Electronic Supplementary Material (ESI) for Green Chemistry
This journal is © The Royal Society of Chemistry 2012

A Practical Solution for Aqueous Reactions of Water-Insoluble High-Melting-Point Organic Substrates

Xiaoxue Cui, Bo Li, Tianzhen Liu and Chunbao Li*

Department of Chemistry, College of Science, Tianjin University, Tianjin 300072, P. R. of China. Fax: +862227403475, E-mail: lichunbao@tju.edu.cn

Contents

General experimental information (2)

General procedure for the oxidation of pseudosapogenins (2)

Control experiments for the function of water in the oxidation reactions (2)

Control experiments for the function of PTC in the oxidation reactions (2-3)

General procedure for the reduction of ketones or aldehydes and ^{1}H NMR spectra for the crude products after filtrations (3-5)

Recycling procedure for the reduction of **3d** (5-6)

Control experiments for the function of PTC and PTFE sand in the reduction reactions (6-7)

Control experiments for the function of water in the reduction reactions (7-8)

Control experiment for the reduction of estrone benzoate in ethanol and the HPLC analyses (8-9)

General procedure for the condensation of sinomenine (9-10)

Control experiments for the function of Aliquat 336 and PTFE sand in the condensation reactions (10)

General procedure for the hydrolysis of esters (10)

Hydrolysis of **7f** in 10 gram scale (10-11)

Control experiments for the function of PTC and PTFE sand in the hydrolysis reactions (11-12)

^{1}H NMR and ^{13}C NMR spectra for new products (12-14)

References (14-15)

General experimental information

All of the chemicals were obtained from commercial sources or prepared according to standard methods. The ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) were recorded on a Bruker AM-400 spectrometer. Chemical shifts (δ) are reported relative to TMS (^{1}H) or $CDCl_3$ (^{13}C). IR spectra were recorded on BIO-RAD FTS 3000 spectrometer. Melting points were obtained on an X-4 Micro-melting Point Apparatus. Mass spectra (ESI) were obtained on a Finnigan LCQ Advantage MAX spectrometer. High resolution mass spectra (ESI) were obtained on Bruker micrOTOF-QII. The size of PTFE sand is 70 pieces/g.

General procedure for the oxidation of pseudosapogenins

To a mixture of pseudosapogenin (2 g), V_2O_5 (0.04 equiv), Aliquat 336 (0.15 equiv), NaOAc (0.1 equiv), PTFE sand (2 g) and water (10 mL) was added H_2O_2 (30 %, 2.5 equiv). The reaction mixture was heated to 75°C and mechanically stirred (400 rpm, Teflon blade, D = 4 cm) for 5-10 h. TLC showed the completion of the reaction. After the decantation of the aqueous phase, the solid residue was mixed with silica gel (2 g) and extracted by Soxhlet extractor with petroleum ether containing 2% ethyl acetate, which was concentrated and crystallized from methanol to give 16-dehydropregenolone acetate and its analogues **2a**-**2e**. Product **2a**,[1] **2b**,[2] **2c**,[3] **2d**[4] and **2e**[5] are all identical to the references. The yields and reaction durations are listed in Table 1 in the text.

Control experiments for the function of water in the oxidation reactions

To a mixture of **1a** (2 g), V_2O_5 (0.16 mmol, 0.04 equiv), Aliquat 336 (0.6 mmol, 0.15 equiv), NaOAc (0.4 mmol, 0.1 equiv), PTFE sand (2 g) and water (30 mL) was added H_2O_2 (30 %, 10 mmol, 2.5 equiv). The reaction mixture was heated to 75°C and mechanically stirred (400 rpm, Teflon blade, D = 4 cm) for 6.5 h. TLC showed that the reaction was completed. The work up was performed as above to give **2a** in 70% yield.

Control experiments for the function of PTC in the oxidation reactions

1. Catalyzed by Aliquat 336 (0.3 equiv)

To a mixture of **1a** (2 g), V_2O_5 (0.16 mmol, 0.04 equiv), Aliquat 336 (1.2 mmol, 0.3 equiv), NaOAc (0.4 mmol, 0.1 equiv), PTFE sand (2 g) and water (10 mL) was added H_2O_2 (30 %, 10 mmol, 2.5 equiv). The reaction mixture was heated to 75°C and mechanically stirred (400 rpm, Teflon blade, D = 4 cm) for 4.5 h. TLC showed that the reaction was completed. The work up was performed as above to give **2a** in 73% yield.

2. Catalyzed by benzyltriethylamonium chloride

To a mixture of **1a** (2 g), V_2O_5 (0.16 mmol, 0.04 equiv), benzyltriethylamonium chloride (0.6 mmol, 0.15 equiv), NaOAc (0.4 mmol, 0.1 equiv), PTFE sand (2 g) and water (10 mL) was added H_2O_2 (30 %, 10 mmol, 2.5 equiv). The reaction mixture was heated to 75°C and mechanically stirred (400 rpm, Teflon blade, D = 4 cm) for 10 h. the reaction did not take place as checked by TLC and the NMR of the concentrated reaction mixture.

4. Catalyzed by tetraethylamonium chloride

To a mixture of **1a** (2 g), V_2O_5 (0.16 mmol, 0.04 equiv), tetraethylamonium chloride (0.6 mmol, 0.15 equiv), NaOAc (0.4 mmol, 0.1 equiv), PTFE sand (2 g) and water (10 mL) was added H_2O_2 (30 %, 10 mmol, 2.5 equiv). TLC and the NMR both indicated that the reaction did not take place when the reaction mixture was heated to 75°C and mechanically stirred (400 rpm, Teflon blade, D = 4 cm) for 10 h.

5. Catalyzed by octadecyltrioctylamonium chloride

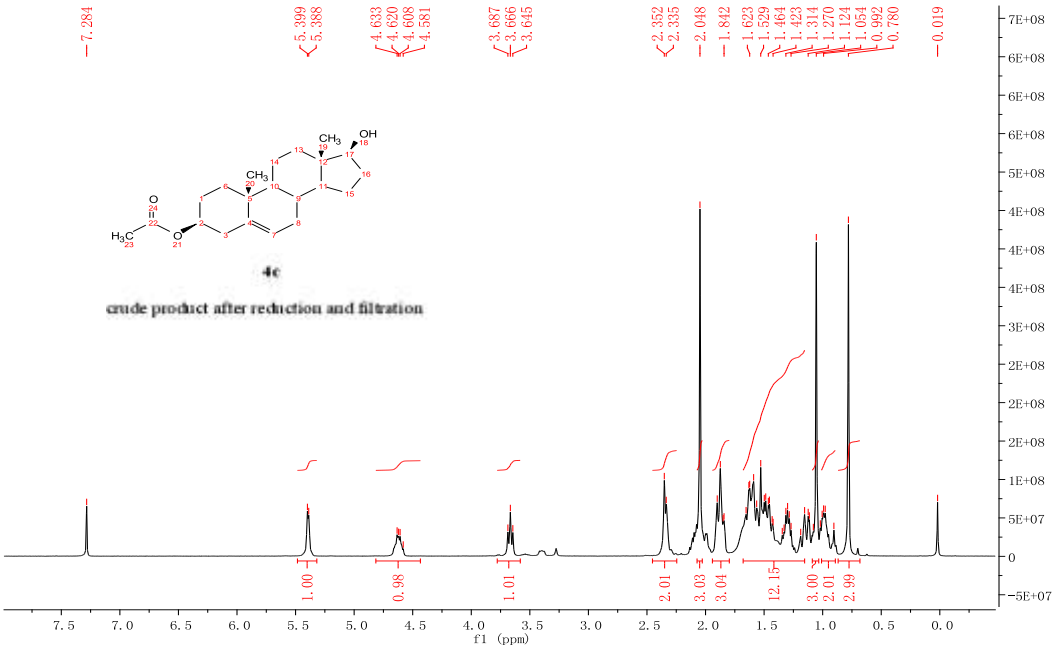
To a mixture of **1a** (2 g), V_2O_5 (0.16 mmol, 0.04 equiv), octadecyltrioctylamonium chloride (0.6 mmol, 0.15 equiv), NaOAc (0.4 mmol, 0.1 equiv), PTFE sand (2 g) and water (10 mL) was added H_2O_2 (30 %, 10 mmol, 2.5 equiv). The reaction mixture was heated to 75°C and mechanically stirred (400 rpm, Teflon blade, D = 4 cm) for 8 h. TLC showed that the reaction was completed. Flash chromatography with silica gel gave **2a** in 60% yield.

General procedure for the reduction of ketones or aldehydes and ^{1}H NMR spectra for the crude products after filtrations

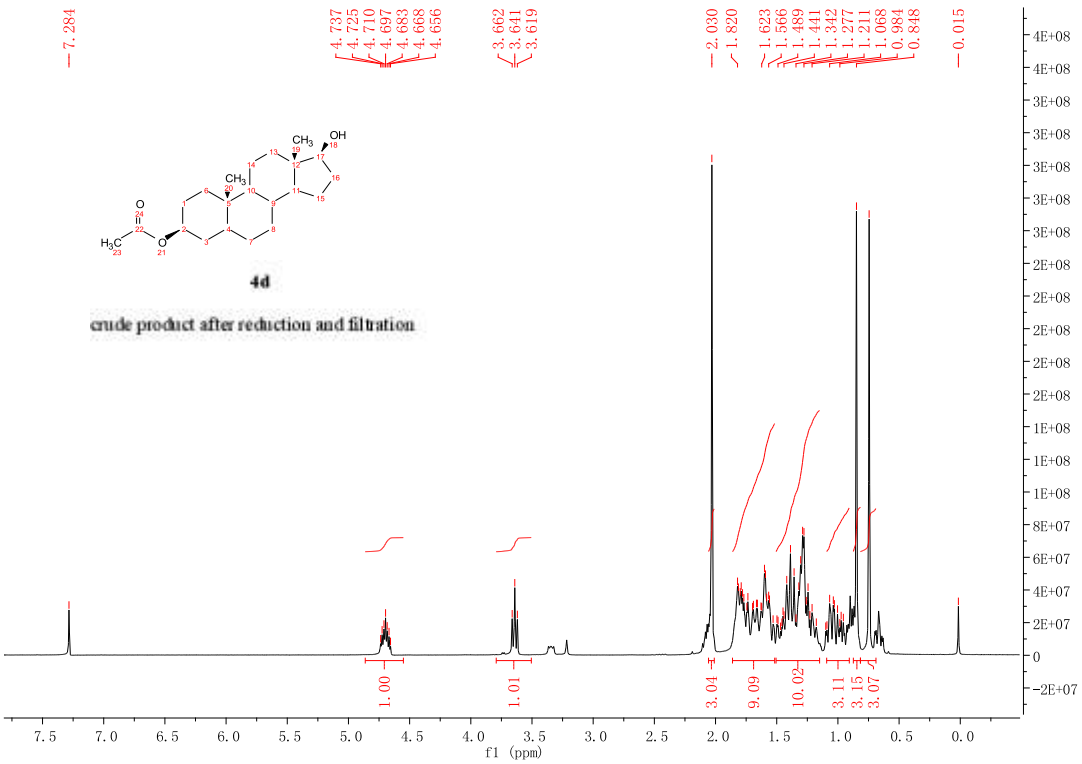
To a mixture of ketone/aldehyde (2 g), Aliquat 336 (0.08 equiv), PTFE sand (2 g) and water (10 mL) was added KBH_4 (0.8 equiv) in portions. The mixture was mechanically stirred (400 rpm, Teflon blade, D = 4 cm) at 20°C or 60°C for 1- 6.5 h. TLC showed the completion of the reaction. After stopping the reaction, the crystalline product was suspended in water while the sand precipitated on the bottom. The suspension was filtrated to give **4a**-**4i** in quantitative yields leaving the sand to be recovered. After recrystallization, product **4a** was obtained in 92% yield, **4b** in 85% yield. Products **4a**,[6] **4b**,[7] **4c**,[8] **4d**,[9] **4e**,[10] **4f**,[11] **4g**[12] and **4i**[13] are known compounds. The yields, reaction temperatures and durations are listed in Table 2 in the text.

4-(4-Nitrobenzoxy)benzyl 4-nitrobenzoate (**4h**): ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.40 (q, J= 8.8 Hz, 4H), 8.30 (dd, J= 8.8 Hz, J= 22 Hz, 4H), 7.22-7.24 (m, 1H), 7.14-7.15 (m, 2H), 5.44 (s, 2H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.7, 163.0, 151.4, 151.1, 150.9, 139.9, 135.6, 134.9, 131.7, 131.1, 123.9, 123.8, 123.1, 121.3, 113.1, 67.5, 56.3; IR (KBr): 1738, 1730, 1607, 1520, 1263, 1099, 852, 717 cm^{-1}; Mp: 198-201°C; MS (ESI): *m/z* (%) $[M + Na]^+$= 475.4 (5); HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{22}H_{16}N_2O_9$ + Na: 475.0753; found 475.0761.

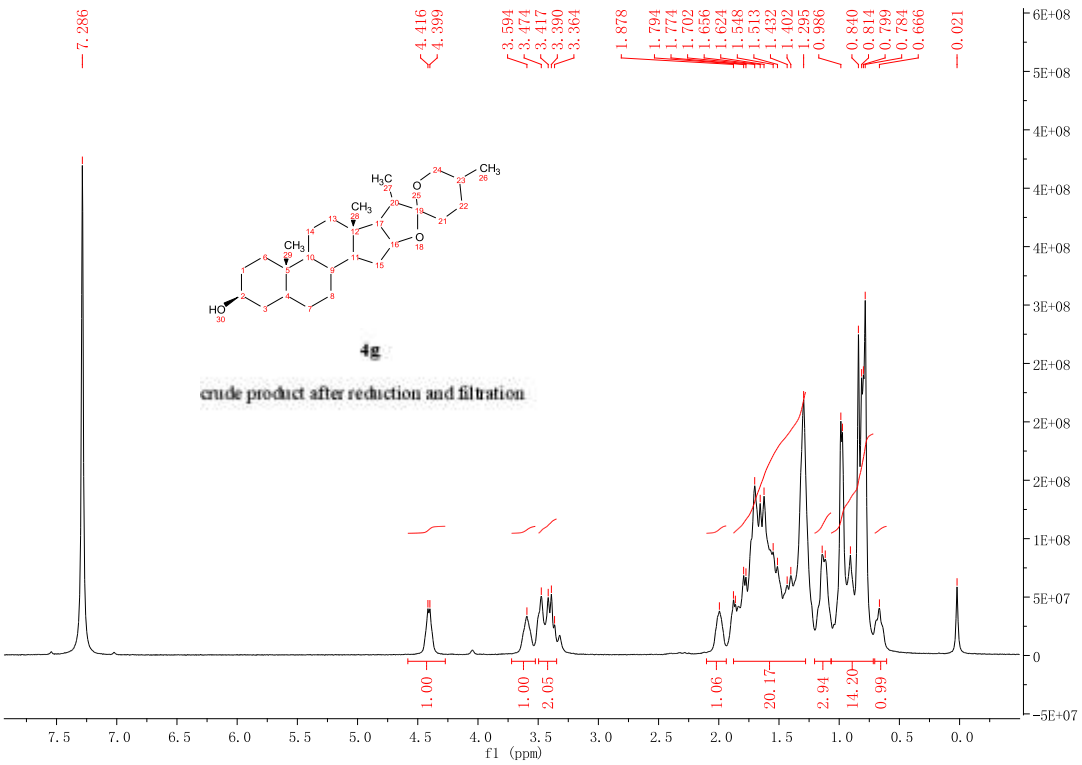
Following is the ^{1}H NMR spectrum of crude **4c** after filtration.



Following is the ^{1}H NMR spectrum of crude **4d** after filtration.



Following is the ^{1}H NMR spectrum of crude **4g** after filtration.



Recycling procedure for the reduction of 3d

A mixture of **3d** (2 g), KBH_4 (4.8 mmol, 0.8 equiv), Aliquat 336 (0.48, 0.08 equiv), PTFE sand (2 g), and water (10 mL) was mechanically stirred (400 rpm, Teflon blade, D = 4 cm) at 20°C for 4 h. TLC showed that the reaction was completed. After stopping the reaction, the crystalline product was suspended in water while the sand precipitated on the bottom. The suspension was filtrated to give **4d** in quantitative yield leaving the sand to be recovered. After recrystallization from methanol, the mother liquor was concentrated and combined with the sand and water from the previous pot, to which were again added **3d** (2 g) and KBH_4 (4.8 mmol, 0.8 equiv). The mixture was treated as in the first pot. This is the second cycle. In this manner, the reaction was cycled from the third to the tenth. The reaction yields and times remained the same from 1st to 10th cycles.

Control experiments for the function of PTC and PTFE sand in the reduction reactions

1. Without Aliquat 336 and PTFE sand

A mixture of **3e** (2 g), KBH_4 (3.7 mmol, 0.8 equiv) and water (10 mL) was stirred at 60°C for 10 h. The reaction did not take place as indicated by TLC and the NMR of the concentrated reaction mixture. The suspension was filtrated to give starting material **3e** (1.9 g).

A mixture of **3h** (2 g), KBH_4 (5.3 mmol, 0.8 equiv) and water (10 mL) was stirred at 20°C for 6 h. The reaction did not take place as indicated by TLC and the NMR of the concentrated reaction mixture. The suspension was filtrated to give starting material **3h** (1.95 g).

A mixture of **3i** (2 g), KBH_4 (6.2 mmol, 0.8 equiv) and water (10 mL) was stirred at 20°C for 1 h. The reaction did not take place as indicated by TLC and the NMR of the concentrated reaction mixture. The suspension was filtrated to give starting material **3i** (2 g).

2. Catalyzed by tetrabutylammonium bromide, without PTFE sand

A mixture of **3g** (2 g), tetrabutylammonium bromide (0.39 mmol, 0.08 equiv), KBH_4 (3.9 mmol, 0.8 equiv) and water (10 mL) was stirred at 60°C for 7 h. The reaction did not take place as indicated by TLC and the NMR of the concentrated reaction mixture. The suspension was filtrated to give starting material **3g** (1.89 g).

3. Catalyzed by benzyltriethylammonium chloride, without PTFE sand

To a mixture of **3a** (2 g), benzyltriethylammonium chloride (0.59 mmol, 0.08 equiv) and water (10 mL) was added KBH_4 (5.9 mmol, 0.8 equiv) in portions. The mixture was stirred at 60°C for 9 h. The reaction did not take place as indicated by TLC and the NMR of the concentrated reaction mixture. The suspension was filtrated to give starting material **3a** (1.92 g).

Control experiments for the function of water in the reduction reactions

1. without water

A mixture of **3c** (2g), KBH_4 (4.8 mmol, 0.8 equiv), Aliquat 336 (0.48 mmol, 0.08 equiv) and PTFE sand (2g) was mechanically stirred (400 rpm, Teflon blade, D = 4 cm) at 60°C for 1h, ^{1}H NMR showed that the reaction did not take place.

A mixture of **3g** (2g), KBH_4 (3.9 mmol, 0.8 equiv), Aliquat 336 (0.39 mmol, 0.08 equiv) and PTFE sand (2g) was mechanically stirred (400 rpm, Teflon blade, D = 4 cm) at 60°C for 1h, ^{1}H NMR showed that the reaction did not take place.

2. without water and PTFE sand

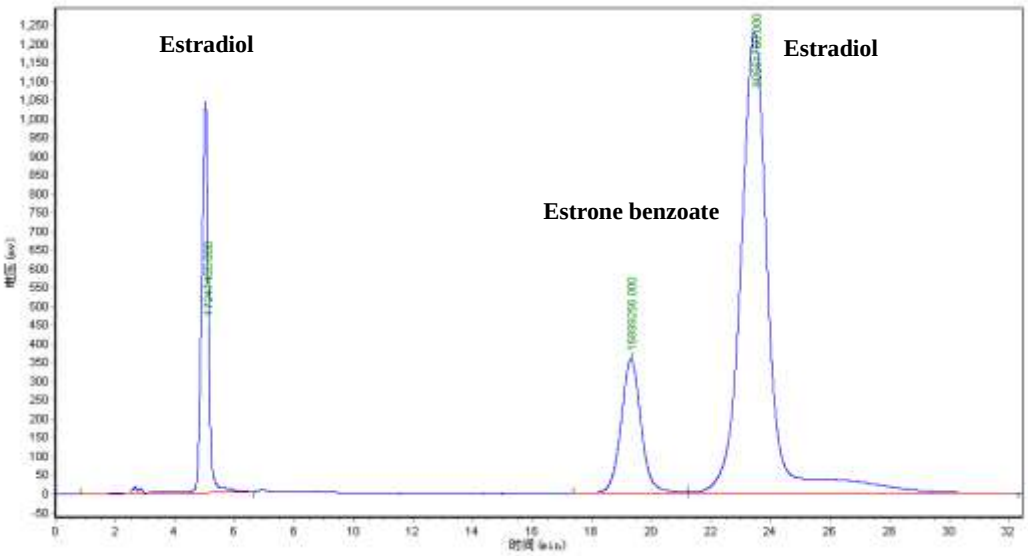
A mixture of **3c** (2g), KBH_4 (4.8 mmol, 0.8 equiv) and Aliquat 336 (0.48 mmol, 0.08 equiv) was mechanically stirred (400 rpm, Teflon blade, D = 4 cm) at 60°C for 1h, the reaction did not take place as analyzed by ^{1}H NMR.

A mixture of **3g** (2g), KBH_4 (3.9 mmol, 0.8 equiv) and Aliquat 336 (0.39 mmol, 0.08 equiv) was mechanically stirred (400 rpm, Teflon blade, D = 4 cm) at 60°C for 1h, the reaction did not take place as analyzed by ^{1}H NMR.

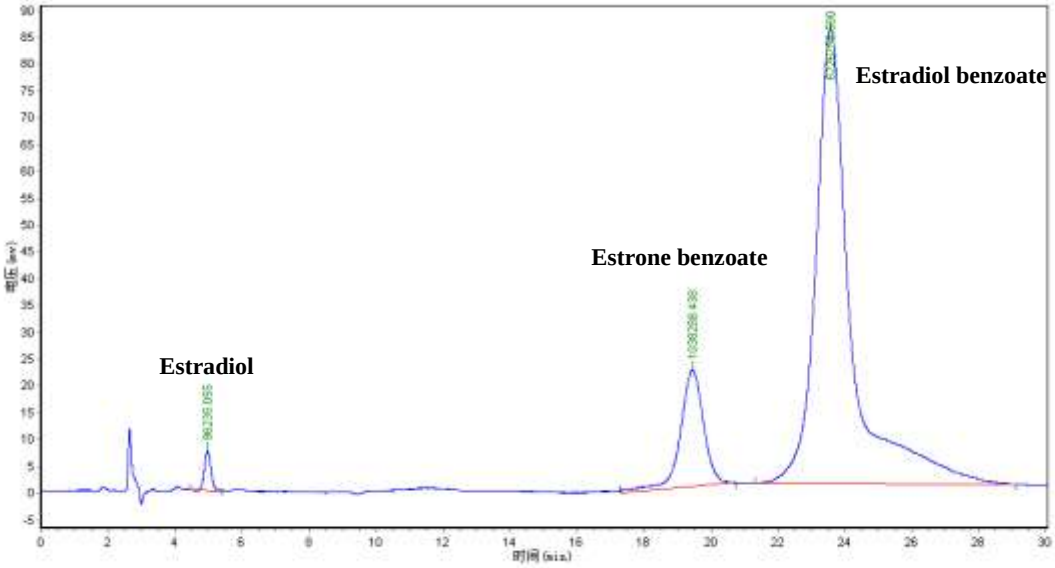
Control experiment for the reduction of estrone benzoate in ethanol and the HPLC analyses

To a solution of estrone benzoate (**3b**) (2 g) in ethanol (20 mL) was added KBH_4 (4.3mmol, 0.8 equiv), the mixture was stirred at 20°C for 4 h. HPLC showed that the product was a mixture of estradiol and estradiol benzoate.

HPLC analysis for the reduction of estrone benzoate in ethanol at 4 h was performed on an ODS column (BaseLine C_{18}, 250×4.6 mm, 10 μm), and the elution with methanol and water (4:1) was monitored at 230 nm. A large amount of estradiol from the hydrolysis of estradiol benzoate was detected.



HPLC analysis for the reduction of estrone benzoate in H_2O at 4 h was performed as above. Small amount of estradiol from the hydrolysis of estradiol benzoate was detected.



General procedure for the condensation of sinomenine

A mixture of sinomenine **5a** (2 g), $NH_2OH \cdot HCl$ / $PhNHNH_2 \cdot HCl$ (1.0 equiv), Aliquat 336 (0.08 equiv), PTFE sand (2 g) and water (10 mL) was mechanically stirred (400 rpm, Teflon blade, D = 4 cm) at 60°C for 1 h or 3 h. TLC showed the completion of the reaction. The reaction mixture was decanted from the sand and neutralized with ammonium hydroxide, and filtrated to give **6a**/**6b** in quantitative yields. The yields and reaction durations are listed in Table 3 in the text.

(Z, E)-Sinomenine oxime (**6a**): ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.95 (s, 1H), 6.62 (d, J= 8.4 Hz, 1H), 6.53 (d, J= 8 Hz, 1H), 5.99 (s, 1H), 5.14 (d, J= 16 Hz, 1H), 4.90 (s, 1H), 3.80 (s, 3H), 3.52, (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.9, 150.8, 144.9, 144.8, 131.0, 123.7, 118.0, 108.5, 104.6, 57.1, 55.9, 54.7, 47.8, 44.3, 42.7, 37.3, 35.9, 33.3, 24.1; IR (KBr): 3402, 2911, 2836, 1638, 1611, 1583, 1485, 1438, 1277, 1205, 1152, 1067, 809, 746 cm^{-1}; MS (ESI): *m/z* (%) $[M + H]^+$= 345.6 (100), 346.8 (40), 348.3 (8), $[2M + H]^+$= 689.6 (35), 690.5 (17), 691.4 (9), $[3M + H]^+$= 1033.1 (3), $[M + Na]^+$= 367.5 (4), $[2M + Na]^+$= 711.5 (30), 712.6 (15), 713.7 (5), $[3M + Na]^+$= 1055.2 (25), 1056.3 (15), 1057.3 (5); HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{19}H_{24}N_2O_4$ + H: 345.1814; found 345.1816.

(Z, E)-N-phenyl sinomenine hydrazone (**6b**): ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.84 (s, 1H), 6.53-7.27 (m, 7H), 6.03 (s,1H), 4.61-4.83 (m, 2H), 3.75-3.82 (m, 3H), 3.51-3.57 (m, 3H),

2.41-2.45 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.2, 152.6, 145.5, 144.8, 144.5, 139.3, 131.1, 129.0, 128.9, 123.4, 119.7, 118.8, 118.5, 117.9, 114.3, 113.1, 112.2, 108.9, 102.3, 57.3, 56.0, 54.9, 54.3, 48.0, 47.7, 47.1, 44.8, 43.2, 42.7, 38.0, 37.8, 35.5, 34.0, 31.6, 29.0, 24.2, 22.5, 14.0; IR (KBr): 3492, 3346, 2933, 2839, 1601, 1503, 1485, 1438, 1278, 1204, 1160, 1055, 796, 750 cm^{-1}; MS (ESI): *m/z* (%) $[M + H]^+$= 420.6 (100), 421.7 (70), 422.7 (33); HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{25}H_{29}N_3O_3$ + H: 420.2287; found 420.2288.

Control experiments for the function of Aliquat 336 and PTFE sand in the condensation reactions

1. A mixture of sinomenine **5a** (2 g), $NH_2OH \cdot HCl$ (6.1 mmol, 1.0 equiv) and water (10 mL) was stirred at 60°C for 1 h. TLC showed that the reaction was a mixture and incomplete.

2. A mixture of sinomenine **5a** (2 g), $PhNHNH_2 \cdot HCl$ (6.1 mmol, 1.0 equiv) and water (10 mL) was stirred at 60°C for 3 h. TLC showed that the reaction was a mixture and incomplete.

General procedure for the hydrolysis of esters

A mixture of ester (2 g), Aliquat 336 (0.08 equiv), KOH (1.5 equiv), PTFE sand (2 g) and water (10 mL) was mechanically stirred (400 rpm, Teflon blade, D = 4 cm) at 60°C for 1-7 h. TLC showed the completion of the reaction. After stopping the reaction, the crystalline product was suspended in water while the sand precipitated on the bottom. The suspension was filtrated to give the corresponding products in quantitative yields leaving the sand to be recovered. Product **5a**,[14] **8b**,[15] **8c**,[16] **8d**[17] and **8e**[18] are known compounds. The yields and reaction durations are listed in Table 4 in the text.

Hydrolysis of 7f in 10 gram scale

A mixture of ester **7f** (10 g), Aliquat 336 (2.1 mmol, 0.08 equiv), KOH (38.8 mmol, 1.5 equiv), PTFE sand (10 g) and water (20 mL) was mechanically stirred (400 rpm, Teflon blade, D = 4 cm) at 60°C for 1.5 h. TLC showed that the reaction was completed. After stopping the reaction, the

crystalline product was suspended in water while the sand precipitated on the bottom. The suspension was filtrated to give **8e** in 99% yield.

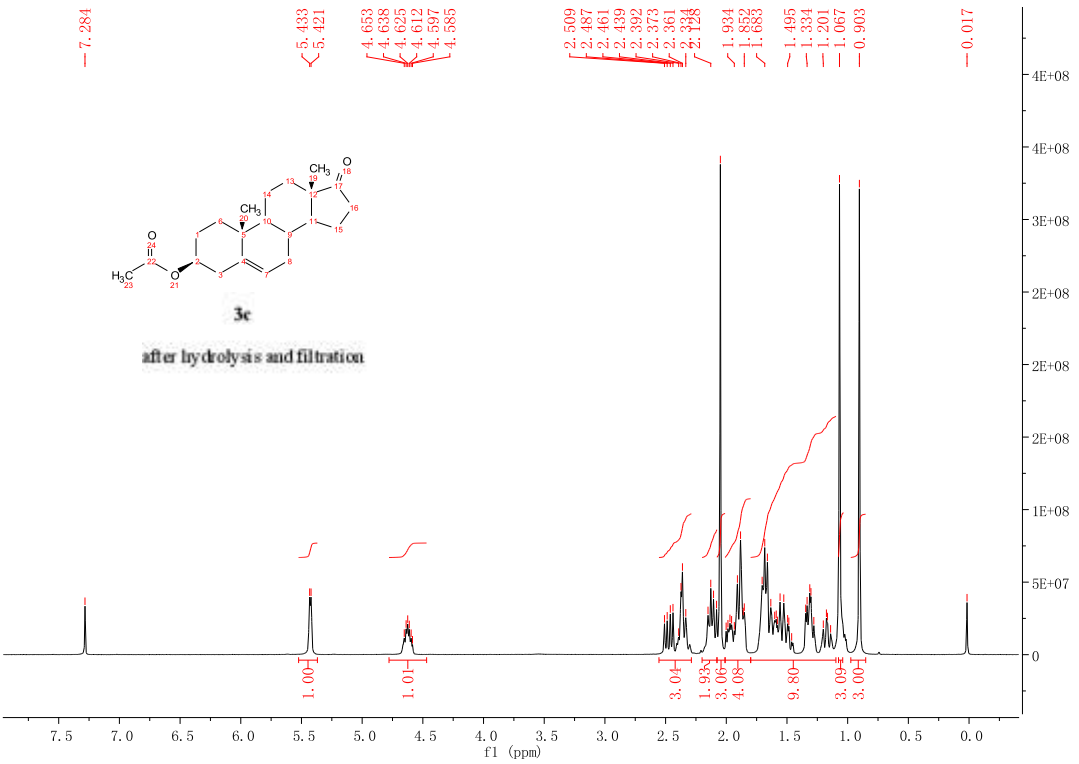
Control experiments for the function of PTC and PTFE sand in the hydrolysis reactions

1. Without Aliquat 336 and PTFE sand

A mixture of **2a** (2 g), KOH (8.4 mmol, 1.5 equiv) and water (10 mL) was stirred at 60°C for 5.5 h. TLC and the NMR showed that the reaction did not take place. After 24 h, trace amounts of product were detected by TLC.

2. Catalyzed by tetrabutylammonium bromide without PTFE sand

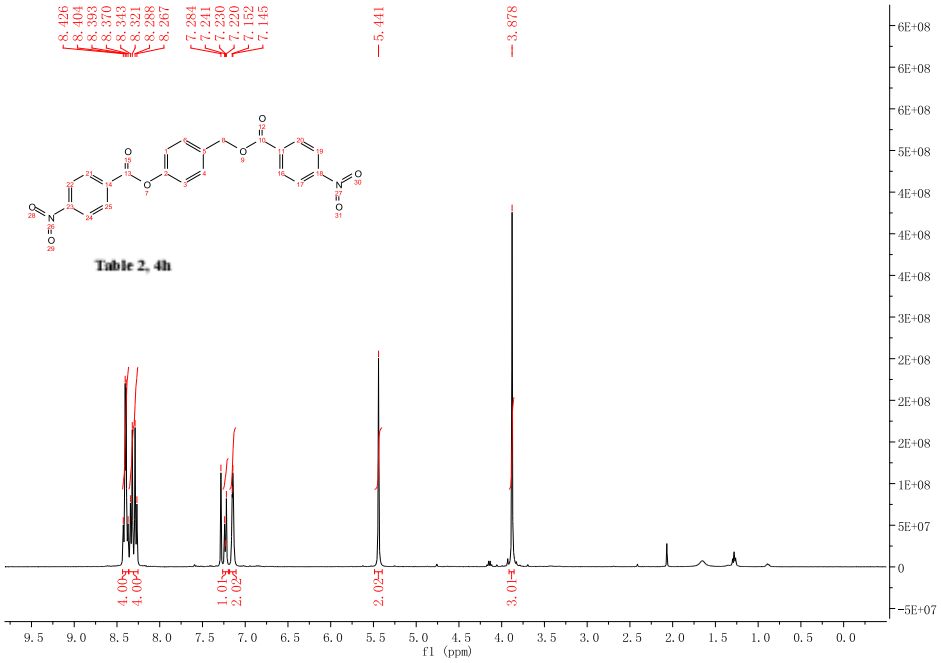
A mixture of **3c** (2 g), KOH (9.1 mmol, 1.5 equiv), tetrabutylammonium bromide (0.5 mmol, 0.08 equiv) and water (10 mL) was stirred at 60°C for 1.5 h. The reaction did not take place as indicated in the following ^{1}H NMR of the crude product.

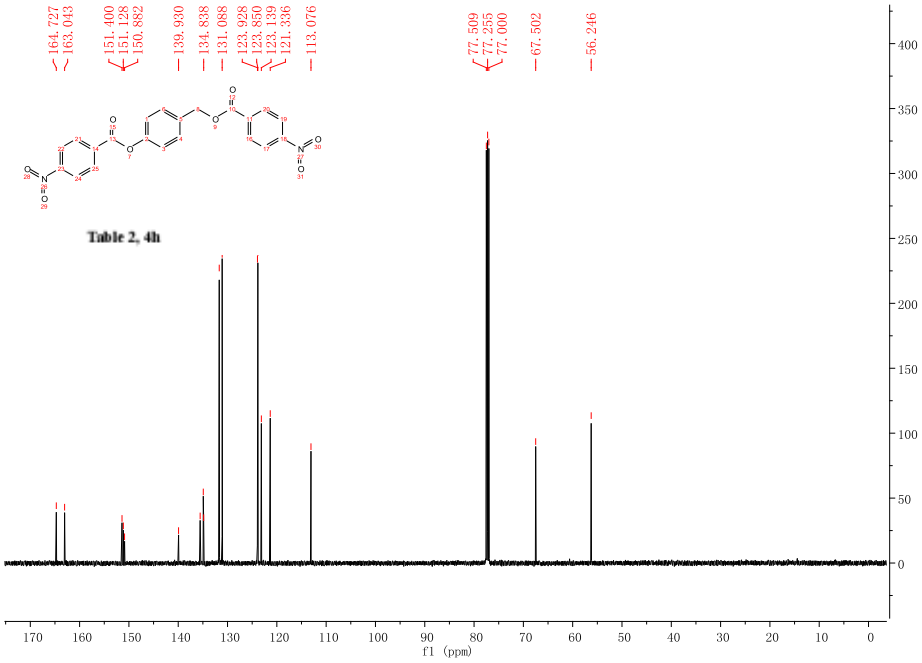


3. Catalyzed by benzyltriethylamonium chloride without PTFE sand

A mixture of **3c** (2 g), KOH (9.1 mmol, 1.5 equiv), benzyltriethylamonium chloride (0.5 mmol, 0.08 equiv) and water (10 mL) was stirred at 60°C for 1.5 h. TLC and the NMR showed that the reaction did not take place.

^{1}H NMR and ^{13}C NMR spectra for new products





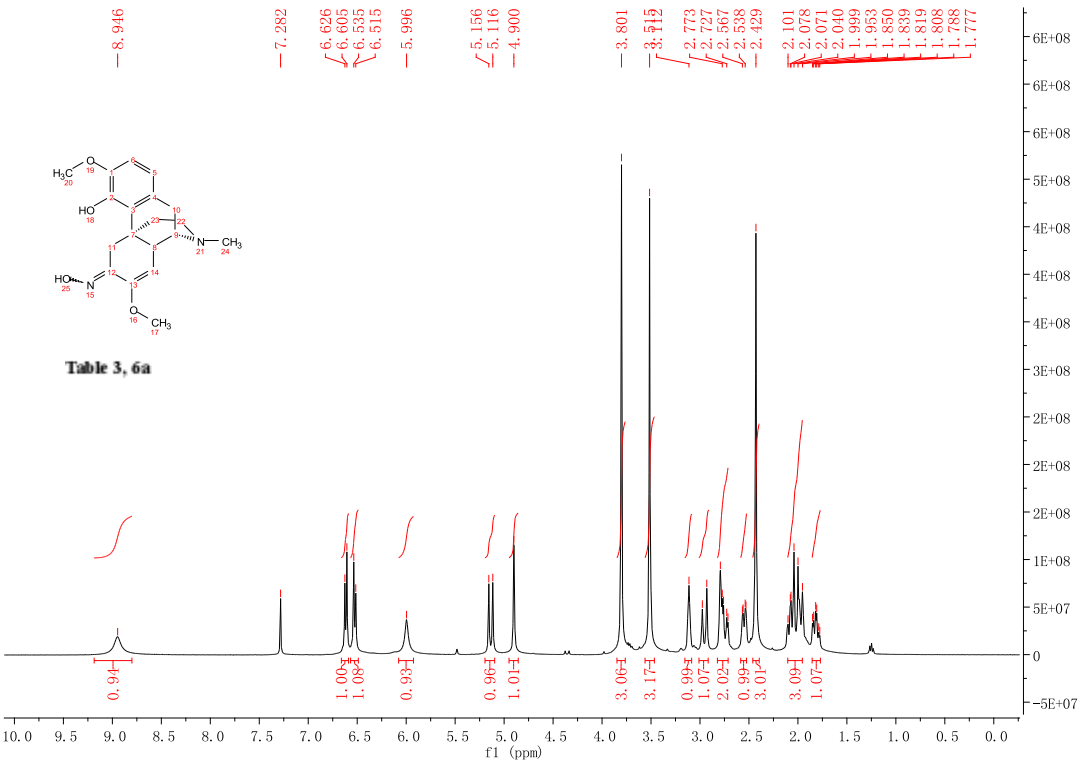


Table 3, 6a
f1 (ppm)

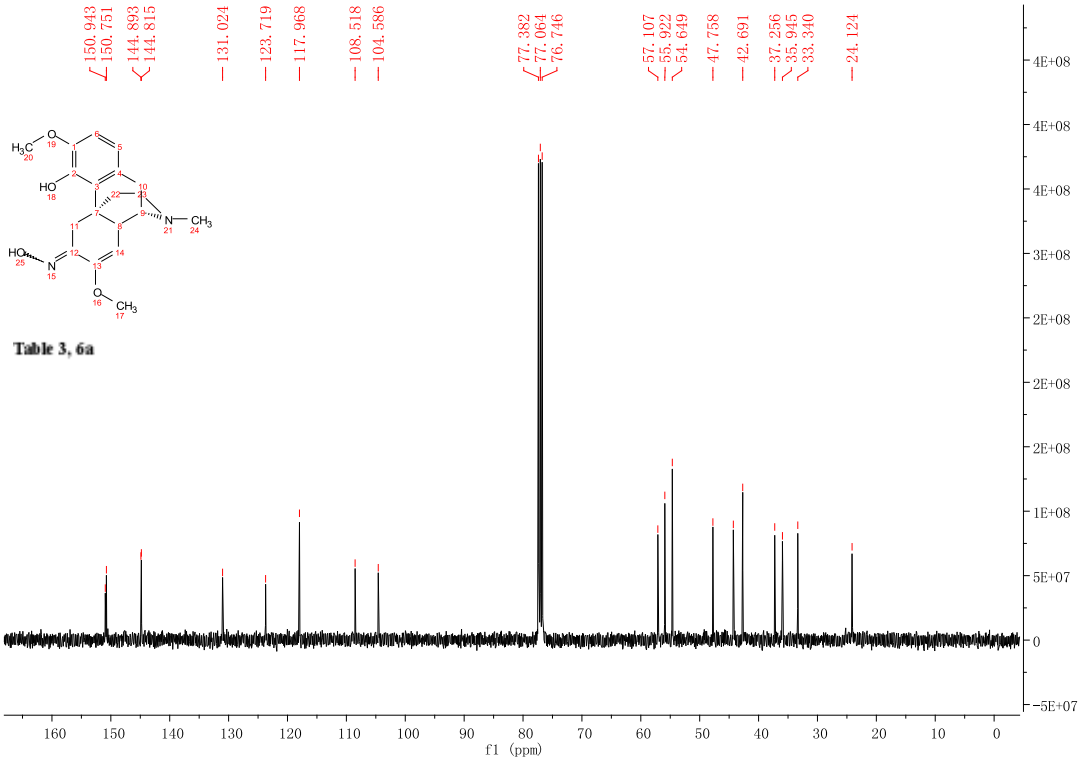
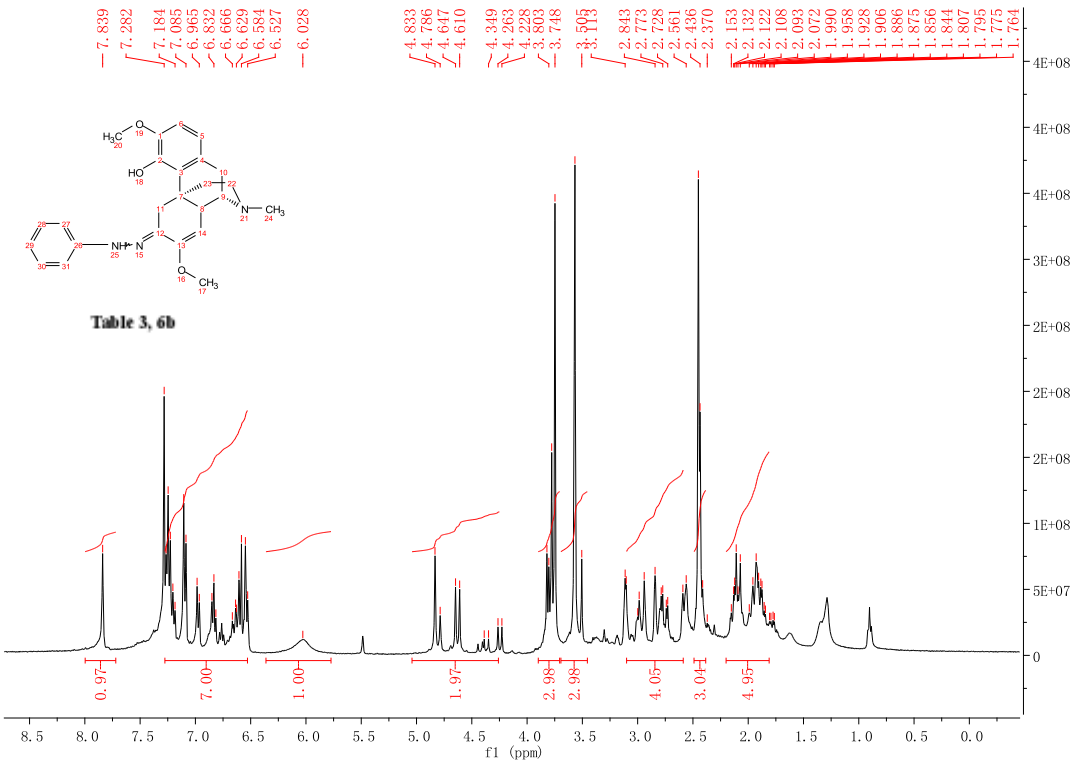
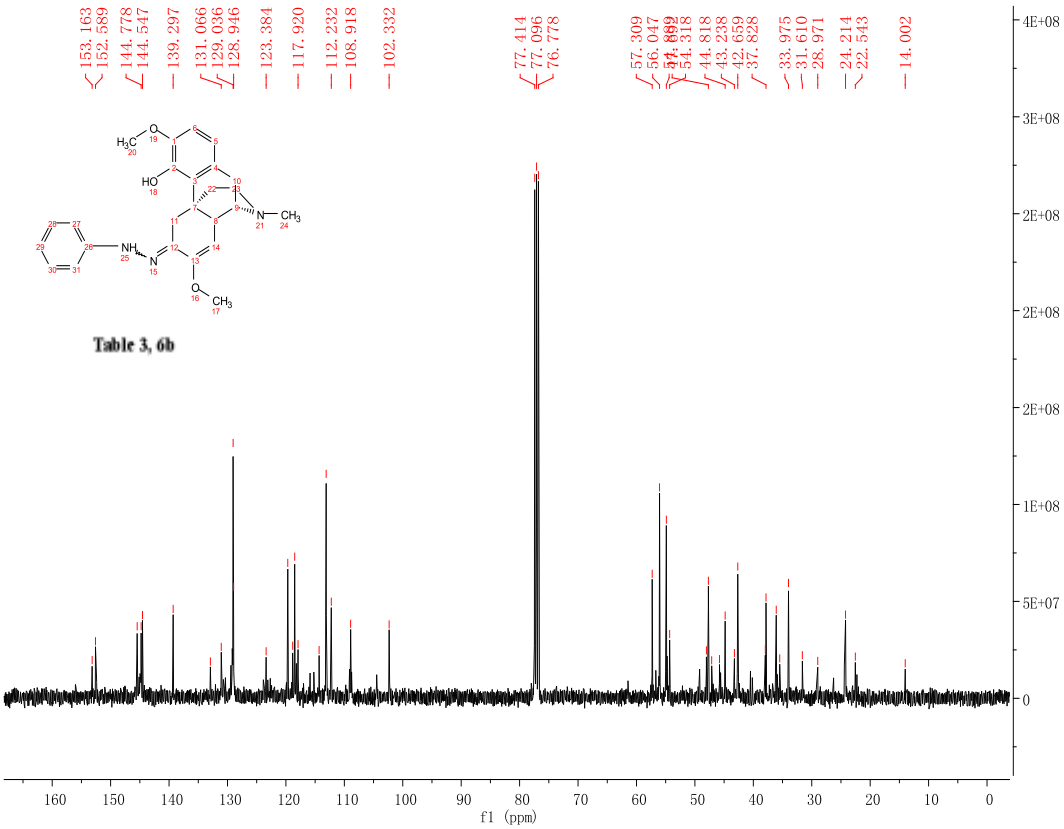


Table 3, 6a
f1 (ppm)





References:

1 R. W. Hartmann, *et al*., *J. Med. Chem*., 2000, **43**, 4266-4277.

2 P. Bunyathaworn, S. Boonananwong, B. Boonsong and N. Kongkathip, *Steroids*, 2010, **75**, 432-444.

3 N. Kongkathip, B. Kongkathip and N. Noimai, *Synth*. *Commun*., 2006, **36**, 865-874.

4 R. C. Boruah, S. Ahmed, U. Sharma and J. S. Sandhu, *Indian J*. *Chem*. *Section B*., 1999, **38**, 274-282.

5 F. Liu, H. Liu, Y. Zhang, J. Zhang and L. Tian, *Steroids*, 2005, **70**, 825-830.

6 B. Wang, *et al*., *Org*. *Lett*., 2010, **12**, 3352-3355.

7 L. A. Castagnetta, *et al*., *Steroids*, 1992, **57**, 437-443.

8 V. M. A. Moreira, T. S. Vasaitis, Z. Guo, V. C. O. Niar and J. A. R. Salvador, *Steroids*, 2008, **73**, 1217-1227.

9 C. R. Engel, *et al*., *J*. *Org*. *Chem*., 1983, **48**, 1954-1966.

10 K. Yamamoto and C. H. Heathcock, *Org*. *Lett*., 2000, **2**, 1709-1712.

11 A. E. Leontjev, L. L. Vasiljeva and K. K. Pivnitsky, *Russ*. *Chem*. *B+*., 2004, **53**, 703-708.

12 K. Tori, *et al*., *Steroids*, 1982, **39**, 73-80.

13 C. Dugave, *J*. *Org*. *Chem*., 1995, **60**, 601-607.

14 G. Bao, G. Qin, R. Wang and X. Tang, *J*. *Nat*. *Prod*., 2005, **68**, 1128-1130.

15 B. B. Shingate, B. G. Hazra, V. S. Pore, R. G. Gonnade and M. M. Bhadbhade, *Tetrahedron*, 2007, **63**, 5622-5635.

16 H. Li, H. Liu, W. Ge, L. Huang and L. Shan, *Steroids*, 2005, **70**, 970-973.

17 M. Itabashi, *et al*., *Carbohyd*. *Res*., 2000, **323**, 57-62.

18 N. R. Schmuff and B. M. Trost, *J*. *Org*. *Chem*., 1983, **48**, 1404-1412.