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A New Chiral Director for the Highly Diastereoselective Borane Reduction of Steroid-20-ones

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Summary. The synthesis of a new chiral boroxazolidine was achieved which was used to control the stereochemistry of the borane reduction of the 20-keto group of steroids. The otherwise hardly accessible 20α-(20*S*)-alcohol can thus be prepared in a yield of 91%.

Keywords. Asymmetric reduction; Chiral boranes; Steroid-20-one.

Introduction

High enantioselectivity has been reported in the asymmetric reduction of prochiral ketones with mixtures of borane and chiral aminoalcohols in tetrahydrofuran [1–5]. The asymmetric reduction of chiral 20-keto-steroids with nucleophilic organoborohydrides and electrophilic organoboranes has likewise been studied [6]. The hydroboration of steroid-20-ones *via anti-Cram* addition provided predominantly the (20*S*)-(20α)-hydroxy products [6]. We have found that the asymmetric reduction of chiral steroid-20-ones with borane-methyl sulfide (*BMS*) in the presence of (*R*)-(−)-2-amino-2-phenyl-1-ethanol gives a moderate excess of the (20*S*) products [7].

Corey et al. have prepared the sterically hindered β-aminoalcohol (*S*)-diphenylprolinol ((*S*)-**4**) and the corresponding B-methyl-oxazaborolidine (*S*)-**7** which provided useful enantioselectivity in the reduction of prochiral ketones [2]. They have further proposed that the borane complex of the resulting oxazaborolidine [8, 9] is an important intermediate responsible for the enantioselectivity of ketone reduction. This phenomenon is supported by recent results found in the literature [11].

Results and Discussion

In order to achieve a higher diastereoselectivity for the preparation of the (20*S*)-hydroxy isomer **2** in the reduction of 5β-pregnan-3α-ol-20-one (**1**) than previously

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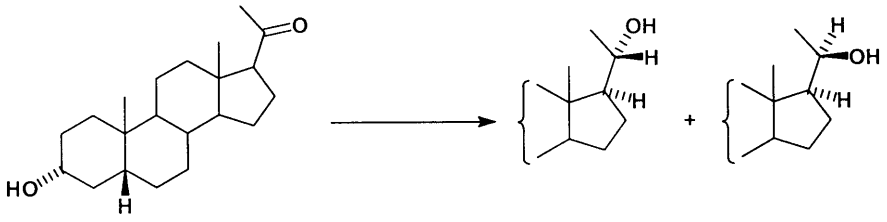


1 (20*S*)-**2** (20*R*)-**3**

Scheme 1

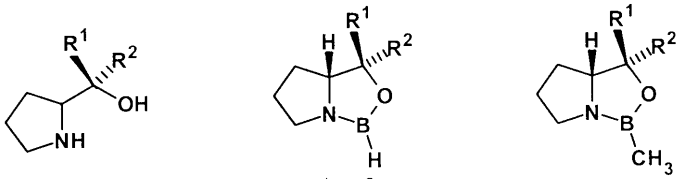
Table 1. Asymmetric reduction of 5β-pregnan-3α-ol-20-one (**1**) in the presence of various chiral directors with borane at room temperature

Entry	Chiral director	Reaction time (h)	Yield[a] (%)	Product/%[b] **2** (20*S*-OH)	**3** (20*R*-OH)
1	(*R*)-(+)-**4**	48.0	39	34.0	66.0
2	(*S*)-(−)-**4**	48.0	30	0.0	100.0
3	(*R*)-(+)-**7**	40.0	25	18.0	82.0
4	(*S*)-(−)-**7**	40.0	27	28.0	72.0
5	(*R*)-(−)-**5**	0.5	99	75.6	24.4
6	(*S*)-(+)-**5**	0.5	97	0.0	100.0
7	(*R*)-(−)-**6**	24.0	45	48.8	51.2
8	(*R*)-(−)-**8**	0.5	100	91.5	8.5

[a] Isolated product; [b]HPLC, Merck Partisil PXS 10/25, $CHCl_3$: MeOH = 95 : 5 or CH_2Cl_2 : MeOH = 95 : 5

reported [7], we applied the (*R*)-(+)- and (*S*)-(−)-diphenylprolinols ((*R*)-**4** and (*S*)-**4**) [2] and the corresponding (*R*)-(+)- and (*S*)-(−)-B-methyl-oxazaborolidines ((*R*)-**7** and (*S*)-**7**) [5] as chiral directors. Initially, **1** was reduced with *BMS* in the presence of (*R*)-**4** and (*S*)-**4** applying a method published earlier [7] (Scheme 1). The resulting diastereoisomeric ratios are listed in Table 1.

High diastereoselectivity was achieved with (*S*)-**4**, but the common (20*R*)-hydroxy isomer was formed in a large excess (Table 1, entry 2). Lower diastereoselectivity was observed in the presence of (*R*)-**4**, but the (20*S*)-hydroxy isomer was obtained in higher quantity (Table 1, entry 1) compared to Ref. [7]. However, the selectivity for the (20*S*)-hydroxy isomer was insufficient. The stoichiometric reaction of ketone **1** with the enantiomeric borane complexes (*R*)-**7** and (*S*)-**7** was achieved by the method reported by *Mathre et al.* [10]. It was found that the selectivity of the reductions were high, but both products contained a large excess of the (20*R*)-diastereoisomer (Table 1, entries 3 and 4). It is noteworthy that with (*S*)-**7** the yield of the (20*S*)-hydroxy isomer was much higher than with (*R*)-**7**. The data in Table 1 indicate that the yields of the reductions with all chiral directors mentioned above were very low. We suppose this to be due to the steric



4: $R^1 = R^2 =$ Ph
5: $R^1 = R^2 =$ H
6: $R^1 = R^2 =$ H
7: $R^1 = R^2 =$ Ph
8: $R^1 = R^2 =$ H

Scheme 2

hindrance of the applied chiral reagents. When the two phenyl substituents were removed from the reagents **4** and **7** and the reductions were performed with *BMS* in the presence of (R)-$(-)$-prolinol (R)-**5** employing our previous method [7], the major product was the (20*S*)-hydroxy isomer (**2**, Table 1, entry 5) rather than the (20*R*)-hydroxy isomer (**3**). However, when **1** was reduced with *BMS* in the presence of (S)-**5**, **3** was formed exclusively (Table 1, entry 6). Reactions were carried out under very mild conditions and were complete after 30 minutes.

In order to increase the amount of **2** in the resulting mixture of diastereoisomers **2** and **3**, the corresponding oxazaborolidine **6** was prepared in crystalline form by sublimation of the residue obtained from a molar equivalent mixture of (R)-**5** and *BMS*. When the reduction of **1** was attempted with two equivalents of *BMS* in the presence of the chiral director **6** *via* the method reported by *Youn et al*. [3], both diastereoselectivity and yield (Table 1, entry 7) were lower than expected from the previous experiment where **6** was generated *in situ*. In accordance with literature data [10] we presume that **6** was partly converted to the corresponding dimer before the reduction occurred. To avoid this problem, we prepared a new B-methyl-boroxazolidine ((R)-**8**) from (R)-**5** (Scheme 2).

The synthesis of (R)-**8** could be driven to completion by sequential addition of trimethylboroxine (molar equivalent) to a toluene solution of (R)-**5** and azeotropic removal of both water and the excess of methylboronic acid as described by *Mathre et al*. [10].

The solution of (R)-**8** itself in toluene did not reduce ketone **1**. However, a mixture of (R)-**8** and $BMS \cdot BH_3$ (1–1.2 molar equivalents) afforded complete reduction of **1** in 30 min at ambient temperature with excellent yield (98%) and considerable diastereoselectivity ($(20S) : (20R) = 91.5 : 8.5$; Table 1, entry 8).

Experimental

Melting points were determined on a Boetius apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were run at ambient temperature on a Bruker AVANCE DRX 400 spectrometer at 400.24 and 100.06 MHz, respectively, with *TMS* as internal standard using the deuterium signal of $CDCl_3$ (solvent) to lock the field.

5β-Pregnan-3α-ol-20-one (**1**) and (R)-$(-)$- and (S)-$(+)$-prolinols ((R)-**5** and (S)-**5**) were purchased from Aldrich, (R)-$(+)$- and (S)-$(-)$-α,α-diphenyl-prolinols ((R)-**4** and (S)-**4**) from Lancaster Synthesis Ltd. (England); all substances were used as received. (R)- and (S)-Tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole ((R)-**7** and (S)-**7**) was kindly supplied by Dr. *D. J. Mathre* from Merck Sharp & Dohme Research Laboratories (New Jersey, USA) and used without further purification.

The ratios of steroid alcohol isomers (**2** and **3**) were determined by TLC and HPLC as described earlier [7]. The physical and spectroscopic data of compounds **2** and **3** are available from Ref. [7].

(R)-(−)-Tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole (**6**; $C_5H_{10}BNO$)

To a stirred solution of 0.1 g aminoalcohol **5** (1 mmol) in 5 cm^3 *THF*, 0.6 cm^3 *BMS* (1.2 mmol; 2 M solution in *THF*, Aldrich) were added at −70°C. The resulting solution was gradually warmed to 50°C and stirred for 5 h. Removal of solvent, sublimation at 145–160°C (0.8 mbar), and resublimation of 145–160°C (0.3 mbar), afforded **6** as a white solid.

Yield: 0.097 g (88.18%); m.p.: 61–65°C (decomp); EIMS: $m/z = 110.95$ (calcd.: 110.94); ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.5–1.9 (m, 4H, 4-CH_2, 5-CH_2), 3.0 (m, 1H, 3a-CH), 3.4 (m, 2H, 6-CH_2), 3.6 (m, 2H, 3-CH_2), 5.0 (b, 1H, 1-BH) ppm.

(R)-(+)-Tetrahydro-1-methyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole (**8***R*; $C_6H_{12}BNO$)

A solution of 103 mg **5** (1 mmol) in 6 cm^3 toluene was treated with 125 mg trimethylboroxine (1 mmol) at room temperature for 1 h. The flask was fitted with a distillation head, toluene (50 cm^3) was added, and the mixture was heated and concentrated by distillation (1 atm) to 50 cm^3. During distillation the vessel was swept with N_2. The toluene addition followed by concentration was repeated three times to insure complete removal of H_2O and excess of methylboronic acid. Removal of the excess of solvent *in vacuo* yielded **8** (116 mg, 92.8%) as a pale yellow oil.

EIMS: $m/z = 124.95$ (calcd.: 124.976); ^{1}H NMR ($CDCl_3$, δ, 400 MHz):-0.06 (s, 3H, B-CH_3), 1.4–1.8 (m, 4H, 4-CH_2, 5-CH_2), 2.8 (m, 1H, 3a-CH), 3.3 (m, 2H, 6-CH_2), 3.5 (m, 2H, 3-2CH_2) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 26.7 and 28.2 (4- and 5-C, respectively), 47.0 (6-C), 60.2 (3a-C), 65.5 (3-C) ppm.

Stoichiometric reduction of ketone **1**

To a stirred solution of 124.9 mg boroxazolidine **8** (1 mmol) and 75.9 mg *BMS* (1 mmol) in 5 cm^3 dry *THF*, a *THF* (3 cm^3) solution of 318.5 mg ketone **1** (1 mmol) was added over 20 min at room temperature under N_2. The reaction mixture was stirred at room temperature for 30 min, and 2 cm^3 15% aqueous HCl were added at 5°C. The precipitated steroid alcohol was extracted three times with 15 cm^3 ether, and the combined extracts were washed with H_2O until neutral and dried over anhydrous Na_2SO_4. After removal of the solvent the residue was analyzed by TLC and HPLC as described earlier [7].

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