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PREPARATION OF 3α- AND 3β-(ω–AMINOALKOXY)-7α,12α-DIHYDROXY-5β-CHOLANOIC ACID ESTERS: VERSATILE SHUTTLES FOR DRUG TARGETING

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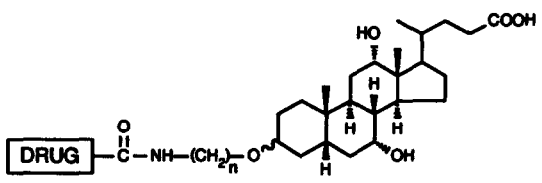
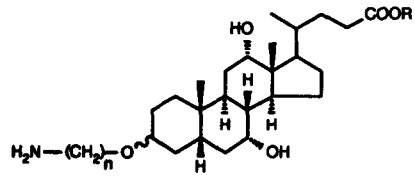
Abstract: *Simple methodology for the preparation of 3α- and 3β-(ω-aminoalkoxy)-cholanoic acid esters 7, 9, 11, 13 and 15 is described starting from readily available bile acid derivatives. Protecting groups are not required.*

Bile acid-drug conjugates **1** might be useful for liver selective drug targeting.[1] In these molecules the bile acid part is supposed to serve as a drug shuttle providing molecular recognition and transport by the specific ileal and hepatic bile acid transport systems.[2] For the design of molecules **1** modified bile acid esters **2** are required that have not yet been described. We wish to report efficient methodology for the preparation of these versatile building blocks giving entry into the 3α- and 3β-series.



1



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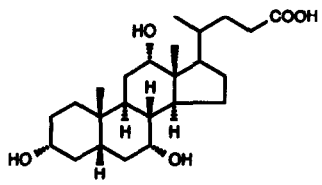
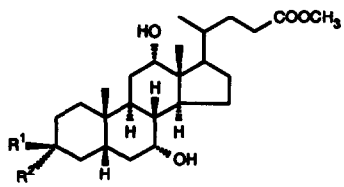


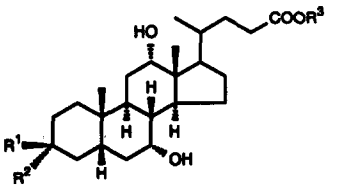
3 Cholic acid



4 $R^1 = OCH_2CH_2OH$, $R^2 = H$
5 $R^1 = OCH_2CH_2OSO_2CH_3$, $R^2 = H$
6 $R^1 = OCH_2CH_2N_3$, $R^2 = H$
7 $R^1 = OCH_2CH_2NH_2$, $R^2 = H$
8 $R^1 = H$, $R^2 = OCH_2CH_2OH$
9 $R^1 = H$, $R^2 = OCH_2CH_2NH_2$

For the synthesis of 3β-amine **7** alcohol **4** readily prepared from cholic acid[3a] was transformed quantitatively to mesylate **5** using 1.05 equiv. methanesulfonyl chloride in pyridine at 0°C for 30 min. and at room temperature for 1 h. Without further purification **5** was reacted with 1.15 equiv. sodium azide in DMF at 90°C for 3.5 h to give **6** in 82% yield after chromatography (silica gel, n-heptane/ethyl acetate = 3:7). Catalytic hydrogenation with Pd/C in methanol at room temperature gave **7**[4] in 70% yield after chromatogaphy (silica gel, ethyl acetate/ethanol/triethylamine = 5:1:1). The 3α-isomer **9**[4] was prepared from alcohol **8**[3] in 75% total yield following the same sequence of reactions. For the synthesis of amines **11**, **13** and **15** (table 1) alcohols **10**, **12** and **14** served as starting materials.

Table 1.



no	R^1	R^2	R^3	no	R^1	R^2	R^3	yield[a]
10[3b]	H	$O(CH_2)_3OH$	Me	11[4]	H	$O(CH_2)_3NH_2$	Me	55%
12[3b]	$O(CH_2)_3OH$	H	Me	13[4]	$O(CH_2)_3NH_2$	H	Me	58%
14[5]	$O(CH_2)_5OH$	H	t-Bu	15[4]	$O(CH_2)_5NH_2$	H	t-Bu	58%

(a) total yield following the sequence of reactions according to the preparation of 7.

This sequence of reactions requires no protecting groups and offers an easy access to a variety of modified bile acids. The methodology can be extended to functionalize steroidal positions 7 and 12. Besides their use as shuttle molecules for drug targeting amines 2 are versatile building blocks for various applications in bile acid chemistry.

Acknowledgments: We wish to thank Dr. Fehlhaber and Dr. Kogler for analytical support.

REFERENCES AND NOTES

1. Kramer, W.; Wess, G.; Schubert, G.; Bickel, M.; Girbig, F.; Gutjahr, U.; Kowalewski, S.; Baringhaus, K.-H.; Enhsen, A.; Glombik, H.; Müllner, S.; Neckermann, G.; Schulz, S.; Petzinger, E., J. Biol. Chem. **1992**, *267*, in press.

2. see following paper.

3. (a) Wess, G.; Kramer, W.; Bartmann, W.; Enhsen, A.; Glombik, H.; Müllner, S.; Bock, K.; Dries, A.; Kleine, H.; Schmitt, W., Tetrahedron Lett. **1992**, *33*, 195-198.
(b) EP 0417725 A2.

4. Characteristic analytical data:
7 amorphous solid, mp 50-55°C; ^{1}H-NMR 270 MHz ($CDCl_3$) δ 0.68 (s, 3 H), 0.90 (s, 3 H), 0.97 (d, J = 6.4 Hz, 3 H), 1.10 - 2.45 (m, 24 H), 2.82 (t, J = 4.8 Hz, 2 H), 3.38 (t, J = 4.8 Hz, 2 H), 3.53 (m, 1 H), 3.67 (s, 3 H), 3.83 (m, 1 H), 3.97 (m, 1 H);
9 amorphous solid, mp 55-60°C; ^{1}H-NMR 270 MHz ($CDCl_3$) δ 0.70 (s, 3 H), 0.91 (s, 3 H), 1.00 (d, J = 6.0 Hz, 3 H), 1.05 - 2.45 (m, 24 H), 2.83 (t, J = 4.8 Hz, 2 H), 3.12 (m, 1 H), 3.50 (t, J = 4.8 Hz, 2 H), 3.68 (s, 3 H), 3.85 (m, 1 H), 3.98 (m, 1 H);
11 amorphous solid, mp 47-50°C; ^{1}H-NMR 270 MHz ($CDCl_3$) δ 0.69 (s, 3 H), 0.90 (s, 3 H), 1.00 (d, J = 5.2 Hz, 3 H), 1.05 - 2.45 (m, 26 H), 2.91 (t, J = 6.0 Hz, 2 H), 3.08 (m, 1 H), 3.58 (t, J = 6.0 Hz, 2 H), 3.67 (s, 3 H), 3.83 (m, 1 H), 3.96 (m,1 H);
13 amorphous solid; ^{1}H-NMR 270 MHz ($CDCl_3$) δ 0.70 (s, 3 H), 0.91 (s, 3 H), 0.99 (d, J = 6.0 Hz, 3 H), 1.05 - 2.45 (m, 26 H), 2.80 (t, J = 7.2 Hz, 2 H), 3.42 (m, 2 H), 3.51 (m, 1 H), 3.68 (s, 3 H), 3.85 (m, 1 H), 3.99 (m, 1 H);
15 amorphous solid; ^{1}H-NMR 270 MHz ($CDCl_3$) δ 0.70 (s, 3 H), 0.91 (s, 3 H), 0.98 (d, J = 6.0 Hz, 3 H), 1.05 - 2.47 (m, 39 H), 2.69 (t, J = 7.2 Hz, 2 H), 3.45 (m, 2 H), 3.52 (m, 1 H), 3.86 (m, 1 H), 3.99 (m, 1 H).

5. t-Butylester 14 was prepared from the corresponding carboxylic acid[3] following the sequence (1) formylation (HCO_2H, cat. $HClO_4$), (2) acid cloride formation ($SOCl_2$, toluene), (3) alcoholysis (t-BuOH, pyridine), (4) deformylation (aqueous NaOH).

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