Concomitant Catalytic Transformations of Geminal Ethynyl and Hydroxy Groups of Steroids into Acetyl and Ester Functions with Retention of Configuration by $[Ru(\mu\text{-}O_2CH)(CO)_2(PPh_3)]_2$

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Steroids **1**, **2**, **3** containing both hydroxy and ethynyl groups at C(17) are selectively transformed by reaction with carboxylic acids, catalysed by $[Ru(\mu\text{-}O_2CH)(CO)_2(PPh_3)]_2$ complex, into β-oxopropyl esters **4**, **5**, **6** with retention of configuration.

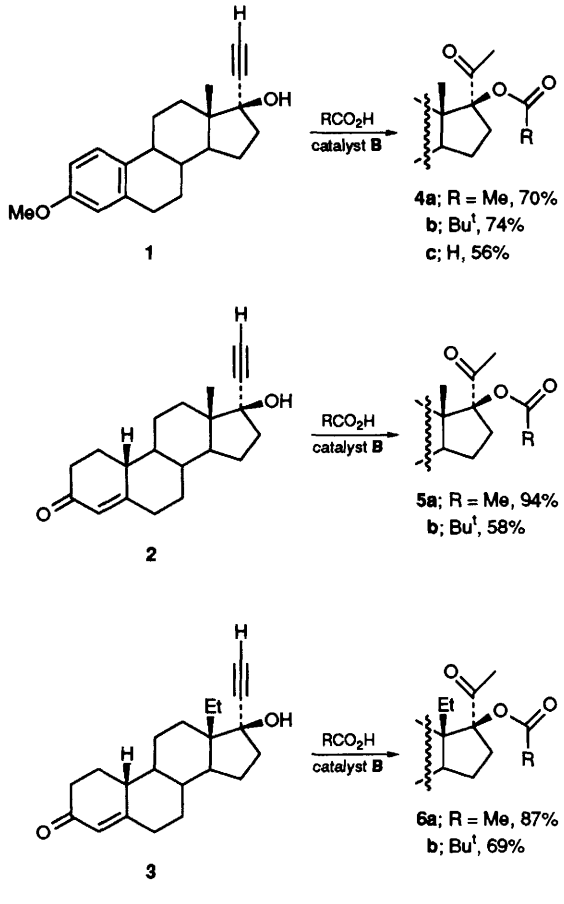
Stereoselective modifications of steroids play an important role in pharmaceutical chemistry as the nature of the side chain, associated with the suitable configuration at carbon C(17), modulates the biological activity of steroids.[1] Steroids having both ethynyl and hydroxy groups at carbon C(17) as in ring *D* of **I** are of special interest[2,3] not only for their specific properties but also as precursors, *via* side-chain modification, of drugs such as those containing the hydrocortisone skeleton and moiety **III**. It has been shown that prop-2-yn-1-ol, and its non sterically hindered 1,1-dimethyl derivative, could be selectively transformed into β-oxopropyl esters in the presence of $RuCl_2(PR_3)$(arene) complexes of type **A** but the stereochemistry of this reaction could not be established.[4] We now report that, whereas the complex $RuCl_2(PPh_3)$-(*p*-cymene) **A** appears inefficient with sterically hindered 1-hydroxy prop-2-yn-1-yl derivatives such as moiety **I** containing steroids, the binuclear complex $Ru_2(\mu\text{-}O_2CH)_2(CO)_4(PPh_3)_2$ **B** (*i*) is a powerful catalyst precursor for the selective addition of carboxylic acids to hindered steroids containing the moiety **I** and (*ii*) allows the stereospecific transformation of steroids of type **I** into their acetyl ester derivatives **II** in one step with retention of configuration at carbon C(17).

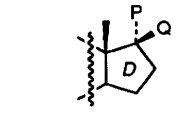
Mestranol **1** (1.6 mmol) and acetic acid (3 equiv.) in toluene in the presence of a catalytic amount of $RuCl_2(PPh_3)$-(*p*-cymene) **A** (16×10^{-3} mmol, 1 mol%) were heated at 90 °C. After 15 h, only 30% of compound **1** was converted. The same rection but in the presence of 8×10^{-3} mmol (0.5 mol%) of $Ru_2(\mu\text{-}O_2CH)_2(CO)_4(PPh_3)_2$ **B**[5] led, after 15 h, to a complete conversion of **1** and the isolation of **4a** in 70% yield.† In a similar way norethindrone **2** and levonorgestrel **3** were selectively transformed into acetates **5a** (94%) and **6a** (87%),† respectively (Scheme 1).

The addition of the bulky pivalic acid to steroids **1–3** is much slower, and the reaction with Bu^tCO_2H (1 equiv.) in the presence of catalyst **B** affords the pivalate derivatives **4b** (74%), **5b** (58%) and **6b** (69%)† after 42, 64 and 100 h of reaction at 90 °C in toluene, respectively (Scheme 1). Addition of formic acid to **1** in the presence of **B** allows the formation of **4c**† in 56% yield.

The ^1H NMR spectra of derivatives **4–6** showed the presence of only one stereoisomer as indicated by the C(17) α-acetyl, β-carboxylate and C(13) β-methyl or C(13) β-ethyl group proton resonances {**4a** (300.13 MHz, $CDCl_3$), δ: 2.13 (β-OCOMe), 2.10 [α-COMe(20)], 1.02 (β-Me)}. The ^1H NMR data easily show that the compounds **4a**,[6] **5a**,[7] **6a**[8] are identical to the known derivatives previously obtained by hydrolysis of the ethynyl group and do not contain their C(17) epimer, for instance δ 18-Me is 1.02 for **4a** and 0.69 for its C(17) epimer.[9] Thus, the overall transformation of **1–3** into **4–6** takes places with retention of configuration at C(17).

The transformations **1–3** → **4–6a,b** in the presence of the formate containing $[Ru_2(\mu\text{-}O_2CH)_2]$ complex **B** show that

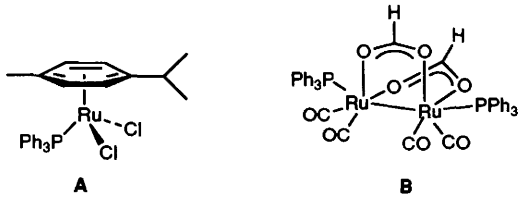




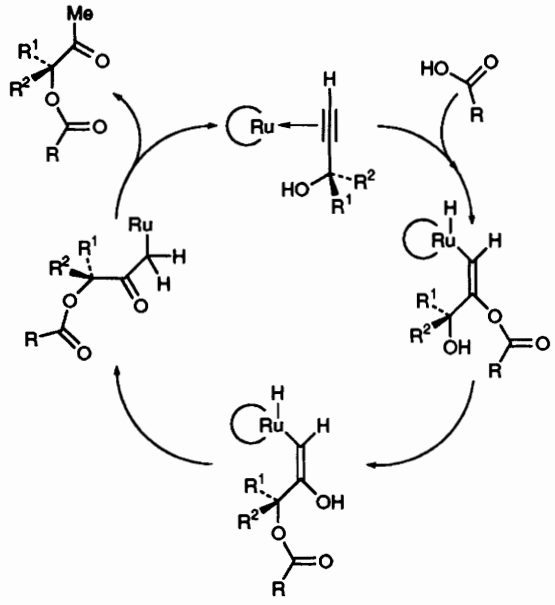
I P = ≡—H; Q = OH

II P = C(O)Me; Q = OC(O)R

III P = $C(O)CH_2OC(O)R^1$; Q = OH



Scheme 1 *Conditions*: **1**, **2** or **3** (1.6 mmol) in 5 ml of toluene, catalyst **B** (8×10^{-3} mmol, 0.5 mol%) at 90 °C; i, 3 equiv. acetic acid for 15 h; ii, 1 equiv. pivalic acid for 42 h **4b**, 64 h **5b** and 100 h **6b**; iii, 3 equiv. formic acid for 16 h



Scheme 2

there is no exchange between the external carboxylic acid (Bu^tCO_2H or $MeCO_2H$) and the bridging formate of **B** and thus that reaction does not proceed *via* insertion of the C≡C bond in the ruthenium–O_2CR bond. As ruthenium catalysts are known to promote the addition of carboxylic acids to C≡C bonds,[5,10] although it is not possible to precise the specific role of the binuclear system **B**, the retention of configuration **I** → **II** can be explained by addition of carboxylic acid to the ruthenium(II) activated C≡C bond, followed by intramolecular transesterification according to the proposed catalytic cycle (Scheme 2).

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Footnote

† Satisfactory elemental analyses were obtained for derivatives **4a–6b** and **4c**. Selected spectroscopic data for: **4a** IR (KBr) ν/cm^{-1} 1735 (s, νC=O ester), 1710 (s, νC=O ketone); ^{1}H NMR (300.13 MHz) δ 2.13 (s, 3H, $MeCO_2$), 2.10 (s, 3H, MeCO), 1.02 (s, 3H, ^{18}Me); MS *m/z* 370.214 (M^+); $C_{23}H_{30}O_4$ requires 370.2144. **5a**: IR (KBr) 1736 (s, νC=O ester), 1710 (s, νC=O ketone); ^{1}H NMR (300.13 MHz) δ 2.12 (s, 3H, $MeCO_2$), 2.05 (s, 3H, MeCO), 1.06 (s, 3H, ^{18}Me); MS *m/z* 358.215 (M^+); $C_{22}H_{30}O_4$ requires 358.2144. **6a**: IR (KBr) 1738 (s, νC=O ester), 1711 (s, νC=O ketone); ^{1}H NMR (300.13 MHz) δ 2.11 (s, 3H, $MeCO_2$), 2.04 (s, 3H, MeCO), 0.72 (t, 3H, ^3J 7.4 Hz, Me-$^{18}CH_2$); MS *m/z* 372.229 (M^+); $C_{23}H_{32}O_4$ requires 372.2300. **4b**: IR (KBr) 1739 (s, νC=O ester), 1728 (s, νC=O ketone); ^{1}H NMR (300.13 MHz) δ 2.00 (s, 3H, MeCO), 1.19 (s, 9H, Me_3C-CO_2), 0.99 (s, 3H, ^{18}Me); MS *m/z* 412.260 (M^+); $C_{26}H_{36}O_4$ requires 412.2613. **5b**; IR (KBr) 1735 (s, νC=O ester), 1728 (s, νC=O ketone), 1671 (vs, νC=O); ^{1}H NMR (300.13 MHz) δ 2.03 (s, 3H, MeCO), 1.26 (s, 9H, Me_3C-CO_2), 1.09 (s, 3H, ^{18}Me); MS *m/z* 400.261 (M^+); $C_{25}H_{36}O_4$ requires 400.2613. **6b**: IR (KBr) 1732 (s, νC=O ester), 1728 (s, νC=O ketone), 1671 (vs, νC=O); ^{1}H NMR (300.13 MHz); δ 1.95 (s, 3H, MeCO), 1.19 (s, 9H, Me_3C-CO_2), 0.73 (m, 3H, Me-$^{18}CH_2$); MS *m/z* 414.277 (M^+); $C_{26}H_{38}O_4$ requires 414.2770. **4c**: IR (KBr) 1710 (s, νC=O ester); ^{1}H NMR (300.13 MHz) δ 8.06 (s, 1H, CHO), 2.07 (s, 3H, MeCO), 0.99 (s, 3H, ^{18}Me); MS *m/z* 356.199 (M^+); $C_{22}H_{28}O_4$ requires 356.1988.

References

1 R. Wiechert, *L'actualité Chimique*, 1992, 221; D. M. Piatak and J. Wicha, *Chem. Rev.*, 1978, **78**, 199; M. Goodman and Gillman, *The Pharmacological Basis of Therapeutics*, seventh ed., MacMillan, New York, 1985, pp. 1360–1459.
2 J. Redpath and F. J. Zeelen, *Chem. Soc. Rev.*, 1983, **12**, 75.
3 B. M. Trost, R. J. Kulawiec and A. Hammes, *Tetrahedron Lett.*, 1993, **34**, 587; N. R. Schmuff and B. M. Trost, *J. Org. Chem.*, 1983, **48**, 1404.
4 D. Devanne, C. Ruppin and P. H. Dixneuf, *J. Org. Chem.*, 1988, **53**, 926.
5 M. Neveux, B. Seiller, F. Hagedorn, C. Bruneau and P. H. Dixneuf, *J. Organomet. Chem.*, 1993, **451**, 133.
6 K. Prezewowsky, R. Wiechert and W. Hohlweg, *Liebigs Ann. Chem.*, 1971, **752**, 68.
7 H. Hofmeister, K. Annen, H. Laurent and R. Wiechert, *Chem. Ber.*, 1978, **111**, 3086.
8 US Patent 4,029,777, *Schering AG.*, 1977.
9 P. Crabbe, A. Cruz and J. Iriarte, *Can. J. Chem.*, 1968, **46**, 349.
10 C. Bruneau, M. Neveux, Z. Kabouche, C. Ruppin and P. H. Dixneuf, *Synlett.*, 1991, 755.