Pergamon

Tetrahedron Letters 43 (2002) 2499–2503

TETRAHEDRON LETTERS

O-Silylated steroidal *cis*-aminoalcohols as chiral auxiliaries: highly diastereoselective Pd-catalyzed cyclopropanation of α,β-unsaturated aldimines†

M. Dubs,[a] H. Dieks,[a] W. Günther,[a] M. Kötteritzsch,[a] W. Poppitz[b] and B. Schönecker[a,*]

[a]*Institut für Organische Chemie und Makromolekulare Chemie, Friedrich-Schiller-Universität Jena, Humboldtstr. 10, D-07743 Jena, Germany*

[b]*Institut für Anorganische und Analytische Chemie, Friedrich-Schiller-Universität Jena, Humboldtstr. 10, D-07743 Jena, Germany*

Received 15 February 2002; accepted 16 February 2002

Abstract—α,β-Unsaturated imines, obtained from *cis*-17-silyloxy-16-amino steroids and α,β-unsaturated aldehydes, react with diazomethane in the presence of a catalytic amount of $Pd(OAc)_2$ with high chemo- and diastereoselectivities to form steroidal cyclopropanocarbaldimines; chromatography on silica gel gives the substituted cyclopropanocarbaldehydes with a high enantiomeric excess and allows recovery of the chiral steroidal auxiliaries.

Steroids have a great unexplored potential as chiral auxiliaries and chiral ligands, which has previously been demonstrated for only a few examples.[1,2] In connection with our investigations employing differently substituted chiral steroids with different configurations as model compounds in stereoselective synthesis,[2] we became interested in using these compounds as chiral auxiliaries for the cyclopropanation of cinnamic acid and cinnamic aldehyde derivatives. In particular, we employ D-ring substituted 3-methoxy-estra-1,3,5(10)-trienes because of the well-defined and restricted conformation of the anellated cyclopentane ring.[2]

Chiral 1,2-disubstituted cyclopropanes are important natural products and synthetic compounds which possess biological activities.[3] One way to synthesize substituted cyclopropanes is the Pd-catalyzed reaction of substituted olefins with diazomethane.[4] In contrast to the well-known enantioselective copper- or rhodium-catalyzed addition of diazoesters to simple olefins,[4] the former reaction seems to be unsuccessful as an enantioselective route using chiral ligands. In a careful study of Denmark and co-workers on this reaction, only racemates were obtained in the chiral ligand mediated Pd-catalyzed cyclopropanation.[5] Simple procedures using chiral auxiliaries should therefore be useful to obtain the desired cyclopropanes. An advantage of this method is the synthesis of only *cis*- or *trans*-1,2-disubstituted cyclopropanes depending on wether the *cis*- or *trans*-olefin is employed, whereas the cyclopropanation of simple olefins with diazoesters normally gives a mixture of *cis*- and *trans*-1,2-disubstituted cyclopropanes. Two kinds of chiral auxiliaries are described for the Pd-catalyzed cyclopropanation of *trans*-olefins.[6,7] (−)-Ephedrine was reacted with (*E*)-cinnamic aldehyde to give an oxazolidine. Cyclopropanation of the double bond proceeded with high diastereoselectivity and the subsequent hydrolysis gave the *trans*-phenyl-cyclopropanecarbaldehyde with the 1*R*,2*R*-configuration.[6] For the success of this method, it is necessary to create the new stereocenter in the oxazolidine ring with high stereoselectivity.[6] The other method started with Oppolzer's sultam. After synthesis of the sultams of (*E*)-α,β-unsaturated carboxylic acids in a two-step sequence, cyclopropanation of the products with diazomethane gave the expected cyclopropanes with good diastereoselectivies. Cleavage under relatively drastic conditions furnished the desired homochiral *trans*-substituted cyclopropanecarboxylic acids.[7]

We synthesized a number of cinnamic esters of the 17β- and 17α-alcohols of the estratriene series[8] that also contain neighboring groups in the 16-position for the Pd-catalyzed cyclopropanation reaction with di-

Keywords: steroids; aminoalcohols; catalysis; cyclopropanes; stereochemistry.

* Corresponding author. Tel.: 03641 948225; fax: 03641 948292; e-mail: c8scbr@uni-jena.de

† Dedicated to Professor E.-G. Jäger on the occasion of his 65th birthday.

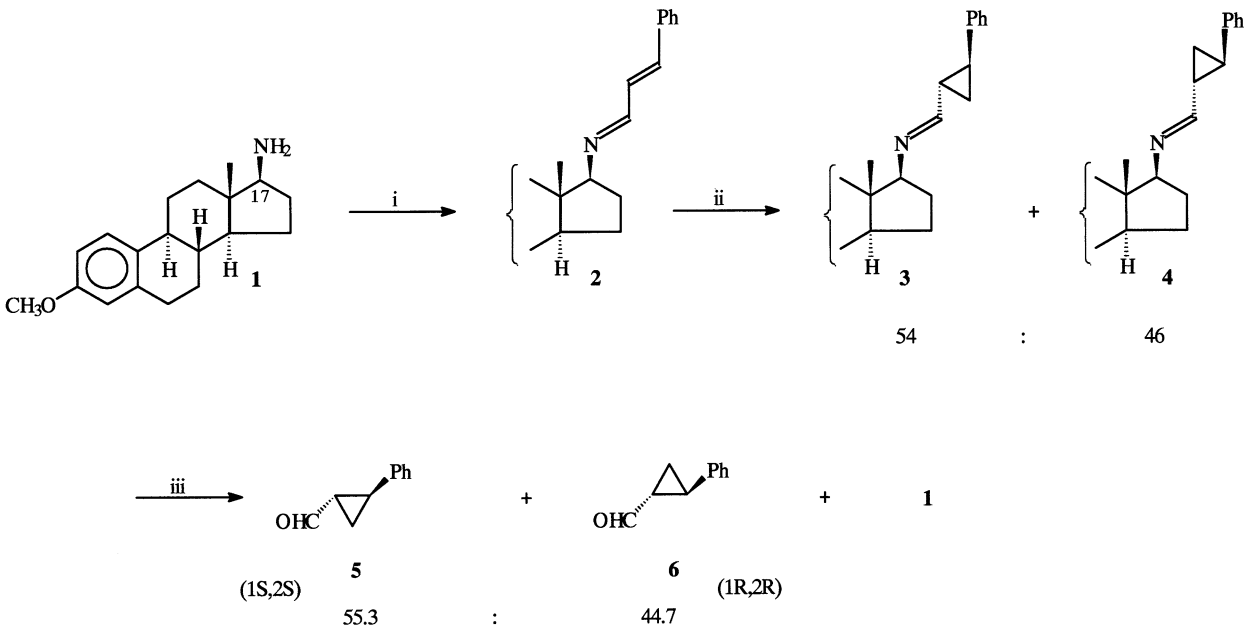
0040-4039/02/$ - see front matter
PII: S0040-4039(02)00334-9

azomethane. In all cases, only low diastereoselectivies could be observed. Recently, we described the condensation products of (*E*)-cinnamic aldehydes with primary 17- and 16-amines and aminoalcohols of steroids.[2a] These chiral α,β-unsaturated imines can be transformed into planar-chiral stable (1-azadiene)$Fe(CO)_3$ complexes and to 1,3-dihydro-pyrrol-2-ones, in some cases with high diastereoselectivies.[2a,d] Surprisingly, the reaction of α,β-unsaturated aldimines with diazomethane has not yet been described. Only the cyclopropanation of such compounds with a phenylchromium Fischer carbene complex has been reported.[9] No face discrimination has been observed for the reaction of the azadiene obtained from (+)-Ph(Me)$CHNH_2$ and (*E*)-cinnamic aldehyde.[9] Therefore, we have investigated the reactions of steroidal α, β-unsaturated imines with diazomethane for their chemo- and stereoselectivities. Our first attempt with the (*E*,*E*)-azadiene 2, [obtained from the 17β-amine **1** and (*E*)-cinnamic aldehyde[2a]] $Pd(OAc)_2$ and diazomethane proceeded with high chemoselectivity at the C=C double bond (Scheme 1).

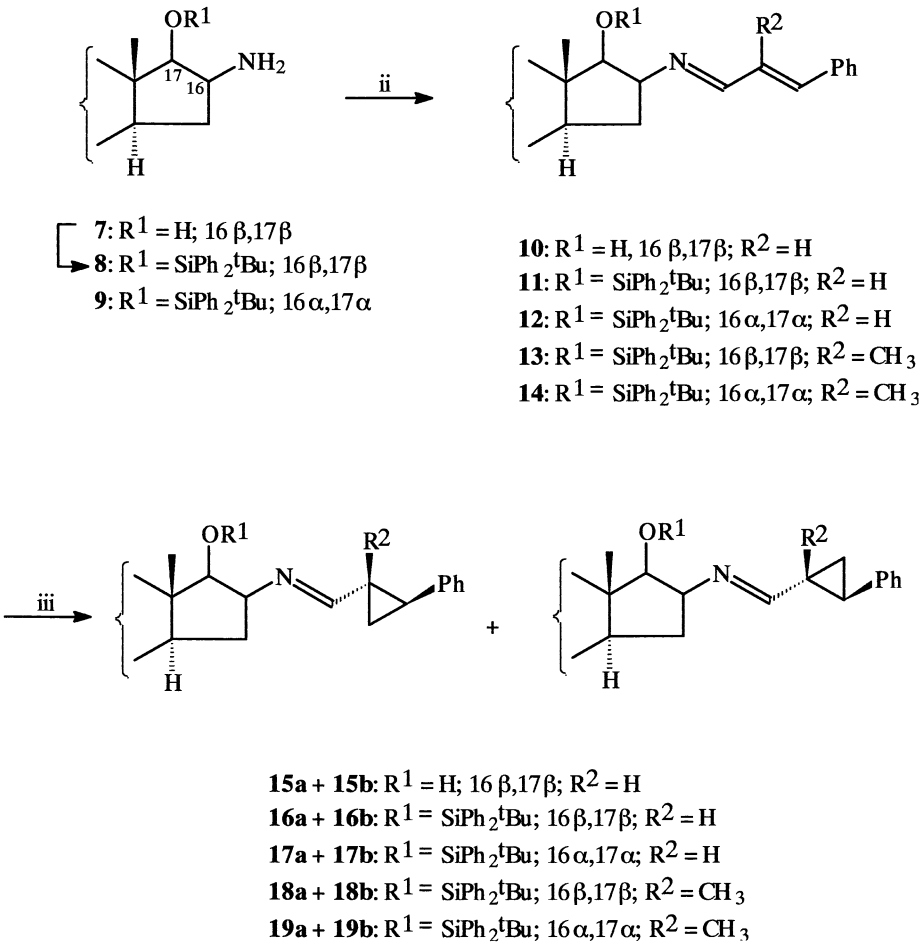
In a smooth reaction, a mixture of the diastereomeric *trans*-substituted cyclopropanes **3** and **4** could be isolated in a high yield. Detailed ^1H NMR analysis (400 MHz, $CDCl_3$; two signals for the angular 13β-methyl group, $\delta = 0.801$ and 0.825 ppm, ratio 54:46; TOCSY experiments for the cyclopropane protons show signal doubling) pointed to a low diastereoselectivity with a nearly 1:1 ratio for the diastereomeric steroidal cyclopropanes. After hydrolysis of the diasteromeric steroidal aldimines **3** and **4** by a simple chromatography on silica gel (Fa. Merck, 0.04–0.06 mm, elution with CH_2Cl_2/CH_3OH 20:1), a mixture of the enantiomeric (1*S*,2*S*)- and (1*R*,2*R*)-*trans*-phenyl-cyclopropanocarbaldehydes **5** and **6** (^1H NMR, 400 MHz, $CDCl_3$; δ [ppm] = 1.51, m, 1H; 1.70, m, 1H; 2.15, m, 1H; 2.60, m, 1H; 7.09–7.30, m, 5H; 9.31, d, $J = 4.57$ Hz, 1H) was obtained in a yield higher than 80% as well as the steroid amine ligand **1** (90%). ^1H NMR shift experiments employing (*S*)-2,2,2-trifluoro-1-(9-anthranyl)-ethanol were successful in differentiating the signals of the enantiomers **5** and **6**, especially for the aldehydic proton. We could observe two doublets in a ratio of nearly 1:1. However, an exact determination of the ratio was impossible because a large amount of the shift reagent was necessary for differentiation.

A similar stereochemical result has been obtained by cyclopropanation of the imine **10** synthesized from the 16β,17β-aminoalcohol **7**[2a] (Schemes 2 and 3) (**15a** and **15b**) although **10** reacted to only one diastereomeric $Fe(CO)_3$ complex.[2a] We therefore synthesized the 17β-(*tert*-butyl-diphenyl)silyloxy-16β-cinnamic aldimine **11** from **7** (Scheme 2) for cyclopropanation experiments. In this compound, one face of the unsaturated imine should be blocked by the 13β-methyl- and the 17β-silyloxy group.

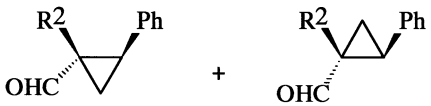
The ^1H NMR spectrum of the cyclopropanation product pointed to two diastereomers (**16a** and **16b**), with one diastereomer dominating (two N=C–H signals in a ratio of 98.5:1.5, $\delta = 6.31$ and 6.39 ppm; selective TOCSY to the cyclopropane proton signals). The *trans*-phenyl-cyclopropanocarbaldehyde, obtained after chromatography in a high yield in addition to the chiral auxiliary **8**, was determined as a mixture of the two enantiomers **5** and **6** by ^1H NMR spectroscopy employing the chiral shift reagent (two doublets of the aldehyde proton signal with strong different intensity). An exact determination of the ratio could be achieved by GC with a chiral column (CP 9000, Chirasil-Dex CB, DF = 0.25μm, $l = 25$ m, ∅ = 0.25 mm; 120°C, isother-



Scheme 1. Cyclopropanation of cinnamic aldimine from the 17β-amine. *Reagents and conditions*: (i) cinnamic aldehyde/CH_3OH, rt; (ii) CH_2Cl_2, $Pd(OAc)_2$, CH_2N_2/ether, −10°C to rt, 18 h; (iii) silica gel, elution with CH_2Cl_2/CH_3OH 20:1 and CH_3OH.



Scheme 2. Cyclopropanation of cinnamic aldimines from the 16,17-*cis*-aminoalcohols and *O*-silylated derivatives. *Reagents and conditions:* (i) CH_2Cl_2/$ClSiPh_2{}^tBu$, 4-*N*,*N*-dimethyl-aminopyridine, triethylamine, rt, 4 days; (ii) cinnamic aldehyde/CH_3OH, rt, 5 h; (iii) CH_2Cl_2, $Pd(OAc)_2$ (3–5 mol%), CH_2N_2/ether, −10°C to rt, 18 h.



	5: R^2 = H	+	**6**: R^2 = H	
15a + 15b —i→	54.6	:	46.4	+ **7**
16a + 16b —i→	98.6	:	1.4	+ **8**
17a + 17b —i→	4.9	:	95.1	+ **9**
	20: R^2 = CH_3	+	**21**: R^2 = CH_3	
18a + 18b —i→	94.2	:	5.8	+ **8**
19a + 19b —i→	20.0	:	80.0	+ **9**

Scheme 3. Hydrolysis of steroidal cyclopropano imines. Stereochemical outcome. *Reagents and conditions*: chromatography at silica gel with CH_2Cl_2/CH_3OH (20:1) and CH_3OH.

mic). The ratio of the two peaks was 98.6:1.4 (lower retention time) in very good agreement with the ratio given by the NMR method.

The absolute configuration of the enantiomer (ee = 97%) is 1*S*,2*S* as could be determined from the high positive optical rotation as compared to the reported high negative value for the 1*R*,2*R* configuration ($[\alpha]_D$ −340, $CHCl_3$).[6] The GC determination of the ratios for the two enantiomeric aldehydes **5** and **6**, synthesized from the 17-imino compounds **2** and **10**, gave values of 55.3:44.7 and 54.6:46.4, respectively (Scheme 3).

In order to determine the stereochemical outcome of the cyclopropanation reaction with the opposite configuration at C17 and C16, we synthesized the 17α-(*tert*-butyl-diphenyl)silyloxy-16α-cinnamic aldimine **12** from the 17α,16α-aminoalcohol[10] by silylation (**9**) and condensation (**12**). The cyclopropanation products from **12**[11] (Scheme 2 **17a** and **17b**) were investigated by ^{1}H NMR spectroscopy. Two signals for the angular 13β-methyl group ($\delta = 0.644$ and 0.614 ppm) in a ratio of 95:5 pointed to a high excess of one diastereomer. After chromatography, the mixture of the enantiomeric cyclopropanes **5** and **6** and the chiral auxiliary **9** could be obtained in high yields. The ratio of the enantiomers **6** and **5**, determined by GC, was 95.1:4.9 (higher retention time), which is again in very good agreement with the NMR method (Scheme 3). The high enantiomeric excess (ee>90%) of **6** with the (1*R*,2*R*) configuration, obtained from the 17α,16α-configurated steroid **12**, is remarkable and demonstrates that the other asymmetric centers of the steroid core are not determining the stereochemistry of the cyclopropanation reaction. The stereochemical outcome of the cyclopropanation is in good agreement with our stereochemical model for imines which includes a preferred conformation with a small torsional angle 16H–C16–N=C[2a,b] and a transoid arrangement of the unsaturated imino group, also confirmed by an X-ray analysis of **12**.

This reaction is also useful for the synthesis of cyclopropanes with a new quaternary chiral center as we could demonstrate with the reaction at the compounds **13** and **14**, obtained by condensation of the *O*-silylated aminoalcohols **8** and **9** with (*E*)-α-methylcinnamaldehyde (Scheme 2). After hydrolysis of the steroidal cyclopropanes **18** and **19** 94.2:5.8 and 20.0:80.0 mixtures of the enantiomeric cyclopropano aldehydes **20** and **21** (ee = 88.4 and 60.0%) could be obtained (Scheme 3). Also, in these cases the auxiliaries could be recovered easily and in high yields.

Using (1*S*,2*R*)-*cis*-1-amino-2-hydroxyindane (Aldrich) for the described procedure (*O*-silylation, condensation with cinnamic aldehyde, cyclopropanation, hydrolysis) gave **5** and **6** in a ratio of 74:26 (ee = 48%). A further disadvantage are the oily products in this series in contrast to the crystalline steroid compounds, which can be easily recovered.

In summary, we have demonstrated for the first time that the Pd-catalyzed cyclopropanation of α,β-unsaturated aldimines with diazomethane leads to cyclopropanocarbaldimines. Using diastereomeric steroidal *cis*-17-silyloxy-16-cinnamic aldimines, high diastereoselectivities of the cyclopropanation reaction could be observed. Simple chromatography gave the enantiomeric *trans*-phenyl-cyclopropanocarbaldehydes with high enantiomeric excess and the steroidal chiral auxiliaries. The steroidal *cis*-aminoalcohols are available from 3-*O*-methylestrone, a pharmaceutical.[10]

Acknowledgements

We thankfully acknowledge financial support from the Deutsche Forschungsgemeinschaft, Sonderforschungsbereich 436 and the Fonds der Chemischen Industrie. We thank Schering AG for the gift of 3-*O*-methylestrone and S. Göttke for experimental assistance.

References

1. (a) Soulivong, D.; Matt, D.; Ziessel, R. *J. Chem. Soc., Chem. Commun.* **1999**, 393–394; (b) Enev, V. S.; Mohr, J.; Harre, M.; Nickisch, K. *Tetrahedron: Asymmetry* **1998**, *9*, 2693–2699; (c) Enev, V. S.; Ewers, Ch. L. J.; Harre, M.; Nickisch, K.; Mohr, J. T. *J. Org. Chem.* **1997**, *62*, 7092–7093; (d) Strickler, R. R.; Schwan, A. L. *Tetrahedron: Asymmetry* **1999**, *10*, 4065–4069; (e) Mathivanan, P.; Maitra, U. *J. Org. Chem.* **1995**, *60*, 364–369; (f) Roy, D.; Birney, D. M. *Synlett* **1994**, 798–800; (g) Huang, D.-L.; Draper, R. W. *Tetrahedron Lett.* **1994**, *35*, 661–662; (h) Maitra, U.; Mathiranan, P. *Tetrahedron: Asymmetry* **1994**, *5*, 1171–1174; (i) Maitra, U.; Mathiranan, P. *J. Chem. Soc., Chem. Commun.* **1993**, 1469–1471; (j) Kaufmann, M. D.; Grieco, P. A.; Bougie, D. W. *J. Am. Chem. Soc.* **1993**, *115*, 11648–11649; (k) Kostova, K.; Genov, M.; Philipova, V. *Tetrahedron: Asymmetry* **2000**, *11*, 3253–3256; (l) Enev, V. S.; Harre, M.; Nickisch, K.; Schneider, M.; Mohr, J. *Tetrahedron: Asymmetry* **2000**, *11*, 1767–1779; (m) Bandyopadhyaya, A. K.; Sangeetha, N. M.; Radha, A.; Maitra, U. *Tetrahedron: Asymmetry* **2000**, *11*, 3463–3466.
2. (a) Berger, D.; Dubs, M.; Göbel, A.; Imhof, W.; Kötteritzsch, M.; Rost, M.; Schönecker, B. *Tetrahedron: Asymmetry* **1999**, *10*, 2983–2995; (b) Dubs, M.; Krieg, R.; Görls, H.; Schönecker, B. *Steroids* **2000**, *65*, 305–318; (c) Gonschior, M.; Kötteritzsch, M.; Rost, M.; Schönecker, B.; Wyrwa, R. *Tetrahedron: Asymmetry* **2000**, *11*, 2159–2182; (d) Imhof, W.; Berger, D.; Kötteritzsch, M.; Rost, M.; Schönecker, B. *Adv. Synth. Catal.* **2001**, *343*, 795–801.
3. Salaün, J. *Topics Curr. Chem.* **2000**, *207*, 1–67.
4. (a) Cornils, B.; Hermann, W. A. *Applied Homogeneous Catalysis with Organometallic Compounds*; VCH: Weinheim, New York, Basel, Cambridge, Tokyo, 1996; Vol. 2, pp. 733–747; (b) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*; Wiley-VCH: Weinheim, New York, Chichester, Brisbane, Singapore, Toronto, 1998; Vol. 1, pp. 107–113.
5. Denmark, S. E.; Stavenger, R. A.; Fauchier, A.-M.; Edwards, J. P. *J. Org. Chem.* **1997**, *62*, 3375–3389.

6. Abdallah, H.; Grée, R.; Carrié, R. *Tetrahedron Lett*. **1982**, *23*, 503–506.
7. Vallgårda, J.; Hacksell, U. *Tetrahedron Lett*. **1991**, *32*, 5625–5628.
8. All new steroidal compounds were characterized by elemental analysis, $[\alpha]_D$, and ^{1}H NMR spectra. Details will be reported later in a full paper.
9. Barluenga, J.; Tomás, M.; López-Pelegrin, J. A.; Rubio, E. *J. Chem. Soc., Chem. Commun*. **1995**, 665–666.
10. Schönecker, B.; Ponsold, K. *Tetrahedron* **1975**, *31*, 1113–1118.
11. Procedure for the cyclopropanation: A stirred solution of the steroid imine **12** (654 mg, 1.0 mmol) in dry CH_2Cl_2 (20 ml) was treated at −10°C with $Pd(OAc)_2$ (6.7 mg, 30 μmol) and an etheral solution of diazomethane (15 ml, 7.5 mmol CH_2N_2, prepared from *N*-methyl-*N'*-nitro-*N*-nitroso guanidine, Fluka). After 18 h at rt, the mixture was filtered and the solvents were evaporated in vacuo. The solid residue [660 mg, 98.8%, diastereomeric mixture of **17a** and **17b**, ratio 5:95, ^{1}H NMR: $CDCl_3$, δ [ppm]: 0.614 and 0.644 (2×s, 3H, $18H_3$, 5:95)] was hydrolyzed by column chromatography on silica gel with CH_2Cl_2/CH_3OH (20:1) and CH_3OH; fraction 1: *trans*-2-phenyl-cyclopropano-1-carbaldehyde as an oil (120 mg, 82%, mixture of the enantiomers **5** and **6**, ratio 4.9:95.1, determined by GC with a chiral column Chirasil-Dex CB, 120°C, isothermic, minor component **5** with higher retention time). ^{1}H NMR: $CDCl_3$, δ [ppm]: 1.51, m, 1H; 1.70, m, 1H; 2.15, m, 1H; 2.60, m, 1H; 7.09–7.30, m, 5H, arom. H; 9.31, d, $J=4.57$ Hz, aldehyde H; fraction 2: *O*-silylated steroidal aminoalcohol **9** (490 mg, 90.8%, white foam). ^{1}H NMR: identical with **9** synthesized from the 16α,17α-amino alcohol.[10]