Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 6, pp. 1763-1770, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00211-X

INTRAMOLECULAR VS. INTERMOLECULAR INDUCTION IN THE DIASTEREOSELECTIVE CATALYTIC REDUCTION OF 17-OXO-STEROIDS

I. Reiners, J. Martens*

Fachbereich Chemie der Universität Oldenburg, Ammerländer Heerstraße 114-118, D-26129 Oldenburg i.O., Germany

S. Schwarz, H. Henkel

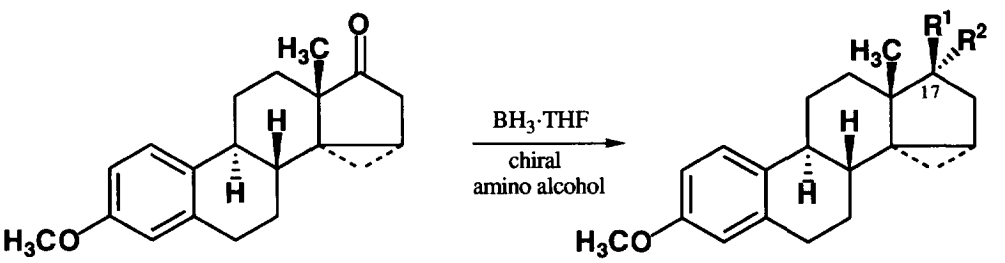
Geschäftsbereich Forschung und Entwicklung, Jenapharm GmbH, D-07745 Jena, Germany

Abstract: The asymmetric reduction of enantiomerically pure steroid ketones was carried out by using oxazaborolidine catalysts with a variety of achiral or chiral ligands. The efficiency of chiral ligands (1,2-amino alcohols) as well as the effect of the stereogenic centers in the substrate on the catalytic asymmetric reduction were studied. It was found that the diastereoselectivity is mainly controlled by the absolute configuration of the chiral ligand. The reduction gave either the 17α- or 17β-alcohol with high diastereomeric purity. This catalytic reduction represents a very practical solution to the problem of controlling C(17)-stereochemistry in synthesis of steroid compounds.

Introduction

The biological activity of steroidal hormones is controlled to a large degree by the distance and orientation of functional groups bound to the steroid skeleton.

Esters of 14α,14α-methylenestra-1,3,5(10)-triene-3,17β-diol are highly active estrogens upon oral application. In particular the sulfamates show a promising dissociation between uterine and hepatic estrogenicity[1]. Because of these effects the esters may have potential use in fertility control and hormone replacement therapy.



1

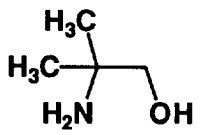
17α-2 (R^1= H, R^2= OH)
17β-2 (R^1= OH, R^2= H)

The reduction of 17-oxo-steroids represents a key step in the synthesis of these compounds and a high stereoselectivity is required. In almost every case, reduction of steroid ketones by conventional reducing

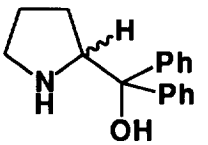
agents such as sodium tetrahydroborate leads to a mixture containing predominantly one of the two possible isomeric alcohols.

Results and discussion

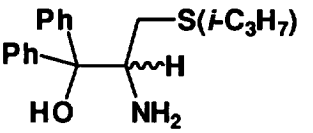
We report here on a new method for the synthesis of key substances 17β-**2** and 17α-**15**, mainly from the stereochemical point of view. The multi-step synthesis[2] of the orally active 14α,15α-methylene estradiol J 824 includes the C(17)-reduction of **1** to the 17β-alcohol 17β-**2**. In this paper we describe the reduction of 3-methoxy-14α,15α-methylen-estra-1,3,5(10)-trien-17-one **1** with borane in the presence of achiral or chiral amino alcohols. In these cases oxazaborolidines[3] formed *in situ* are the active reducing agents. An interesting point involved in this reaction is how the stereogenic centers of the steroid ketone affect the way of asymmetric induction by the chiral catalyst. In an earlier report we described the stereoselective reduction of other enantiomerically pure ketones like camphor and menthone[4].



3

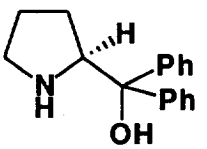


rac-**4**

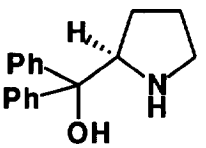


rac-**5**

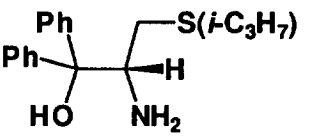
Reduction with diborane[5] in the absence of any amino alcohol afforded an 85:15 mixture of 17β-**2** and 17α-**2** which was separated by chromatography. We found that treatment of **1** with borane and catalytic amounts of achiral **3**, *rac*-**4**[6] and *rac*-**5**[7] gave the secondary alcohols in high yields (table 1, entry 1-3). These results show that the chirality of the substrate **1** forces the reaction to give the desired alcohol 17β-**2** in excess.



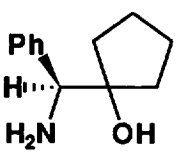
(*S*)-**4**



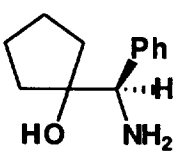
(*R*)-**4**



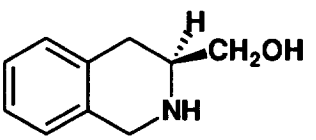
(*R*)-**5**



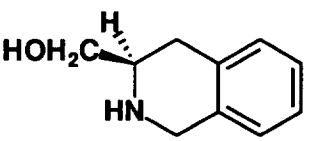
(*S*)-**6**



(*R*)-**6**



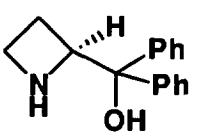
(*S*)-**7**



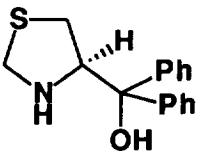
(*R*)-**7**

Borane reduction of **1** in the presence of homochiral amino alcohols (*R*)-**4**[8], (*R*)-**6**[9] and (*R*)-**7**[10] increased the stereoselectivity, providing 99% 17β-**2** and 1% 17α-**2** (entry 5). In this case we observed a large double

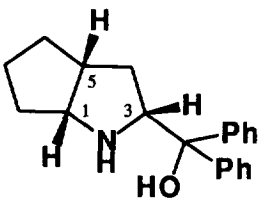
asymmetric induction. This chiral double recognition could also be achieved with (*R*)-**9**[11], (1*R*,3*R*,5*R*)-**10**[12] and (1*R*,3*R*,5*R*)-**11**[13].



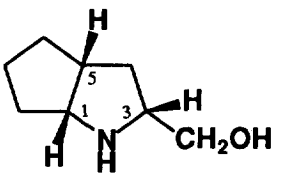
(*S*)-**8**



(*R*)-**9**



(1*R*,3*R*,5*R*)-**10**



(1*R*,3*R*,5*R*)-**11**

On the other hand 87% of the secondary alcohol 17α-**2** was obtained by changing the configuration of the homochiral catalyst (table 1, entry 4). Thus, the amino alcohols (*S*)-**4**[14], (*R*)-**5**[15], (*S*)-**6**[4], (*S*)-**7**[16] and (*S*)-**8**[17] are able to supersede the intramolecular induction.

Table 1. Diastereoselective reduction of 3-methoxy-14α,15α-methylen-estra-1,3,5(10)-trien-17-one **1**

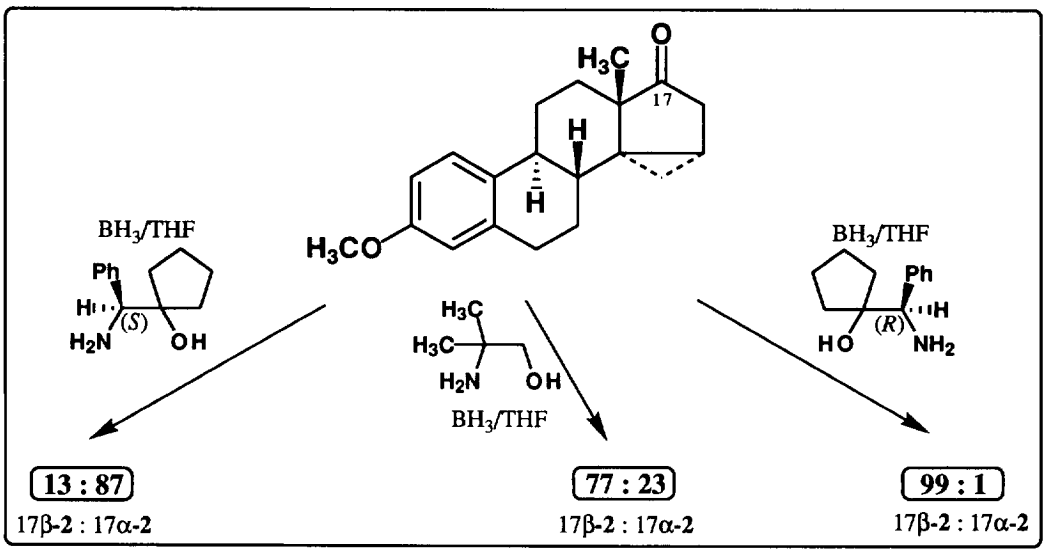
entry	catalyst	catalyst concentration [mol%]	temperature [°C]	time [h]	yield [%]	17α-**2**:17β-**2**[a]
1	**3**	10	30	4	94	23:77
2	*rac*-**4**	10	30	4	94	37:63
3	*rac*-**5**	10	35	16	98	32:68
4	(*S*)-**6**	10	30	48	95	87:13
5	(*R*)-**6**	10	30	48	94	1:99
6	(*S*)-**4**	10	30	4	91	86:14
7	(*R*)-**4**	10	30	4	94	5:95
8	(*S*)-**7**	10	30	48	91	57:43
9	(*R*)-**7**	10	30	48	90	5:95
10	(*S*)-**8**	10	30	4	66	78:22
11	(*R*)-**9**	10	65	16	79	13:87
12	(*R*)-**5**	5	30	4	90	80:20
13	(1*R*,3*R*,5*R*)-**10**	10	30	48	91	8:92
14	(1*R*,3*R*,5*R*)-**11**	10	30	48	92	7:93

[a] The ratio of the alcohols 17α-**2**:17β-**2** was determined by HPLC analysis of the recovered residue.

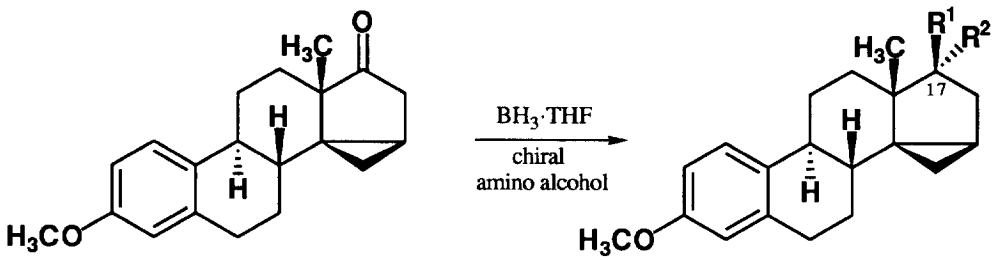
The stereochemistry of the new stereogenic center in **2** is affected mainly by the configuration of the homochiral amino alcohol. The catalyst can clearly control the stereoselectivity of the reaction to a large

degree, although the chiral centers of the ketone **1** have a strong influence upon the diastereoselectivity in reductions with achiral or racemic amino alcohols.

A summary is given below:



These results are transferable to the reduction of other 17-oxo-steroids for example 3-methoxy-14β,15β-methylen-estra-1,3,5(10)-trien-17-one **12**. Reduction of this 14β,15β-methylene derivative gave a mixture of C(17)-epimeric alcohols 17α-**13** and 17β-**13** in a ratio of 69: 31 with sodium tatrahydroborate and a ratio of 90:10 with diborane[5].



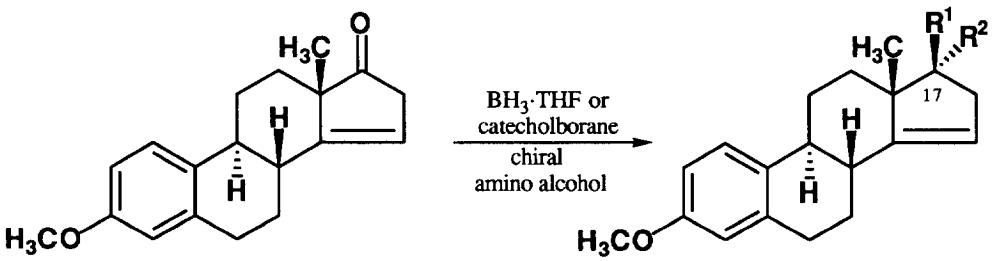
Treatment of the β-bridged steroid ketone **12** with borane-THF complex in the presence of the homochiral amino alcohol (*S*)-**6** gave the 17α-alcohol 17α-**13** in excellent yield and no 17β-alcohol 17β-**13** could be determined by HPLC (table 2, entry 3). On the other hand is it possible to invert the intramolecular induction with a good yield and a product ratio 17α-**13**:17β-**13** of 12:88 using the same amino alcohol with opposite configuration.

Table 2. Diastereoselective reduction of 3-methoxy-14β,15β-methylen-estra-1,3,5(10)-trien-17-one **12**

entry	reducing agent	catalyst [mol%]	temperature [°C]	time [h]	yield [%]	17α-**13**:17β-**13**[a]	ref.
1	$NaBH_4$	–	20	24	75	69:31	5
2	B_2H_6	–	20	1	80	90:10	5
3	BH_3·THF	(*S*)-**6** (10)	30	48	97	>99:1	–
4	BH_3·THF	(*R*)-**6** (10)	30	48	95	12:88	–

[a] The ratio of the alcohols 17α-**13**:17β-**13** was determined by HPLC analysis of the recovered residue.

The advantage of this method can be seen in the synthesis of the key compound 17α-**15**. The stereochemistry in position 17 of **15** is essential for the stereoselective carbene addition at the 14-double bond from the rear side of the molecule[5]. In particular the reduction with sodium tetrahydroborate of the precursor 14-dehydro-estrone-3-methylether **14** suffers from only 10% yield of 17α-**15** upon chromatography[18].



14

17α-**15** (R^1= H, R^2= OH)
17β-**15** (R^1= OH, R^2= H)

This counterproductive substrate-controlled diastereoface differentiation in the key reductive step represents an inefficient route to 17α-**15**. Another purpose of this paper is to present a highly stereocontrolled catalytic *one-step*[19] procedure for the conversion of **14** into 17α-**15**.

Table 3. Diastereoselective reduction of 14-dehydro-estrone-3-methylether **14** with BH_3·THF

entry	reducing agent [equiv]	catalyst [mol%]	temperature [°C]	time [min]	yield [%]	17α-**15**:17β-**15**[a]
1	BH_3·THF (1)	(*S*)-**6** (10)	–20	180	69	68:32
2	BH_3·THF (1)	(*S*)-**6** (10)	0	240	43	74:26
3	BH_3·THF (1)	(*S*)-**8** (10)	20	60	19	67:33
4	BH_3·THF (0.6)	(*S*)-**8** (10)	20	15	47	82:18
5	BH_3·THF (0.9)	(*S*)-**8** (10)	20	10	45	86:14

[a] The ratio of the alcohols 17α-**15**:17β-**15** was determined by HPLC analysis of the recovered residue.

The chiral 17-oxo steroid **14** underwent reduction with borane in THF in the presence of 10 mol% of (*S*)-**8** as catalyst to give the 17α-**15** alcohol and the 17β-**15** diastereomer in a ratio up to 86:14 with a chemical yield of

19% up to 69% (table 3). We could improve the process by using catecholborane as reducing agent[20], but associated with the catalyst prepared from amino alcohol and borane-THF complex, instead of the usual *n*-butyl boron related oxazaborolidine catalyst. Thus, side reactions such as hydroboration of the C=C-double bond can be avoided. We obtained 17α-**15** alcohol and 17β-**15** epimer in a ratio of 76:24 with a chemical yield of 98% using (*S*)-**8** and a reaction temperature of 0°C (table 4, entry 7). As can be seen from table 4 we achieve the same ratio with a temperature of 30°C but the chemical yield decreases to 75% (table 4, entry 5).

Table 4. Diastereoselective reduction of 14-dehydro-estrone-3-methylether **14** with catecholborane

entry	catalyst	catalyst concentration [mol%]	temperature [°C]	time [h]	yield [%]	17α-**15**:17β-**15**[a)]
1	–	–	20	72	97	15:85
2	(*S*)-**4**	10	20	20	95	31:69
3	(*S*)-**6**	10	20	20	76	46:54
4	(*S*)-**8**	10	20	18	66	71:29
5	(*S*)-**8**	10	30	20	75	76:24
6	(*S*)-**8**	20	30	1	79	72:28
7	(*S*)-**8**	10	0	3	98	76:24
8	(*S*)-**8**	10	40	2	87	61:39
9	(*S*)-**8**	10	– 15	4	93	75:25
10	(*S*)-**8**	5	20	20	99	49:51

[a] The ratio of the alcohols 17α-**15**:17β-**15** was determined by HPLC analysis of the recovered residue.

In summary this catalytic reduction of 17-keto steroids using optically active amino alcohols as dominating source of chirality shows a very efficient solution to the problem of controlling C(17)-stereochemistry in synthesis of C(14)/C(15)-bridged steroid derivatives. The inherent preference for one isomer was increased or overridden by use of homochiral amino alcohols. The desired 17-hydroxy steroids 17β-**2** and 17α-**15** could be obtained *via* an *one-step* procedure controlled by the configuration of the chiral catalyst.

Experimental Section

All reactions were carried out in oven dried glassware and under argon atmosphere. THF and toluene were freshly distilled from sodium. Melting points were taken on a melting point apparatus according to Dr. Linström and are uncorrected. High pressure liquid chromatography (HPLC) was performed using a Shimadzu LC-6A/C-R4A instrument. Commercially available chemicals were used. The amino alcohols **4-11** were prepared according to the literature[4,6–17].

Asymmetric reduction of ketone 1 with borane-THF complex (typical procedure): In a typical procedure a mixture of the steroid ketone **1** (0.40g, 1.35 mmol) in 3 mL dry THF was slowly added within 1 hour to a solution of the catalyst (mol% see table 1) and borane-THF complex (1.5 mmol) in 5 mL dry THF at 30°C or 65°C. After stirring until the reaction was complete as determined by tlc analysis (eluent: cyclohexane/ethyl acetate 7:3 v/v) the mixture was hydrolyzed with 10 mL 2 N HCl and extracted three times with 4 mL *tert-*

butylmethyl ether. The combined organic layers were successively washed with 5 mL 2N NaOH and two times 5 mL NaCl solution, dried ($MgSO_4$) and concentrated under reduced pressure. The obtained crude product was analysed by HPLC in order to avoid enrichment of one diastereomer by crystallization. HPLC was performed using a Hypersil ODS 5 µm (250x4 mm I. D.) column and acetonitrile-H_2O (6:4) as the mobile phase at 1 mL/min to estimate the ratio of the 17α-**2**- and 17β-**2**-diastereomers (17α-**2**: 11.3 min, 17β-**2**: 8.7 min.). The products werde identified via HPLC by comparison with authentic samples prepared according to the literature[2]. The results are listed in table 1. The crude product was subjected to chromatography (eluent: cyclohexane/ethyl acetate 7:3 v/v) or crystallization (CH_3OH) to give 17α-**2** and 17β-**2**. 17α-**2**: m.p. 138-143°C (ref.[2] 139-143°C). 17β-**2**: m.p. 118-123°C (ref.[2] 118-122°C).

Asymmetric reduction of ketone 12 with borane-THF complex (typical procedure): A mixture of the steroid ketone **12** (0.30g, 1 mmol) in 3 mL dry THF was slowly added within 1 hour to a solution of the catalyst (10 mol%) and borane-THF complex (1.1 mmol) in 3 mL dry THF at 30°C. After stirring until the reaction was complete as determined by tlc analysis (eluent: cyclohexane/ethyl acetate 7:3 v/v) the mixture was hydrolyzed with 10 mL 2 N HCl and extracted three times with 4 mL *tert*-butylmethyl ether. The combined organic layers were successively washed with 5 mL 2N NaOH and two times 5 mL NaCl solution, dried ($MgSO_4$) and concentrated under reduced pressure. The obtained crude product was analysed by HPLC, using a Hypersil ODS 5 µm (250x4 mm I. D.) column and acetonitrile-H_2O (6:4) as the mobile phase at 1 mL/min to estimate the ratio of the 17α-**13**- and 17β-**13**-diastereomers (17α-**13**: 11.0 min, 17β-**13**: 8.4 min.). The products werde identified via HPLC by comparison with authentic samples prepared according to the literature[5]. The results are listed in table 2. The crude product was subjected to chromatography (eluent: cyclohexane/ethyl acetate 7:3 v/v) or crystallization (CH_3CH_2OH) to give 17α-**13** and 17β-**13**. 17α-**13**: m.p. 119-121°C (ref.[5] 119-121°C). 17β-**13**: m.p. 139-141°C (ref.[5] 140-142°C).

Asymmetric reduction of ketone 14 with borane-THF complex (typical procedure): A solution of the 17-oxo steroid **14** (0.42 g, 1.5 mmol) was added within 5 min to a mixture of catalyst (10 mol%) and BH_3-THF complex (equiv see table 3) in 3 mL dry THF at the respective temperature. After stirring until the reaction was complete as determined by tlc analysis (eluent: $CHCl_3$) the mixture was hydrolyzed with 10 mL 2 N HCl and extracted three times with 4 mL *tert*-butylmethyl ether. The resulting alcohol could be isolated by washing with 5 mL 2N NaOH, two times 5 mL NaCl solution, drying with anhydrous magnesium sulphate and removal of solvent under reduced pressure. The ratio of the alcohols 17α-**15**:17β-**15** was determined by HPLC analysis of the recovered residue (see table 3). HPLC was performed using a Chiralpak AD (250x4.4 mm I. D.) column and acetonitrile-H_2O (6:4) as the mobile phase at 1 mL/min to estimate the ratio of the 17α-**15**- and 17β-**15**-diastereomers (17α-**15**: 12.6 min, 17β-**15**: 9.3 min.). The products werde identified via HPLC by comparison with authentic samples prepared according to the literature[18]. The crude product was subjected to chromatography ($CHCl_3$) or crystallization (Et_2O/light petroleum) to give 17α-**15** and 17β-**15**. 17α-**15**: m.p. 105-107°C (ref.[18] 105-108°C). 17β-**15**: m.p. 115-117°C (ref.[18] 116-118°C).

Asymmetric reduction of ketone 14 with catecholborane (typical procedure): To the amino alcohol (mol% see table 1) in 3 mL dry THF at – 70°C was added borane-THF complex (3 equiv). The reaction mixture was stirred for 1/2 h at 20°C and 2 h at 60°C. The solvent was then removed at room temperature

under reduced pressure. It remains a white solid. This oxazaborolidine was dissolved in 4 mL dry toluene and the steroid ketone **14** (0.42 g, 1.5 mmol) in 3 mL dry toluene was added at the respective temperature. To this mixture was added slowly (20 min) a solution of freshly distilled catecholborane (0.54 g, 4.5 mmol) in 3 mL dry toluene. The solution was stirred until the reaction was complete as determined by tlc analysis (eluent: $CHCl_3$) and quenched with 15 mL water. The organic layer was washed three times with 20 mL 2N NaOH to remove catechol, extracted three times with 15 mL 2 N HCl to remove the amino alcohol for reuse and washed with 15 mL NaCl solution. Drying with $MgSO_4$ and concentration in vacuo afforded the crude product. The ratio of the alcohols 17α-**15**:17β-**15** was determined by HPLC analysis (Conditions see above, comparison with authentic samples[18]) of the recovered residue. The results are listed in table 4. The crude product was subjected to chromatography ($CHCl_3$) or crystallization (Et_2O/light petroleum) to give 17α-**15** and 17β-**15**. 17α-**15**: m.p. 104-107°C (ref.[18] 105-108°C). 17β-**15**: m.p. 115-118°C (ref.[18] 116-118°C).

Acknowledgements : Thanks are due to *Degussa AG, Hermann-Schlosser-Stiftung* and *Fonds der Chemischen Industrie* for support.

References and Notes

1 S. Schwarz, W. Elger, G. Reddersen, B. Schneider, *German Patent Appl.* 44 29 397.6, 44 29 398.4, **1994**.

2 H.-J. Siemann, P. Droescher, B. Undeutsch, S. Schwarz, Steroids **1995**, 60, 308-315.

3 (a) A. Hirao, S. Itsuno, S. Nakahama, N. Yamazaki, *J. Chem. Soc. Chem. Commun.* **1981**, 315-317. (b) S. Itsuno, A. Hirao, S. Nakahama, Y. Yamazaki, *J. Chem. Soc. Perkin I* **1983**, 1673-1676. (c) S. Itsuno, K. Ito, A. Hirao, S. Nakahama, *J. Chem. Soc. Perkin I* **1984**, 2887. Reviews: (d) S. Wallbaum, J. Martens, *Tetrahedron: Asymmetry* **1992**, *3*, 1475-1504. (e) L. Deloux, M. Screbnik, *Chem. Rev.* **1993**, *93*, 763-784.

4 I. Reiners, J. Wilken, J. Martens, *Tetrahedron: Asymmetry* **1995**, *6*, 3063-3070.

5 R. Prousa, B. Schönbecker, D. Tresselt, K. Ponsold, *J. prakt. Chem.* **1986**, *328*, 55-70.

6 E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 7925-7926.

7 T. Mehler, J. Martens, unpublished results.

8 E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 7925-7926.

9 Ch. Dauelsberg, J. Martens, *Synth. Commun.* **1993**, *23*, 2091-2099.

10 D. Farge, A. Jossin, G. Ponsinet, D. Reisdorf, Deutsches Patent 2 635 516, **1977**.

11 W. Trentmann, J. Martens, unpublished results.

12 S. Wallbaum, J. Martens, *Tetrahedron: Asymmetry* **1991**, *2*, 1093-1096.

13 Ch. Döbler, U. Schmidt, H. W. Krause, H.-J. Kreuzfeld, M. Michalik, *Tetrahedron: Asymmetry* **1995**, *6*, 385-388.

14 E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553.

15 T. Mehler, J. Martens, *Tetrahedron: Asymmetry* **1993**, *4*, 2299-2302.

16 K. Stingl, J. Martens, S. Wallbaum, *Tetrahedron: Asymmetry* **1992**, *3*, 223-226.

17 W. Behnen, Ch. Dauelsberg, S. Wallbaum, J. Martens, *Synth. Commun.* **1992**, *22*, 2143-2153.

18 K. Ponsold, G. Schubert, M. Wunderwald, R. Prousa, *Pharmazie* **1979**, *34*, 250.

19 H. Künzer and M. Thiel reported on a synthesis of the intermediate 17α-**15** in a *four-step* reaction: H. Künzer, M. Thiel, *Tetrahedron Lett.* **1995**, *36*, 1237-1238.

20 (a) E. J. Corey, E. J. Bakshi, *Tetrahedron Lett.* **1990**, *31*, 611-614. (b) E. J. Corey, J. O. Link, *Tetrahedron Lett.* **1992**, *33*, 4141-4144.

(*Received in UK* 22 *March* 1996; *accepted* 30 *April* 1996)