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A concise synthesis of the steroidal core of clathsterol

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ABSTRACT

The protected steroidal core of clathsterol, a marine natural product with remarkable inhibitory activity against HIV-1 reverse transcriptase, was synthesized starting from readily available tigogenin. The synthetic strategy involved three key reactions: abnormal Baeyer–Villiger rearrangement of the spiroketal of tigogenin, xanthation of steroidal 16-hydroxyl-22-carboxylate dianion and regioselective epoxide-opening lactonization.

In 2001, Kashman and his co-workers isolated a novel sterol sulfate, clathsterol (**1**, Scheme 1), from the Red Sea sponge *Clathria* sp.[1] It can inhibit human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) at a concentration of 10 μM. The basic structure of clathsterol was established by spectral data and a chemical transformation. However, the stereochemistry of C-22, C-23 and C-24 in its side chain has not been assigned due to conformational lability.

Intrigued by its potent biological activity, low abundance and unique structure, along with our perennial interest in the synthesis of steroidal natural products,[2] we first investigated the synthesis of its steroidal core (**2**, Scheme 1) as a part of our project toward the synthesis, structural determination and biological evaluation of clathsterol. Target molecule **2** bears all functional groups of the steroidal core of clathsterol with right configuration, and its 16,22-lactone moiety could serve as the precursor for the construction of the side chain.[3]

Our retrosynthetic analysis of compound **2** is illustrated in Scheme 1. The 2β,3α-dihydroxy group can be constructed by acid-catalyzed ring opening of the corresponding epoxide **3** according to the Fürst–Plattner rule.[4] Compound **3** in turn can be synthesized from acid **4** via epoxidation and regioselective intramolecular epoxide-opening reaction. The Δ^{15} double bond of **4** would be formed regioselectively by Chugaev elimination of the C-16 xanthate of **5**. Compound **5** would be prepared from tigogenin via regioselective degradation[5] of the E/F rings followed by elimination of the C-3 hydroxyl group.

The synthesis of the target molecule **2** is described in Scheme 2. Tigogenin is a best choice as the starting material because it not only is cheap and readily available but also possesses the basic skeleton and requisite functional groups for the synthesis of clathsterol. Mesylation of **6** with MsCl afforded mesylate **7** in quantitative yield, which realized the protection of the C-3 hydroxy group and the preparation of the precursor for constructing the Δ^2 double bond at the same time. Mesylate **7** was degradated regioselectively to the corresponding 16,22-γ-lactone **8** in 78% yield by utilizing abnormal Baeyer–Villiger reaction of steroidal sapogenins found by our group.[5] Elimination of the C-3 mesyl group of lactone **8** with lithium bromide in DMF at 120 °C provided the desired Δ-2 alkene **5** and its regioisomer Δ-3 alkene in 98% combined yield in a ratio of 11.5:1 according to ^{1}H NMR analysis. A similar reaction result has been reported by Takatsuto and Ikekawa in 1986.[6] The mixture of isomers was employed in the following steps because they were inseparable. Treatment of alkene **5** with NaOH in aqueous MeOH gave the corresponding sodium salt **9** quantitatively.

With compound **9** in hand, we set out to explore the preparation of 16-xanthate-22-acid **10**. Compared with other alcohols,[7] xanthation of the C-16 hydroxyl group of **9** proved to be much harder due to the effect of its C-22 carboxy group. After repeated try, however, we finally synthesized the desired 16-xanthate-22-acid **10** in 51% yield (brsm 61%) and its 22-acid ester **10a** as the major by-product in 14% yield (brsm 16%) by increasing the reaction temperature to 80 °C and adding excess reagents. Chugaev *syn*-elimination of **10** at 160 °C in free solvent system provided diene **4** in 95% yield. Compound **4** could also be prepared from **10a** via pyrolysis followed by hydrolysis in 89% yield over two steps. Epoxidation of diene **4** with *m*-CPBA in CH_2Cl_2 resulted in the formation of diepoxide **11**, which is unstable and can transformed into lactone **3** and **3a** partially when purified on silica gel column chromatography. The attempts to convert diepoxide **11** into **3** by adding various acids such as PTSA, CSA and $BF_3{\cdot}Et_2O$ or bases such as NaH, LiOH and $LiOH/H_2O_2$ were all unsuccessful.[8]

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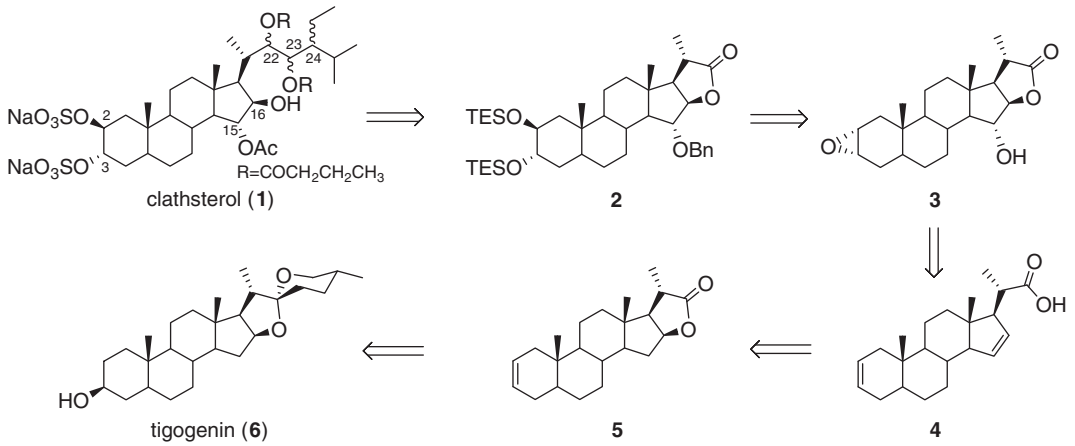
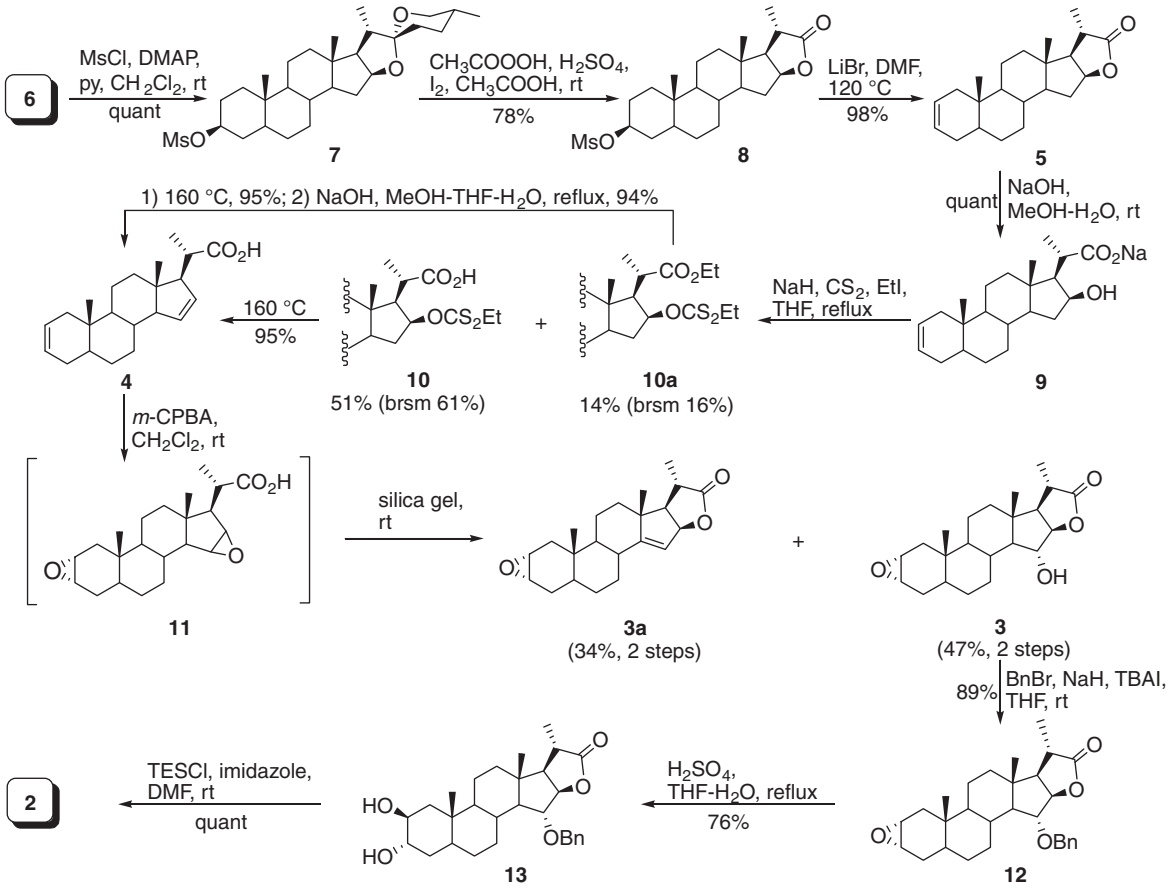


Scheme 1. Retrosynthetic analysis of the steroidal core of clathsterol.



Scheme 2. Synthesis of compound **2**.

The reaction system became quite complex when these acids were used, while no reaction occurred under basic conditions. Finally, this problem was solved by adsorbing crude **11** on excess silica gel (w/w = 1/10) at room temperature for two days to furnish the desired lactone **3** in 47% yield over two steps along with Δ-14 alkene **3a** as a serious side product in 34% yield over two steps. The α configuration of the 2,3-epoxide was assigned due to the presence of the C-19 angular methyl group which blocks the β-face of the A ring when the Δ^2 double bond of **4** was epoxidized.[9] The coupling constant between 15-H and 14-H in **3** is 10.5 Hz, which shows the 15-H should be in β position. Through further observation, it was found that the ratio of **3** and **3a** was not related to the reaction time. These facts suggest us that **11** is a mixture of 15α,16α- and 15β,16β-epoxide.[10] Compound **3a** is considered to be generated from 15β,16β-epoxide and could also be used to synthesize the target molecule **2**.[11] Benzyl protection of the C-15 hydroxy group of lactone **3** took place readily in the presence of tetrabutylammonium iodide (TBAI) to afford ether **12** in 89% yield.

Treatment of **12** with sulfuric acid in aqueous THF at reflux for one hour provided the desired 2β,3α-diol **13** exclusively[12] according to the Fürst–Plattner rule. The ^{1}H NMR signals of 2-H and 3-H in **13** (broad singlet at 3.88 ppm and broad singlet at 3.84 ppm) also confirm that C-2 hydroxy group and C-3 hydroxy group are situated in the axial positions. Protection of the resulting hydroxy groups as the triethylsilyl (TES) ethers finished the synthesis of **2**.

In summary, the protected steroidal core of clathsterol **2** has been synthesized in 12% overall yield over 11 steps starting from tigogenin. This concise synthesis involves the following three key points: (1) applying abnormal Baeyer–Villiger rearrangement of steroidal sapogenin to the synthesis of the steroidal core of clathsterol for the first time; (2) successful preparation of the C-16 xanthate of steroidal 16-hydroxyl-22-carboxylate dianion and successive regioselective construction of its Δ^{15} double bond through Chugaev elimination; and (3) regioselective intramolecular epoxide-opening lactonization catalyzed by silica gel. It is also noteworthy to mention here that all the newly-built stereocenters of **2** were constructed skillfully relying on substrate control without using any chiral catalysts in this synthesis.

Supplementary data

Supplementary data (experimental procedures, analytical data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.072.

References and notes

1. Rudi, A.; Yosief, T.; Loya, S.; Hizi, A.; Schleyer, M.; Kashman, Y. *J. Nat. Prod.* **2001**, *64*, 1451–1453.
2. (a) Zhu, Z.; Tian, W.; Liao, Q. *Tetrahedron Lett.* **1996**, *37*, 8553–8556; (b) Tian, W.; Zhu, Z.; Liao, Q.; Wu, Y. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1949–1952; (c) Xu, Q.; Peng, X.; Tian, W. *Tetrahedron Lett.* **2003**, *44*, 9375–9377.
3. For two examples of using steroidal 16,22-lactone to introduce the side chain, see: (a) Wojtkielewicz, A.; Długosz, M.; Maj, J.; Morzycki, J. W.; Nowakowski, M.; Renkiewicz, J.; Strnad, M.; Swaczynová, J.; Wilczewska, A. Z.; Wójcik, J. *J. Med. Chem.* **2007**, *50*, 3667–3673; (b) Jiang, B.; Shi, H.; Tian, W.; Zhou, W. *Tetrahedron* **2008**, *64*, 469–476.
4. Fürst, A.; Plattner, P. A. *Helv. Chim. Acta* **1949**, *32*, 275–283.
5. (a) Li, M. Doctoral Dissertation of Shanghai Institute of Organic Chemistry, Shanghai, China, 2001.; (b) Tian, W.; Li, M.; Yin, H.; Tang, X. Chinese Patent CN 1299821 (A), 2001; *Chem. Abstr.* **2003**, *136*, 340870.
6. Takatsuto, S.; Ikekawa, N. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2269–2272.
7. (a) Nakagawa, H.; Sugahara, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 3181–3183; (b) Meulemans, T. M.; Stork, G. A.; Macaev, F. Z.; Jansen, B. J. M.; Groot, A. *J. Org. Chem.* **1999**, *64*, 9178–9188.
8. (a) Paquette, L. A.; Sturino, C. F.; Wang, X.; Prodger, J. C.; Koh, D. *J. Am. Chem. Soc.* **1996**, *118*, 5620–5633; (b) Marcos, I. S.; Moro, R. F.; Carballares, M. S.; Urones, J. G. *Synlett* **2000**, 541–543; (c) Morzycki, J. W.; Gryszkiewicz, A.; Jastrzebska, I. *Tetrahedron Lett.* **2000**, *41*, 3751–3754.
9. (a) Pataki, J.; Rosenkranz, G.; Djerassi, C. *J. Am. Chem. Soc.* **1951**, *73*, 5375–5377; (b) Comin, M. J.; Elhalem, E.; Rodriguez, J. B. *Tetrahedron* **2004**, *60*, 11851–11860.
10. (a) Williams, J. R.; Chai, D.; Bloxton, J. D., II; Gong, H.; Solvibile, W. R. *Tetrahedron* **2003**, *59*, 3183–3188; (b) Kabat, M. M. *J. Org. Chem.* **1995**, *60*, 1823–1827.
11. For two examples of using steroidal Δ-14 double bond to introduce the corresponding C-15α hydroxy group, see: (a) Gong, H.; Williams, J. R. *Org. Lett.* **2006**, *8*, 2253–2255; (b) Jung, M. E.; Johnson, T. W. *J. Am. Chem. Soc.* **1997**, *119*, 12412–12413.
12. Voigt, B.; Porzel, A.; Adam, G.; Golsch, D.; Adam, W.; Wagner, C.; Merzweiler, K. *Collect. Czech. Chem. Commun.* **2002**, *67*, 91–102.