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Homogeneous catalytic hydrogenation of steroidal dehydroamino acid esters

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Abstract

Steroidal dehydroamino acid methyl esters (methyl α-acetamino-β-(cholesta-3,5-dien-3-yl)acrylate (**1**), methyl α-acetamino-β-(pregna-3,5-dien-3-yl)acrylate (**2**), methyl α-acetamino-β-(3-methoxy-estra-1,3,5,(10),16-tetraene-17-yl)acrylate (**3**), methyl α-acetamino-β-(3β-acetoxy-androsta-16-en-17-yl)acrylate (**4**), methyl α-acetamino-β-(3β-benzoyloxy-androsta-16-en-17-yl)acrylate (**5**)) have been hydrogenated to the corresponding α-amino acid methyl esters in the presence of rhodium–phosphine in situ catalysts. The hydrogenation is highly chemoselective in case of 3,5-dienes. Reduction takes place exclusively in the side-chain. On the other hand, both olefinic double bonds were saturated when the 17-(methyl acetamidoacrylate) moiety was bonded to steroids possessing Δ^{16}. Although the diastereoselectivity of hydrogenation is mainly determined by the steroid skeleton itself in the case of substrates possessing the acetamidoacrylate moiety in position-17, the ratio of epimers can be modified by the structure of the tertiary phosphine ligand varied systematically in rhodium–phosphine in situ catalysts. The highest diastereoselectivity (75/25) was obtained when estra-1,3,5-triene derivative was used as substrate in the presence of achiral rhodium–triphenylphosphine catalyst. The stereochemistry of hydrogenation resulting in new stereogenic centers is discussed on the base of NMR investigations.

Keywords: Hydrogenation; Phosphine complexes; Rhodium; Steroidal esters

1. Introduction

One of the most archetypal reactions in asymmetric homogeneous hydrogenation is reduction of dehydroamino acid derivatives to the corresponding α-amino acids. Excellent optical yields have been obtained using various bidentate chiral phosphines bound to rhodium [1–4]. This reaction represents an extremely efficient route to introduction of a new chiral center.

The pioneering work of Knowles and co-workers at Monsanto led to the catalytic synthesis of L-DOPA in high optical yields [5,6]. In addition to L-DOPA analogues there is an increasing demand for uncommon α-amino acids in organic and bioinorganic chemistry [7,8]. Although many various skeletons possessing α-amino acid moiety have been synthesized and in some cases the biological activity has been investigated, according to our knowledge there is no example for the synthesis of steroids containing related structure.

The application of α-acetamidoacrylic acid and α-acetamidoacrylates is well known in coupling

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reactions [9–12]. The palladium-catalysed homogeneous coupling reaction provides an efficient way for the synthesis of steroidal dehydroamino acid derivatives as obvious substrates for the synthesis of α-amino acid derivatives. Various steroidal vinyl and dienyl triflates react with methyl α-acetamidoacrylate in the presence of palladium(0) catalysts to give dehydroamino acids bound to estra-1,3,5,(10)-triene, androstane and cholestane backbone [13,14]. These compounds are interesting targets as precursors of α-steroidal amino acids and are of practical interest also on their own [15].

The hydrogenation of an unsaturated steroidal skeleton with heterogeneous catalysts is the subject of many publications [16–18]. Relatively little information is available on homogeneous catalytic reduction of steroids [19]. The hydrogenation of carbon–carbon double bonds (Δ^4, Δ^5 $\Delta^{9(11)}$, etc.) plays an important role in determining the geometry of molecule. The anellation of rings (e.g. *cis* or *trans* fused A/B rings) is determined by the stereochemistry of the reaction resulting in epimers of different biological activity. There is no example for the hydrogenation of a side chain of steroids resulting in novel chirality centers not involved in the cyclic steroidal backbone. The resulting amino acids of novel type are of trivial pharmacological importance. Their epimeric composition depends on the structure of the catalyst.

In this work catalytic hydrogenation of various steroidal dehydroamino acids will be described. The influence of the structure of unsaturated steroids and that of the catalyst on the stereochemical outcome of the reaction will be discussed.

2. Experimental

2.1. General method for hydrogenation of steroidal dehydroamino acid derivatives

In a typical experiment, a solution of 5.8 mg (0.0125 mmol) $[Rh(nbd)Cl]_2$ and 0.025 mmol optically active ditertiary phosphine (or 13.1 mg (0.05 mmol) triphenylphosphine) in 10 ml toluene was transferred under argon into a 100 ml stainless steel autoclave containing 0.5 mmol steroidal dehydroamino acid derivative (e.g. 255 mg of **1**). The autoclave was pressurized to 80 bar with H_2, placed in an oil bath. After carrying out the reaction, cooling and venting the autoclave, the solution was evaporated to dryness and analyzed immediately by ^1H NMR in order to determine the epimeric composition of the amino acid derivative formed in the hydrogenation. The residue was subjected to column chromatography on silica gel with chloroform as eluent. The isolated products were characterized by IR, MS, and various NMR techniques including 2D NMR experiments such as ^1H–^1H COSY, ^1H–^{13}C HETCOR.

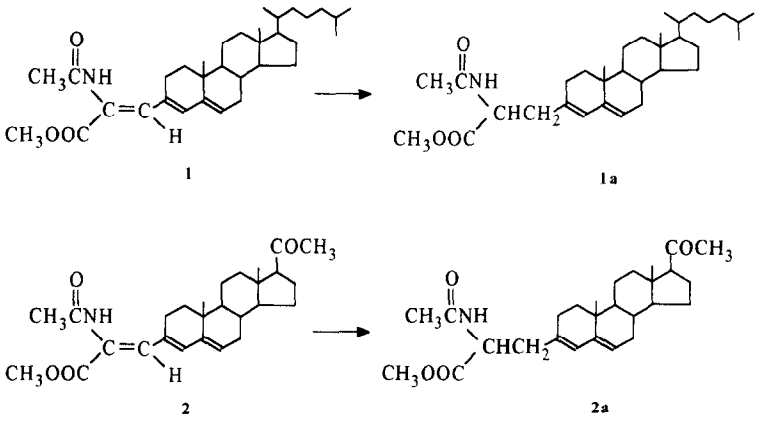
2.2. Characterization of the products

1a: ^1H-NMR (δ, $CDCl_3$): (5.97 (d, J=7.6 Hz), 5.90 (d, J=8.6 Hz), 1H, N*H*) * [1]; 5.72 (brs, 1H, C^4*H*); 5.35 (brs, 1H, C^6*H*); 4.70 (m, 1H, NH–C*H*); (3.724; 3.717 (s, 3H, OC*H*$_3$)) *; 0.80–2.30 (m, 33H, skeleton protons); 2.60–2.30 (m, 2H, C*H*$_2$CH); 2.20 (m, 2H, C^7*H*$_2$); (2.00; 1.994 (s, 3H, CO–C*H*$_3$)) *; 0.90 (s, 3H, C^{19}*H*$_3$); 0.68 (s, 3H, C^{18}*H*$_3$). IR (KBr, ν, cm^{-1}): 1751 (*CO*OCH$_3$), 1652 (NH*CO*); Analysis calculated for $C_{33}H_{53}NO_3$ (511.79): C, 77.43; H, 10.44; N, 2.74. Found: C, 77.72; H, 10.64; N, 2.87; mp. 220°C; Yield 86%.

2a: ^1H-NMR (δ, $CDCl_3$): (6.05, 5.95 (brd, 1H, N*H*)) *; 5.72 (brs, 1H, C^4*H*); 5.35 (brs, 1H, C^6*H*); 4.70 (m, 1H, NHC*H*); 3.70 (s, 3H, OC*H*$_3$); 0.80–2.60 (m, 20H, ring protons + =C^3–C*H*$_2$); 2.10 (s, 3H, COC*H*$_3$); 2.00 (s, 3H, NHCOC*H*$_3$); 0.90 (s, 3H, C^{19}*H*$_3$); 0.65 (s, 3H, C^{18}*H*$_3$). Analysis calculated for $C_{27}H_{39}NO_4$ (441.61): C, 73.43; H, 8.90; N, 3.17. Found: C, 73.70; H, 9.04; N, 3.29; mp. 200–201°C; Yield 82%.

3a: ^1H-NMR (δ, $CDCl_3$): 7.20 (m, 1H, C^1*H*); 6.75 (brd, 1H, C^2*H*); 6.60 (s, 1H, C^4*H*); (6.09 (d, J=7.5 Hz); 5.96 (d, J=8.4 Hz), 1H, N*H*) *;

[1] The asterisk (*) indicates signals of two epimers formed in the hydrogenation of the Δ^{20} or the $\Delta^{3'}$ double bond.



Scheme 1. Hydrogenation of steroidal 3,5-dienes containing acetamidoacrylate moiety in the presence of rhodium–phosphine catalysts.

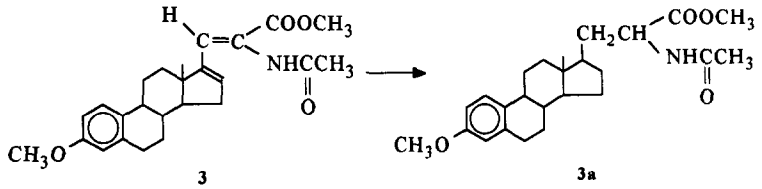
4.65 (m, 1H, NH–C*H*); 3.80 (s, 3H, OCH_3); 3.78 (s, 3H, COOCH_3); 2.85 (m, 2H, C$^6H_2$); 0.80–2.40 (m, 14H, ring protons); 2.05 (s, 3H, NHCOCH_3); 0.60 (s, 3H, C$^{18}H_3$). ^{13}C-NMR (δ, $CDCl_3$): 173.8 (*C*OO); 170.0 (*C*ON); 157.5 (C^3); 138.1 (C^5); 133.2 (C^{10}); 126.2 (C^1); 113.8 (C^4); 111.5 (C^2); 55.2 (O*C*H$_3$); 54.5 (COO*C*H$_3$); 52.4 (*C*H–NH); 51.6; 47.1; 44.1; 42.7; 38.8; 37.5; 33.6; 29.9; 28.4; 27.8; 26.4; 24.5; 23.2; 12.6 (C^{18}). MS (*m*/*z*/rel. intensity): 413/880 (M$^+$); 227/330; 173/440; 131/1000; 99/310; 78/390; 43/440. Analysis calculated for $C_{25}H_{35}NO_4$ (413.56): C, 72.61; H, 8.53; N, 3.39. Found: C, 72.76; H, 8.70; N, 3.47; mp. 228–230°C; Yield 85%.

4a: ^{1}H-NMR (δ, $CDCl_3$): (6.15 (d, J=7.5 Hz); 6.01 (d, J=8.2 Hz),1H, N*H*)*; 5.0 (brs, 1H, C^3*H*); 4.60 (m, 1H, NH–C*H*); (3.70; 3.71 (s, 3H, OCH_3))*; 2.04 (s, 3H, OOCCH_3); (2.00; 2.015 (s, 3H, NHCOCH_3))*; 0.80–1.90 (m, 26H, ring protons + CH_2–C*H*–NH); 0.78 (s, 3H, C$^{19}H_3$); 0.55 (s, 3H, C$^{18}H_3$). ^{13}C-NMR (δ, $CDCl_3$): (173.6, 173.5 (*C*OOCH$_3$))*; 170.6 (CH$_3$*C*OO); (169.8,169.4 (*C*ONH))*; 70.0 (C^3); ((55.5, 55.4), (54.5, 54.50), (52.2, 52.1), (51.9, 51.5), (46.9, 46.8) (C^9, C^{14}, C^{17}, *C*H(CO)NH, COO*C*H$_3$))*; (42.5, 42.3)*; 40.0 (C^5); 37.4; 36.0; 35.8; 35.4 (C^8); 33.4; 32.8; 31.9; 28.3; 26.0; (24.7, 24.6)*; 23.1 (*C*H$_3$(CO)NH); 21.5 (*C*H$_3$COO); 20.4; (12.6, 12.4 (C^{18}))*; 11.3 (C^{19}). IR (KBr, ν, cm^{-1}): 1728 (br, *C*OOCH$_3$ + CH$_3$*C*OO); 1660 (NH*C*O); MS (*m*/*z*/rel.intensity): 461/14 (M$^+$); 131/1000; 107/120; 99/110; 81/100; 43/210. Analysis calculated for $C_{27}H_{43}NO_5$ (461.64): C, 70.25; H, 9.39; N, 3.03. Found: C, 70.51; H, 9.55; N, 3.25; mp. 192–193°C; Yield 74%.

5a: ^{1}H-NMR (δ, $CDCl_3$): 8.05 (d, J=8.5 Hz, 2H, Ph-*ortho*); 7.55 (t, J=8.5 Hz, 1H, Ph-*para*); 7.45 (t, J=8.5 Hz, 2H, Ph-*meta*); (5.98 (d, J=7.8 Hz); 5.85 (d, J=8.1 Hz), 1H, N*H*)*; 4.95 (m, 1H, C^3*H*); 4.60 (m, 1H, NH–C*H*); 3.75 (s, 3H, OCH_3); 2.02 (s, 3H, NHCOCH_3); 0.80–1.90 (m, 26H, ring protons + CH_2–C*H*–NH); 0.88 (s, 3H, C$^{19}H_3$); 0.58 (s, 3H, C$^{18}H_3$). ^{13}C-NMR (δ, $CDCl_3$): (173.6, 173.5 (*C*OOCH$_3$))*; (169.8, 169.4 (*C*ONH))*; 166.1 (Ph*C*OO); 125.2; 128.2; 129.4; 130.9; 74.2 (C^3); ((55.4, 55.2)*, 54.6, (52.2, 52.1)*, (51.9, 51.5)*, (46.9, 46.8)* (C^9, C^{14}, C^{17}, *C*H(CO)NH, COO*C*H$_3$))*; 44.8 (C^5); 35.4 (C^8); 23.1 (*C*H$_3$(CO)NH); (14.0, 12.6 (C^{18}))*; (12.4; 12.3(C^{19}))*. MS (*m*/*z*/rel.intensity): 523/14 (M$^+$); 491/55; 271/190; 131/1000; 105/370; 77/180. Analysis calculated for $C_{32}H_{45}NO_5$ (523.71): C, 73.39; H, 8.66; N, 2.67. Found: C, 73.60; H, 8.84; N, 2.76; mp. 177–178°C; Yield 72%.

3. Results and discussion

Dehydroamino acid derivatives of cholesta-3,5-diene (**1**) and pregna-3,5-diene (**2**) have been



3 3a

Scheme 2. Hydrogenation of estra-1,3,5,(10)-triene derivative containing acetamidoacrylate moiety in the presence of rhodium–phosphine catalysts.

hydrogenated to the corresponding steroidal acetylated amino acids (**1a**, **2a**) possessing a new stereogenic center in the side chain (Scheme 1). Phosphine–rhodium catalysts prepared in situ from $[Rh(nbd)Cl]_2$ and triphenylphosphine have been used. Surprisingly, the conjugated double bond system in ring-A and B ($\Delta^{3,5}$) remained intact even at moderate pressure and 60°C.

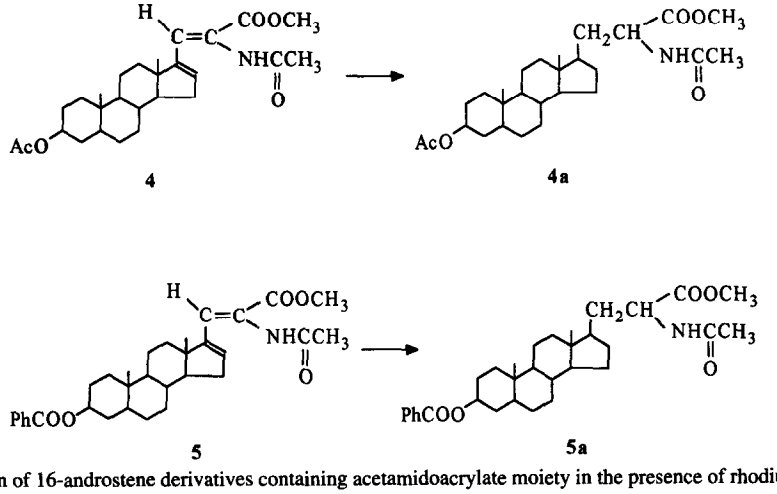
However, complete hydrogenation of the conjugated double bonds takes place when Δ^{16} steroids bearing the acetamidoacrylate moiety in position-17 were used. The hydrogenation of **3** possessing aromatic A-ring resulted in the formation of **3a** of saturated ring-D (Scheme 2).

The hydrogenated products of **4** and **5** have been obtained regardless of the substituents at position-3 of the androstane skeleton (Scheme 3). On the basis of NMR studies (NOE experiments) the substituent at C-17 was found to be in the β-position in the major products as a consequence of the α-side coordination of the catalyst.

The hydrogenation of all of the substrates (**1**–**5**) at atmospheric pressure was failed. In the pressure range of 80–110 bar complete conversion has been obtained in all cases regarding the hydrogenation of the C=C double bond of the acrylic moiety (Table 1).

3.1. *The stereochemistry of the hydrogenation*

The epimeric composition of the resulted products has been analyzed by ^1H NMR spectroscopy. Completely resolved peaks (baseline separation) are obtained in case of CH*NH*COCH$_3$ protons for all products (**1a**–**5a**) (See also Section 2.2. *Characterization of the products*). The amide protons show a doublet due to the ^3J coupling to CH proton. The CON rotation is hindered and the steric interaction between the N-alkyl group (containing the steroid moiety itself) and the CH_3CO group leads to predominance of the *s-trans* isomer [20]. The modest lability of amide protons was shown by D_2O exchange experiments. Complete H–D exchange has taken place in some hours at room temperature or in few minutes upon heating at 50°C. A typical 300 MHz ^1H NMR spectrum of



4 4a

5 5a

Scheme 3. Hydrogenation of 16-androstene derivatives containing acetamidoacrylate moiety in the presence of rhodium–phosphine catalysts.

Table 1
Hydrogenation of steroidal dehydroamino acid methyl esters (**1–5**) in the presence of $[Rh(nbd)Cl]_2$ + tertiary phosphine in situ system [a]

Run	Substrate	$p(H_2)$ (bar)	Conversion (%)	Phosphine [b]	Rh/substrate	Ratio of epimers [c]
1	**1**	105	100	PPh_3	0.21	50:50
2	**1**	80	100	(*S,S*)-DIOP	0.10	60:40
3	**1**	80	100	(*R,R*)-DIOP	0.10	35:65
4	**2**	90	100	PPh_3	0.14	50:50
5	**3**	110	100	PPh_3	0.38	75:25
6	**4**	1	0	PPh_3	0.24	–
7	**4**	85	100	PPh_3	0.125	57:43
8	**4**	80	100	DPPB	0.16	45:55
9	**4**	80	100	(*S,S*)-DIOP	0.05	37:63
10	**4**	80	100	(*R,R*)-DIOP	0.15	52:48
11	**4**	80	100	(*S,S*)-CHIRAPHOS	0.23	50:50
12	**5**	80	100	PPh_3	0.27	70:30

[a] Reaction temperature: 60°C; reaction time 10 h; 10 ml toluene; 0.025 mmol $[Rh(nbd)Cl]_2$; Rh/P = 1/2.
[b] DIOP = 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane, DPPB = 1,4-bis(diphenylphosphino)butane, CHIRAPHOS = 2,3-bis(diphenylphosphino)butane.
[c] The determination of the ratio of enantiomers was carried out on the basis of the integral of N*H* protons (downfield NH/upfield NH).

diastereomers of **1a** is given in Fig. 1. The well-separated broad doublets of NH are at 5.90 and 5.97 ppm. In addition to NH protons some epimeric separation could be observed in case of OCH_3 ($\Delta\delta = 0.007$ ppm) and $COCH_3$ ($\Delta\delta = 0.006$ ppm) protons. The side-chain protons (the neighbour protons of the newly formed stereogenic center) could easily be assigned by ^1H–^1H COSY experiment (Fig. 2).

Although no stereospecific reactions were obtained in the hydrogenation of the above substrates the epimeric composition of the resulted products shows strong dependence on the skeleton. By using **1** as substrate and a PPh_3-containing rhodium catalyst the cholestadiene skeleton does not affect the stereoselectivity of hydrogenation of the unsaturated side-chain, approximately 1/1 mixture of epimers was formed (Run 1). This fact could be explained by the rather long distance between the stereogenic centers of the steroidal backbone (C-8, C-9, C-10) and the C=C double bond of acrylic moiety as well as by the planarity of A,B-rings caused by 3,5-diene system. The same phenomenon was observed for **2** (Run 4).

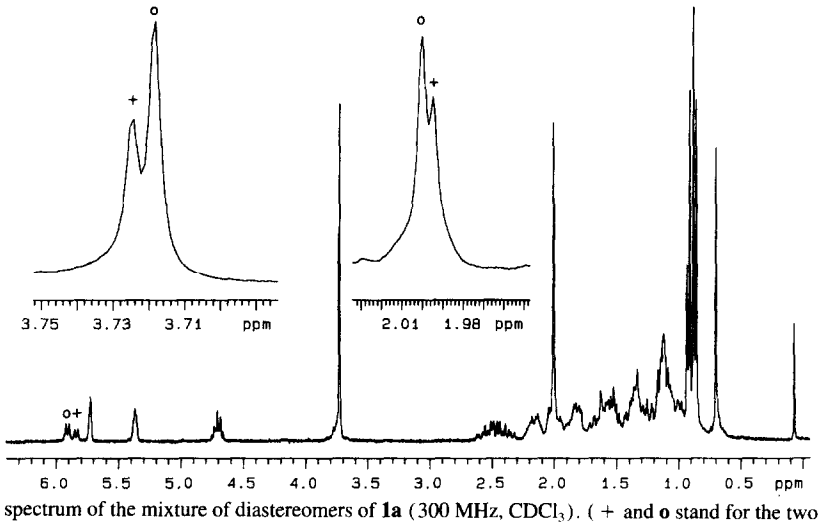


Fig. 1. ^1H NMR spectrum of the mixture of diastereomers of **1a** (300 MHz, $CDCl_3$). (+ and **o** stand for the two C-3″ epimers).

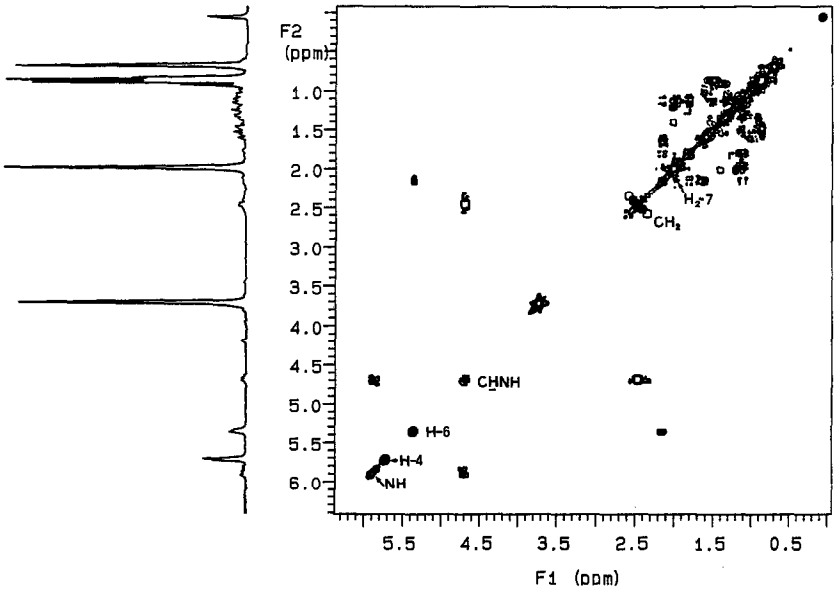


Fig. 2. ^1H–^1H COSY spectrum of the mixture of diastereomers of **1a**.

The use of the two enantiomers of DIOP resulted in some diastereoselection, as expected (Run 2 and 3).

The substrates possessing the acetamidoacrylate moiety in position-17 (**3**, **4**, **5**) have been reduced to mixture of epimers different from 1/1 even in the case of achiral Rh–PPh_3 catalyst (Run 5 and 12). The relatively high diastereoselectivity can be explained by the proximity of stereogenic centers C-13 and C-14. The effect of the structure of steroidal backbone on the stereochemical outcome of the reaction is more significant than in the case of the trienes, **1** and **2**. The importance of chelation is shown by the use of achiral bisphosphine, DPPB (Run 8). The enantiomers of DIOP yielded opposite epimeric ratios, the (*S*,*S*) enantiomer resulted in much higher diastereoselectivity showing some role of chelation and optical activity of the phosphine ligand (Run 9, 10). It is difficult to explain, but interesting to note, that the diastereoselectivity seems to be influenced by the aromatic groups of the steroidal skeleton (A-ring) or that of the 3-benzoyloxy moiety in spite of their long distance from the reaction center (compare Run 5 and 12 with 7).

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