J.Serb.Chem.Soc. *69*(5)349–351(2004) UDC 547.932+542.913
JSCS – 3161 *Note*

N O T E

Synthesis of 3α,12α-dihydroxy-23a,23b-dihomo-5β-cholan-24-oic acid

VERA ĆIRIN-NOVTA*#, KSENIJA KUHAJDA*#, JULIJAN KANDRAČ**# and SLAVKO KEVREŠAN**#

**Department of Chemistry, Faculty of Science, Trg Dositeja Obradovića 3, 21000 Novi Sad and **Faculty of Agriculture, Trg Dositeja Obradovića 3, 21000 Novi Sad, Serbia and Montenegro*

(Received 8 September, revised 1 December 2003)

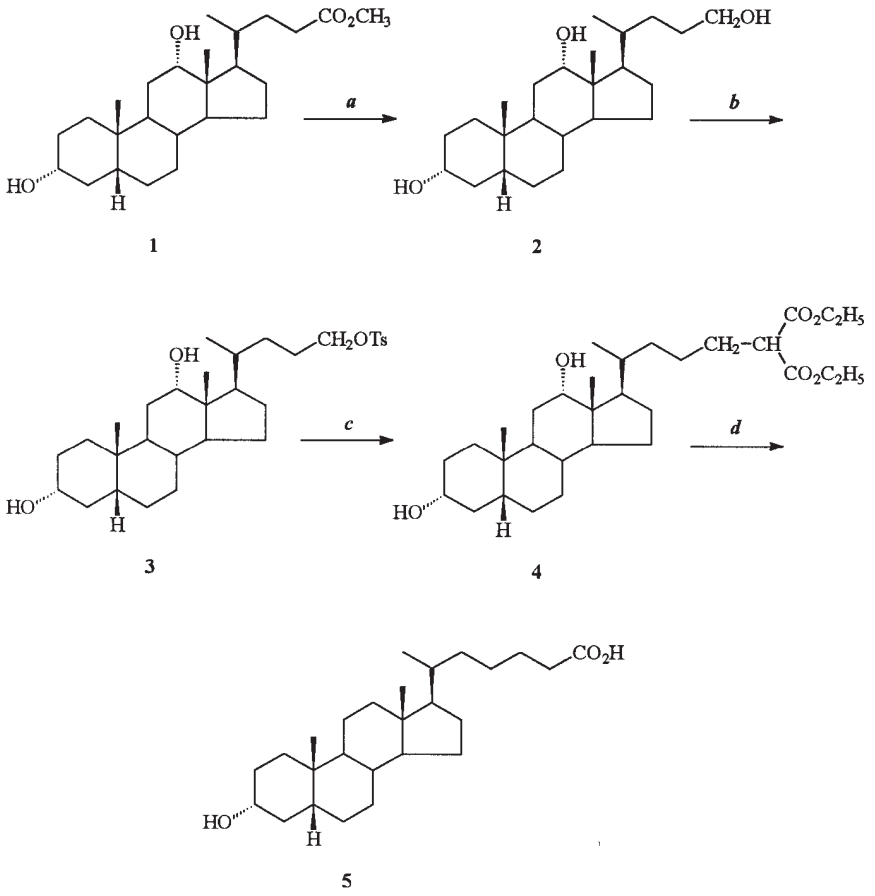
Abstract: A novel multi-step synthesis of 3α,12α-dihydroxy-23a,23b-dihomo-5β-cholan-24-oic acid (23a,23b-dihomodeoxycholic acid) (**5**) has been achieved from methyl 3α,12α-dihydroxy-5β-cholanoate (**1**). Reduction of compound **1** with $LiAlH_4$ in dry ether gave the corresponding alcohol **2** in 83 % yield. Selective esterification of compound **2** with tosyl chloride in dry piridine at 0–5 ºC for 12 h afforded the 3α,12α-dihydroxy-5β-24-cholanyl tosylate (**3**) in 64 % yield. The reaction of the tosyl derivative **3** with sodium diethyl malonate gave compound **4** which was first subjected to hydrolysis under basic conditions, followed by decarboxylation under acidic conditions to afford 3α,12α-dihydroxy-5β-23a,23b-dihomocholan-24-oic acid in 84 % yield.

Keywords: 26-homodeoxycholic aicd, bile acids.

In the commercial synthesis of corticosteroids, the starting material is usually cholic or deoxycholic acid, both readily available from bovine bile. A key reaction in these syntheses is the shortening of the side chain by three carbon atoms. For given reasons, many scientific papers in the chemical literature are devoted to this problem.[1] With the aim of studying the biosynthesis and metabolism of bile acids, 23a-homo and 23a,23b-dihomocholanoic acids were synthesized starting from selected natural (C 24) bile acids.[2–4] Further, using the Arndt-Eister's reaction, deoxycholic acid may be converted into 3α,12α-dihydroxy-5β-cholane-24-carboxylic acid.[5]

In this paper, the synthesis of 3α,12α-dihydroxy-23a,23b-dihomo-5β-cholan-24-oic acid (**5**) starting from methyl 3α,12α-dihydroxy-5β-cholanoate[6] (**1**) (Scheme 1), whereby the deoxycholic acid side chain was extended by two additional carbon atoms, is reported.

* Corresponding author.
\# Serbian Chemical Society active member.



Scheme 1. a) $LiAlH_4$, Et_2O, reflux; 8 h; b) TsCl, Py, 0 ºC, 12 h; c) $NaCH(CO_2Et)_2$, EtOH, reflux, 5 h; d) KOH, pH = 11, reflux, 12 h; then H_2SO_4, pH = 1, reflux, 5 h.

Reduction of methyl 3α,12α-dihydroxy-5β-cholanoate (**1**) was achieved with $LiAlH_4$ in dry ether, at reflux temperature for 8 h. The corresponding alcohol **2** was isolated after purification on a column of silica gel (CH_2Cl_2 : Me_2CO 7 : 3), as a colorless oil in 83 % yield. [IR (film): 3550–3300, 2960, 2850, 1380, 1050 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 0.69 (*s*, 3H, H-18), 0.91 (*s*, 3H, H-19), 1.01 (*d*, J = 6.0 Hz, 3H, H-21), 3.45 (*m*, 1H, H-3), 3.63 (*m*, 2H, H-24), 4.00 (*m*, 1H, H-12). ^{13}C-NMR (DMSO-d_6): 71.5 (C-12); 70.4 (C-3), 61.5 (C-24), 23.0 (C-21), 17.4 (C-19), 12.5 (C-18)].[7]

Selective tosylation of the primary hydroxyl group was carried out by treatment of alcohol **2** with tosyl chloride in pyridine at 0 ºC for 12 h. After purification on a silica gel column (EtOAc : toluene 1:1), the 3α,12α-dihydroxy-5β-24-cholanyl tosylate was obtained in 64 % yield. [IR(film): 3480, 2960, 2880, 1600, 1380, 1180, 1050 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.63 (*s*, 3H, H-18), 0.96 (*s*, 3H, H-19), 0.99 (*d*, J = 6.0 Hz, 3H, H-21), 2.45 (*s*, 3H, Me$C_6H_4SO_2$), 3.50 (*m*, 1H, H-3), 4.00 (*m*,

2H, H-24), 4.20 (*m*, 1H, H-12), 7.25 and 7.80 (4H, Ts). ^{13}C-NMR ($CDCl_3$): 144.59, 133.21, 129.76, 127.83 (C-Ar), 73.10 (C-12), 71.77 (C-3), 23.09 ($\underline{Me}C_6H_4SO_2$), 21.61 (C-21), 17.39 (C-19), 12.65 (C-18)].

Nucleophilic displacement of the tosyloxy function in **3** with the diethyl malonate anion gave the intermediate **4**, which was successively treated with boiling aqueous KOH for 12 h, then with aqueous H_2SO_4 at reflux temperature for 5 h, to accomplish decarboxylation. Crude product **5** was purified on a silica gel column (EtOAc : cyclohexane 2:1), to afford the 3α,12α-dihydroxy-23a,23b-dihomo-5β-cholan-24-oic acid in 84 % yield (m.p. 173 ºC, from benzene : EtOAc). [IR (KBr): 3450–3330, 2930, 2870, 1710, 1410, 1380, 1080 cm^{-1}. ^{13}C-NMR (DMSO-d_6): 175.21 (C-26, COOH), 71.20 (C-12), 70.14 (C-3), 23.25 (C-21), 17.06 (C-19), 12.60 (C-18) from 23.70 to 47.64 signals for the other twenty C-atoms].

ИЗВОД

СИНТЕЗА 3α,12α-ДИХИДРОКСИ-23a,23b-ДИХОМО-5β-ХОЛАНСКЕ КИСЕЛИНЕ

ВЕРА ЋИРИН-НОВТА*, КСЕНИЈА КУХАЈДА*, ЈУЛИЈАН КАНДРАЧ** и СЛАВКО КЕВРЕШАН**

**Департман за хемију, Природно-математички факултет, Трг Доситеја Обрадовића 3, 21000 Нови Сад и **Пољопривредни факултет, Трг Доситеја Обрадовића 8, 21000 Нови Сад*

Полазећи од метил–3α,12α-дихидрокси-5β-холаната (**1**) синтетизован је 5β-холан-3α,12α,24-триол (**2**) који је селективним тозиловањем преведен у 24-О-тозил дериват **3**. Дејством натријум-диетил – малоната на добијени тозилат **3** настаје једињење **4** које је прво хидролизовано у базној, а потом декарбоксиловано у киселој средини при чему је добијена 3α,12α-дихидрокси-23a,23b-дихомо-5β-холанска киселина (**5**).

(Примљено 8. септембра, ревидирано 1. децембра 2003)

REFERENCES

1. D. H. R. Barton, J. Wozniak, S. Z. Zard, *Tetrahedron* **45** (1989) 3741, and references therein
2. S. Lindesedt, N. Tryding, *Ark. Kemi*. **11** (1954) 137
3. T. Kuramoto, T. Kawamoto, S. Mariwaki, T. Hoshita, *Steroids* **44** (1984) 549
4. T. Kuramoto, S. Mariwaki, K. Kawamoto, T. Hoshita, *J. Pharmacobiodin* **10** (1987) 309
5. K. Kuhajda, J. Petrović, V. Ćirin-Novta, D. Miljković, *J. Serb. Chem. Soc.* **57** (1992) 625
6. B. Dayal, Y. Speck, E. Bagan, G. S. Tint, G. Salen, *Steroids* **37** (1981) 239
7. IR spectra (wave numbers in cm^{-1}) were recorded using a Perkin-Elmer 457 spectrophotometer. The ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker AC 250 E instrument, with tetramethylsilane as an internal standard. The chemical shifts are given in ppm (δ-scale). The melting point was determined on a Buchi SMP-20 apparatus and was not corrected.