Stereoselective Construction of Steroidal Side Chain from 16-Dehydropregnenolone Acetate

Nilkanth G. Aher,[a] Rajesh G. Gonnade,[b] Vandana S. Pore*[a]

[a] Organic Chemistry Division, National Chemical Laboratory, Pune 411008, India
Fax +91(20)25902624; E-mail: vs.pore@ncl.res.in

[b] Centre for Material Characterization, National Chemical Laboratory, Pune 411008, India

Received 1 April 2009

Abstract: Stereoselective construction of steroidal side chain at C-20 having 'natural' configuration using 16-dehydropregnalone acetate (16-DPA) as a starting material has been carried out. Palladium-catalyzed carbon–carbon bond-forming Heck reaction between C-20 vinyl iodide with methyl acrylate and transfer hydrogenation with triethylsilane and Pd/C are the key steps for stereoselective side-chain synthesis.

Key words: stereoselectivity, 16-dehydropregnenolone acetate, Heck coupling, transfer hydrogenation, steroidal side chain

The introduction of the properly functionalized side chains onto tetracyclic steroidal starting materials has been the subject matter of several investigations.[1,2] Most of the naturally occurring steroids isolated from plant, marine, and animal sources have the C(20*R*) stereochemistry, for example, cholesterol (**1**), brassinolide (**2**),[3] squalamine (**3**),[4] OSW-1 (**4**),[5] vitamin D_3 (**5**)[6] (Figure 1) and many other biologically important steroids with modified side chains such as ecdysones,[7] contignasterol,[8] and marine sterols.[9] Due to high biological activity of single isomer and their scarcity from natural resources, methods for their stereoselective synthesis are highly desirable.

Synthetic methods for stereoselective construction of steroidal side chain have involved the use of Michael addition,[10] palladium-catalyzed reactions,[11] alkylation at C-20,[12] Claisen sigmatropic rearrangement,[13] ene reaction,[14] Wittig rearrangement,[15] aldol condensation,[16] use of organoborane,[17] organozirconium[18] and organoruthenium[19] reagents, etc. The focal point of any such synthesis is the stereospecific introduction of the asymmetric center at C-20.

Catalytic hydrogenation of double bonds formed between C-20 and one of the adjacent carbons at C-17 and C-21 or C-22 is one of the most attractive methods for introduction of chiral centre at C-20. Hydrogenation of the 20(21)/20(22) by using different catalysts affording the C-20 epimeric mixture has been reported.[1a] Construction of side chain by Wittig reaction on C-20 oxo steroids followed by selective hydrogenation is the simplest and most versatile method. Hydrogenation of C-20(22) double bond using different catalysts such as H_2 Pd/C, Pt/C, Ra-Ni (W-2), $(Ph_3P)_3RhCl$, 5% Rh/Al_2O_3 afforded the C-20 epimeric mixture,[20] while hydrogenation using PtO_2 in EtOH showed better selectivity.[21] Older literature reports showed inconsistency in selectivity using PtO_2 catalyst.[1a,20a] The C-22 furan derivative of pregnenolone acetate having C-20(21) double bond, on hydrogenation using H_2 and Pd/C in benzene afforded the compound having C-(20*R*) natural stereochemistry.[22] There is a recent report on introduction of side chain on the estrane skeleton in which hydrogenation using Pd/C gave a mixture of C-20(*R*) and C-20(*S*) compounds in a 7:3 ratio.[23]

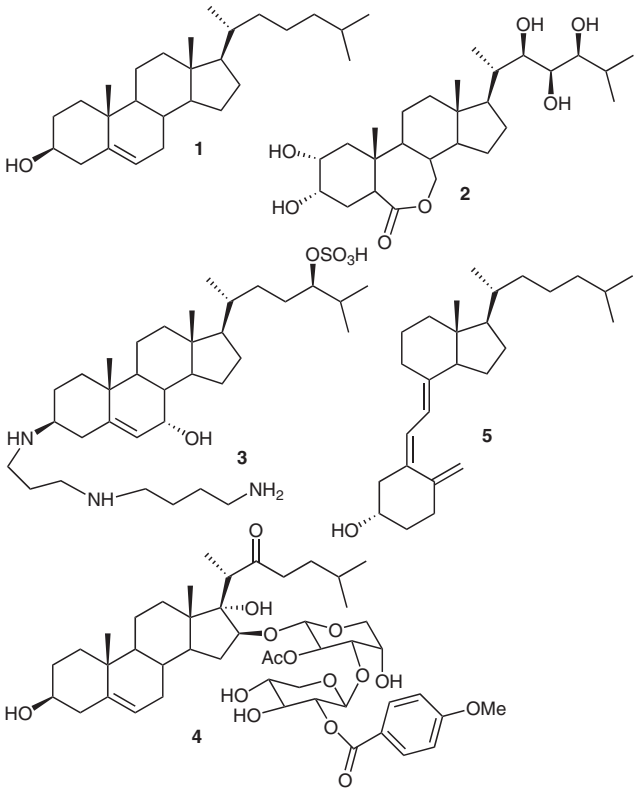


Figure 1 Natural steroids having C-(20*R*) configuration

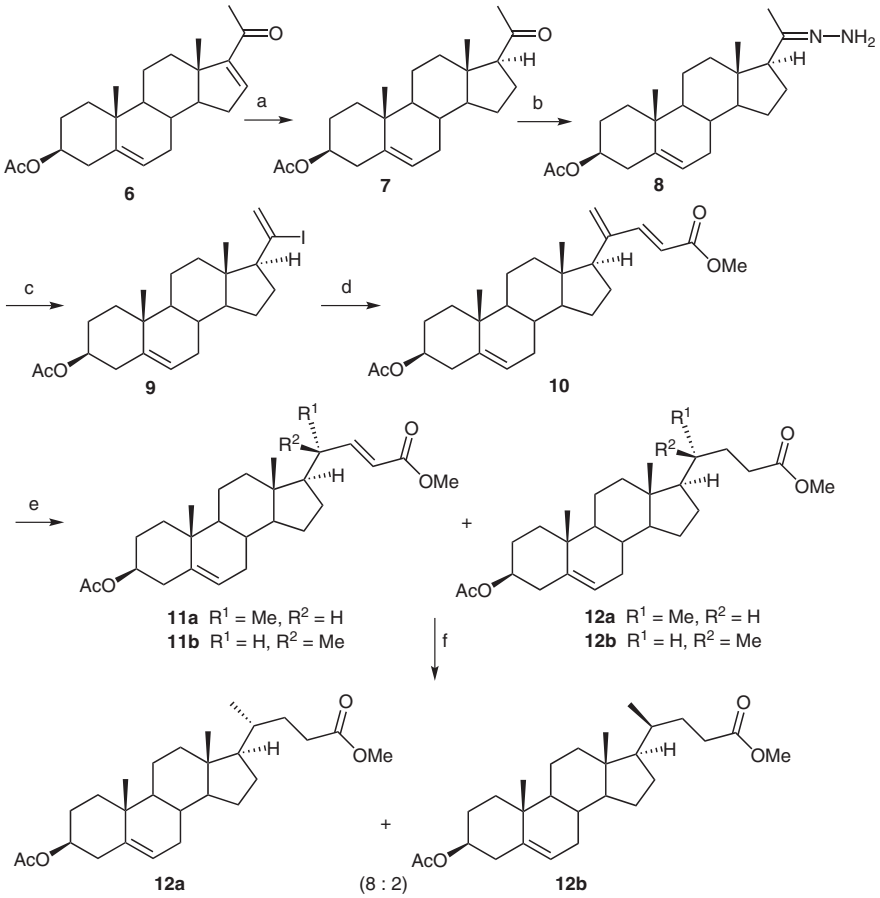
In continuation of our interest in stereoselecive construction of steroidal side chain,[14c–e] we recently developed new methods for a highly stereoselective synthesis of unnatural C-20(*R*)-aldehydes starting from 16-dehydropregnenolone acetate (16-DPA) by ionic hydrogenation of C-20(22)-ketene dithioacetal[24a] and C-20 tertiary alcohols.[24b] These aldehydes were used for the synthesis of

SYNLETT 2009, No. 12, pp 2005–2009
Advanced online publication: 01.07.2009
DOI: 10.1055/s-0029-1217521; Art ID: G11209ST

20-epicholanic acid derivatives.[24c] In this paper we wish to report a short route for stereoselective synthesis of C-20(*R*) cholanic acid derivative from 16-DPA (**6**). Palladium-catalyzed Heck coupling of C-20 vinyl iodide compound **9** with methyl acrylate and Pd/C-induced catalytic transfer hydrogenation with triethylsilane are the key steps in this synthesis.

Chemoselective catalytic hydrogenation of C-16 double bond of 16-DPA (**6**) with 10% Pd/C in ethyl acetate resulted into saturated ketone **7** in 98% yield[24c] (Scheme 1). The ^{1}H NMR spectrum of this compound showed chemical shifts of δ = 0.63 (s, 3 H, 18-CH_3) and 2.13 (s, 3 H, 21-CH_3) ppm. Reaction of **7** with hydrazine hydrate in MeOH afforded C-20 hydrazone product **8** in almost quantitative yield. This compound **8** showed characteristic up field chemical shift of δ = 0.59 (s, 3 H, 18-CH_3) and 1.76 (s, 3 H, 21-CH_3) ppm in comparison with compound **7**. In the ^{13}C NMR spectrum quaternary carbon (C-20 hydrazone) was observed at δ = 151.5 ppm. Oxidation of hydrazone was carried out using iodine in the presence of organic base, triethylamine, to give vinyl iodide **9** in good yield.[25] In the ^{1}H NMR spectrum of compound **9** the geminal C-21 methylene protons showed different chemical shifts [δ = 5.98 (d, *J* = 1.51 Hz, 1 H) and 6.15 (br s, 1 H) ppm]. In the ^{13}C NMR spectrum methylene at C-21 was observed at δ = 126.1 ppm. There are reports in the literature on palladium-catalyzed carbon–carbon bond-forming reactions of steroidal vinyl iodide or vinyl triflate with alkenes and terminal alkynes.[26]

Heck coupling of steroidal vinyl iodides at C-17, with allyl acetates or methyl acrylate in the presence of catalytic amount of $Pd(OAc)_2$ and triethyl amine or K_2CO_3 at 60–100 °C, is known in the literature.[27] When we carried out coupling reaction of C-20 vinyl iodide **9** with methyl acrylate using the literature procedure,[27] afforded the complex mixture of products which could not be identified. However, when the same reaction was carried out using catalytic amount of $Pd(OAc)_2$ and K_2CO_3 in DMF at 25–30 °C, 80% conversion of starting material was observed (on the basis of recovered starting material) and expected product **10** was obtained as a single product.[28] Increase in amount of the catalyst or extended reaction time did not improve the complete conversion of the starting material into the product. Use of $Pd(PPh_3)_4$ resulted in 45% conversion while addition of $Pd(OAc)_2$ and Ph_3P as catalysts resulted in the complete conversion of starting material but the expected product **10** was isolated in poor yield along with many unidentified products. The IR spectrum of **10** showed bands at 1724 and 1668 cm^{-1} for C-3 acetate carbonyl and C-24 methyl ester carbonyl respectively. Its ^{1}H NMR spectrum showed characteristic signals at δ = 5.34 and 5.55 ppm as two singlets for C-21-CH_2 and



Scheme 1 *Reagents and conditions*: a) 10% Pd/C, H_2, EtOAc, 3.1 bar, 25–30 °C, 12 h, 98%; b) hydazine hydrate, Et_3N, MeOH, 25–30 °C, 4 h, 98%; c) I_2, Et_3N, THF, 25–30 °C, 3 h, 74%; d) $Pd(OAc)_2$ (0.04%) K_2CO_3, methyl acrylate, DMF, 25–30 °C, 12 h, 77%; e) 10% Pd/C (15% by weight), MeOH, TES (excess), 10 min; f) H_2, Pd/C, EtOAc, 3.1 bar, 30 °C, 10 h (overall 90% after two steps; ratio of **12a**/**12b** = 8:2).

δ = 6.02 (d, 1 H, *J* = 15.95 Hz), 7.36 (d, 1 H, *J* = 15.95 Hz) ppm for C-23 and C-22 CH, respectively. In the ^{13}C NMR spectrum C-24 carbonyl was observed at δ = 167.6 ppm and C-21-CH_2 at δ = 122 ppm.

Our next goal was to obtain single C-20(*R*) isomer by stereoselective hydrogenation of C-20(21) double bond. Catalytic hydrogenation of **10** on Pd/C in ethyl acetate at 3.1 bar for 10 hours afforded the epimeric mixture **12a** and **12b** in the ratio of 6:4. Recently, there is a report[29] on Pd/C-induced catalytic transfer hydrogenation using triethylsilane to give efficient reduction of multiple bonds, azides, imines, and nitro groups as well as benzyl and allyl group deprotection, under mild neutral conditions. Transfer hydrogenation[29] of compound **10** using catalytic amount of 10% Pd/C and excess of triethylsilane in MeOH afforded compounds **11a**,**b** and **12a**,**b** as an epimeric mixture at C-20 in 10 minutes. Various attempts of purification of this mixture and to determine the ratio of the products obtained did not fructify. In ^1H NMR of this mixture (Figure 2), C-20(21) double bond was observed to be completely hydrogenated (disappearance of chemical shift at δ = 5.34 and 5.55 ppm while C-22(23) double bond was partially hydrogenated and 5(6) double bond remained unaffected. The major chemical shifts in the ^1H NMR spectrum of this mixture (Figure 2) were found to be at δ = 6.90 (dd, 1 H, *J* = 10, 16 Hz, C-22H) and 5.73 (d, 1 H, *J* = 16 Hz, C-23H), 1.09 (d, 3 H, *J* = 6.57 Hz, C-21CH_3) ppm. These chemical shifts matches with the literature values[30] of compound **11a** having C-20(*R*) natural stereochemistry.

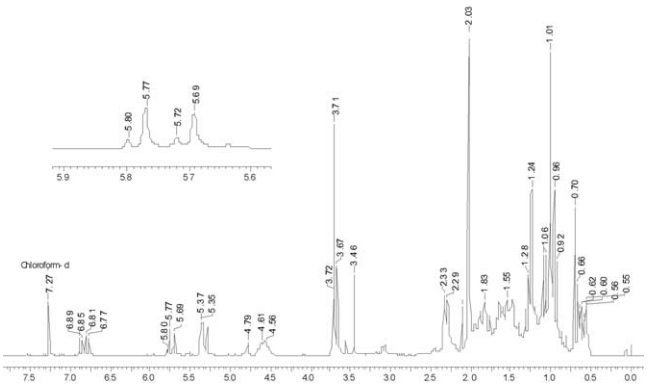


Figure 2 ^1H NMR of epimeric mixture of **11a**,**b** and **12a**,**b**

For complete conversion of **11a**,**b** into **12a**,**b** further hydrogenation of this mixture was carried out using H_2 and Pd/C in EtOAc. It gave C-20 epimeric mixture of compounds **12a** and **12b** in 8:2 ratio[31] (calculated by ^1H NMR chemical shift of methyl ester and C-21 methyl protons as shown in Figure 3). In the ^1H NMR spectrum of the mixture of compounds **12a**,**b** (Figure 3) major peaks were observed at δ = 0.67 (s, 3 H, 18-CH_3), 0.92 (d, 3 H, *J* = 6.33 Hz, 21-CH_3), 3.67 (s, 3 H, $COOCH_3$) ppm while minor peaks observed at δ = 0.69 (s, 3 H, 18-CH_3), 0.85 (d, 3 H, *J* = 6.33 Hz, 21-CH_3), 3.69 (s, 3 H, $COOCH_3$). These chemical shifts match with the literature data[30] of compounds **12a** and **12b** having C-20(*R*)- and C-20(*S*) configuration, respectively. The mixture of compounds **12a** and **12b** was purified by crystallization in CH_2Cl_2–MeOH (1:9) to get pure cholanic acid derivative **12a** in 62% yield as a major compound.

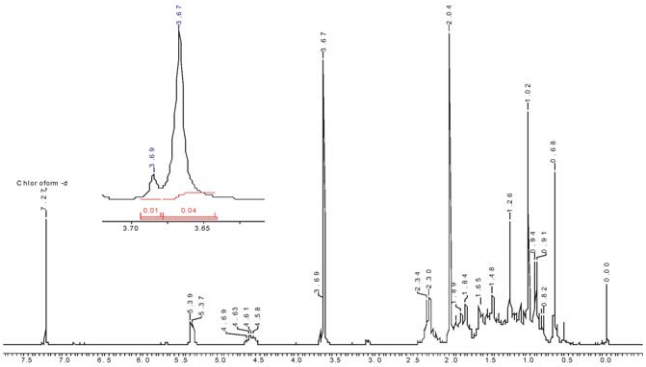


Figure 3 ^1H NMR of epimeric mixture of **12a** and **12b**

The stereochemistry of compound **12a** at C-20 was finally confirmed by single crystal X-ray diffraction (Figure 4).[31,32]

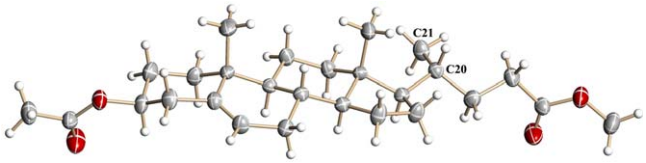


Figure 4 ORTEP view of methyl (20*R*)-3β-acetoxychol-5-enoate **12a**

From the mother liquor compound **12b** was isolated in 8% yield after several crystallizations. Cholanic acid derivatives with natural configuration at C-20 are important compounds for an investigation of the biological fat of cholesterol and for the treatment of gallstones. They are also key intermediates for the synthesis of large number of biologically active steroids having natural C-20(*R*) configuration.

In conclusion, stereoselective construction of steroidal side chain at C-20 position having 'natural' C-20(*R*) configuration from 20 oxo steroid (16-DPA) (**6**) has been achieved. Palladium-catalyzed carbon–carbon bond-forming Heck reaction has been used for coupling between C-20 vinyl iodide **9** and methyl acrylate to form unsaturated compound **10**. Transfer hydrogenation using triethylsilane and Pd/C is the key step for stereoselective side-chain synthesis.

Acknowledgment

VSP thanks Director, NCL, for In-House funding (MLP 13126). NGA thanks CSIR-UGC, New Delhi, for the award of Junior Research Fellowship.

References and Notes

(1) (a) For a review on the construction of steroid side chain, see:Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199. (b) Redpath, J.; Zeelan, F. *Chem. Soc. Rev.* **1983**, *12*, 75.

(2) (a) Ibuka, T.; Taga, T.; Shingu, T.; Saito, M.; Nishii, S.; Yamamoto, Y. *J. Org. Chem.* **1988**, *53*, 3947. (b) He, Z.; Yi, C. S.; Donaldson, W. A. *Org. Lett.* **2003**, *5*, 1567; and references cited therein. (c) Harada, S.; Kiyono, H.; Nishio, R.; Tagushi, T.; Hanzawa, Y. *J. Org. Chem.* **1997**, *62*, 3994.

(3) (a) Adam, G.; Marquardt, V. *Phytochemistry* **1986**, *25*, 1787. (b) Lokhvich, F. A.; Khripach, V. A.; Zhabinskii, V. N. *Russ. Chem. Rev.* **1991**, *60*, 658. (c) Kovganko, N. V.; Ananich, S. K. *Chem. Nat. Compd.* **2002**, *38*, 122. (d) Massey, A. P.; Pore, V. S.; Hazra, B. G. *Synthesis* **2003**, 426. (e) Ramirez, J. A.; Brosa, C.; Galagovsky, L. R. *Phytochemistry* **2005**, *66*, 581.

(4) (a) Brunel, J. M.; Letourneux, Y. *Eur. J. Org. Chem.* **2003**, 3897; and references cited therein. (b) Zhang, D. H.; Cai, F.; Zhou, X.-D.; Zhou, W.-S. *Org. Lett.* **2003**, *5*, 3257. (c) Okumura, K.; Nakamura, Y.; Takeuchi, S.; Kato, I.; Fujimoto, Y.; Ikekawa, N. *Chem. Pharm. Bull.* **2003**, *51*, 1177. (d) Zhang, D.-H.; Cai, F.; Zhou, X.-D.; Zhou, W.-S. *Chin. J. Chem.* **2005**, *23*, 176.

(5) Morzycki, J. W.; Wojtkielewicz, A. *Phytochem. Rev.* **2005**, *4*, 259; and references cited therein.

(6) (a) Georghiou, P. E. *Chem. Soc. Rev.* **1977**, *6*, 83. (b) Taber, D. F.; Jiang, Q.; Chen, B.; Zhang, W.; Campbell, C. L. *J. Org. Chem.* **2002**, *67*, 4821. (c) Gorobets, E.; Stepanenko, V.; Wicha, J. *Eur. J. Org. Chem.* **2004**, 783.

(7) (a) Nakanishi, K. *Pure Appl. Chem.* **1971**, *25*, 167. (b) Kovganko, N. V.; Kashkan, Zh. N.; Chernov, Y. G.; Ananich, S. K.; Sokolov, S. N.; Survilo, V. L. *Chem. Nat. Compd.* **2003**, *39*, 411.

(8) (a) Burgoyne, D. L.; Andersen, R. J.; Allen, T. M. *J. Org. Chem.* **1992**, *57*, 525. (b) Izzo, I.; Avallone, E.; Monica, C. D.; Casapullo, A.; Amigo, M.; Riccardis, D. *Tetrahedron* **2004**, *60*, 5587.

(9) (a) Nes, W. R.; Mckean, M. L. *Biochemistry of Steroids and other Isoprenoids*; University Park: Baltimore MD, **1977**. (b) D'Aura, M. V.; Minale, L.; Ricco, R. *Chem. Rev.* **1993**, *93*, 1839. (c) Stonik, V. A. *Russ. Chem. Rev.* **2001**, *70*, 673.

(10) (a) Yu, W.; Jin, Z. *J. Am. Chem. Soc.* **2001**, *123*, 3369. (b) Yu, W.; Jin, Z. *J. Am. Chem. Soc.* **2002**, *124*, 6576.

(11) (a) Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *J. Org. Chem.* **1992**, *57*, 6090. (b) Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *Tetrahedron* **1999**, *50*, 475.

(12) (a) Kurek-Tyrlik, A.; Michalak, K.; Urbanczyk-Lipkowska, Z.; Wicha, J. *Tetrahedron Lett.* **2004**, *45*, 7479. (b) Kurek-Tyrlik, A.; Michalak, K.; Wicha, J. *J. Org. Chem.* **2005**, *70*, 8513.

(13) (a) Tanabe, M.; Hayashi, K. *J. Am. Chem. Soc.* **1980**, *102*, 862. (b) Mikami, K.; Kawamoto, K.; Nakai, T. *Tetrahedron Lett.* **1986**, *27*, 4899.

(14) (a) Yamamoto, S.; Watanabe, B.; Otsuki, J.; Nakagawa, Y.; Akamatsu, M.; Miyagawa, H. *Bioorg. Med. Chem.* **2006**, *14*, 1761. (b) Houston, T. A.; Tanaka, Y.; Koreeda, M. *J. Org. Chem.* **1993**, *58*, 4287. (c) Hazra, B. G.; Joshi, P. L.; Pore, V. S. *Tetrahedron Lett.* **1990**, *31*, 6227. (d) Hazra, B. G.; Pore, V. S.; Joshi, P. L. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1819. (e) Hazra, B. G.; Joshi, P. L.; Bahule, B. B.; Argade, N. P.; Pore, V. S.; Chordia, M. D. *Tetrahedron* **1994**, *50*, 2523.

(15) (a) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885. (b) Castedo, L.; Granja, J. R.; Mouriño, A. *Tetrahedron Lett.* **1985**, *26*, 4959.

(16) (a) Shi, B.; Wu, H.; Yu, B.; Wu, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 4324. (b) Shi, B.; Tang, P.; Hu, X.; Liu, J. O.; Yu, B. *J. Org. Chem.* **2005**, *70*, 10354.

(17) Katoch, R.; Korde, S. S.; Deodhar, K. D.; Trivedi, G. K. *Tetrahedron* **1999**, *55*, 1741.

(18) (a) Temple, J. S.; Riediker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 1310. (b) Harada, S.; Kiyono, H.; Nishio, R.; Taguchi, T.; Hanzawa, Y.; Shiro, M. *J. Org. Chem.* **1997**, *62*, 3994.

(19) He, Z.; Yi, C. S.; Donaldson, W. A. *Org. Lett.* **2003**, *5*, 1567.

(20) (a) DuBois, G. E. *J. Org. Chem.* **1982**, *47*, 5035. (b) Kametani, T.; Katoh, T.; Fujio, J.; Nogiwa, I.; Tsubuki, M.; Toshio Honda, T. *J. Org. Chem.* **1988**, *53*, 1982.

(21) Fukumoto, K.; Suzuki, K.; Nemoto, H.; Kametani, T.; Furuyama, H. *Tetrahedron* **1982**, *38*, 3701.

(22) (a) Kametani, T.; Masayoshi, T.; Nemoto, H. *Tetrahedron Lett.* **1981**, *22*, 2373. (b) Kametani, T.; Suzuki, K.; Nemoto, H. *J. Org. Chem.* **1982**, *47*, 2331.

(23) Jogireddy, R.; Rullkotter, J.; Christoffers, J. *Synlett* **2007**, 2847.

(24) (a) Shingate, B. B.; Hazra, B. G.; Pore, V. S.; Gonnade, R. G.; Bhadbhade, M. M. *Chem. Commun.* **2004**, 2194. (b) Shingate, B. B.; Hazra, B. G.; Pore, V. S.; Gonnade, R. G.; Bhadbhade, M. M. *Tetrahedron Lett.* **2006**, *47*, 9343. (c) Shingate, B. B.; Hazra, B. G.; Pore, V. S.; Gonnade, R. G.; Bhadbhade, M. M. *Tetrahedron* **2007**, *63*, 5622.

(25) (a) Barton, D. H. R.; O'Brien, R. E.; Sternhell, S. *J. Chem. Soc.* **1962**, 470. (b) Barton, D. H. R.; Bashiardes, G.; Fourrey, J.-L. *Tetrahedron Lett.* **1983**, *24*, 1605. (c) Barton, D. H. R.; Bashiardes, G.; Fourrey, J.-L. *Tetrahedron* **1988**, *44*, 147.

(26) Skoda-Földes, R.; Kollár, L. *Chem. Rev.* **2003**, *103*, 4095.

(27) Skoda-Földes, R.; Bodnar, M.; Kollár, L.; Horvath, J.; Tuba, Z. *Steroids* **1998**, *63*, 93.

(28) **Methyl [20 (21),22]-3β-Acetoxychol-5-trienoate (10)**
To a solution of vinyl iodide **9** (0.234 g, 0.5 mmol) in dry DMF (10 mL), methyl acrylate (0.9 mL 1 mmol), Pd catalyst (0.005 g, 0.02 mmol), and K_2CO_3 (0.414 g, 1.5 mmol) were added, and the reaction mixture was stirred under argon at 25–28 °C for 12 h. Ice was added to the reaction mixture, and it was extracted with EtOAc (3 × 25 mL). The extract was washed 5% HCl (2 × 25 mL), sat. aq $NaHCO_3$ (20 mL) and brine, and dried over Na_2SO_4. The product was purified by chromatography on silica gel (2% EtOAc–PE) to give pure product **10** (0.163 g) in 77% yield and starting material **9** (0.047 g). Colorless solid; mp 93–94 °C; $[\alpha]_D^{26}$ –32.0 (*c* 2.58, $CHCl_3$); IR (mull): 1691, 1724 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.56 (s, 3 H, 18-CH_3), 1.02 (s, 3 H, 19-CH_3), 2.04 (s, 3 H, $OCOCH_3$), 3.76 (s, 3 H, $COOCH_3$), 4.61 (m, 1 H, 3-CH), 5.34 (s, 1 H, 21-CH_2), 5.38 (d, *J* = 5.0 Hz, 1 H, 6-CH), 5.55 (s, 1 H, 21-CH_2), 6.02 (d, *J* = 16.0 Hz, 1 H, 23-CH), 7.36 (d, *J* = 16.0 Hz, 1 H, 22-CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.8, 19.2, 20.9, 21.3, 24.2, 26.3, 27.6, 31.7, 32.3, 36.5, 36.9, 38.0, 38.6, 43.2, 50.0, 51.1, 51.5, 56.6, 73.8, 117.3, 122.0, 122.3, 139.6, 144.0, 149.1, 167.6, 170.4. Anal. Calcd for $C_{27}H_{38}O_4$: C, 76.02; H, 8.98. Found: C, 75.79; H, 8.78. ESI-LCMS: *m/z* = 427.58 [M^+ + 1].

(29) Mandal, P. K.; McMurray, J. S. *J. Org. Chem.* **2007**, *72*, 6599.

(30) Vanderah, D. J.; Djerassi, C. *J. Org. Chem.* **1978**, *43*, 1442.

(31) **Hydrogenation of Compound 10**
To a stirred solution of compound **10** (0.100 g 0.24 mmol) in MeOH (4 mL) 10% Pd/C (0.015 g, 15% by weight) was added under an argon-filled balloon. Neat TES (0.4 mL, 2.4 mmol) was added dropwise to the reaction mixture. Within 10 min the reaction was complete. The reaction mixture was filtered through Celite, and the solvent was removed under

vacuum. The product was purified by column chromatography on silica gel (2% EtOAc–hexane) to furnish a mixture of compounds **11a**,**b** and **12a**,**b** (0.094 g). Catalytic hydrogenation of this mixture (0.094 g) was carried out using 10% Pd/C (0.009 g) at 3.1 bar, in 10 mL EtOAc at 30 °C for 10 h. The reaction mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure to obtain diastereomeric mixture of **12a/12b** (0.091 g) in 90% yield (Overall after 2 steps). Crystallization of the crude product from 10 mL MeOH–CH_2Cl_2 (9:1) gave major product C-20 (*R*)-ol, **12a** (0.063 g) in 62% yield and after several crystallization minor product C-20 (*R*)-ol **12b** (0.008 g) in 8% yield.

Methyl (20*R*)-3β-Acetoxychol-5-en-24-oate (12a)

Colorless solid; mp 160–162 °C; $[\alpha]_D^{26}$ ($CHCl_3$, *c* 2.0) –46.0. IR (mull): 1724 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.67 (s, 3 H, 18-CH_3), 0.92 (d, *J* = 6.3 Hz, 3 H, 21-CH_3), 1.01 (s, 3 H, 19-CH_3), 2.03 (s, 3 H, $OCOCH_3$), 3.66 (s, 3 H, $COOCH_3$), 4.60 (m, 1 H, 3-CH), 5.36 (d, *J* = 5.0 Hz, 1 H, 6-CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.8, 18.3, 19.3, 21.0, 21.4, 24.2, 27.7, 28.1, 31.0, 31.0, 31.8, 31.9, 35.3, 36.5, 37.0, 38.1, 39.7, 42.3, 50.0, 51.4, 55.7, 56.6, 73.9, 122.5, 139.6, 170.4, 174.7. Anal. Calcd for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.27; H, 9.71. ESI-LCMS: *m/z* = 431.62 [M^+ + 1].

(32) **Crystallographic Data for Compound 12a**

Empirical formula: $C_{27}H_{42}O_4$; formula weight: 430.61, temp, 297 (2) K, wavelength, 0.71073 A; crystal system; space group, monoclinic, P21; unit cell dimensions, *a* = 11.0178 (18) A, α = 90°, β = 7.4633 (13) A, β = 92.080 (3)°, *c* = 14.950 (3) A, γ = 90°; volume, 1228.5 (4) A^3, Z; calcd density, 2, 1.164 mg/m^3; absorption coefficient, 0.076 mm^{-1}, *F*(000) 472; crystal size, 0.40 × 0.29 × 0.03 mm; θ range for data collection 1.36–25.99°; limiting indices, –13< = h< = 13, –9< = k< = 9, –18< = l < = 17, reflections collected/unique 9650/4755 [*R*(int) = 0.0275]; completeness to θ = 25.99, 99.9%; absorption correction, semi-empirical from equivalents; max. and min. transmission 0.9977 and 0.9702; refinement method, full-matrix least-squares on F^2; data/restraints/ arameters, 4755/1/285; goodness-of-fit on F^2, 1.182; final *R* indices [I > 2σ(I)] *R*1 = 0.0655, *wR*2 = 0.1285, *R* indices (all data), *R*1 = 0.0784, *wR*2 = 0.1346; largest diff. peak and hole, 0.194 and –0.174 e A^{-3}. CCDC 725609 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Methyl (20*S*)-3β-Acetoxychol-5-en-24-oate (12b)

Colorless solid; mp 120–121 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.69 (s, 3 H, 18-CH_3), 0.85 (d, *J* = 4.0 Hz, 3 H, 21-CH_3), 1.02 (s, 3 H, 19-CH_3), 2.03 (s, 3 H, $OCOCH_3$), 3.67 (s, 3 H, $COOCH_3$), 4.63 (m, 1 H, 3-CH), 5.38 (d, *J* = 5.0 Hz, 1 H, 6-CH).