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A new family of substituted steroidal BINOL-type ligands†

Matthias F. Schneider,* Michael Harre and Christian Pieper

Process Research, Schering AG-Berlin, Müllerstraße 170–178, D-13342 Berlin, Germany

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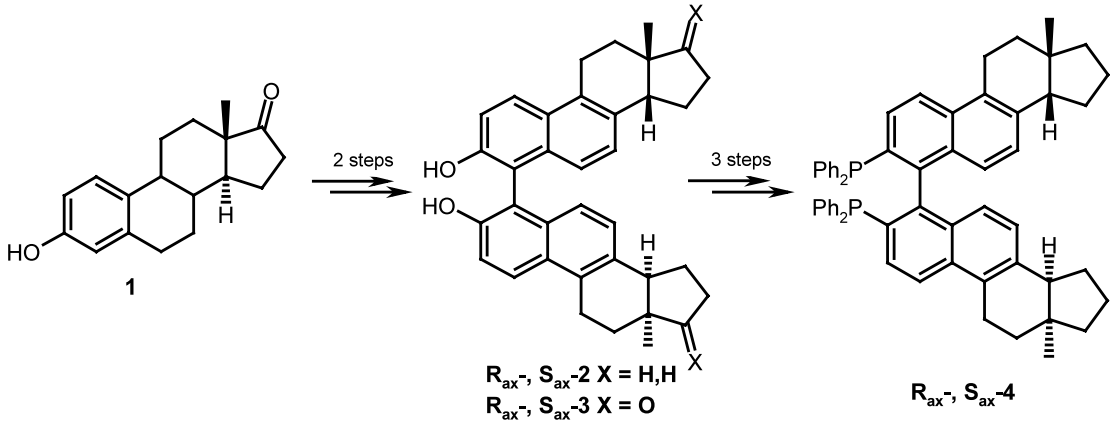
Abstract—The short and high yielding synthesis of a new family of substituted bissteroidal BINOL-type ligands employing the bisketone derivatives $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**3** as the centre point of a 'chemical modular construction system' is reported.

1. Introduction

BINOL[1] and BINAP,[2] which have been employed in numerous catalytic and stoichiometric asymmetric reactions, have attracted great attention over the last several years as chiral auxiliaries and ligands with C_2-symmetry. Nevertheless there are at least two drawbacks for these compounds. The enantiomers of BINOL and/or of BINAP have to be separated by (i) transforming the racemic compounds into diastereomeric derivatives; (ii) separation of these derivatives; and (iii) retransformation into BINOL or BINAP. There are still reactions where BINOL or BINAP give only unsatisfactory results concerning the degree of enantioselection.

Therefore we have developed approaches towards a 13,14-*trans* (steroid nomenclature) configured bissteroidal phosphine[3] starting from equilenine and recently towards the 13,14-*cis* configured phosphine **4**[4] using estrone as relatively cheap starting material. We have employed these phoshines as chiral ligands in ruthenium based asymmetric hydrogenation catalysts.[3,4]

Even having accomplished the second synthesis of steroidal BINAP-type ligands ($\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**4**), we still saw room for improvement due to some difficulties we had encountered during our synthesis. The chemistry from **1** to the diastereomeric mixture of **2** proceeded uneventful, but we were by no means able to separate the deoxygenated ligands $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**2** by column chromatography on a preparative scale. Therefore we had to go via the bisketone derivatives $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**3** which we were able to separate via a preparative HPLC even on a kilogram scale.



Keywords: steroids; polycyclic aromatic compounds; naphthalenes; biaryls.

* Corresponding author. Tel.: +49-(0)30-468-17190; fax: +49-(0)30-468-97190; e-mail: matthias.schneider@schering.de

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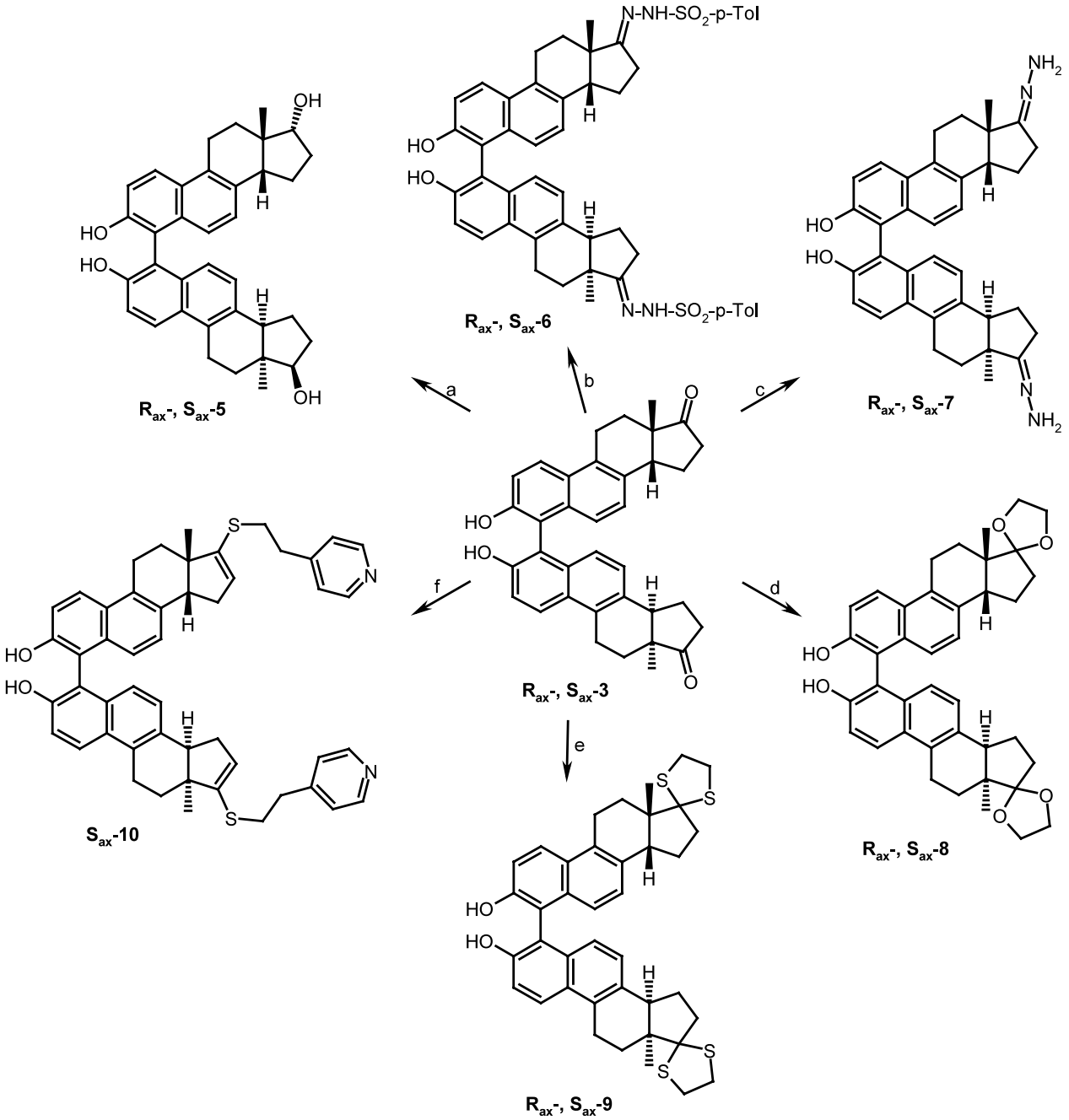
Our new goals were (i) to generate a new family of substituted BINOL-like structures which could also be of interest as potential ligands; and (ii) to discover a synthetic route making the BINOL-type ligands $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**2** available in its diastereopure forms.

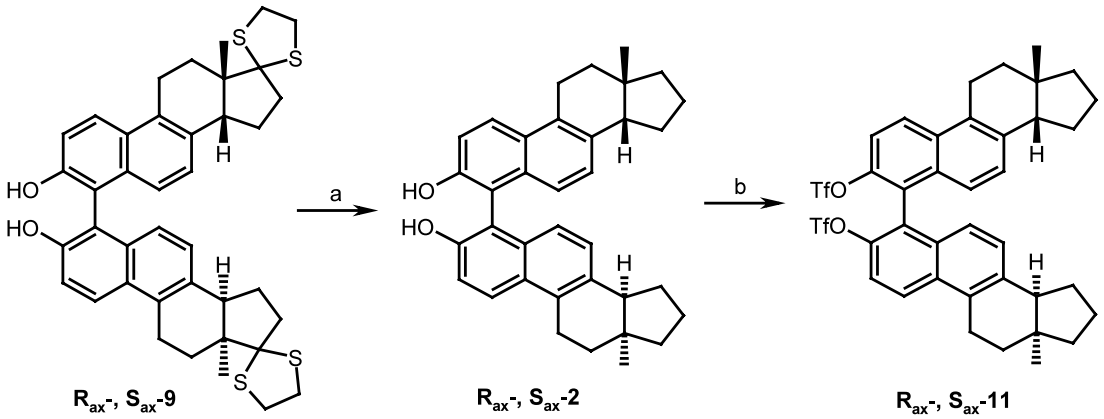
2. Results and discussion

The starting point of our investigation was the bisketone derivatives $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**3** (Scheme 1).

As we had envisioned, we were able to use $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**3** as the centre of a 'chemical modular construction system' to obtain a new family of differently substituted steroidal BINOL-type structures. The reduction of **3** using $NaBH_4$ gave rise to the tetraols $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**5** in quantitative yield.[5] The hydrazone derivatives $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**6** and $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**7** were obtained in 100% and 98% yield, respectively, by simply refluxing **3** with 4.2 equiv. of the necessary hydrazine derivative in EtOH.[6] The employment of an excess of ethyleneglycol and of triethyl orthoformate in toluene using catalytic amounts of *p*-toluenesulfonic acid furnished the desired bisketals



Scheme 1. *Reagents and conditions*: (a) $NaBH_4$, MeOH/THF 1:1, quant.; (b) *p*-toluenesulfonylhydrazine, EtOH, quant.; (c) hydrazine hydrate, EtOH, 98%; (d) 11 equiv. triethyl orthoformate, 0.1 equiv. PTSA, ethyleneglycol/toluene 1/6; 92%; (e) ethane dithiole, $BF_3{\cdot}Et_2O$, CH_2Cl_2, quant.; (f) 4-pyridylethylmercaptan, excess $BF_3{\cdot}Et_2O$, CH_2Cl_2/dichloroethane 1/1, 18% $\mathbf{S_{ax}}$-**19**.



Scheme 2. *Reagents and conditions*: (a) excess Raney-nickel, THF/EtOH 1:4, 95% $\mathbf{R_{ax}}$-**2**/91% $\mathbf{S_{ax}}$-**2**; (b) Tf_2O, NEt_3, toluene; 100% $\mathbf{R_{ax}}$-**11**/85% $\mathbf{S_{ax}}$-**11**.

$\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**8** in very good yield (92%).[7] The bisthioketals $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**9** were available via Lewis acid ($BF_3{\cdot}Et_2O$) mediated ketalisation with ethane dithiole.[8] This reaction was scaled up to 500 g batch sizes without decreasing yields, which were quantitative. As a last example the thioenolether $\mathbf{S_{ax}}$-**10** was synthesized by treating $\mathbf{S_{ax}}$-**3** with an excess of 4-pyridylethylmercaptan and BF_3Et_2O at 50°C.[8] The yield of $\mathbf{S_{ax}}$-**19** is only moderate up to now (18%), but nevertheless this compound could possibly exhibit interesting properties against metals (e.g. Cu) (Scheme 1).

Having in hand the bisthioketals $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**9**, we were now able to obtain the desired compounds $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**2** in its enantiopure forms in only one additional step. Treatment of $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**9** with an excess (15-fold) Raney-Nickel furnished $\mathbf{R_{ax}}$-**2** and $\mathbf{S_{ax}}$-**2** in 95 and 91% yield, respectively, as crystalline compounds after work-up.[8,9] Again the batch sizes have been scaled up to 700 g of starting materials $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**9** without decreasing yields. In addition, this achievement leads the way towards an easier and cheaper way of synthesizing the bistriflates $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**11**, which are the final intermediates in the synthesis of $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**4**.[4] Our original route also started with the bisketone derivatives $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**3** which were transformed into the corresponding tetra-triflates (excess Tf_2O) first and then the enol triflates in position 17 (steroid nomenclature) were reduced using hydrogen and PtO_2 as catalyst to obtain $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**11**. This procedure was not very reliable and in addition is very costly regarding scale-up. In contrast, reaction of $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**2** with triethylamine and triflic acid anhydride in toluene at 0°C, coupled with easy scale-up, gave rise to $\mathbf{R_{ax}}$-**11** in excellent yield (100%) and $\mathbf{S_{ax}}$-**11** in good yield (85%).[2,3] The difference in yield is probably due to different solubilities of the *R*- versus the *S*-compounds influencing the work-up as well as the purification of **2** and **11** (Scheme 2).

3. Conclusion

In conclusion, we have reached all our goals by creating a new family of bissteroidal BINOL-type ligands with the bisketone derivatives $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**3** as centre point thereby affording the ligands $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**2** in its diastereopure forms. In addition a more (cost) efficient way of synthesizing the bistriflates $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**11** has been developed.

The bisketone derivatives $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**3** have already been used as chiral ligands in the addition of diethyl zinc to aldehydes by Dimitrov et al.[10] In addition phosphate derivatives of $\mathbf{R_{ax}}$-, $\mathbf{S_{ax}}$-**2** have been employed successfully as ligands for enantioselective 1,3-dipolar cycloaddition of carbonyl ylides by Hodgson et al.[11] Currently the chiral ligands described therein are tested in different asymmetric reactions. The results will be published in due course.

Acknowledgements

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References

1. (a) For a review, see: Rosoni, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503 and references cited therein; (b) For applications, see: Bao, J.; Wulff, W. D.; Dominy, J. B.; Fumo, M. J.; Grant, E. B.; Rob, A. C.; Whitcomb, M. C.; Yeung, S.-M.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 3392 and references cited therein.
2. (a) Cai, D.; Payack, J. F.; Verhoeven, T. R. US Patent 5,399,771; (b) Cai, D.; Payack, J. F.; Bender, D. R.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 7180 and references cited therein.
3. Enev, V.; Ewers, Ch. L. J.; Harre, M.; Nickisch, K.; Mohr, J. T. *J. Org. Chem.* **1997**, *62*, 7092.
4. Enev, V.; Harre, M.; Nickisch, K.; Schneider, M.; Mohr, J. *Tetrahedron: Asymmetry* **2000**, *11*, 1767–1779 and references cited therein.
5. All new compounds have been unambigously characterized by NMR (^1H and ^{13}C), IR and MS (high resolution).

6. Kabalka, G. W.; Maddox, J. T.; Bogas, E.; Kelley, S. W. *J. Org. Chem.* **1997**, *62*, 3688–3695 and references cited therein.
7. Schering procedure.
8. Ihara, M.; Suzuki, T.; Katogi, M.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 865–873.
9. Kluge, A. F.; Maddox, M. L.; Partridge, L. G. *J. Org. Chem.* **1985**, *50*, 2359–2365.
10. Kostova, K.; Genov, M.; Philipova, I.; Dimitrov, V. *Tetrahedron: Asymmetry* **2000**, *11*, 3253–3256.
11. Hodgson, D. M.; Stupple, P. A.; Pierard, F. Y. T. M.; Labande, A. H.; Johnstone, C. *Chem. Eur. J.* **2001**, *7*, 4465–4476.