Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 1067–1068

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis of FF-MAS from Lithocholic Acid

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Received 14 January 2000; accepted 9 March 2000

Abstract—An effective synthesis of 4,4 dimethyl-cholest-8,14,24-trien-3β-ol (FF-MAS) from lithocholic acid is described, utilising a double oxidation and regioselective Wittig reaction as key steps. © 2000 Elsevier Science Ltd. All rights reserved.

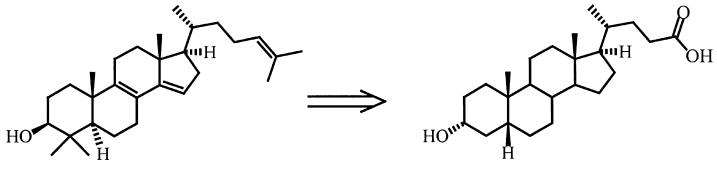
During ongoing research into compounds affecting meiosis it was our goal to find a suitable synthetic route for the synthesis of additional quantities of 4,4-dimethyl-cholest-8,14,24-trien-3β-ol (**1**) (FF-MAS), a naturally occurring sterol isolated from human follicular fluid, and reported from our laboratories[1] to have a positive meiosis inducing effect on immature mouse oocytes.

Successful approaches to FF-MAS have been reported by Dolle et al.,[2] and more recently by Schroepfer et al.[3] However, after initial attempts to follow the former route we found some of the synthetic steps problematic in our hands. As a result of our efforts in finding an alternative route, we report here the synthesis of FF-MAS from lithocholic acid.

Lithocholic acid was transformed in five steps[4] to ester **2**, which was reduced with lithium aluminium hydride to afford the corresponding diol in 97% yield, and protected (92%) as the di-TBS ether **3**. To provide a suitable precursor to the required delta-8, delta-14 diene system, further unsaturation to give delta-7 was introduced via an allylic bromination/elimination sequence[5] using 1,3-dibromo-5,5-dimethyl hydantoin followed by quinaldine, affording diene **4** in 48% yield. Exposure of **4** to HCl in refluxing methanol induced deprotection of both silyl groups and concomitant isomerisation to the required 8,14 diene system giving **5** in 55% yield (Scheme 1).

Attempts to selectively oxidise the primary side chain alcohol in **5** proved ineffective using either Swern, conventional chromium or ruthenium reagents, with irreproducible and generally low conversion to **7**. In each case competitive dioxidation to keto aldehyde **6** usually predominated, and since the subsequent Wittig step on **7** to give FF-MAS was also low yielding, we decided therefore to utilise the 3-keto aldehyde **6** and investigate the feasability of a regioselective Wittig reaction. Diol **5** was smoothly oxidised with TPAP/NMO[6] in 70% yield to **6**, and the homologation step proceeded in 50% yield to afford the complete sterol side chain. A final reduction at C-3 with lithium aluminium hydride afforded FF-MAS (**1**) in 72% yield[7] (Scheme 1), which was identical to that isolated from the natural source.[1a]

In summary, we have developed an effective synthesis of FF-MAS from lithocholic acid, which allows access to gram quantities of the endogenous ligand. Further synthesis of meiosis activating sterols[8] analogous to FF-MAS will be reported in due course.



FF-MAS (**1**) Lithocholic acid

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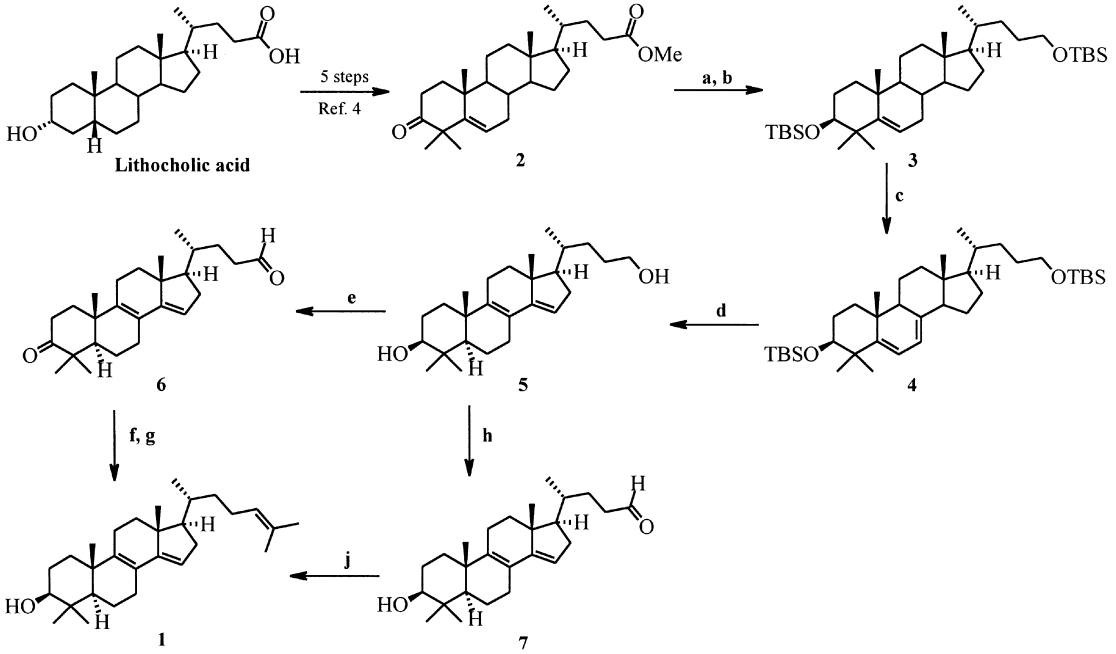
PII: S0960-894X(00)00160-8



Scheme 1. Reagents and conditions: (a) $LiAlH_4$, THF (97%); (b) TBSCl, imidazole, DMF (92%); (c) (i) dimethyl bromohydantoin, hexane/benzene (48%); (ii) quinaldine/*o*-xylene (80%); (d) HCl, EtOH, benzene (55%); (e) TPAP, NMO, DCM (70%); (f) Me_2CHPPh_3I, BuLi, THF (50%); (g) $LiAlH_4$, THF (72%); (h) $(PPh_3)_3RuCl_2$, benzene (30-60%); (j) as for f (19%).

Acknowledgements

We thank Jens Breinholdt for NMR and HLPC assistance.

References and Notes

1. (a) Byskov, A. G.; Andersen, C. Y.; Nordholm, L.; Thøgersen, H.; Guoliang, X.; Wassman, O.; Andersen, J. V.; Guddal, E.; Roed, T. *Nature* **1995**, *374*, 559. (b) Grøndal, C.; Ottesen, J. L.; Lessl, M.; Faarup P.; Murray, A.; Grønvald, F, C.; Hegle-Hartung, C.; Ahnfelt-Rønne, I. *Biology of Reproduction* **1998**, *58*, 1297.
2. (a) Dolle, R. E.; Schmidt, S. J.; Erhard, K. F.; Kruse, L. I. *J. Am. Chem. Soc*. **1989**, *111*, 278. (b) Dolle, R. E; Kruse, L. I *J. Org. Chem*. **1986**, *51*, 4047.
3. (a) Ruan, B.; Wilson, W. K.; Schroepfer, G. J. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 233. (b) Ruan, B.; Watanabe, S.; Eppig, J. J.; Kwoh, C; Dzidic, N; Pang, J; Wilson, W. K.; Schroepfer, G. *J. Lipid Research* **1998**, *39*, 2005.
4. Aranda, G.; Fetizon, M.; Tayeb, N. *Tetrahedron* **1987**, *43*, 4147.
5. Prelle, A.; Winterfeldt, E. *Heterocycles* **1989**, *28*, 333.
6. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* 1994, 641.
7. Physical data: **6**, mp 96.5–97 °C. ^{1}H NMR ($CDCl_3$, 300 MHz); 9.79 (1H, s, CHO), 5.40 (1H, s, H-15), 1.10 and 1.04 (3H each, s, CH_3-4α and 18), 0.93 (3H, d, $J=6$ Hz, CH_3-20), 0.82 (6H, s, CH_3-4β and 19), 2.6.8 (m, remaining H).^{13}C NMR ($CDCl_3$, 75 MHz); 218.1 (C-3), 203.3 (C-24), 151.1 (C-8), 140.3 (C-9), 126.2 (C-14), 118.2 (C-15), 57.3, 51.3, 47.6, 45.5, 41.3, 38.0, 37.4, 36.7, 36.2, 34.8, 34.0, 28.2, 28.1, 27.2, 21.8, 21.3, 20.5, 19.9, 19.0, 16.1. Anal. calcd for $C_{26}H_{38}O_2$: C, 81.62; H, 10.01. Found: C, 81.85; H, 10.56. MS: calcd for $C_{26}H_{38}O_2$: 382.6. Found: 382.3.

1, mp 126.5.5°C. ^{1}H NMR ($CDCl_3$, 300 MHz); 5.35 (1H, s, H-15), 5.10 (1H, t, $J=6$ Hz, H-24), 3.22 (1H, dd, $J=12$, 5 Hz, H-3), 1.69 and 1.61 (3H each, s, CH_3-26 and 27), 1.04 and 1.02 (3H each, s, CH_3-4α and 18), 0.94 (3H, d, $J=6$ Hz, CH_3-20), 0.83 and 0.80 (3H each, s, CH_3-4β and 19), 2.4.8 (m, remaining H). ^{13}C NMR ($CDCl_3$, 75 MHz) 151.4 (C-8), 142.1(C-9), 131.3 (C-25), 125.5 (C-14), 123.2 (C-24), 117.7 (C-15), 79.0 (C-3). Anal. calcd for $C_{29}H_{46}O$: C, 84.81; H, 11.29. Found: C, 84.72; H, 11.75. MS: calcd for $C_{29}H_{46}O$: 410.7. Found: 411.
8. For an initial publication see Wenckens, M.; Grønvald, F.; Bondo Hansen, J. *Acta Chem. Scand*. **1998**, 52, 503.