Pergamon

Tetrahedron Letters 41 (2000) 389–392

TETRAHEDRON LETTERS

Glucuronide and sulfate conjugates of ICI 182,780, a pure anti-estrogenic steroid. Order of addition, catalysis and substitution effects in glucuronidation

John R. Ferguson,[a] John R. Harding,[b] Keith W. Lumbard,[a] Feodor Scheinmann [a] and Andrew V. Stachulski [a,*]

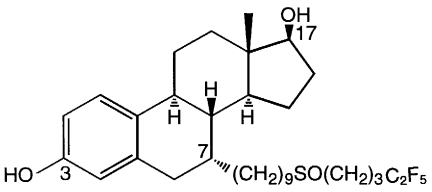
[a] *Ultrafine UFC Ltd, Synergy House, Guildhall Close, Manchester Science Park, Manchester M15 6SY, UK*
[b] *AstraZeneca Pharmaceuticals, Safety of Medicines Department, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK*

Received 6 August 1999; revised 26 October 1999; accepted 2 November 1999

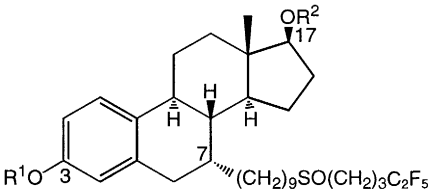
Abstract

The 3-sulfate **4** and 3- and 17-glucuronide conjugates **5** and **6** of the pure anti-estrogenic steroid ICI 182,780 **1**, which is expected to be an effective agent for the treatment of breast cancer, have been prepared. The synthesis of **6** could only be satisfactorily achieved using an inverse addition technique, not previously employed in the glucuronic acid series: the value of this technique for some other aglycones is discussed.

The 7α-substituted estradiol derivative, ICI 182,780 (7α-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)-nonyl]estra-1,3,5,(10)-triene-3,17β-diol) **1**, is a pure receptor antagonist of estrogen[1] and should be an effective treatment for estrogen dependent breast cancer[2] and non-malignant estrogen dependent conditions.



1



2 R^1 = H, R^2 = $COCH_3$

3 R^1 = PhCO, R^2 =H

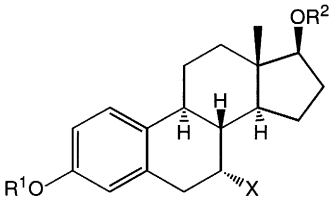
As part of a continuing programme to define the metabolism and distribution of **1** in animals and man, a number of putative metabolites, in particular the 3-sulfate, 3-glucuronide and 17-glucuronide,

* Corresponding author.

0040-4039/00/$ - see front matter
PII: S0040-4039(99)02067-5

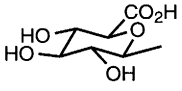
were required as metabolic standards. This paper both describes the efficient syntheses of the above metabolites and presents a study of the scope of an inverse addition technique applied to glucuronidation.

Acid-catalysed transesterification of **1** (EtOAc, tosic acid)[3] delivered the 17-acetate **2** which was a suitable protected version for the synthesis of the 3-sulfate **4** (using $Et_3N \cdot SO_3$)[4] and the 3-glucuronide **5** (using imidate **7**); [5,6] full details will be published later. Synthesis of the 17-glucuronide **6**, however, from the 3-benzoate **3** (**1**+PhCOCl, CH_2Cl_2, aq. KOH) proved much more difficult.

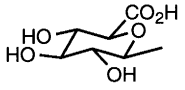


X = as **1** in all cases.

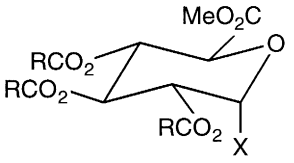
4 $R^1 = HO_3S$, $R^2 = H$



5 R^1 = , $R^2 = H$



6 $R^1 = H$, R^2 =

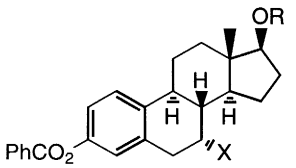


7 R = CH_3, X = OC(=NH)CCl_3

8 R = CH_3, X = Br

9 R = ^{i}Pr, X = OC(=NH)CCl_3

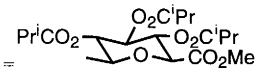
Reaction of the 3-benzoate **3** with **7** using 1.5 equiv. of $BF_3 \cdot Et_2O$ (this unusually large quantity of catalyst was required during the synthesis of **5** also: we assume the first equivalent binds strongly to the sulfoxide) gave almost entirely the 17-acetate **10** with no detectable glucuronide. It had been reported[7] that reaction of a 3-protected androstane-3,17-diol derivative with **7** gave only 8% of the desired 17-glucuronide, though in that case a Koenigs–Knorr reaction with bromosugar **8** and Ag_2CO_3 gave a 34% yield. We obtained no glucuronide on reaction of **3** with **8** and Ag_2CO_3; when $CdCO_3$[8] was used as catalyst, an orthoester was produced in 75% yield [δ_H, inter alia, 1.8 (3H, s) and 5.9 (1H, d)]. Attempted acid-catalysed rearrangement of the orthoester led only to decomposition.



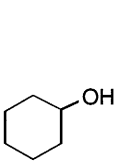
X = as **1** in all cases

10 R = $COCH_3$

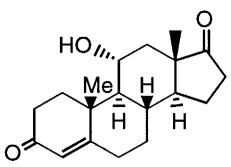
11 R = $COPr^i$



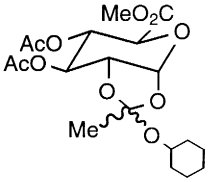
12 R =



13



14



15

$Ph(CH_2)_2OH$

16

Even when the tri-isobutyryl imidate **9** [9,10] was used, the transacylated compound **11** was still by far the major product, with just 7% of the desired conjugate **12** being formed. At this point, however, we found that the order of addition had a profound influence on the course of this reaction. *When **9** was added slowly to a solution of **3** and 1.5 equiv. $BF_3 \cdot Et_2O$ in 1,2-dichloroethane at −15°C, rather than adding $BF_3 \cdot Et_2O$ to **3**+**9**, the desired conjugate **12** was obtained in 50% yield after chromatography with **11** now*

a minor by-product (15%). Schmidt has noted[11] a similarly advantageous inverse addition when using a much more reactive donor (sc. a fucosyl imidate). Finally, hydrolysis of **12** was performed using NaOH in aq. *i*-PrOH and **6** was isolated as its sodium salt, followed by reverse-phase silica chromatography to give material of >98% purity as assayed by analytical reverse-phase HPLC. Characterisation by ^{1}H NMR (300 MHz), negative-ion mode electrospray (ES) and positive-ion mode fast-atom bombardment (FAB) MS confirmed the structure.[12]

The value of the inverse addition technique was further studied using other alcohols. In the case of cyclohexanol **13**, using either imidate **7** or **9** with 0.5 equiv. $BF_3 \cdot Et_2O$, the inverse addition gave a slightly but consistently higher yield, although not nearly so dramatic as with **3** (Table 1). Using either normal or inverse addition, **9** gave double the yield of **7**. Another steroidal aglycone, 11α-hydroxyprogesterone **14**, gave a vastly better yield by the inverse technique. It appears likely that the effect is most pronounced with aglycones bearing groups such as C=O and S=O which can strongly complex the Lewis acid: we note this was the case in Schmidt's example cited above.

Table 1
Glucuronidation of alcohols using the normal (method **A**) and inverse (method **B**) procedures (see text). [a]Using 1.5 equiv. imidate. [b]Using 1 equiv. imidate

Alcohol	Imidate	Method	Yield of glucuronide%
3	**9**[a]	**A**	7
3	**9**[a]	**B**	50
13	**7**[b]	**A**	18
13	**7**[b]	**B**	24
13	**9**[b]	**A**	39
13	**9**[b]	**B**	49
14	**9**[a]	**A**	31
14	**9**[a]	**B**	77
16	**7**[b]	**A**	27
16	**9**[b]	**A**	57

In the case of a primary alcohol, 2-phenylethanol **16**, the inverse method offered no advantage but again the tri-isobutyryl imidate **9** was greatly superior to the tri-acetyl imidate **7** by virtue of reduced transacylation.[10]

When only 0.2 equiv. $BF_3 \cdot Et_2O$ was used in the reaction of **13** with **9**, considerable amounts of the orthoester **15** resulted in addition to the glucuronide even when the inverse technique was used. Prolonged reaction (40 h) with addition of further catalyst gave steady conversion of **15** to glucuronide in a virtually identical yield (51%) to that obtained before. Using $ZnCl_2$ (0.5 equiv.), **15** was the major product in the early stages: after prolonged reaction the glucuronide was obtained in satisfactory (39%) yield. With the stronger Lewis acid catalyst trimethylsilyl trifluoromethanesulfonate (TMSOTf, 0.25 equiv.), 'inverse' reaction of **13** with **9** was complete in <1 h at −10°C and the glucuronide was isolated in 52% yield with no orthoester seen.

We conclude that order of addition, catalyst and acyl substitution are all important variables in the trichloroacetimidate glucuronidation of alcohols and that the inverse addition technique may offer a significant advantage, particularly for complex aglycones.

Acknowledgements

We are grateful to Dr. G. Robinson (Process Development Department, AstraZeneca Pharmaceuticals) for valuable technical discussions on the chemistry of **1**, to Mr. I. Cumpstey (St. John's College, Oxford) for skilled experimental assistance and to Mrs. V. Boote (University of Manchester) for high-resolution MS in the FAB mode.

References

1. Wakeling, A. E.; Bowler, J. *J. Steroid Biochem. Mol. Biol.* **1992**, *43*, 173.
2. DeFriend, D. J.; Howell, A.; Nicholson, R. I.; Anderson, E.; Dowsett, M.; Mansell, R. E.; Blamey, A. W.; Bundred, N. J.; Robertson, J. F.; Saunders, C.; Baum, W.; Walton, P.; Sutcliffe, F.; Wakeling, A. E. *Cancer Res.* **1994**, *54*, 408.
3. Tsuneda, K.; Yamada, J.; Yasuda, K.; Mori, H. *Chem. Pharm. Bull. Jpn.* **1963**, *11*, 510.
4. Dusza, J. P.; Joseph, J. P.; Bernstein, S. *Steroids* **1968**, *12*, 49.
5. Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21.
6. Brown, R. T.; Scheinmann, F.; Stachulski, A. V. *J. Chem. Res. (S)* **1997**, 370.
7. Rao, P. N.; Rodriguez, A. M.; Miller, D. W. *J. Steroid Biochem.* **1986**, *25*, 417.
8. Conrow, R. B.; Bernstein, S. *J. Org. Chem.* **1971**, *36*, 863.
9. Brown, R. T.; Mayalarp, S. P.; McGown, A. T.; Hadfield, J. A. *J. Chem. Res. (S)* **1993**, 496.
10. Brown, R. T.; Carter, N. E.; Lumbard, K. W.; Scheinmann, F. *Tetrahedron Lett.* **1995**, *36*, 8661.
11. Schmidt, R. R.; Toepfer, A. *Tetrahedron Lett.* **1991**, *32*, 3353.
12. Selected spectroscopic data for **6**: δ_H (300 MHz, CD_3OD) 0.88 (3H, s, 18-CH_3), 3.65 (1H, d, 5′-H), 3.85 (1H, t, 17-H), 4.40 (1H, d, J 8 Hz, 1′-H), 6.46 (1H, d, 4-H), 6.53 (1H, dd, 2-H) and 7.08 (1H, d, 1-H); *m/z* (ES −ve mode) 781 (M−Na, 100%). Found (FAB +ve mode): *m/z*, 827.3207. $C_{38}H_{54}F_5Na_2O_9S$ requires: MNa^+, 827.3191. Consistent 300 MHz ^1H NMR and high resolution FAB mass spectra were also obtained for **4** and **5**.