.

2.4 Hydrolysis of 140 and 141

Hydrolysis of ketals **140** and **141** occurred readily with pyridinum *para*-toluenesulfonate and ketones **142** and **143** were obtained in good yield (scheme 96). Hydrolysis of **142** was accompanied by elimination and 10% of **144** were found in the crude mixture.



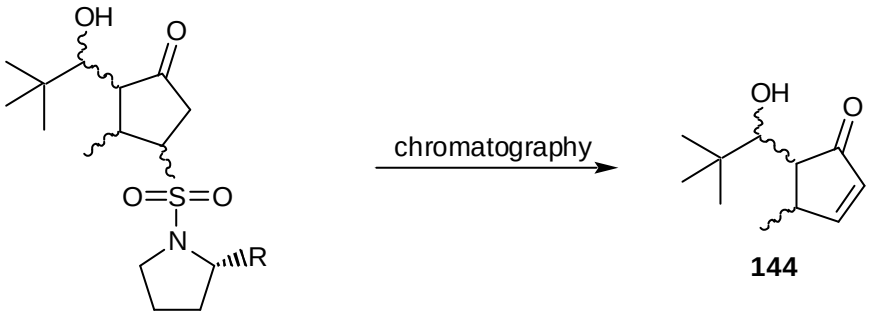
140 R = $C(CH_3)_2OMe$
141 R = H

142 R = $C(CH_3)_2OMe$ ~79% ~10%
143 R = H 76%

Scheme 96

2.5 Elimination of the chiral inductor

The crude product of the previous reaction was passed on a silicagel chromatography column. This led to a β-elimination and product **144** was obtained in good yields (scheme 97).



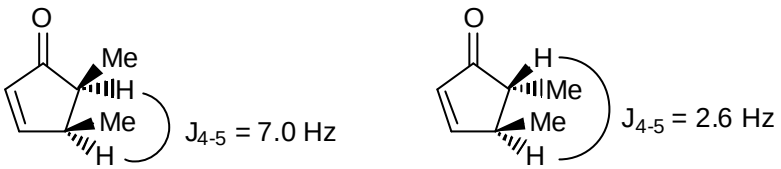
142 R = $C(CH_3)_2OMe$ 78%
143 R = H 75%

Scheme 97

2.6 Stereochemistry

One diastereomer of **144** was formed in both cases. The coupling constants for 4,5-dimethylcyclopent-2-enone **145** have been described in the literature.[162] Coupling constants between the two protons on the sp^3 carbons were 7.0 Hz in ***cis*-145** and 2.6 Hz in ***trans*-145** (figure 25).

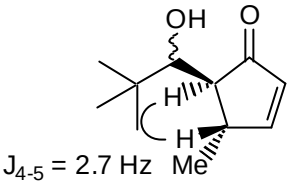
[162] Karpf, M.; Huguet, J.; Dreiding, A. S. *Helv. Chim. Acta*, **1982**, *65*, 13-25.



***cis*-145** ***trans*-145**

Figure 25

For compound **144** we measured a coupling constant of 2.7 Hz. This led us to the conclusion that cyclopentenone **144** had the *tert*-butyl group *trans* to the methyl group (figure 26).



144

Figure 26

Thus the cyclopentannulation sequence was stereoselective: a *cis*-enone yielded a pentenone with a *syn*-configuration, whereas a *trans*-enone led to an *anti*-configuration.

For the relative configuration of the hydroxyl group, we have the following informations. The coupling constant between H5 and H6 was 5.25 Hz (figure 27). Shibasaki measured a coupling constant of 5.5 Hz in ***syn*-146**, whereas it was 7.8 Hz in ***anti*-146**.[163] In pentanone ***syn*-147** the corresponding coupling constant was 3.9 Hz, in ***anti*-147** it was 9.3 Hz.[164] Kobayashi was interested in cyclopentenones, and he observed coupling constants of ca. 3 Hz in ***syn*-148** and of 9-9.6 Hz in ***anti*-148**.[165] Finally, C. Huart[67] and we measured a coupling constant of 5.7 Hz for the corresponding proton in bicycle **134**.

[163] Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.*, **1999**, *121*, 4168-4178.
[164] Ishihara, K.; Kondo, S.; Yamamoto, H. *J. Org. Chem.*, **2000**, *65*, 9125-9128.
[165] Kobayashi, Y.; Murugesh, M. G.; Nakano, M.; Takahisa, E.; Usmani, S. B.; Ainai, T. *J. Org. Chem.*, **2002**, *67*, 7110-7123.

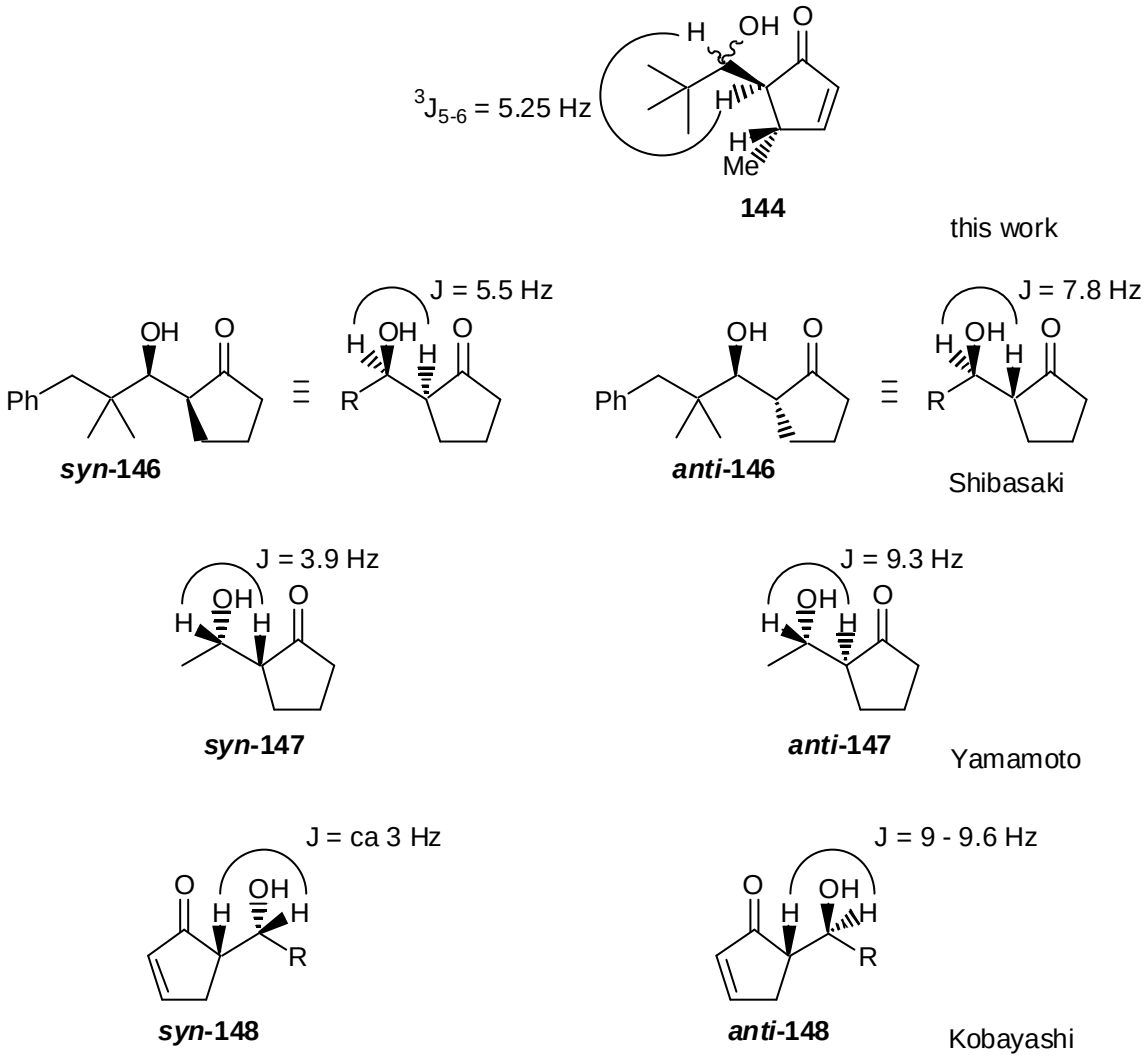


Figure 27

These results strongly suggest that the relative configuration of the hydroxyl group in **144** is *syn*. Also a coupling constant of 5.25 Hz corresponds to a dihedral angle of 35° which is the angle we obtain when we assume the existence of a hydrogen bridge between the alcohol and the ketone. We therefore propose the relative configuration shown in figure 28: a *trans* relation between the two substituents on the ring and a *syn* configuration for the hydroxyl group.

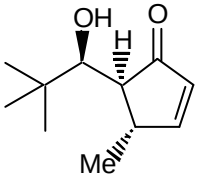
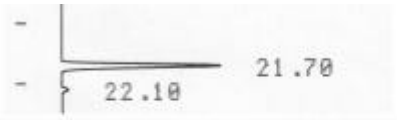


Figure 28

Enantioselectivities have been measured by chiral GC and an enantiomeric excess of 91% has been observed (figure 29).

NO.	RT	AREA	CONC	BC
1	21.63	18638	50.239	BB
2	22.00	18460	49.760	BB



NO.	RT	AREA	CONC	BC
1	21.70	10317	95.580	BB
2	22.10	477	4.419	BB

Figure 29

The cyclopentannulation of an acyclic enone could thus be realized with nearly as good enantioselectivities than with cyclic enones.