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(54) Title: PROCESS FOR PREPARING NONAETHYLENE GLYCOL MONOMETHYL ETHER

(57) Abstract: The present invention provides a process for preparing nonethylene glycol monomethyl ether.



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PROCESS FOR PREPARING NONAETHYLENE GLYCOL MONOMETHYL ETHER

BACKGROUND OF THE INVENTION

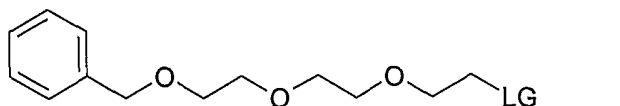
5 The present invention relates to a novel process for preparing nonaethylene glycol. More specifically, the present invention relates to a process for preparing nonaethylene glycol monomethyl ether.

Various processes are known for the synthesis of polyethylene glycols. See, for
10 example, R.A. Bartsch et al, *J. Org. Chem.* 1989, **54**:857-860; J.M. Harris,
Macromol. J.Sci. Rev. Polymer Phys. Chem. 1985, **C25 (3)**:325-373; and S.
Zalipsky, *Bioconjugate Chem.* 1995, **6**: 150-165.

U.S. Patent Nos. 6355646 and 6437124, both to Daluge et al., and PCT Publication
15 No. WO 98/35966, published 20 Aug 1998 to Glaxo Group Limited, disclose a
process for preparing nonaethylene glycol using hexaethyleneglycol as a starting
material].

BRIEF SUMMARY OF THE INVENTION

20 The present invention provides a novel process for preparing nonaethylene glycol monomethyl ether. The process comprises the steps of:
a) reacting a compound of formula (I):



wherein LG is a suitable leaving group,

25 with triethylene glycol monomethyl ether in the presence of a coupling agent, to
prepare hexaethylene glycol monobenzyl monomethyl ether;
b) hydrogenating hexaethylene glycol monobenzyl monomethyl ether to prepare
hexaethylene glycol monomethyl ether;

- c) reacting hexaethylene glycol monomethyl ether with a compound of formula (I) in the presence of a coupling agent to prepare nonaethylene glycol monobenzyl monomethyl ether; and
- d) hydrogenating nonaethylene glycol monobenzyl monomethyl ether to prepare
- 5 nonaethylene glycol monomethyl ether.

Additional aspects and advantages of the present invention will be apparent from the description and example which follow.

10 DETAILED DESCRIPTION OF THE INVENTION

Polyethylene glycols, such as nonaethylene glycol monomethyl ether, are useful in a number of areas, including for example, as plasticizers, softeners, humectants, ointments, polishes, paper coatings, mold lubricants, bases for cosmetics and pharmaceuticals, solvents, binders, metal and rubber processing, food additives,

15 chemical intermediates, phase transfer catalysts, polymer-bound reagents, reagents for binding assays, processes for protein and cell purification, peptide synthesis and as modifiers for a variety of substrates, including pharmaceutically active agents.

In particular, polyethylene glycols have been used as covalent modifiers of both low

20 molecular weight compounds and biological macromolecules, predominantly to allow for the alteration of one or more of the properties of the substrate. For example, polyethylene glycol may be used to improve solubility, increase molecular weight or change a substrate's partition properties in a biphasic system. S. Zalipsky, *Id.*

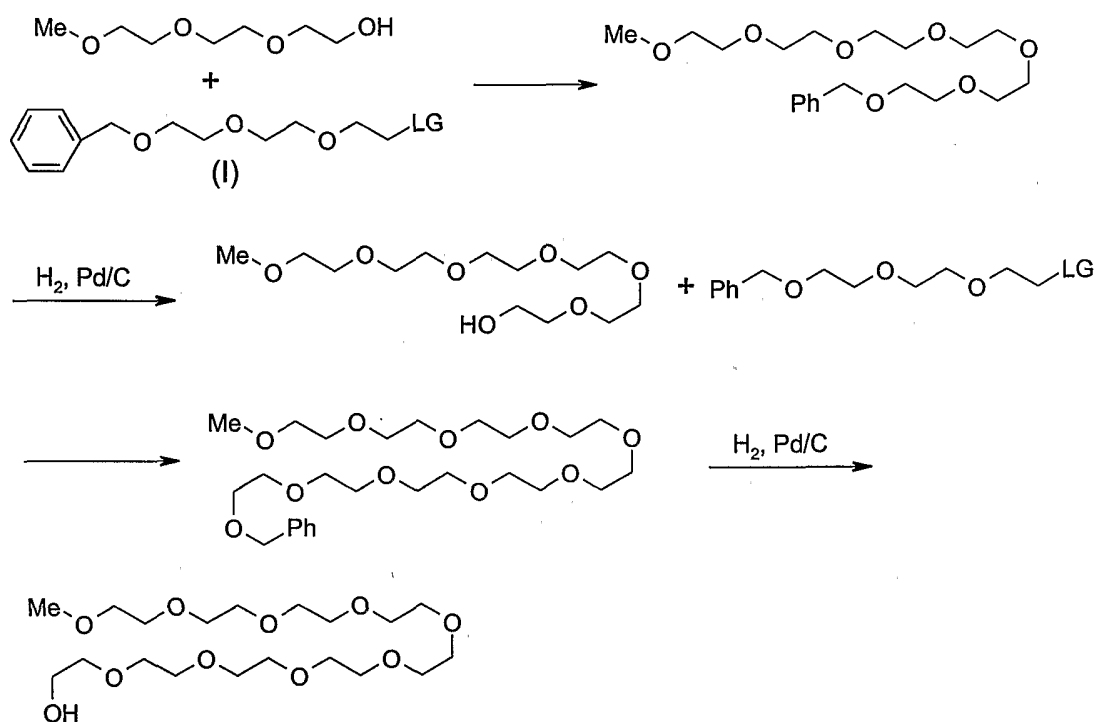
25 U.S. Patent Nos. 6355646 and 6437124, both to Daluge et al., and PCT Publication No. WO 98/35966, published 20 Aug 1998 to Glaxo Group Limited, relate to substituted 1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)phenyl polyethylene glycol derivatives. U.S. Patent No. 6608069 to Daluge et al., and PCT Publication No. WO 00/09507, published 24 Feb 2000 to Glaxo Group

30 Limited, relate to phenyl xanthine derivatives which incorporate polyethylene glycol chains. The processes of the present invention are useful, among other things for

the preparation nonaethylene glycol monomethyl ether, which is useful for the synthesis of the compounds described in the foregoing patents and publications.

The present invention provides a process for preparing nonaethylene glycol monomethyl ether, as illustrated in Scheme 1 below.

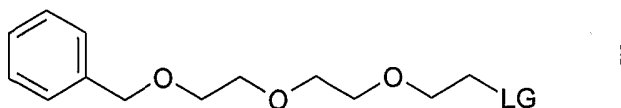
Scheme 1



wherein LG is a suitable leaving group, Me refers to methyl and Ph refers to phenyl.

Generally, the process comprises the steps of:

a) reacting a compound of formula (I):



wherein LG is a suitable leaving group,

with triethylene glycol monomethyl ether in the presence of a coupling agent, to prepare hexaethylene glycol monobenzyl monomethyl ether;

- b) hydrogenating hexaethylene glycol monobenzyl monomethyl ether to prepare hexaethylene glycol monomethyl ether;
- c) reacting hexaethylene glycol monomethyl ether with a compound of formula (I) in the presence of a coupling agent to prepare nonaethylene glycol monobenzyl monomethyl ether; and
- 5 d) hydrogenating nonaethylene glycol monobenzyl monomethyl ether to prepare nonaethylene glycol monomethyl ether.

More specifically, a triethylene glycol monobenzyl ether compound of formula (I) is reacted with triethylene glycol monomethyl ether. The leaving group in the compound of formula (I) may be any suitable leaving group known to those skilled in the art of organic chemistry to be useful in such synthesis. Suitable leaving groups include activated esters. Specific examples of suitable leaving groups including but are not limited to tosyl; mesylate; and tresylate. In one embodiment, the leaving group is tosyl.

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The reaction of the compound of formula (I) with triethylene glycol monomethyl ether is carried out in the presence of a coupling agent. Suitable coupling agents are known in the art. In particular, suitable coupling agents include bases. Specific examples of suitable coupling agents include but are not limited to potassium *tert*-butoxide, sodium *tert*-butoxide, sodium hydride, potassium hydride, potassium hydroxide, sodium metal, sodium hexamethyldisilazide, potassium hexamethyldisilazide and the like.

20

In one embodiment, the coupling agent for the reaction of step (a) is potassium *tert*-butoxide.

25

The coupling reaction of step (a) preferably carried out in a polar aprotic solvent at reduced temperature (e.g., below room temperature). Examples of suitable solvents include, but are not limited to tetrahydrofuran, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, hexamethylphosphoramide and dioxane. In one embodiment, the coupling reaction of step (a) is carried out using tetrahydrofuran as the solvent.

30

The preparation of the compound of formula (I) involves the installation of the leaving group on commercially available triethylene glycol monobenzyl ether.

Methods for the installation of such leaving groups are known in the art. *See, e.g.,*

- 5 A. Bouzide, et al., *Tetrahedron Letters* 2001 42:8781; L. Jullien, et al., *J. Chem Soc. Perkin Trans.2* 1994 2:989-1002; A. M. Reichwein, et al., *Recl. Trav. Chim. Pays-Bas* 1993 112:595-608; A. M. Reichwein, et al. *Recl. Trav. Chim. Pays-Bas* 1993, 112:358-366; J. Ipaktschi, et al., *Liebigs Ann. Chem.* 1992, 1029-1032; W. Walkowiak, et al., *Anal. Chem.* 1992, 64:1685-1690; C. Selve, et al., *Synth. Commun.* 1990 20: 799-807; D. Bethell, et al., *J. Chem. Soc. Perkin Trans.* 1988 2:2035-2044; S. Svedhem, et al., *J. Org. Chem.* 2001 66: 4494-4503; G. Herve, *Org. Biomol. Chem.* 2003, 1:427-435; B. Mulley, *J. Chem. Soc. A* 1970 1459-1464; M. Carissimi, et al. *J. Med. Chem.* 1965 8: 542-545; Z. Grobelny, et al., *J. Org. Chem.* 1999 64:8990-8994; and C. Vitali, et al., *Tetrahedron* 1989 45: 2213-2222.

15

Optimal reaction conditions will depend upon the particular leaving group to be installed, and will be within the skill of the synthetic organic chemist. For example, a tosyl leaving group may be installed on triethylene glycol monobenzyl ether by reacting triethylene glycol monobenzyl ether with 4-toluenesulfonyl chloride in a suitable solvent and basic additive. Suitable solvents and basic additives for installing the tosylate or mesylate include

20

pyridine (as both solvent and basic additive), dichloromethane and triethylamine, dichloromethane and pyridine, and sodium, potassium or cesium hydroxide in dioxane. In one embodiment, the the leaving group is tosyl and the solvent and basic additive are both pyridine.

25

Examples of compounds of formula (I) which are useful in the process of the present invention include but are not limited to triethylene glycol benzyl tosyl ether, triethylene glycol benzyl mesyl ether.

30

The coupling reaction of step (a) produces hexaethylene glycol monobenzyl monomethyl ether. This compound is then subjected to hydrogenation conditions to yield hexaethylene glycol monomethyl ether. Suitable techniques for the

hydrogenation of hexaethylene glycol monobenzyl monomethyl ether are analogous to techniques for the hydrogenation of similar compounds. *See, e.g.,* C. Selve, et al., *J. Chem. Soc. Chem. Commun.* 1990, 911-912; and E. Weber, *Liebigs Ann. Chem.* 1983, 770-801.

5

In one embodiment, the hydrogenation step (b) is carried out using palladium catalyzed hydrogenation in a hydrogen atmosphere. Suitable palladium catalysts include palladium on carbon. Suitable solvents for the hydrogenation step (b) include the solvents described above for use in step (a) of the process as well as
10 alcohol solvents. In one embodiment, the process is conveniently carried out using the same solvent for both the couplings step (a) and the hydrogenation step (b).

The hydrogenation of step (b) yields hexaethylene glycol monomethyl ether. Conveniently, hexaethylene glycol monomethyl ether is then reacted with the
15 compound of formula (I). This coupling reaction (step (c)) may conveniently be carried out using the same reaction conditions as described above for the reaction of step (a). In one embodiment, the coupling agent in step (c) is selected from potassium *tert*-butoxide, potassium hydride and potassium hexamethyldisilazide. Advantageously, the same coupling agent may be employed for both step (a) and
20 step (c) of the process of the present invention. In one embodiment, the coupling agent for both step (a) and step (c) is potassium *tert*-butoxide. The coupling step (c) may be carried out in a suitable solvent selected from those described above for the coupling step (a). In one convenient embodiment of the process of the present invention, step (a) and step (c) are carried out in the same solvent, e.g.,
25 tetrahydrofuran.

The coupling reaction of step (c) yields nonaethylene glycol monobenzyl monomethyl ether, which is then subjected to hydrogenation to provide nonaethylene glycol monomethyl ether. The hydrogenation of step (d) may be
30 carried out using the same reaction conditions described above for the hydrogenation of step (b). Conveniently, the hydrogenation may be carried out in the same solvent.

In one embodiment, the process of the present invention is carried out in solvent. Suitable solvents are selected from tetrahydrofuran, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, hexamethylphosphoramide and dioxane. In one embodiment,
5 the process of the invention is carried out using tetrahydrofuran as the solvent.

The process of the present invention provides a number of unique advantages over conventional processes for preparing nonaethylene glycol monomethyl ether. In particular, the process of the present invention employs only two starting materials,
10 both of which are available in high oligomeric purity, the compound of formula (I) and triethylene glycol monomethyl ether. Triethylene glycol monomethyl ether (which is employed to prepare the compounds of formula (I)) is commercially available in large quantities and at costs that permit commercial-scale synthesis of the desired nonaethylene glycol monomethyl ether product. Further the process of the present
15 invention is carried out using only four steps and reaction conditions which are suitable for scale-up production of commercial quantities. Conventional processes employing hexaethylene glycol or hexaethylene glycol monobenzyl ethers suffer key disadvantages compared to the process of the present invention. In particular, availability of hexaethylene glycol in quantities suitable for synthesis of commercial
20 quantities of the desired nonaethylene glycol monomethyl ether product is uncertain and the purchase of such quantities may be cost prohibitive. Further it has been found that synthesis of nonaethylene glycol monomethyl ether by coupling hexaethylene glycol monobenzyl ether to triethylene glycol monomethyl ether results in a "chain clipping" reaction whereby one ethylene glycol unit is removed from the
25 chain. This chain clipping side reaction produces higher quantities of ethylene glycol monomethyl ether chains of varying lengths, including the octaethylene glycol monomethyl ether, as side products. Such side products negatively impact production costs and increase risk particularly when the PEG chains are to be incorporated into pharmaceutically active agents for human use. The process of the
30 present invention does not appear to initiate the chain clipping side reaction. Thus, the process of the present invention provides nonaethylene glycol monomethyl ether in a high level of oligomeric purity.

The following example is intended for illustration only and is not intended to limit the scope of the invention in any way, the invention being defined by the claims which follow.

5

Reagents are commercially available or are prepared according to procedures in the literature.

Example 1: Synthesis of Nonaethylene Glycol MonoMethyl Ether

10 A. Triethylene Glycol MonoBenzyl Tosyl Ether

4-Toluenesulfonyl chloride (20.9 g, 0.11 mol) was added to a cold (0 °C) solution of triethylene glycol monobenzyl ether ("BnO-3EG-OH," 24.0 g, 0.1 mol) in pyridine (100 mL) in portions over a period of two minutes. A precipitate formed over 20 minutes. After 70 minutes the reaction mixture was allowed to warm to room temperature overnight. After 16 hours the reaction was diluted with ethyl acetate (100 mL) and quenched with water (50 mL) to dissolve the solids. The layers were separated and the organic layer was washed with aqueous hydrochloric acid till the aqueous layer was about pH 1. The organic solution was dried over magnesium sulfate and concentrated to dryness to give the title compound (28.94 g). ¹H NMR (400 MHz, CDCl₃, A10899) indicated an ca 4:1 mixture of desired triethylene glycol monobenzyl ether tosylate and undesired ({2-[2-(2-chloroethoxy)ethoxy]-ethoxy)methyl)benzene.

Triethylene glycol monobenzyl ether tosylate: δ_H (CDCl₃, ppm from TMS) 7.79 (2 H, d, $J = 8.3$ Hz, Ar-H), 7.4-7.2 (7 H, m, Ar-H), 4.55 (2 H, s, PhCH₂O-), 4.15 (2 H, t, $J = 4.7$ Hz, CH₂) 3.7-3.5 (10 H, m, CH₂ x 5), 2.43 (3 H, s, ArCH₃).

25 ({2-[2-(2-Chloroethoxy)ethoxy]ethoxy)methyl)benzene: δ_H (CDCl₃, ppm from TMS) 7.4-7.2 (5 H, m, Ar-H), 4.57 (2 H, s, PhCH₂O-), 3.76 (2 H, t, $J = 5.9$ Hz, CH₂Cl) 3.7-3.5 (10 H, m, CH₂ x 5).

Mixture calculated to contain 88.4 wt% tosylate (25.58 g, 64.9% theory) and 11.6 wt% chloride (3.36 g, 13.0 % theory).

30

B. Triethylene Glycol MonoBenzyl Tosyl Ether

4-Toluenesulfonyl anhydride (25 g, 76.6 mmol, 1.1 equiv) was added to a cold (5 °C) solution of triethylene glycol monobenzyl ether (BnO-3EG-OH, 24.0 g, 0.1 mol, 1 equiv) in pyridine (67 mL) in portions to control the exotherm. More pyridine (40 mL) was added to maintain stirring of the resultant slurry. After 5 hours the reaction was diluted with ethyl acetate (80 mL) and quenched with water (40 mL) to dissolve the solids. The layers were separated and the organic layer was washed with aqueous sulfuric acid till the aqueous layer was about pH 1. The organic solution was dried over magnesium sulfate and concentrated to dryness to give triethylene glycol monobenzyl ether tosylate (22.69 g, 83% theory). ¹H NMR (400 MHz, CDCl₃) consistent with above.

C. Hexaethylene Glycol MonoBenzyl Monomethyl Ether

A solution of potassium *tert*-butoxide in tetrahydrofuran (1 M, 17.5 mL, 17.5 mmol) was added to a solution of triethylene glycol monomethyl ether ("MeO-3EG-OH," 2.58 mL, 16.13 mmol) in tetrahydrofuran (20 mL) maintaining an internal temperature of less than 10 °C. After 15 minutes a solution of a mixture of triethylene glycol monobenzyl ether 4-toluenesulfonate ("BnO-3EG-OTs") and corresponding chloride (88.4 wt% tosylate; 5.00 g, 11.2 mmol of tosylate) in tetrahydrofuran (10 mL) was added. A colorless precipitate formed immediately.

After 2 hours, the reaction was quenched with saturated aqueous sodium bicarbonate solution (25 mL) at a rate to control gas evolution. Water (20 mL) was added and the tetrahydrofuran was removed by distillation under reduced pressure. The resulting aqueous layer was washed with diisopropyl ether (50 mL) then ethyl acetate (50 mL). The ethyl acetate layer was dried over magnesium sulfate, filtered and concentrated to dryness to provide the coupled benzyl ether (2.66 g, 61.5% theory based on input tosylate). ¹H NMR (400 MHz, CDCl₃, A10919) δ_H (CDCl₃, ppm from TMS) 7.4-7.2 (5 H, m, Ar-H), 4.57 (2 H, s, PhCH₂O-), 3.7-3.6 (22 H, m, CH₂ x 11), 3.6-3.5 (2 H, m, CH₂), 3.38 (3 H, s, OCH₃).

D. Hexaethylene Glycol Monomethyl Ether

A 50% wet paste of 10% palladium on carbon (0.71 g, 5 mol%) was charged to a nitrogen purged flask. A solution of hexaethylene glycol monomethyl monobenzyl

ether ("BnO-6EG-OMe"; 2.66g, 6.88 mmol) in tetrahydrofuran (26.6 mL) was added. The mixture was stirred under an atmosphere of hydrogen for 90 minutes. The mixture was filtered through celite to remove the catalyst. The solids were washed with tetrahydrofuran (20 mL). The filtrate was concentrated to dryness to give
5 hexaethylene glycol monomethyl ether (2.01 g, 99% theory). ^1H NMR (250 MHz, CDCl_3 , S44238) δ_{H} (CDCl_3 , ppm from TMS) 3.8-3.5 (24 H, m, $\text{CH}_2 \times 12$), 3.38 (3 H, s, OCH_3), 2.08 (1 H, brs, OH).

E. Nonaethylene Glycol Monobenzyl Monomethyl Ether

10 A solution of potassium *tert*-butoxide (0.78 g, 6.8 mmol) in tetrahydrofuran (7.5 mL) was cooled to 5 °C. A solution of hexaethylene glycol monomethyl ("MeO-6EG-OH", 1.83 g, 6.19 mmol) in tetrahydrofuran (10 mL) was added dropwise over ten minutes. After 12 minutes, a solution of triethylene glycol monobenzyl ether 4-
15 toluenesulfonate ("BnO-3EG-OTs", 3.17 g, 8.04 mmol) in tetrahydrofuran (7.5 mL) was added over four minutes. The mixture was allowed to warm to room temperature. After 19.5 hours, a solution of potassium *tert*-butoxide (0.45 g, 4.0 mmol) in tetrahydrofuran (5.0 mL) was added. After 90 minutes more the reaction was quenched with water (15 mL) and the tetrahydrofuran was removed by
20 distillation under reduced pressure. The resulting aqueous layer was washed with diisopropyl ether (3 x 20 mL) then extracted with dichloromethane (2 x 20 mL). The dichloromethane layers were combined and washed with water (2 x 20 mL) then saturated aqueous sodium bicarbonate (4 x 20 mL) then concentrated to dryness to
25 give nonethylene glycol monomethyl monobenzyl ether (2.52 g, 79% theory). ^1H NMR (400 MHz, CDCl_3 , A11016) δ_{H} (CDCl_3 , ppm from TMS) 7.4-7.2 (5 H, m, Ar-H), 4.57 (2 H, s, $\text{PhCH}_2\text{O-}$), 3.7-3.6 (34 H, m, $\text{CH}_2 \times 17$), 3.6-3.5 (2 H, m, CH_2), 3.38 (3 H, s, OCH_3).

F. Nonaethylene Glycol Monomethyl Ether

30 A 50% wet paste of 10% palladium on carbon (0.53 g, 5 mol%) was charged to a nitrogen purged flask. A solution of nonaethylene glycol monomethyl monobenzyl ether ("BnO-9EG-OMe," 2.52g, 4.86 mmol) in tetrahydrofuran (25 mL) was added. The mixture was stirred under an atmosphere of hydrogen for 65 minutes. The

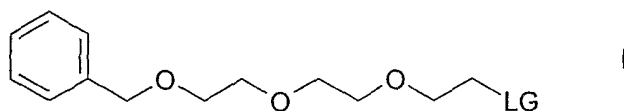
mixture was filtered through celite to remove the catalyst. The solids were washed with tetrahydrofuran (3 x 5 mL). The filtrate was concentrated to dryness to give nonaethylene glycol monomethyl ether (2.02 g, 97% theory). ¹H NMR (400 MHz, CDCl₃, A11021) δ_H (CDCl₃, ppm from TMS) 3.8-3.6 (34 H, m, CH₂ x 17), 3.6-3.5 (2
5 H, m, CH₂), 3.38 (3 H, s, OCH₃), 2.58 (1 H, t, J = 5.9 Hz, OH).

CLAIMS

That Which Is Claimed Is:

1. A process for preparing nonaethylene glycol monomethyl ether, said process comprising the steps of:

a) reacting a compound of formula (I):



wherein LG is a suitable leaving group,

with triethylene glycol monomethyl ether in the presence of a coupling agent, to prepare hexaethylene glycol monobenzyl monomethyl ether;

b) hydrogenating hexaethylene glycol monobenzyl monomethyl ether to prepare hexaethylene glycol monomethyl ether;

c) reacting hexaethylene glycol monomethyl ether with a compound of formula (I) in the presence of a coupling agent to prepare nonaethylene glycol monobenzyl monomethyl ether; and

d) hydrogenating nonaethylene glycol monobenzyl monomethyl ether to prepare nonaethylene glycol monomethyl ether.

2. The process according to claim 1, wherein said compound of formula (I) is selected from triethylene glycol benzyl tosyl ether and triethylene glycol benzyl mesyl ether.

3. The process according to claim 1, wherein said coupling agent of step a) and step c) is the same.

4. The process according to claim 1, wherein said coupling agent of step a) is selected from potassium *tert*-butoxide, sodium *tert*-butoxide, sodium hydride, potassium hydride, sodium metal, sodium hexamethyldisilazide, and potassium hexamethyldisilazide.

5. The process according to claim 1, wherein said coupling agent of step c) is selected from potassium *tert*-butoxide, potassium hydride, potassium hexamethyldisilazide.
6. The process according to claim 1, wherein said coupling agent for step a) and step c) is potassium *tert*-butoxide.
7. The process according to claim 1, wherein said hydrogenation step b) and step d) is a palladium catalyzed hydrogenation.
8. The process according to claim 1, wherein said steps (a), (b), (c), and (d) are carried out in a solvent.
9. The process according to claim 8, wherein said solvent is selected from tetrahydrofuran, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, hexamethylphosphoramide and dioxane.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/013392

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C43/11 C07C41/16 C07C41/26

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)

IPC 7 C07C

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 355 646 B1 (S. M. DALUGE) 12 March 2002 (2002-03-12) cited in the application example 10	1
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

15 September 2005

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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