Title: PROCESS FOR THE PREPARATION OF 1,2,6,7,8,8A-HEXAHYDRO-BETA,DELTA,6-TRIHYDROXY-2-METHYL-8-{(2S)-2-METHYL-1-OXOBUTOXY}-(BETA R,DELTA R,1S,2S,6S,8S,8AR)-1-NAPHTHALENETHPTANONIC ACID, SODIUM SALT.

Abstract: A process for the preparation of substantially pure 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-{(2S)-2-methyl-1-oxobutoxy}-(beta R,delta R,1S,2S,6S,8S,8AR)-1-naphthaleneheptanonic acid, sodium salt is disclosed.
PROCESS FOR THE PREPARATION OF 1,2,6,7,8,8a-
HEXAHYDRO-BETA,DELTA,6-TRIHYDROXY-2-METHYL-8-
[(2S)-2-METHYL-1-OXOBUTOXY]-, (BETA R,DELTA
R,1S,2S,6S,8S,8AR)- 1-NAPHTHALENEHEPTANOIC ACID,
SODIUM SALT

FIELD OF THE INVENTION

The present invention relates to a novel process for the
preparation of substantially pure 1,2,6,7,8,8a-hexahydro-
beta, delta, 6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-,
(beta R, delta R, 1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid, sodium salt.

BACKGROUND OF THE INVENTION

US 4,346,227 discloses 1,2,6,7,8,8a-hexahydro-beta, delta, 6-
trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R, delta
R, 1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid, sodium salt.
The compound is also known by the synonyms 3-beta-
Hydroxycompactin; Eptastatin and Pravastatin. The compound is
used as cholesterol lowering agent which inhibit the enzyme HMG
CoA reductase.

The step of conversion of 1,2,6,7,8,8a-hexahydro-
beta, delta, 6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-,
(beta R, delta R, 1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid to
its sodium salt is crucial. The prior art methods convert the acid
form into sodium salt form as final step to afford the sodium salt.

The prior art methods for the preparation of sodium salt from
the 1,2,6,7,8,8a-hexahydro-beta, delta, 6-trihydroxy-2-methyl-8-
[(2S)-2-methyl-1-oxobutoxy]-, (beta R, delta R, 1S, 2S, 6S, 8S, 8aR)-1-Naphthaleneheptanoic acid are disclosed herein as reference.

WO 98/45410 discloses preparation of 1,2,6,7,8,8a-hexahydro-beta,delta, 6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R, delta R, 1S, 2S, 6S, 8S, 8aR)-1-

Naphthaleneheptanoic acid sodium by feeding compactin sodium to the microorganism *Streptomyces exfoliatus* and recovering the hydroxylated compactin sodium (1,2,6,7,8,8a-hexahydro-

beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R, delta R, 1S, 2S, 6S, 8S, 8aR)-1-Naphthaleneheptanoic acid sodium salt) by extraction, purification by semi preparative HPLC and crystallization.

The process involves use of HPLC, which is a tedious and expensive technique and cannot be scaled up beyond a limit.

WO 00/46175 discloses a process for preparation of

1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R, delta R, 1S, 2S, 6S, 8S, 8aR)-1-

Naphthaleneheptanoic acid sodium salt from lactone by hydrolyzing with sodium hydroxide.

Also amine salts can be transformed to sodium salt by treating with sodium hydroxide and/or sodium alkoxide.

When amine salts are employed, it involves an extra step i.e., the preparation of the amine salt.

US 2003/0050502 discloses a process for preparation of sodium salt of a statin by contacting a solution of hydroxy acid of the statin with sodium-2-ethylhexanoate and recovering the corresponding sodium salt.
The process involves use of expensive reagent sodium-2-ethyl hexanoate.

The prior art methods suffer from one or more disadvantages like use of expensive reagents, need of special equipment to carry out the operation or increased number of steps for the preparation of sodium salt of 1,2,6,7,8,8a-hexahydro-beta, delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid.

The present invention relates to a process, which overcomes all the disadvantages of the prior art and results in substantially pure product in high yields.

**SUMMARY OF THE INVENTION**

The present invention relates to a novel process for the preparation of 1,2,6,7,8,8a-hexahydro-beta, delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid sodium salt (FORMULA I).

![Formula I](image)

**FORMULA I**
The process of present invention comprises treatment of a solution of 1,2,6,7,8,8a-hexahydro-beta, delta, 6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]- (beta R, delta R, 1S, 2S, 6S, 8S, 8aR)- 1-Naphthaleneheptanoic acid in a suitable solvent with solid sodium carbonate to afford sodium salt of 1,2,6,7,8,8a-hexahydro-beta, delta, 6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]- (beta R, delta R, 1S, 2S, 6S, 8S, 8aR)- 1-Naphthaleneheptanoic acid (FORMULA I).

**DETAILED DESCRIPTION OF THE INVENTION**

As mentioned earlier, the present invention relates to a novel process for the preparation of 1,2,6,7,8,8a-hexahydro-beta, delta, 6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R, delta R, 1S, 2S, 6S, 8S, 8aR)- 1-Naphthaleneheptanoic acid sodium salt (FORMULA I).

![Chemical Structure](image)

**FORMULA I**

The important aspect of the present invention is to overcome the problems associated with the prior art methods. Thus the important aspect of the invention is to provide a simple, economic, industrially scalable process with high yields and purity.
The present invention specifically claims a process for the preparation of sodium salt of 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid.

The process of the present invention comprises: contacting 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid in a suitable solvent with solid sodium carbonate to afford sodium salt of 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid.

The process can be carried out in a suitable solvent wherein the solvent is such a solvent in which 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid is soluble and the sodium salt of 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid is insoluble.

The suitable solvent can be selected from a group comprising ester, ether, alcohol, halogenated hydrocarbon and ketone. The suitable solvent can be water miscible or water immiscible. Preferably the solvent is selected from ethyl acetate, isobutyl acetate or butyl acetate.

Sodium bicarbonate can also be used place of sodium carbonate of the instant invention.
Reagents like sodium alkanoate e.g. sodium acetate and sodium 2-ethylhexanoate as used in the prior art methods, results in the formation of the byproducts like acetic acid and ethylhexanoic acid. These byproducts increase solubility of the sodium salt of 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid in the solvent resulting in low yields.

The other important aspect of the present invention is that the gaseous byproduct formed, carbon dioxide, escapes from the reaction mixture. Thus the process of the present invention increases the yield.

Yet another aspect of the present invention is that since the sodium salt of 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid is insoluble in the suitable solvent of the process, it can be isolated with ease without employing expensive and tedious processes like freeze drying.

Yet another aspect of the present invention is that the sodium salt of 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid is insoluble in the solvent of the process and can be easily isolated by simple techniques like filtration, thereby eliminating all impurities which do not have functionality to form sodium salt in the mother liquor, resulting in high purity of the product.
In particular, the process of present invention comprises:
contacting 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-
methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta
R,1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid in a suitable
solvent with solid sodium carbonate to afford insoluble sodium salt
of 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-
[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)-
1-Naphthaleneheptanoic acid.

The following examples are used to illustrate the invention
which are not to be considered as limiting the scope of the
invention.

EXAMPLES

Example 1

To a solution of 3,5-Dihydroxy-7-[6-hydroxy-2-methyl-8-(2-
methyl-butyryloxy)-1,2,6,7,8,8a-hexahydro-naphthalen-1-yl]-
heptanoic acid (70 g, 0.165 mol) in ethyl acetate (500 ml), solid
sodium carbonate (8.76 g, 0.0825 mol) was added and stirred for 2
hours. 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-
[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)-
1-Naphthaleneheptanoic acid sodium salt was precipitated. The
reaction mixture was filtered and cake was washed with ethyl
acetate to get free flowing crystals of 1,2,6,7,8,8a-hexahydro-
beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-,
(beta R,delta R,1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid
sodium (FORMULA I). Yield: 65 g, 88%
Example 2

To a solution of 3,5-Dihydroxy-7-[6-hydroxy-2-methyl-8-(2-methyl-butryloxy)-1,2,6,7,8,8a-hexahydro-naphthalen-1-yl]-heptanoic acid (10 Kg, 23.6 mol) in isobutyl acetate (60 L), solid sodium carbonate (1.25 Kg, 11.8 mol) was added and stirred for 3 hours. 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)-1-Naphthaleneheptanoic acid sodium salt was precipitated. The reaction mixture was filtered and cake was washed with isobutyl acetate to get free flowing crystals of 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid sodium (FORMULA I). Yield: 9 Kg, 85%

Example 3

To a solution of 3,5-Dihydroxy-7-[6-hydroxy-2-methyl-8-(2-methyl-butryloxy)-1,2,6,7,8,8a-hexahydro-naphthalen-1-yl]-heptanoic acid (100 Kg, 236 mol) in butyl acetate (600 L), solid sodium carbonate (12.5 Kg, 118 mol) was added and stirred for 3 hours. 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)-1-Naphthaleneheptanoic acid sodium salt was precipitated. The reaction mixture was filtered and cake was washed with butyl acetate to get free flowing crystals of 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid sodium (FORMULA I). Yield: 95 Kg, 90%
We claim

1. A process for the preparation of compound of formula I comprising

   a) treating 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)- 1-
   Naphthaleneheptanoic acid in a suitable solvent with solid sodium carbonate to afford insoluble 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid sodium salt.

   b) isolating the 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)- 1-
   Naphthaleneheptanoic acid sodium salt (FORMULA I).
2. A process as in claim 1, wherein the solvent is selected in such a way that the 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid is soluble in the solvent.

3. A process as in claim 1, wherein the solvent is selected in such a way that the 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid sodium salt is insoluble in the solvent.

4. A process as in claim 1, wherein the solvent is selected from water miscible solvent or water immiscible solvent.

5. A process as in claim 4, wherein the solvent is an organic solvent.

6. A process as in claim 5, wherein the solvent is selected from a group comprising ester, ether, alcohol, halogenated hydrocarbon and ketone.

7. A process as in claim 6, wherein the solvent is selected from ethyl acetate, butyl acetate or isobutyl acetate.

8. A process as in claim 1, wherein the 1,2,6,7,8,8a-hexahydro-beta,delta,6-trihydroxy-2-methyl-8-[(2S)-2-methyl-1-oxobutoxy]-, (beta R,delta R,1S,2S,6S,8S,8aR)- 1-Naphthaleneheptanoic acid sodium salt is isolated by filtration.

9. A process as in claim 1, wherein the sodium carbonate is replaced with sodium bicarbonate.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

Int. Cl.: C07C 69/03.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

See electronic database consulted below.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

STN File Registry: Registry number search on pravastatin sodium salt.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>A</td>
<td>WO 01/44144 A2 (RANBAXY LABORATORIES LIMITED) 21 June 2001</td>
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☐ Further documents are listed in the continuation of Box C  
X See patent family annex

* Special categories of cited documents:
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Date of the actual completion of the international search: 13 November 2003

Date of mailing of the international search report: 17 NOV 2003

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This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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