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(54) **PROCEDURE FOR CRYSTALLIZATION OF (22E)-(24R)-2-METHYLENE-22-DEHYDRO-1 $\alpha$ ,24,25-TRIHYDROXY-19-NOR-VITAMIN D<sub>3</sub>**

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**A61P 3/04** (2006.01)  
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**A61P 35/00** (2006.01)  
**C07C 35/21** (2006.01)  
**C07C 29/78** (2006.01)

(52) **U.S. Cl.**  
CPC ..... **C07C 401/00** (2013.01); **A61K 31/593** (2013.01); **A61P 3/02** (2018.01); **A61P 3/04** (2018.01); **A61P 35/00** (2018.01); **C07C 29/78** (2013.01); **C07C 35/21** (2013.01); **C07B 2200/13** (2013.01); **C07C 2601/14** (2017.05); **C07C 2602/24** (2017.05)

(58) **Field of Classification Search**  
None  
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,168,535 A \* 2/1965 Martin ..... C07C 401/00  
552/653  
8,404,874 B2 3/2013 Deluca  
8,420,839 B1 \* 4/2013 DeLuca ..... C07C 401/00  
552/653  
8,519,169 B2 8/2013 DeLuca  
8,884,039 B2 11/2014 DeLuca  
8,940,916 B2 1/2015 DeLuca  
9,040,729 B2 5/2015 Lutz  
9,212,137 B2 12/2015 DeLuca  
9,416,102 B2 8/2016 DeLuca  
2013/0324752 A1 \* 12/2013 DeLuca ..... C07C 401/00  
552/653  
2014/0206655 A1 7/2014 DeLuca

FOREIGN PATENT DOCUMENTS

CN 103819379 A \* 5/2014  
WO 2003088977 A1 10/2003  
WO WO-2011002756 A2 \* 1/2011 ..... A23K 20/174  
WO 2014116386 A1 7/2014

OTHER PUBLICATIONS

Mullin ("Crystallization and Precipitation", 2005, pp. 1-51).  
Andrews, D. R., et al. "A direct, regio- and stereoselective 1. alpha.-hydroxylation of (5E)-calciferol derivatives." *The Journal of Organic Chemistry* 51.9 (1986): 1635-1637.  
Caira, M. R. "Crystalline polymorphism of organic compounds." *Design of Organic Solids*. Springer, Berlin, Heidelberg, 1998. 163-208.  
Calverley, M. J. "Synthesis of MC 903, a biologically active vitamin D3 metabolite analogue." *Tetrahedron* 43.20 (1987): 4609-4619.  
Choudhry, S. C., et al. "Synthesis of a biologically active vitamin D2 metabolite." *The Journal of Organic Chemistry* 58.6 (1993): 1496-1500.  
International Searching Authority. International Search Report and Written Opinion for application PCT/US2018/056057, dated Feb. 4, 2019.  
Nerinckx, W., et al. "An improved synthesis of 1 $\alpha$ -hydroxy vitamin D3." *Tetrahedron* 47.45 (1991): 9419-9430.  
Paaren, H.E., et al. "Direct C (1) hydroxylation of vitamin D3 and related compounds." *The Journal of Organic Chemistry* 45.16 (1980): 3253-3258.  
Paaren, H.E., et al. "Direct C-1 hydroxylation of vitamin D compounds: convenient preparation of 1 $\alpha$ -hydroxyvitamin D3, 1 $\alpha$ , 25-dihydroxyvitamin D3, and 1 $\alpha$ -hydroxy vitamin D2." *Proceedings of the National Academy of Sciences* 75.5 (1978): 2080-2081.

(Continued)

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(57) **ABSTRACT**

Disclosed are methods of purifying the compound (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub> to obtain the compound in crystalline form. The methods typically include the steps of dissolving (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub> in a solvent comprising ethyl acetate and hexane to form a solution, allowing crystals of (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub> to form and precipitate from the solution, and recovering the crystals of (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub> from the solution.

**17 Claims, 4 Drawing Sheets**

(56)

**References Cited**

OTHER PUBLICATIONS

Vanmaele, L. J., et al. "A stereocontrolled partial synthesis of 1 $\alpha$ -hydroxy vitamin D<sub>3</sub>." *Tetrahedron Letters* 23.9 (1982): 995-998.

Vanmaele, L. J., et al. "An efficient synthesis of 1 $\alpha$ , 25-dihydroxy vitamin D<sub>3</sub>." *Tetrahedron (Oxford, Print)* 41.1 (1985): 141-144.

Vanmaele, L. J., et al. "1 $\alpha$ -hydroxy previtamin D<sub>3</sub>, and its selective formation from 1-keto previtamin D<sub>3</sub>." *Tetrahedron* 40.7 (1984): 1179-1182.

\* cited by examiner

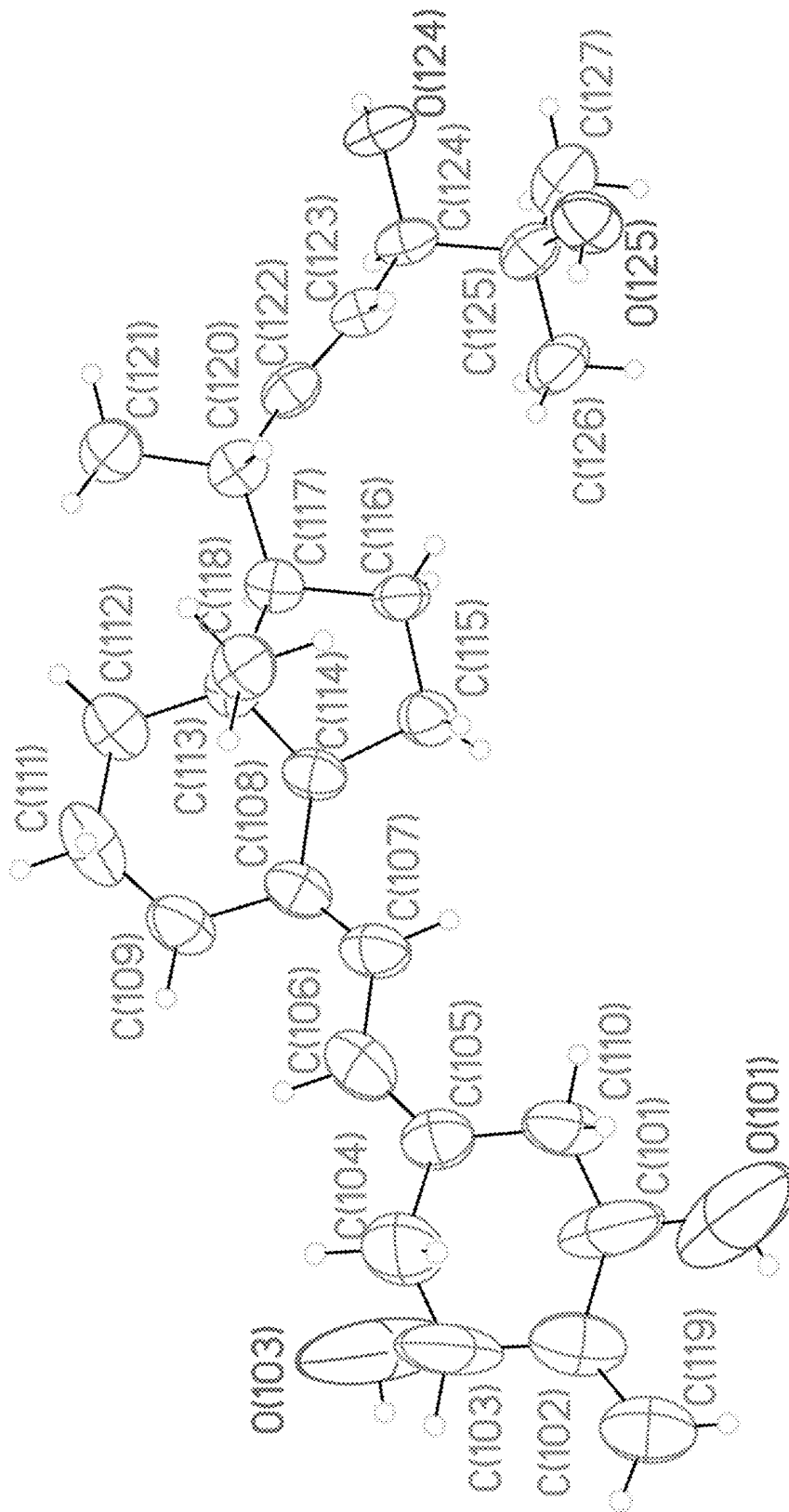


Figure 1

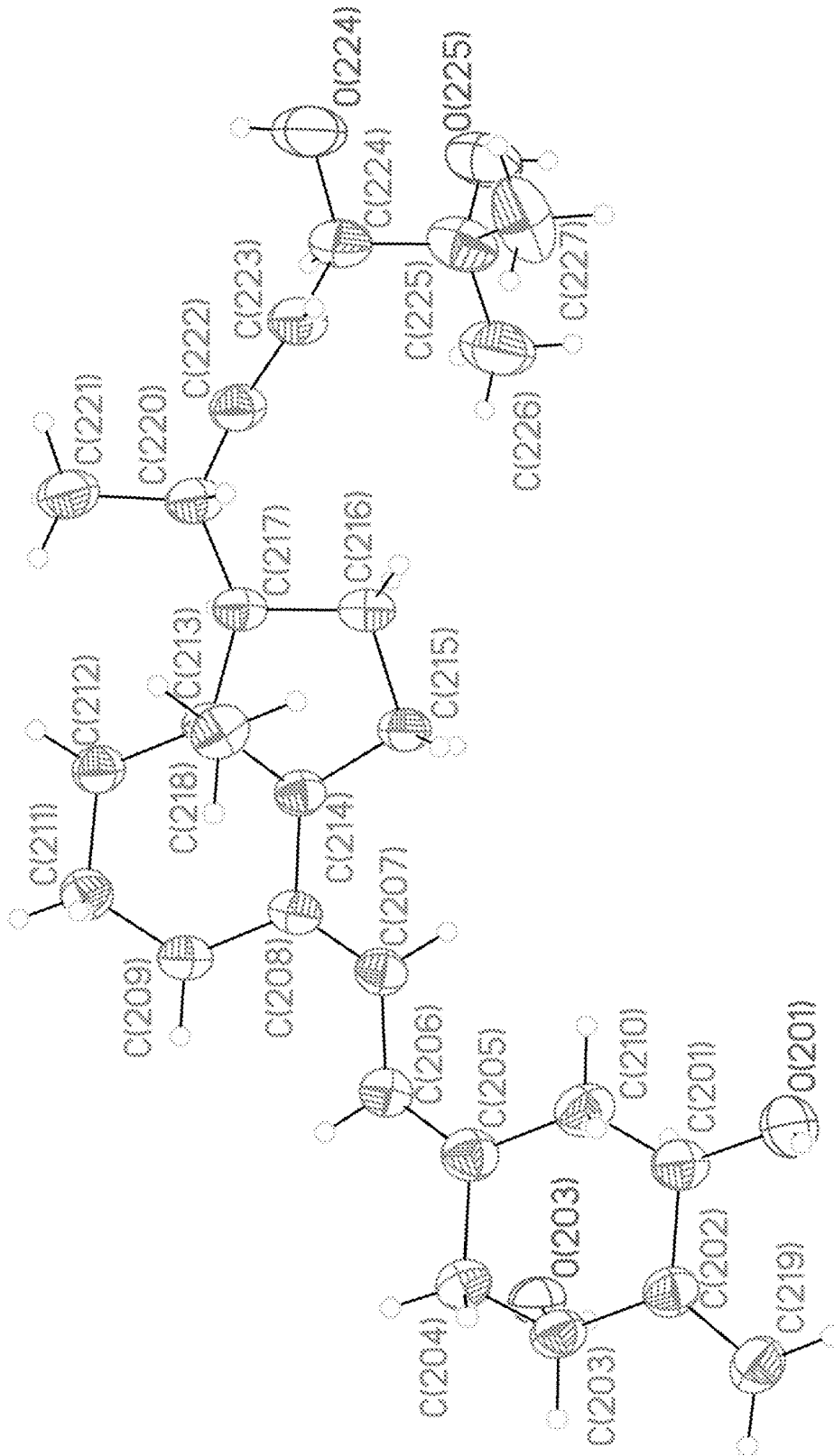


Figure 2

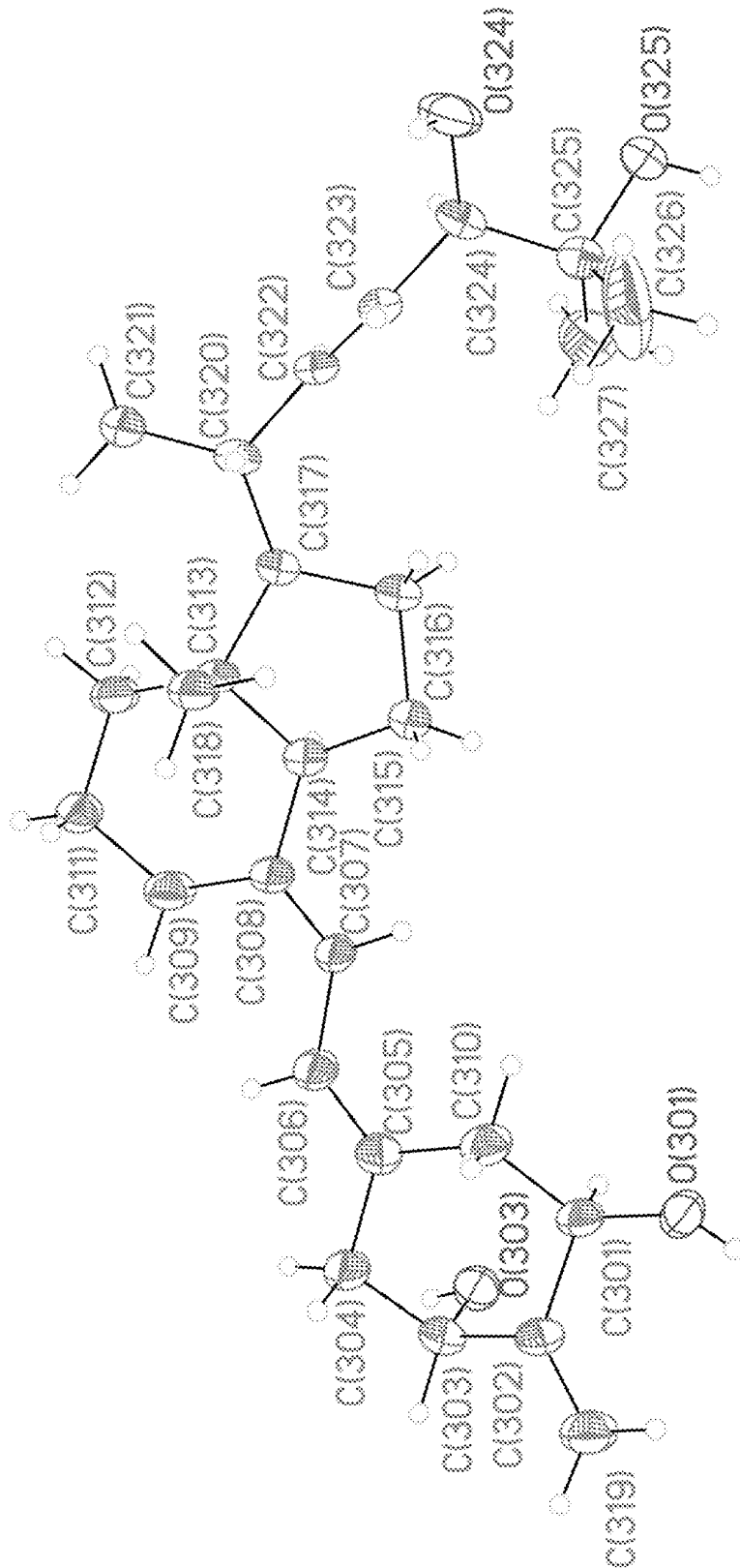


Figure 3

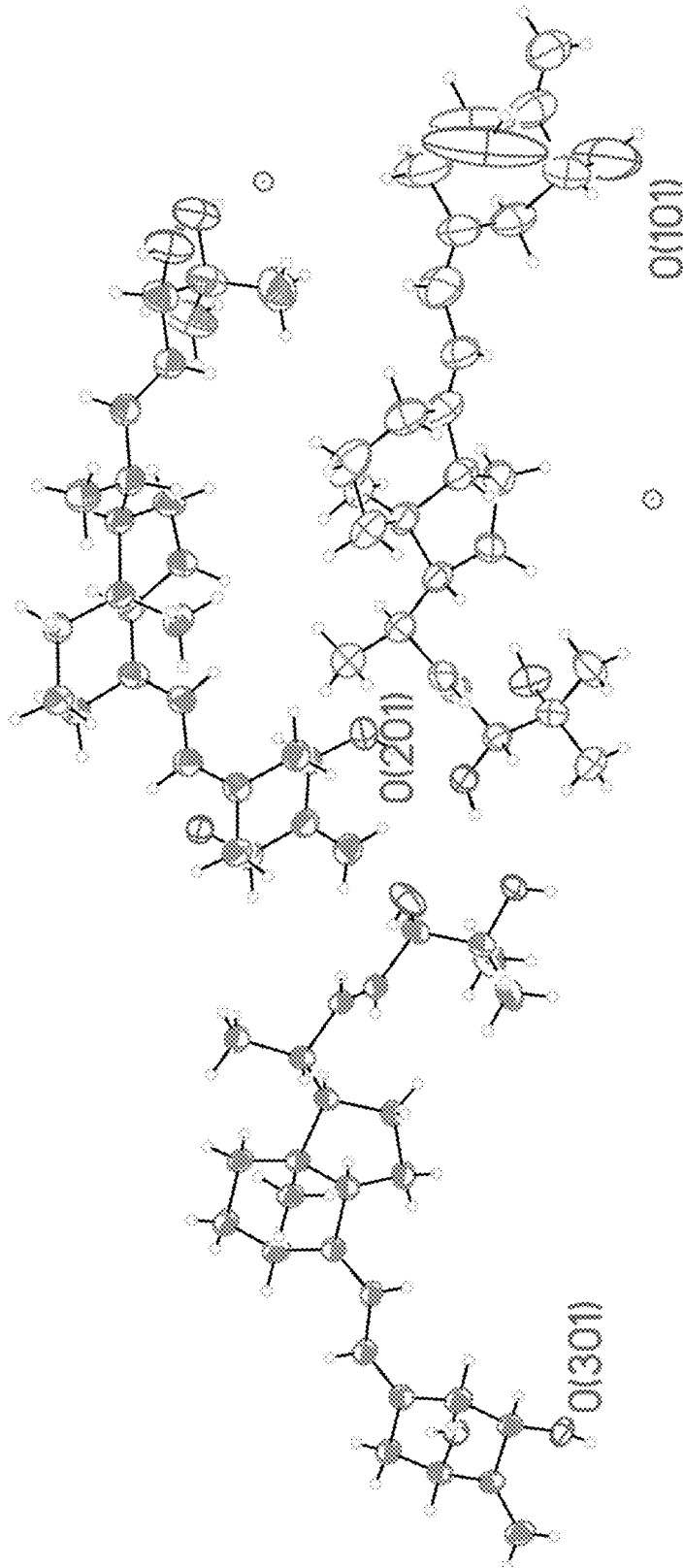


Figure 4

**PROCEDURE FOR CRYSTALLIZATION OF  
(22E)-(24R)-2-METHYLENE-22-DEHYDRO-1 $\alpha$ ,  
24-25-TRIHYDROXY-19-NOR-VITAMIN D<sub>3</sub>**

**CROSS-REFERENCE TO RELATED PATENT  
APPLICATIONS**

The present application is the U.S. National Stage of International Application PCT/US2018/056057, filed on Oct. 16, 2018, which claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 62/573,387, filed on Oct. 17, 2017, the contents of which are incorporated herein by reference in their entireties.

**BACKGROUND**

The field of the invention relates to vitamin D compounds, and more particularly to (22E)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub> analogs and their pharmaceutical uses. In particular, the field of the invention relates to procedures for crystallizing vitamin D compounds such as (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub>.

Purification of organic compounds, especially those designated for pharmaceutical use, is of considerable importance for chemists synthesizing such compounds. Preparation of the compound usually requires many synthetic steps and, therefore, the final product can be contaminated not only with side-products derived from the last synthetic step of the procedure but also with compounds that were formed in previous steps. Even chromatographic purification, which is a very efficient but relatively time-consuming process, does not usually provide compounds which are sufficiently pure to be used as drugs.

Depending on the method used to synthesize 1 $\alpha$ -hydroxyvitamin D compounds, different minor undesirable compounds can accompany the final product. Thus, for example, if direct C-1 hydroxylation of the 5,6-trans geometric isomer of vitamin D is performed, followed by SeO<sub>2</sub>/NMO oxidation and photochemical irradiation, (see Andrews et al., *J. Org. Chem.* 51, 1635 (1986); Calverley et al., *Tetrahedron* 43, 4609 (1987); Choudry et al., *J. Org. Chem.* 58, 1496 (1993)), the final 1 $\alpha$ -hydroxyvitamin D product can be contaminated with 1 $\beta$ -hydroxy- as well as 5,6-trans isomers. If the method consists of C-1 allylic oxidation of the 4-phenyl-1,2,4-triazoline-3,5-dione adduct of the pre-vitamin D compound, followed by cycloreversion of the modified adduct under basic conditions, (see Nevinckx et al., *Tetrahedron* 47, 9419 (1991); Vanmaele et al., *Tetrahedron* 41, 141 (1985) and 40, 1179 (1994); Vanmaele et al., *Tetrahedron Lett.* 23, 995 (1982)), one can expect that the desired 1 $\alpha$ -hydroxyvitamin can be contaminated with the pre-vitamin 5(10), 6,8-triene and 1 $\beta$ -hydroxy isomer. One of the most useful C-1 hydroxylation methods, of very broad scope and numerous applications, is the experimentally simple procedure elaborated by Paaren et al., *J. Org. Chem.* 45, 3253 (1980); and *Proc. Natl. Acad. Sci U.S.A.* 75, 2080 (1978). This method consists of allylic oxidation of 3,5-cyclovitamin D derivatives, readily obtained from the buffered solvolysis of vitamin D tosylates, with SeO<sub>2</sub>/t-BuOOH and subsequent acid-catalyzed cycloreversion to the desired 1 $\alpha$ -hydroxy compounds. Taking into account this synthetic path it is reasonable to assume that the final product can be contaminated with the 1 $\alpha$ -hydroxy epimer, the 5,6-trans isomer and the pre-vitamin D form. 1 $\alpha$ -hydroxyvitamin D<sub>4</sub> is another undesirable contaminant found in 1 $\alpha$ -hydroxyvitamin D compounds synthesized from vita-

min D<sub>2</sub> or from ergosterol. 1 $\alpha$ -hydroxyvitamin D<sub>4</sub> results from C-1 oxidation of vitamin D<sub>4</sub>, which in turn is derived from contamination of the commercial ergosterol material. Typically, the final product may contain up to about 1.5% by weight 1 $\alpha$ -hydroxyvitamin D<sub>4</sub>. Thus, a purification technique that would eliminate or substantially reduce the amount of 1 $\alpha$ -hydroxyvitamin D<sub>4</sub> in the final product to less than about 0.1-0.2% would be highly desirable.

The vitamin D conjugated triene system is not only heat- and light-sensitive but it is also prone to oxidation, leading to the complex mixture of very polar compounds. Oxidation usually happens when a vitamin D compound has been stored for a prolonged time. Other types of processes that can lead to a partial decomposition of vitamin D compounds consist of some water-elimination reactions. The driving force for these reactions is the allylic (1 $\alpha$ -) and homoallylic (3 $\beta$ -) position of the hydroxy groups. The presence of such above-mentioned oxidation and elimination products can be easily detected by thin-layer chromatography.

Usually, all 1 $\alpha$ -hydroxylation procedures require at least one chromatographic purification. However, even chromatographically purified 1 $\alpha$ -hydroxyvitamin D compounds, although showing consistent spectroscopic data that suggests homogeneity, do not meet the purity criteria required for therapeutic agents that can be orally, parenterally or transdermally administered.

Therefore, improved purification procedures for vitamin D compounds are desirable such as crystallization procedures. Here, the present inventors disclose procedures for crystallizing (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub>.

**SUMMARY**

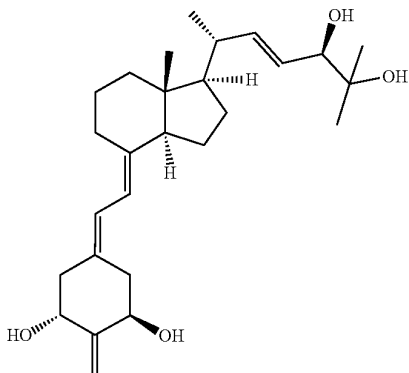
Disclosed herein are procedures for purifying (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub>, otherwise referred to as "WT-51" by means of crystallization to obtain WT-51 in crystalline form.

The disclosed crystallization procedures utilize a solvent to dissolve WT-51. The solvent plays an important role in the crystallization procedure, and is typically an individual liquid substance or a suitable mixture of different liquids. For crystallizing WT-51, the most appropriate solvent and/or solvent system is characterized by the following factors: (1) low toxicity; (2) low boiling point (e.g. less than about 100, 90, or 80° C.); (3) significant dependence of solubility properties with regard to temperature (condition necessary for providing satisfactory crystallization yield); and (4) relatively low cost.

Interestingly, a mixture of ethyl acetate and hexane was found to be a suitable solvent for the crystallization of WT-51. In particular, it was determined that a mixture of about 20% to about 30% ethyl acetate (v/v) with about 80% to about 70% hexane (v/v) was a suitable solvent for the crystallization of WT-51. In the disclosed method, WT-51 first was dissolved in ethyl acetate and hexane was added dropwise to reach a saturation point. After sitting at room temperature, crystals of WT-51 began to grow after about 1 hour. The ethyl acetate/hexane solvent mixture also was easy to remove by evaporation or other well-known methods. The precipitated crystals were sufficiently large to assure their recovery by filtration or other means, and thus were suitable for X-ray diffraction analysis.

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Accordingly, the present invention provides a compound having the formula:



in crystalline form. More specifically, the compound may be referred to as (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub>, or "WT-51" in crystalline form.

The crystalline forms of WT-51 may be formulated as a pharmaceutical composition comprising a crystalline form of WT-51 and a suitable carrier. The pharmaceutical compositions may be administered to a subject in need thereof for treating a variety of conditions that are treated and/or prevented by vitamin D compounds.

In some embodiments, the crystalline forms of WT-51 disclosed herein may be utilized in methods for treating and/or preventing skin diseases, disorders, and conditions in a subject in need thereof. These may include, but are not limited to psoriasis, acne, lack of adequate skin firmness, lack of adequate dermal hydration, and insufficient sebum secretion.

In further embodiments, the crystalline forms of WT-51 disclosed herein may be utilized in methods for treating and/or preventing cell proliferative diseases or disorders such as cancer in a subject in need thereof. These may include, but are not limited to leukemia, colon cancer, breast cancer, skin cancer, and prostate cancer.

In even further embodiments, the crystalline forms of WT-51 disclosed herein may be utilized in methods for treating and/or preventing autoimmune diseases and disorders in a subject in need thereof. These may include, but are not limited to multiple sclerosis, diabetes mellitus, lupus, host versus graft reaction, and rejection of transplants.

In even further embodiments, the crystalline forms of WT-51 disclosed herein may be utilized in methods for treating and/or preventing inflammatory diseases. These may include, but are not limited to rheumatoid arthritis, asthmas, and inflammatory bowel diseases. The crystalline forms of WT-51 may be utilized specifically in methods of treating or preventing inflammatory bowel diseases that include Crohn's disease and ulcerative colitis.

In even further embodiments, the crystalline forms of WT-51 disclosed herein may be utilized in methods for treating and/or preventing obesity, inhibiting adipocyte differentiation, inhibiting SCD-1 gene transcription, and/or reducing body fat.

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is an illustration of one embodiment of a three dimensional molecular structure for WT-51 as defined by the atomic positional parameters discovered and set forth herein.

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FIG. 2 is an illustration of one embodiment of a three dimensional molecular structure for WT-51 as defined by the atomic positional parameters discovered and set forth herein.

FIG. 3 is an illustration of one embodiment of a three dimensional molecular structure for WT-51 as defined by the atomic positional parameters discovered and set forth herein.

FIG. 4 is an illustration of three dimensional molecular structures for WT-51 as defined by the atomic positional parameters discovered and set forth herein.

#### DETAILED DESCRIPTION

The disclosed subject matter further may be described utilizing terms as defined below.

Unless otherwise specified or indicated by context, the terms "a", "an", and "the" mean "one or more." For example, the phrases "a compound" and "an analog" should be interpreted to mean "one or more compounds" and "one or more analogs," respectively.

As used herein, "about", "approximately," "substantially," and "significantly" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which they are used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" and "approximately" will mean plus or minus  $\leq 10\%$  of the particular term and "substantially" and "significantly" will mean plus or minus  $>10\%$  of the particular term.

As used herein, the terms "include" and "including" have the same meaning as the terms "comprise" and "comprising." The transitional term "comprising" should be interpreted as being "open-ended" such that a claim utilizing the term "comprising" should be interpreted as requiring the recited components but being permitted to include other additional components. The transitional term "consisting essentially of" should be interpreted as being "partially closed" such that a claim utilizing the term "consisting essentially of" should be interpreted as requiring the recited components and permitting only other additional components that do not materially affect the basic and novel characteristics of the claimed subject matter. The transitional term "consisting" should be interpreted as being "closed" such that a claim utilizing the term "consisting" should be interpreted as requiring the recited components and permitting no other additional components.

As used herein, the terms "native hormone" and "1 $\alpha$ ,25(OH)<sub>2</sub>D<sub>3</sub>" may be used interchangeably.

As used herein, the compound "WT-51" refers to (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub>. Methods for synthesizing WT-51 are disclosed, for example, in U.S. Pat. No. 9,416,102, the content of which is incorporated herein by reference in its entirety.

As disclosed herein, the crystalline forms of WT-51 may be utilized to treat and/or prevent diseases or disorders in a subject in need thereof. The terms "subject," "patient," and "individual" may be used interchangeably herein.

A subject in need thereof may include any animal. The animal may be a human, a domestic animal such as a dog or a cat, or an agricultural animal, especially those that provide meat for human consumption, such as fowl like chickens, turkeys, pheasant or quail, as well as bovine, ovine, caprine, or porcine animals.

A subject in need thereof may refer to subject having or at risk for acquiring a disease or disorders associated with vitamin D activity. For example, a subject in need thereof



may include a subject having or at risk for acquiring bone diseases and disorders, which may include, metabolic bone diseases and disorders where an increase in bone mass is desirable such as osteoporosis (e.g., senile osteoporosis, postmenopausal osteoporosis, steroid-induced osteoporosis, and low bone-turnover osteoporosis), osteopenia, and osteomalacia. A subject in need thereof may also include a subject in need of an increase in bone strength.

A subject in need thereof may include a subject having or at risk for developing skin diseases, disorders, and conditions. These may include, but are not limited to psoriasis, acne, lack of adequate skin firmness, lack of adequate dermal hydration, and insufficient sebum secretion.

A subject in need thereof may include a subject having or at risk for developing cell proliferative diseases or disorders such as cancer. These may include, but are not limited to leukemia, colon cancer, breast cancer, skin cancer, and prostate cancer.

A subject in need thereof may include a subject having or at risk for developing autoimmune diseases and disorders. These may include, but are not limited to multiple sclerosis, diabetes mellitus, lupus, host versus graft reaction, and rejection of transplants.

A subject in need thereof may include a subject having or at risk for developing an inflammatory disease or disorder. These may include, but are not limited to rheumatoid arthritis, asthmas, and inflammatory bowel diseases. A subject in need thereof may include having or at risk for developing Crohn's disease and ulcerative colitis.

A subject in need thereof may include a subject having or at risk for developing obesity. A subject in need thereof may include a subject in need of or desirous of inhibiting adipocyte differentiation, inhibiting SCD-1 gene transcription, and/or reducing body fat.

A subject in need thereof may include a subject having or at risk for developing secondary hyperparathyroidism. In particular, a subject in need thereof may include a subject having or at risk for developing secondary hyperparathyroidism of renal osteodystrophy.

For prevention and/or treatment purposes, the crystalline forms of WT-51 may be formulated for pharmaceutical applications as a solution in innocuous solvents, or as an emulsion, suspension or dispersion in suitable solvents or carriers, or as pills, tablets or capsules, together with solid carriers, according to conventional methods known in the art. Any such formulations may also contain other pharmaceutically-acceptable and non-toxic excipients such as stabilizers, anti-oxidants, binders, coloring agents or emulsifying or taste-modifying agents.

The crystalline forms of WT-51 may be administered orally, topically, parenterally, rectally, nasally, sublingually or transdermally. The compound is advantageously administered by injection or by intravenous infusion or suitable sterile solutions, or in the form of liquid or solid doses via the alimentary canal, or in the form of creams, ointments, patches, or similar vehicles suitable for transdermal applications.

A dose of from 0.01  $\mu\text{g}$  to 1000  $\mu\text{g}$  per day of the crystalline forms of WT-51, preferably from about 0.1  $\mu\text{g}$  to about 500  $\mu\text{g}$  per day, is appropriate for prevention and/or treatment purposes, such dose being adjusted according to the disease to be treated, its severity and the response of the subject as is well understood in the art. Because the compound exhibits specificity of action, each may be suitably administered alone, or together with graded doses of another active vitamin D compound (e.g., 1 $\alpha$ -hydroxyvitamin D<sub>2</sub> or D<sub>3</sub>, or 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub>) in situations where

different degrees of bone mineral mobilization and calcium transport stimulation is found to be advantageous.

Compositions for use in the above-mentioned treatments comprise an effective amount of crystalline forms of WT-51 as the active ingredient, and a suitable carrier. An effective amount of such compound for use in accordance with this invention is from about 0.01  $\mu\text{g}$  to about 1000  $\mu\text{g}$  per gm of composition, preferably from about 0.1  $\mu\text{g}$  to about 500  $\mu\text{g}$  per gram of composition, and may be administered topically, transdermally, orally, rectally, nasally, sublingually, or parenterally in dosages of from about 0.01  $\mu\text{g}/\text{day}$  to about 1000  $\mu\text{g}/\text{day}$ , and preferably from about 0.1  $\mu\text{g}/\text{day}$  to about 500  $\mu\text{g}/\text{day}$ .

The formulations of the present invention comprise an active ingredient in association with a pharmaceutically acceptable carrier therefore and optionally other therapeutic ingredients. The carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof.

Formulations of the present invention suitable for oral administration may be in the form of discrete units as capsules, sachets, tablets or lozenges, each containing a predetermined amount of the active ingredient, for example, in the form of a crystalline powder or crystalline granules.

The formulations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. By the term "dosage unit" is meant a unitary, i.e. a single dose which is capable of being administered to a subject as a physically and chemically stable unit dose comprising either the active ingredient as such or a mixture of it with solid or liquid pharmaceutical diluents or carriers.

#### EXAMPLES

The following Examples are illustrative and are not intended to limit the scope of the claimed subject matter.

Example 1—Preparation of (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub> (WT-51)

(22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub> (WT-51) was synthesized as previously described. (See U.S. Pat. No. 9,416,102, the content of which is incorporated herein by reference in its entirety).

(22E)-Des-A,B-8 $\beta$ -benzoyloxy-24-oxo-25-[(triethylsilyloxy)-22-dehydrocholestan (3)

To a stirred solution of 2 (Scheme 1; 250 mg; 0.64 mmol) in tetrahydrofuran (1.5 ml) 1 M solution of lithium hexamethyldisilazide in tetrahydrofuran (700  $\mu\text{l}$ ; 0.70 mmol) was added dropwise. After 1 h a solution of 1<sup>1</sup> (200 mg; 0.64 mmol) in tetrahydrofuran (1.5 ml) was added via cannula. The reaction mixture was stirred for 3 days. Then saturated aqueous solution of NH<sub>4</sub>Cl (2 ml), brine (2 ml) and water (5 ml) was added at 0° C. and the resulting mixture was extracted with methylene dichloride (3 $\times$ 50 ml). Organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the residue was purified by column chromatography (2-5% ethyl acetate/hexane) to give 200 mg (0.39 mmol; 61% yield) of 3. [ $\alpha$ ]<sub>D</sub><sup>25</sup>=+94.3 (c 1.1, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.60 (6H, q, J=7.9 Hz), 0.95 (9H, t, J=7.9 Hz), 1.10 (3H, s), 1.12 (3H, d, J=6.6 Hz), 1.34 (6H, s), 2.04 (2H, m), 2.32 (1H, m), 5.42 (1H, br d, J=1.9 Hz), 6.71 (1H, d, J=15.4 Hz), 6.84 (1H, dd, J=15.4

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Hz,  $J=8.6$  Hz), 7.45 (2H, t,  $J=7.4$  Hz), 7.56 (1H, t,  $J=7.4$  Hz), 8.05 (2H, d,  $J=7.4$  Hz);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  6.5, 7.0, 13.8, 18.0, 19.2, 22.6, 27.0, 27.1, 27.2, 30.5, 39.8, 42.2, 51.4, 55.4, 72.0, 78.8, 121.7, 128.4, 129.5, 132.7, 153.2, 166.4, 203.2; Exact mass (ESI) calculated for  $\text{C}_{31}\text{H}_{49}\text{O}_4\text{Si}$  513.3395, found 513.3405.

(22E)-Des-A,B-8 $\beta$ -benzoyloxy-24-hydroxy-25-[(triethylsilyl)oxy]-22-dehydrocholestan (4, Mixture of 24-Isomers)

To a stirred solution of 3 (200 mg; 0.39 mmol) in tetrahydrofuran (1.5 ml) and ethanol (4.5 ml)  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (298 mg; 0.80 mmol) and  $\text{NaBH}_4$  (46 mg; 1.20 mmol) was added at  $0^\circ\text{C}$ . After 30 min. saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (2 ml) and water (5 ml) were added and the mixture was extracted with methylene dichloride ( $3 \times 40$  ml). Organic phase was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , concentrated under reduced pressure and the residue was purified by column chromatography (5-15% ethyl acetate/hexane) to give 180 mg (0.35 mmol; 90% yield) of 4 as a mixture of 24-diastereoisomers. Exact mass (ESI) calculated for  $\text{C}_{31}\text{H}_{50}\text{O}_4\text{SiNa}$  ( $[\text{M}+\text{Na}]^+$ ) 537.3371, found 537.3380.

(22E)-Des-A,B-8 $\beta$ -benzoyloxy-24,25-di-[(triethylsilyl)oxy]-22-dehydrocholestan (5, Mixture of 24-Isomers)

To a stirred solution of 4 (150 mg; 0.29 mmol) and 2,6-lutidine (67  $\mu\text{l}$ ; 62 mg; 0.58 mmol) in methylene dichloride (1 ml) triethylsilyl trifluoromethanesulfonate (79  $\mu\text{l}$ ; 92 mg; 0.35 mmol) was added dropwise at  $-50^\circ\text{C}$ . After 20 min. wet methylene dichloride (1 ml) and water (5 ml) was added and the mixture was extracted with methylene dichloride ( $3 \times 25$  ml). Organic phase was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was purified by column chromatography (hexane—3% ethyl acetate/hexane) to give 165 mg (0.26 mmol; 90% yield) of 5. Exact mass (ESI) calculated for  $\text{C}_{37}\text{H}_{64}\text{O}_4\text{Si}_2\text{Na}$  ( $[\text{M}+\text{Na}]^+$ ) 651.4236, found 651.4234.

(22E)-Des-A,B-24,25-di-[(triethylsilyl)oxy]-22-dehydrocholestan-8 $\beta$ -ol (6, Mixture of 24-isomers)

A solution of 5 (160 mg; 0.25 mmol) in tetrahydrofuran (3 ml) was treated with a 3 M solution of methylmagnesium bromide in diethyl ether (750  $\mu\text{l}$ ; 2.25 mmol) for 5 h at  $0^\circ\text{C}$ . Saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (2 ml), brine (2 ml) and water (5 ml) was carefully added and the mixture was extracted with methylene dichloride ( $3 \times 25$  ml). Organic phase was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was purified on a silica gel Sep-Pack cartridge (5-15% ethyl acetate/hexane) to give 106 mg (0.20 mmol; 81% yield) of 6. Exact mass (ESI) calculated for  $\text{C}_{30}\text{H}_{60}\text{O}_3\text{Si}_2\text{Na}$  ( $[\text{M}+\text{Na}]^+$ ) 547.3974, found 547.3957.

(22E)-Des-A,B-24,25-di-[(triethylsilyl)oxy]-22-dehydrocholestan-8-one (7, Mixture of 24-Isomers)

A solution of 6 (65 mg; 120  $\mu\text{mol}$ ) and pyridinium p-toluenesulfonate (2 crystals) in methylene dichloride (6 ml) was treated with pyridinium dichromate (150 mg; 400  $\mu\text{mol}$ ) for 3 h. The mixture was purified on a silica gel Sep-Pack cartridge (3-7% ethyl acetate/hexane) to give 54

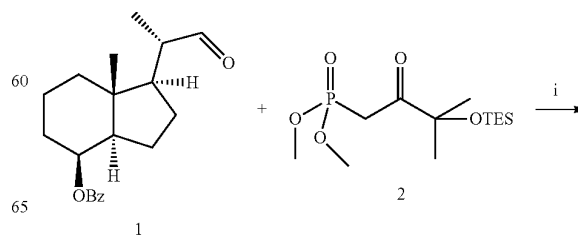
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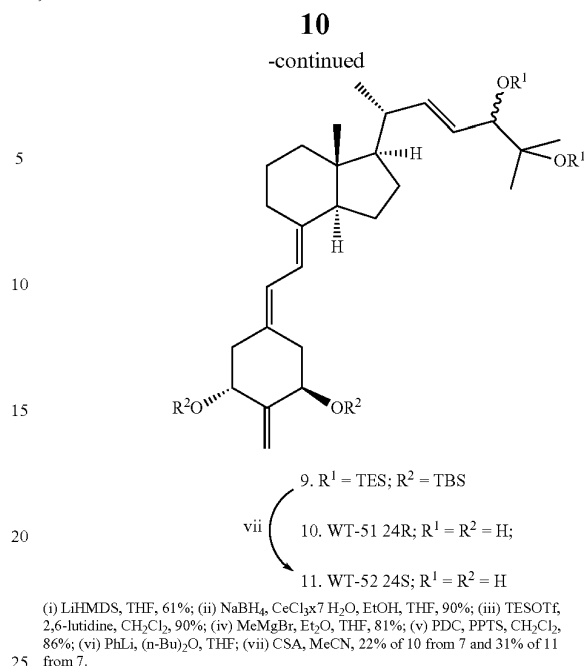
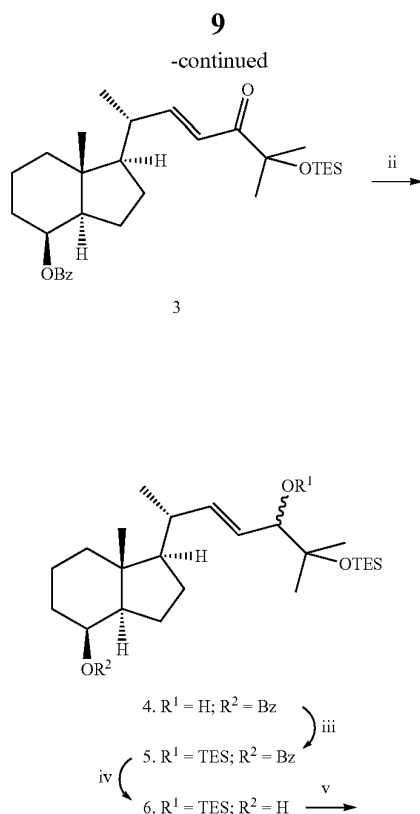
mg (103  $\mu\text{mol}$ ; 86%) of 7. Exact mass (ESI) calculated for  $\text{C}_{30}\text{H}_{58}\text{O}_3\text{Si}_2\text{Na}$  ( $[\text{M}+\text{Na}]^+$ ) 545.3817, found 545.3817.

(22E)-(24R)-2-Methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-norvitamin  $\text{D}_3$  (10, WT-51) and (22E)-(24S)-2-Methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-norvitamin  $\text{D}_3$  (11, WT-52)

To a stirred solution of 8 (87 mg; 150  $\mu\text{mol}$ ) in tetrahydrofuran (1.5 ml) two drops of 1.8 M phenyl lithium solution in di-n-butyl ether was added at  $-25^\circ\text{C}$ . and the solution turned deep orange. Then stoichiometric amount of phenyl lithium solution (78  $\mu\text{l}$ ; 140  $\mu\text{mol}$ ) was added dropwise. After 20 min. the mixture was cooled to  $-78^\circ\text{C}$ . and a solution of 7 (53 mg; 101  $\mu\text{mol}$ ) in tetrahydrofuran (0.75 ml) was transferred via cannula. The mixture was stirred for 2 h, warmed to  $0^\circ\text{C}$ . and stirred for next 2 h. Saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (1 ml), brine (1 ml) and water (5 ml) was carefully added and the mixture was extracted with hexane ( $3 \times 25$  ml). Organic phase was dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was purified on a silica gel Sep-Pack cartridge (hexane—2% ethyl acetate/hexane) to give 90 mg of crude 9. Crude 9 was dissolved in acetonitrile (2 ml) and treated with ( $\pm$ )-camphor-10-sulfonic acid (40 mg; 172  $\mu\text{mol}$ ) for 2 days. The mixture was purified on a previously treated with 10 drops of triethylamine silica gel Sep-Pack cartridge (10-30% 2-propanol/hexane) to give 28 mg (65  $\mu\text{mol}$ ; 64% yield from 7) of 10 and 11 as a mixture of diastereoisomers. The mixture was separated on HPLC (15% water/methanol; Zorbax-Eclipse XDB C18 5  $\mu\text{m}$ ; 3.5 ml/min.;  $R_f=5.30$  min. for 10 and  $R_f=5.80$  min. for 11) to give 9.5 mg (22  $\mu\text{mol}$ ; 22% yield from 7) of 10 and 13.5 mg (31  $\mu\text{mol}$ ; 31% yield from 7) of 11. X-ray analysis of 11 has shown 24S configuration. 10: UV (EtOH)  $\lambda_{\text{max}}=245, 252, 262$  nm;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  0.60 (3H, s), 1.07 (3H, d,  $J=6.6$  Hz),  $2 \times 1.13$  (3H each, s), 2.25-2.31 (2H, m), 2.48 (1H, dd,  $J=13.4$  Hz,  $J=3.8$  Hz), 2.66 (1H, dd,  $J=13.2$  Hz,  $J=4.3$  Hz), 2.85 (1H, dd,  $J=12.2$  Hz,  $J=3.8$  Hz), 3.73 (1H, d,  $J=7.4$  Hz), 4.37 (1H, m), 4.41 (1H, m), 5.04 (1H, s), 5.05 (1H, s), 5.43 (1H, dd,  $J=15.4$  Hz,  $J=7.5$  Hz), 5.52 (1H, dd,  $J=15.4$  Hz,  $J=8.6$  Hz), 5.90 (1H, d,  $J=11.1$  Hz), 6.26 (1H, d,  $J=11.1$  Hz); 11: UV (EtOH)  $\lambda_{\text{max}}=244, 252, 261$  nm;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  0.60 (3H, s), 1.06 (3H, d,  $J=6.6$  Hz), 1.12 (3H, s), 1.13 (3H, s), 1.65-1.70 (2H, m), 1.79-1.83 (1H, m), 1.93-2.07 (2H, m), 2.13 (1H, m), 2.25-2.31 (2H, m), 2.48 (1H, dd,  $J=13.3$  Hz,  $J=3.9$  Hz), 2.67 (1H, dd,  $J=13.2$  Hz,  $J=4.3$  Hz), 2.85 (1H, dd,  $J=12.2$  Hz,  $J=3.7$  Hz), 3.75 (1H, d,  $J=6.7$  Hz), 4.37 (1H, m), 4.41 (1H, m), 5.04 (1H, s), 5.06 (1H, s), 5.45 (1H, dd,  $J=15.4$  Hz,  $J=6.9$  Hz), 5.57 (1H, dd,  $J=15.4$  Hz,  $J=8.4$  Hz), 5.90 (1H, d,  $J=11.1$  Hz), 6.26 (1H, d,  $J=11.1$  Hz); MS (EI)  $m/z$  430 ( $\text{M}^+$ , 10), 396 (7), 253 (22), 91 (100); exact mass (ESI) calculated for  $\text{C}_{27}\text{H}_{42}\text{O}_4\text{Na}$  ( $[\text{M}+\text{Na}]^+$ ) 453.2976, found 453.2977.

Scheme I.





### Example 2—Preparation of 1-(Dimethoxyphosphoryl)-3-methyl-3-[(triethylsilyl)oxy]-2-butanone

#### 3-Methyl-3-[(triethylsilyl)oxy]-2-butanone (13)

To a stirred solution of 3-hydroxy-3-methyl-2-butanone (Scheme 2; 1.20 ml; 1.16 g; 11.4 mmol) and 2,6-lutidine (1.86 ml; 1.71 g; 16.0 mmol) in methylene dichloride (30 ml) triethylsilyl trifluoromethanesulfonate (3.11 ml; 3.61 g; 13.7 mmol) was added dropwise at  $-50^{\circ}\text{C}$ . After 20 min. wet methylene dichloride (5 ml) and water (50 ml) was added and the mixture was extracted with methylene dichloride (3×100 ml). Organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography (hexane—3% ethyl acetate/hexane) to give 2.40 g (10.4 mmol; 91% yield) of 13. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.63 (6H, q, J=7.9 Hz), 0.97 (9H, t, J=7.9 Hz), 1.33 (6H, s), 2.23 (3H, s); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 6.5, 7.0, 27.0, 27.7, 79.7, 214.0; MS (EI) m/z 216 ([M-Et]<sup>+</sup>, 100), 173 (81), 172 (30) 115 (68), 87 (67); exact mass calculated for C<sub>9</sub>H<sub>19</sub>O<sub>2</sub>Si ([M-Et]<sup>+</sup>) 187.1149, found 187.1144.

#### 1-Bromo-3-methyl-3-[(triethylsilyl)oxy]-2-butanone (14)

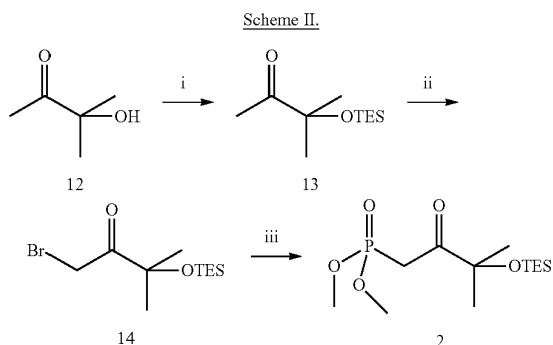
To a stirred solution of 13 (2.40 g; 10.4 mmol) and triethylamine (2.92 ml; 2.12 g; 21.0 mmol) in methylene dichloride (50 ml) triethylsilyl trifluoromethanesulfonate (2.37 ml; 2.75 g; 10.4 mmol) was added dropwise at 0° C. After 15 min. N-bromosuccinimide (2.05 g; 11.5 mmol) was added and a cooling bath was removed. After 30 min. saturated aqueous solution of NH<sub>4</sub>Cl (10 ml) and water (50 ml) was added and the mixture was extracted with methylene dichloride (3×100 ml). Organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography (hexane—5% ethyl acetate/hexane) to give 1.55 g (5.25 mmol; 50% yield) of 14. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.64

## 11

(6H, q, J=7.9 Hz), 0.97 (9H, t, J=7.9 Hz), 1.41 (6H, s), 4.44 (2H, s);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  6.5, 7.0, 27.8, 33.6, 80.4, 206.2; MS (EI)  $m/z$  294 and 296 ( $[\text{M}-\text{Et}]^+$ , 24 and 23), 187 (45), 173 (100); exact mass calculated for  $\text{C}_9\text{H}_{18}\text{O}_2\text{BrSi}$  ( $[\text{M}-\text{Et}]^+$ ) 265.0254, found 265.0247.

1-(Dimethoxyphosphoryl)-3-methyl-3-[(triethylsilyl)oxy]-2-butanone (2)

A solution of 14 (1.55 g; 5.25 mmol) and trimethyl phosphite (514  $\mu\text{l}$ ; 782 mg; 6.31 mmol) in toluene (20 ml) was refluxed for 3 days. The mixture was purified by column chromatography (5-15% 2-propanol/hexane) to give 1.54 g (4.75 mmol; 90% yield) of 2.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.65 (6H, q, J=7.9 Hz), 0.98 (9H, t, J=7.9 Hz), 1.36 (6H, s), 3.40 (2H, d,  $J_{\text{H-P}}=20.7$  Hz) 3.80 (6H, d,  $J_{\text{H-P}}=11.2$  Hz);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  6.4, 6.9, 26.8, 33.7 (d,  $J_{\text{C-P}}=137.8$  Hz), 52.8 (d,  $J_{\text{C-P}}=6.7$  Hz) 80.0, 207.1 (d,  $J_{\text{C-P}}=6.0$  Hz); MS (EI)  $m/z$  324 ( $[\text{M}-\text{Et}]^+$ , 98), 238 (65), 211 (61), 173 (100); exact mass calculated for  $\text{C}_{11}\text{H}_{24}\text{O}_5\text{PSi}$  ( $[\text{M}-\text{Et}]^+$ ) 295.1126, found 295.1126.



Example 3—Crystallization of (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin  $\text{D}_3$  (WT-51) and X-ray Diffraction Analysis

Crystallization of (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin  $\text{D}_3$  (WT-51) from Ethyl Acetate/Hexane

WT-51 (15 mg) was placed in a 4 mL vial and dissolved in ethyl acetate (0.3 mL). Next, hexane (1 mL) was added dropwise to reach a saturation point. The vial then was sealed and left at room temperature. After about 1 hour, crystals began to grow and the mixture was left for the next 2 days at room temperature to obtain crystals. The obtained crystals were filtered off, and washed with a small volume of ethyl acetate/hexane, and dried to give crystalline WT-51.

Experimental. The crystals thus obtained were suitable for X-ray diffraction analysis and were analyzed accordingly. (See, e.g., U.S. Pat. Nos. 9,212,137; 9,040,729; 8,940,916; 8,884,039; 8,519,169; 8,420,839; and 8,404,874; the contents of which are incorporated herein by reference in their entirety). Crystal data and structure refinement are provided in Table 1. Atomic coordinates ( $\text{\AA}\times 10^3$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2\times 10^3$ ) are provided in Table 2. Bond lengths [ $\text{\AA}$ ] and angles [ $^\circ$ ] are provided in Table 3. Anisotropic displacement parameters

## 12

( $\text{\AA}\times 10^3$ ) are provided in Table 4. Hydrogen coordinates ( $\text{\AA}\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2\times 10^3$ ) are provided in Table 5. Torsion angles [ $^\circ$ ] are provided in Table 6. The three dimensional structure of WT-51 as defined by the physical data and atomic positional parameters disclosed in Table 1-6 is illustrated in FIGS. 1-4.

In the foregoing description, it will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention. Thus, it should be understood that although the present invention has been illustrated by specific embodiments and optional features, modification and/or variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention.

Citations to a number of references are made herein. The cited references are incorporated by reference herein in their entirety. In the event that there is an inconsistency between a definition of a term in the specification as compared to a definition of the term in a cited reference, the term should be interpreted based on the definition in the specification.

TABLE 1

Crystal data and structure refinement.	
Empirical formula	$\text{C}_{27}\text{H}_{42}\text{O}_4\cdot 1.33\text{H}_2\text{O}$
Formula weight	454, 430.62 without $\text{H}_2\text{O}$
Temperature	100(2) K
Wavelength	1.54178 $\text{\AA}$
Crystal system	Monoclinic
Space group	$\text{P}2_1$
Unit cell dimensions	$a = 16.3058(9)$ $\text{\AA}$ $\alpha = 90^\circ$ $b = 10.0461(6)$ $\text{\AA}$ $\beta = 109.001(3)^\circ$ $c = 26.0527(15)$ $\text{\AA}$ $\gamma = 90^\circ$
Volume	4035.1(4) $\text{\AA}^3$
Z	6
Density (calculated)	1.076 $\text{Mg}/\text{m}^3$
Absorption coefficient	0.561 $\text{mm}^{-1}$
F(000)	1430
Crystal size	0.05 $\times$ 0.04 $\times$ 0.3 mm
Theta range for data collection	2.843 to 62.415 $^\circ$
Index ranges	-17 $\leq h \leq 18$ , -11 $\leq k \leq 11$ , -29 $\leq l \leq 29$
Reflections collected	32723
Independent reflections	12241 [ $R(\text{int}) = 0.0582$ ]
Completeness to theta = 62.415 $^\circ$	98.4%
Absorption correction	None
Refinement method	Full-matrix least-squares on $F^2$
Data/restraints/parameters	12241/1/874
Goodness-of-fit on $F^2$	0.975
Final R indices	$R1 = 0.0790$ , $wR2 = 0.2184$
[ $I > 2\sigma(I)$ ]	
R indices (all data)	$R1 = 0.1014$ , $wR2 = 0.2408$
Absolute structure parameter	-0.17(18)
Extinction coefficient	n/a
Largest diff. peak and hole	0.567 and -0.300 $\text{e}/\text{\AA}^3$

TABLE 2

Atomic coordinates ( $\text{\AA} \times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ).  
 U(eq) is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor.

	x	y	z	U(eq)
O(301)	6552(3)	2722(4)	428(2)	49(1)
O(303)	4579(3)	5562(4)	-120(2)	46(1)
O(325)	11671(3)	5441(5)	-2184(2)	53(1)
O(203)	11026(3)	12936(5)	-2518(2)	57(1)
C(313)	8967(4)	9428(6)	-546(2)	38(1)
O(124)	11921(4)	7064(5)	-2990(3)	72(2)
C(304)	5725(4)	6688(7)	611(3)	44(2)
O(201)	11630(4)	9648(5)	-3406(2)	66(1)
C(307)	7340(4)	7516(6)	-145(3)	39(1)
O(324)	12479(3)	7376(6)	-1520(2)	75(2)
C(308)	7586(4)	8560(6)	-379(3)	40(1)
C(301)	6137(4)	4013(6)	306(3)	41(1)
C(314)	8188(4)	8424(6)	-713(3)	44(1)
C(305)	6433(4)	6501(7)	367(3)	43(1)
C(208)	14684(4)	13712(7)	-2040(3)	47(2)
C(322)	10647(4)	8846(6)	-1325(3)	43(2)
O(225)	18480(5)	13560(8)	-4317(3)	94(2)
C(318)	9576(4)	9160(7)	29(3)	43(1)
C(206)	13318(4)	12615(7)	-2010(3)	50(2)
C(323)	11278(4)	7972(6)	-1240(3)	43(2)
C(302)	5481(4)	4256(6)	596(3)	41(1)
C(201)	11723(5)	10653(7)	-3010(3)	55(2)
C(324)	11554(4)	7334(7)	-1682(3)	46(2)
C(306)	6697(4)	7526(6)	129(3)	42(1)
C(207)	14030(4)	12840(7)	-2223(3)	48(2)
C(309)	7254(4)	9950(7)	-395(3)	49(2)
C(311)	7985(4)	11008(7)	-264(3)	47(2)
C(214)	15368(4)	13883(7)	-2298(3)	45(2)
C(303)	5043(4)	5572(6)	453(3)	42(1)
C(312)	8602(4)	10837(6)	-598(3)	45(2)
C(320)	10347(4)	9470(6)	-892(3)	43(1)
C(116)	15160(5)	6779(8)	-3503(3)	59(2)
C(213)	16311(4)	13705(6)	-1905(3)	47(2)
C(217)	16828(4)	13959(7)	-2303(3)	47(2)
C(122)	14092(5)	7380(8)	-2811(3)	60(2)
C(310)	6822(4)	5116(6)	441(3)	45(2)
C(218)	16451(4)	12268(7)	-1694(3)	52(2)
C(215)	15340(4)	13101(7)	-2801(3)	51(2)
C(316)	9336(4)	7469(7)	-984(3)	53(2)
C(224)	18653(5)	13644(9)	-3389(3)	65(2)
C(204)	12028(5)	11528(8)	-1886(3)	58(2)
C(317)	9419(4)	9013(6)	-966(3)	40(1)
C(205)	12722(5)	11644(7)	-2149(3)	54(2)
O(224)	19531(4)	13319(8)	-3334(3)	92(2)
C(321)	10433(5)	10985(7)	-917(3)	53(2)
C(202)	11033(5)	10607(7)	-2746(3)	51(2)
C(221)	18384(5)	14028(9)	-1629(3)	65(2)
C(222)	18099(4)	13898(8)	-2615(3)	56(2)
C(211)	15769(5)	14574(8)	-1157(3)	55(2)
C(216)	16251(4)	13334(8)	-2844(3)	52(2)
C(203)	11129(5)	11614(7)	-2305(3)	55(2)
C(315)	8600(5)	7119(7)	-756(4)	56(2)
O(125)	11863(4)	6217(7)	-4057(3)	87(2)
C(123)	13277(5)	7328(7)	-3136(3)	57(2)
C(209)	14825(4)	14636(7)	-1557(3)	50(2)
C(219)	10387(5)	9739(8)	-2883(3)	62(2)
C(223)	18421(4)	13128(8)	-2917(3)	57(2)
C(220)	17787(4)	13490(7)	-2159(3)	52(2)
C(113)	16305(5)	8318(8)	-3020(3)	59(2)
C(319)	5296(4)	3395(8)	927(3)	54(2)
C(212)	16454(5)	14718(7)	-1443(3)	52(2)
C(124)	12621(5)	6367(7)	-3085(3)	58(2)
C(109)	18167(6)	8135(12)	-2900(4)	84(3)
C(118)	15998(6)	9540(8)	-3386(4)	67(2)
C(210)	12638(5)	10600(8)	-2584(3)	58(2)
C(120)	14783(5)	8325(8)	-2834(3)	60(2)
C(325)	11230(5)	5933(7)	-1819(4)	62(2)
C(117)	15515(5)	7568(7)	-2960(3)	56(2)
C(114)	16688(5)	7251(8)	-3298(3)	61(2)
C(125)	12262(6)	5423(9)	-3583(3)	67(2)
C(115)	15894(5)	6740(9)	-3762(4)	70(2)
C(112)	17014(6)	8704(9)	-2482(4)	74(2)
C(108)	17490(5)	7676(9)	-3420(4)	71(2)
C(327)	10241(6)	6013(11)	-2169(5)	92(3)

TABLE 2-continued

Atomic coordinates ( $\text{\AA} \times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ).  
 U(eq) is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor.

	x	y	z	U(eq)
C(225)	18085(6)	13090(11)	-3935(4)	80(3)
C(121)	15094(6)	9096(9)	-2289(4)	76(2)
C(326)	11405(15)	5040(10)	-1354(6)	167(9)
C(110)	18041(6)	7167(12)	-4961(5)	96(3)
C(106)	18316(7)	8145(14)	-4050(6)	111(4)
C(105)	18494(7)	8022(12)	-4501(4)	88(3)
C(126)	12992(7)	4649(11)	-3681(4)	89(3)
C(107)	17582(6)	7649(10)	-3906(4)	77(2)
C(227)	18119(9)	11566(12)	-3930(5)	109(4)
C(127)	11601(8)	4481(10)	-3500(5)	98(3)
C(226)	17180(7)	13662(16)	-4092(5)	111(4)
C(102)	19431(7)	6890(12)	-5163(6)	101(4)
C(111)	17838(7)	9140(12)	-2587(4)	99(4)
C(119)	19688(8)	6800(13)	-5578(6)	108(4)
C(103)	19834(7)	7840(30)	-4706(6)	172(10)
O(101)	18130(18)	5540(30)	-5610(11)	430(20)
C(104)	19200(9)	8823(19)	-4595(6)	139(6)
C(101)	18663(11)	6117(17)	-5085(9)	150(7)
O(103)	20288(7)	7240(30)	-4191(5)	353(19)
O(2)	16200(20)	15120(70)	-5679(17)	630(50)
O(1)	17476(7)	12886(13)	-5340(4)	145(4)
O(3)	14250(30)	3980(130)	-4710(20)	890(110)
O(4)	15000(40)	830(100)	-4827(11)	960(100)

TABLE 3

Bond lengths [ $\text{\AA}$ ] and angles [ $^\circ$ ].

O(301)—C(301)	1.449(8)
O(301)—H(30A)	0.8400
O(303)—C(303)	1.439(8)
O(303)—H(30B)	0.8400
O(325)—C(325)	1.451(8)
O(325)—H(32A)	0.8400
O(203)—C(203)	1.428(9)
O(203)—H(20A)	0.8400
C(313)—C(312)	1.524(9)
C(313)—C(318)	1.526(9)
C(313)—C(317)	1.562(8)
C(313)—C(314)	1.569(8)
O(124)—C(124)	1.427(9)
O(124)—H(12A)	0.8400
C(304)—C(305)	1.500(9)
C(304)—C(303)	1.538(9)
C(304)—H(30C)	0.9900
C(304)—H(30D)	0.9900
O(201)—C(201)	1.417(9)
O(201)—H(20B)	0.8400
C(307)—C(308)	1.338(9)
C(307)—C(306)	1.448(8)
C(307)—H(30E)	0.9500
O(324)—C(324)	1.428(8)
O(324)—H(32B)	0.8400
C(308)—C(309)	1.493(9)
C(308)—C(314)	1.515(8)
C(301)—C(302)	1.518(8)
C(301)—C(310)	1.530(9)
C(301)—H(30F)	1.0000
C(314)—C(315)	1.494(9)
C(314)—H(31A)	1.0000
C(305)—C(306)	1.342(9)
C(305)—C(310)	1.515(10)
C(208)—C(207)	1.342(10)
C(208)—C(214)	1.488(9)
C(208)—C(209)	1.521(10)
C(322)—C(323)	1.316(9)
C(322)—C(320)	1.503(9)
C(322)—H(32C)	0.9500
O(225)—C(225)	1.430(11)
O(225)—H(22A)	0.8400
C(318)—H(31B)	0.9800

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TABLE 3-continued

Bond lengths [Å] and angles [°].	
C(318)—H(31C)	0.9800
C(318)—H(31D)	0.9800
C(206)—C(205)	1.340(10)
C(206)—C(207)	1.459(9)
C(206)—H(20C)	0.9500
C(323)—C(324)	1.510(9)
C(323)—H(32D)	0.9500
C(302)—C(319)	1.324(9)
C(302)—C(303)	1.491(9)
C(201)—C(202)	1.498(10)
C(201)—C(210)	1.543(10)
C(201)—H(20D)	1.0000
C(324)—C(325)	1.506(10)
C(324)—H(32E)	1.0000
C(306)—H(30G)	0.9500
C(207)—H(20E)	0.9500
C(309)—C(311)	1.550(9)
C(309)—H(30H)	0.9900
C(309)—H(30I)	0.9900
C(311)—C(312)	1.539(9)
C(311)—H(31E)	0.9900
C(311)—H(31F)	0.9900
C(214)—C(215)	1.514(10)
C(214)—C(213)	1.555(9)
C(214)—H(21A)	1.0000
C(303)—H(30J)	1.0000
C(312)—H(31G)	0.9900
C(312)—H(31H)	0.9900
C(320)—C(321)	1.531(10)
C(320)—C(317)	1.533(8)
C(320)—H(32F)	1.0000
C(116)—C(115)	1.553(11)
C(116)—C(117)	1.560(11)
C(116)—H(11A)	0.9900
C(116)—H(11B)	0.9900
C(213)—C(212)	1.535(10)
C(213)—C(218)	1.535(10)
C(213)—C(217)	1.555(9)
C(217)—C(216)	1.551(10)
C(217)—C(220)	1.557(9)
C(217)—H(21B)	1.0000
C(122)—C(123)	1.323(11)
C(122)—C(120)	1.489(11)
C(122)—H(12B)	0.9500
C(310)—H(31I)	0.9900
C(310)—H(31J)	0.9900
C(218)—H(21C)	0.9800
C(218)—H(21D)	0.9800
C(218)—H(21E)	0.9800
C(215)—C(216)	1.544(9)
C(215)—H(21F)	0.9900
C(215)—H(21G)	0.9900
C(316)—C(315)	1.542(9)
C(316)—C(317)	1.556(10)
C(316)—H(31K)	0.9900
C(316)—H(31L)	0.9900
C(224)—O(224)	1.429(10)
C(224)—C(223)	1.492(11)
C(224)—C(225)	1.528(13)
C(224)—H(22B)	1.0000
C(204)—C(205)	1.506(10)
C(204)—C(203)	1.519(11)
C(204)—H(20F)	0.9900
C(204)—H(20G)	0.9900
C(317)—H(31M)	1.0000
C(205)—C(210)	1.517(11)
O(224)—H(22C)	0.8400
C(321)—H(32G)	0.9800
C(321)—H(32H)	0.9800
C(321)—H(32I)	0.9800
C(202)—C(219)	1.324(10)
C(202)—C(203)	1.501(10)
C(221)—C(220)	1.507(11)
C(221)—H(22D)	0.9800
C(221)—H(22E)	0.9800
C(221)—H(22F)	0.9800
C(222)—C(223)	1.327(10)
C(222)—C(220)	1.495(10)

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TABLE 3-continued

Bond lengths [Å] and angles [°].	
C(222)—H(22G)	0.9500
C(211)—C(212)	1.539(10)
C(211)—C(209)	1.554(10)
C(211)—H(21H)	0.9900
C(211)—H(21I)	0.9900
C(216)—H(21J)	0.9900
C(216)—H(21K)	0.9900
C(203)—H(20H)	1.0000
C(315)—H(31N)	0.9900
C(315)—H(31O)	0.9900
O(125)—C(125)	1.437(11)
O(125)—H(12C)	0.8400
C(123)—C(124)	1.477(11)
C(123)—H(12D)	0.9500
C(209)—H(20I)	0.9900
C(209)—H(20J)	0.9900
C(219)—H(21L)	0.9500
C(219)—H(21M)	0.9500
C(223)—H(22H)	0.9500
C(220)—H(22I)	1.0000
C(113)—C(114)	1.536(12)
C(113)—C(118)	1.535(11)
C(113)—C(112)	1.549(12)
C(113)—C(117)	1.544(11)
C(319)—H(31P)	0.9500
C(319)—H(31Q)	0.9500
C(212)—H(21O)	0.9900
C(212)—H(21P)	0.9900
C(124)—C(125)	1.558(12)
C(124)—H(12E)	1.0000
C(109)—C(111)	1.503(17)
C(109)—C(108)	1.515(13)
C(109)—H(10A)	0.9900
C(109)—H(10B)	0.9900
C(118)—H(11C)	0.9800
C(118)—H(11D)	0.9800
C(118)—H(11E)	0.9800
C(210)—H(21Q)	0.9900
C(210)—H(21R)	0.9900
C(120)—C(117)	1.539(11)
C(120)—C(121)	1.550(12)
C(120)—H(12F)	1.0000
C(325)—C(326)	1.460(15)
C(325)—C(327)	1.574(13)
C(117)—H(11F)	1.0000
C(114)—C(108)	1.505(11)
C(114)—C(115)	1.544(11)
C(114)—H(11G)	1.0000
C(125)—C(127)	1.502(13)
C(125)—C(126)	1.513(13)
C(115)—H(11H)	0.9900
C(115)—H(11I)	0.9900
C(112)—C(111)	1.520(14)
C(112)—H(11J)	0.9900
C(112)—H(11K)	0.9900
C(108)—C(107)	1.323(13)
C(327)—H(32J)	0.9800
C(327)—H(32K)	0.9800
C(327)—H(32L)	0.9800
C(225)—C(226)	1.511(14)
C(225)—C(227)	1.531(16)
C(121)—H(12G)	0.9800
C(121)—H(12H)	0.9800
C(121)—H(12I)	0.9800
C(326)—H(32M)	0.9800
C(326)—H(32N)	0.9800
C(326)—H(32O)	0.9800
C(110)—C(105)	1.463(16)
C(110)—C(101)	1.569(18)
C(110)—H(11L)	0.9900
C(110)—H(11M)	0.9900
C(106)—C(105)	1.306(16)
C(106)—C(107)	1.453(14)
C(106)—H(10C)	0.9500
C(105)—C(104)	1.489(15)
C(126)—H(12J)	0.9800
C(126)—H(12K)	0.9800
C(126)—H(12L)	0.9800

TABLE 3-continued

Bond lengths [Å] and angles [°].	
C(107)—H(10D)	0.9500
C(227)—H(22J)	0.9800
C(227)—H(22K)	0.9800
C(227)—H(22L)	0.9800
C(127)—H(12M)	0.9800
C(127)—H(12N)	0.9800
C(127)—H(12O)	0.9800
C(226)—H(22M)	0.9800
C(226)—H(22N)	0.9800
C(226)—H(22O)	0.9800
C(102)—C(119)	1.283(17)
C(102)—C(103)	1.50(2)
C(102)—C(101)	1.542(18)
C(111)—H(11N)	0.9900
C(111)—H(11O)	0.9900
C(119)—H(11P)	0.9500
C(119)—H(11Q)	0.9500
C(103)—O(103)	1.436(18)
C(103)—C(104)	1.52(3)
C(103)—H(10E)	1.0000
O(101)—C(101)	1.48(3)
O(101)—H(10J)	0.8400
C(104)—H(10F)	0.9900
C(104)—H(10G)	0.9900
C(101)—H(10H)	1.0000
O(103)—H(10I)	0.8400
C(301)—O(301)—H(30A)	109.5
C(303)—O(303)—H(30B)	109.5
C(325)—O(325)—H(32A)	109.5
C(203)—O(203)—H(20A)	109.5
C(312)—C(313)—C(318)	111.2(5)
C(312)—C(313)—C(317)	116.4(5)
C(318)—C(313)—C(317)	109.6(5)
C(312)—C(313)—C(314)	108.3(5)
C(318)—C(313)—C(314)	111.6(5)
C(317)—C(313)—C(314)	99.1(5)
C(124)—O(124)—H(12A)	109.5
C(305)—C(304)—C(303)	112.7(5)
C(305)—C(304)—H(30C)	109.0
C(303)—C(304)—H(30C)	109.0
C(305)—C(304)—H(30D)	109.1
C(303)—C(304)—H(30D)	109.1
H(30C)—C(304)—H(30D)	107.8
C(201)—O(201)—H(20B)	109.5
C(308)—C(307)—C(306)	126.3(6)
C(308)—C(307)—H(30E)	116.8
C(306)—C(307)—H(30E)	116.9
C(324)—O(324)—H(32B)	109.5
C(307)—C(308)—C(309)	125.9(5)
C(307)—C(308)—C(314)	122.5(5)
C(309)—C(308)—C(314)	111.3(5)
O(301)—C(301)—C(302)	112.9(5)
O(301)—C(301)—C(310)	110.1(5)
C(302)—C(301)—C(310)	110.5(5)
O(301)—C(301)—H(30F)	107.7
C(302)—C(301)—H(30F)	107.7
C(310)—C(301)—H(30F)	107.7
C(315)—C(314)—C(308)	120.9(6)
C(315)—C(314)—C(313)	104.0(5)
C(308)—C(314)—C(313)	113.6(5)
C(315)—C(314)—H(31A)	105.7
C(308)—C(314)—H(31A)	105.7
C(313)—C(314)—H(31A)	105.7
C(306)—C(305)—C(304)	120.4(6)
C(306)—C(305)—C(310)	125.4(6)
C(304)—C(305)—C(310)	114.1(6)
C(207)—C(208)—C(214)	122.7(6)
C(207)—C(208)—C(209)	125.5(6)
C(214)—C(208)—C(209)	111.7(6)
C(323)—C(322)—C(320)	125.4(6)
C(323)—C(322)—H(32C)	117.3
C(320)—C(322)—H(32C)	117.3
C(225)—O(225)—H(22A)	109.4
C(313)—C(318)—H(31B)	109.5
C(313)—C(318)—H(31C)	109.4
H(31B)—C(318)—H(31C)	109.5
C(313)—C(318)—H(31D)	109.5
H(31B)—C(318)—H(31D)	109.5

TABLE 3-continued

Bond lengths [Å] and angles [°].	
H(31C)—C(318)—H(31D)	109.5
C(205)—C(206)—C(207)	127.4(7)
C(205)—C(206)—H(20C)	116.3
C(207)—C(206)—H(20C)	116.3
C(322)—C(323)—C(324)	124.5(6)
C(322)—C(323)—H(32D)	117.8
C(324)—C(323)—H(32D)	117.8
C(319)—C(302)—C(303)	123.3(6)
C(319)—C(302)—C(301)	124.5(6)
C(303)—C(302)—C(301)	112.2(5)
O(201)—C(201)—C(202)	113.2(6)
O(201)—C(201)—C(210)	110.4(6)
C(202)—C(201)—C(210)	111.3(6)
O(201)—C(201)—H(20D)	107.2
C(202)—C(201)—H(20D)	107.2
C(210)—C(201)—H(20D)	107.2
O(324)—C(324)—C(325)	110.7(6)
O(324)—C(324)—C(323)	108.0(5)
C(325)—C(324)—C(323)	114.1(6)
O(324)—C(324)—H(32E)	108.0
C(325)—C(324)—H(32E)	108.0
C(323)—C(324)—H(32E)	107.9
C(305)—C(306)—C(307)	127.9(6)
C(305)—C(306)—H(30G)	116.0
C(307)—C(306)—H(30G)	116.1
C(208)—C(207)—C(206)	127.2(6)
C(208)—C(207)—H(20E)	116.4
C(206)—C(207)—H(20E)	116.4
C(308)—C(309)—C(311)	112.9(5)
C(308)—C(309)—H(30H)	109.0
C(311)—C(309)—H(30H)	109.0
C(308)—C(309)—H(30I)	109.0
C(311)—C(309)—H(30I)	109.0
H(30H)—C(309)—H(30I)	107.8
C(312)—C(311)—C(309)	113.3(6)
C(312)—C(311)—H(31E)	108.9
C(309)—C(311)—H(31E)	108.9
C(312)—C(311)—H(31F)	108.9
C(309)—C(311)—H(31F)	108.9
H(31E)—C(311)—H(31F)	107.7
C(208)—C(214)—C(215)	121.0(6)
C(208)—C(214)—C(213)	114.5(5)
C(215)—C(214)—C(213)	104.8(5)
C(208)—C(214)—H(21A)	105.0
C(215)—C(214)—H(21A)	105.1
C(213)—C(214)—H(21A)	105.1
O(303)—C(303)—C(302)	107.4(5)
O(303)—C(303)—C(304)	111.9(5)
C(302)—C(303)—C(304)	109.5(5)
O(303)—C(303)—H(30J)	109.4
C(302)—C(303)—H(30J)	109.4
C(304)—C(303)—H(30J)	109.4
C(313)—C(312)—C(311)	111.2(5)
C(313)—C(312)—H(31G)	109.4
C(311)—C(312)—H(31G)	109.4
C(313)—C(312)—H(31H)	109.4
C(311)—C(312)—H(31H)	109.4
H(31G)—C(312)—H(31H)	108.0
C(322)—C(320)—C(321)	109.1(5)
C(322)—C(320)—C(317)	109.3(5)
C(321)—C(320)—C(317)	113.1(5)
C(322)—C(320)—H(32F)	108.4
C(321)—C(320)—H(32F)	108.4
C(317)—C(320)—H(32F)	108.4
C(115)—C(116)—C(117)	107.2(6)
C(115)—C(116)—H(11A)	110.3
C(117)—C(116)—H(11A)	110.2
C(115)—C(116)—H(11B)	110.3
C(117)—C(116)—H(11B)	110.3
H(11A)—C(116)—H(11B)	108.5
C(212)—C(213)—C(218)	112.0(6)
C(212)—C(213)—C(217)	115.9(5)
C(218)—C(213)—C(217)	110.1(6)
C(212)—C(213)—C(214)	107.8(5)
C(218)—C(213)—C(214)	110.1(5)
C(217)—C(213)—C(214)	100.2(5)
C(213)—C(217)—C(216)	103.8(5)
C(213)—C(217)—C(220)	120.6(6)

TABLE 3-continued

Bond lengths [Å] and angles [°].	
C(216)—C(217)—C(220)	111.2(5)
C(213)—C(217)—H(21B)	106.8
C(216)—C(217)—H(21B)	106.8
C(220)—C(217)—H(21B)	106.8
C(123)—C(122)—C(120)	128.0(7)
C(123)—C(122)—H(12B)	116.0
C(120)—C(122)—H(12B)	115.9
C(305)—C(310)—C(301)	113.1(5)
C(305)—C(310)—H(31I)	109.0
C(301)—C(310)—H(31I)	109.0
C(305)—C(310)—H(31J)	109.0
C(301)—C(310)—H(31J)	109.0
H(31I)—C(310)—H(31J)	107.8
C(213)—C(218)—H(21C)	109.5
C(213)—C(218)—H(21D)	109.5
H(21C)—C(218)—H(21D)	109.5
C(213)—C(218)—H(21E)	109.4
H(21C)—C(218)—H(21E)	109.5
H(21D)—C(218)—H(21E)	109.5
C(214)—C(215)—C(216)	103.1(5)
C(214)—C(215)—H(21F)	111.1
C(216)—C(215)—H(21F)	111.1
C(214)—C(215)—H(21G)	111.2
C(216)—C(215)—H(21G)	111.2
H(21F)—C(215)—H(21G)	109.1
C(315)—C(316)—C(317)	106.7(5)
C(315)—C(316)—H(31K)	110.4
C(317)—C(316)—H(31K)	110.4
C(315)—C(316)—H(31L)	110.4
C(317)—C(316)—H(31L)	110.4
H(31K)—C(316)—H(31L)	108.6
O(224)—C(224)—C(223)	110.6(7)
O(224)—C(224)—C(225)	107.0(7)
C(223)—C(224)—C(225)	113.7(7)
O(224)—C(224)—H(22B)	108.4
C(223)—C(224)—H(22B)	108.5
C(225)—C(224)—H(22B)	108.5
C(205)—C(204)—C(203)	111.2(6)
C(205)—C(204)—H(20F)	109.4
C(203)—C(204)—H(20F)	109.3
C(205)—C(204)—H(20G)	109.4
C(203)—C(204)—H(20G)	109.4
H(20F)—C(204)—H(20G)	108.0
C(320)—C(317)—C(316)	112.0(5)
C(320)—C(317)—C(313)	120.2(5)
C(316)—C(317)—C(313)	103.3(5)
C(320)—C(317)—H(31M)	106.8
C(316)—C(317)—H(31M)	106.8
C(313)—C(317)—H(31M)	106.8
C(206)—C(205)—C(204)	121.3(7)
C(206)—C(205)—C(210)	125.9(7)
C(204)—C(205)—C(210)	112.7(6)
C(224)—O(224)—H(22C)	109.5
C(320)—C(321)—H(32G)	109.5
C(320)—C(321)—H(32H)	109.5
H(32G)—C(321)—H(32H)	109.5
C(320)—C(321)—H(32I)	109.5
H(32G)—C(321)—H(32I)	109.5
H(32H)—C(321)—H(32I)	109.5
C(219)—C(202)—C(201)	123.2(7)
C(219)—C(202)—C(203)	121.7(7)
C(201)—C(202)—C(203)	115.1(6)
C(220)—C(221)—H(22D)	109.5
C(220)—C(221)—H(22E)	109.4
H(22D)—C(221)—H(22E)	109.5
C(220)—C(221)—H(22F)	109.5
H(22D)—C(221)—H(22F)	109.5
H(22E)—C(221)—H(22F)	109.5
C(223)—C(222)—C(220)	127.9(7)
C(223)—C(222)—H(22G)	116.1
C(220)—C(222)—H(22G)	116.0
C(212)—C(211)—C(209)	112.8(6)
C(212)—C(211)—H(21H)	109.0
C(209)—C(211)—H(21H)	109.0
C(212)—C(211)—H(21I)	109.0
C(209)—C(211)—H(21I)	109.0
H(21H)—C(211)—H(21I)	107.8
C(215)—C(216)—C(217)	107.9(5)

TABLE 3-continued

Bond lengths [Å] and angles [°].	
C(215)—C(216)—H(21J)	110.2
C(217)—C(216)—H(21J)	110.1
C(215)—C(216)—H(21K)	110.1
C(217)—C(216)—H(21K)	110.1
H(21J)—C(216)—H(21K)	108.4
O(203)—C(203)—C(202)	111.1(6)
O(203)—C(203)—C(204)	107.2(6)
C(202)—C(203)—C(204)	110.3(6)
O(203)—C(203)—H(20H)	109.4
C(202)—C(203)—H(20H)	109.4
C(204)—C(203)—H(20H)	109.4
C(314)—C(315)—C(316)	104.7(5)
C(314)—C(315)—H(31N)	110.8
C(316)—C(315)—H(31N)	110.8
C(314)—C(315)—H(31O)	110.8
C(316)—C(315)—H(31O)	110.8
H(31N)—C(315)—H(31O)	108.9
C(125)—O(125)—H(12C)	109.5
C(122)—C(123)—C(124)	125.1(7)
C(122)—C(123)—H(12D)	117.5
C(124)—C(123)—H(12D)	117.4
C(208)—C(209)—C(211)	112.4(6)
C(208)—C(209)—H(20I)	109.1
C(211)—C(209)—H(20I)	109.1
C(208)—C(209)—H(20J)	109.1
C(211)—C(209)—H(20J)	109.1
H(20I)—C(209)—H(20J)	107.9
C(202)—C(219)—H(21L)	120.0
C(202)—C(219)—H(21M)	120.0
H(21L)—C(219)—H(21M)	120.0
C(222)—C(223)—C(224)	122.8(7)
C(222)—C(223)—H(22H)	118.6
C(224)—C(223)—H(22H)	118.6
C(222)—C(220)—C(221)	110.2(6)
C(222)—C(220)—C(217)	107.5(6)
C(221)—C(220)—C(217)	114.2(6)
C(222)—C(220)—H(22I)	108.2
C(221)—C(220)—H(22I)	108.3
C(217)—C(220)—H(22I)	108.2
C(114)—C(113)—C(118)	111.5(6)
C(114)—C(113)—C(112)	107.6(7)
C(118)—C(113)—C(112)	111.0(7)
C(114)—C(113)—C(117)	100.8(6)
C(118)—C(113)—C(117)	109.8(6)
C(112)—C(113)—C(117)	115.6(6)
C(302)—C(319)—H(31P)	120.0
C(302)—C(319)—H(31Q)	120.0
H(31P)—C(319)—H(31Q)	120.0
C(213)—C(212)—C(211)	111.7(6)
C(213)—C(212)—H(21O)	109.3
C(211)—C(212)—H(21O)	109.3
C(213)—C(212)—H(21P)	109.3
C(211)—C(212)—H(21P)	109.3
H(21O)—C(212)—H(21P)	107.9
O(124)—C(124)—C(123)	109.7(6)
O(124)—C(124)—C(125)	109.7(6)
C(123)—C(124)—C(125)	114.3(7)
O(124)—C(124)—H(12E)	107.6
C(123)—C(124)—H(12E)	107.6
C(125)—C(124)—H(12E)	107.6
C(111)—C(109)—C(108)	113.9(8)
C(111)—C(109)—H(10A)	108.8
C(108)—C(109)—H(10A)	108.8
C(111)—C(109)—H(10B)	108.8
C(108)—C(109)—H(10B)	108.8
H(10A)—C(109)—H(10B)	107.7
C(113)—C(118)—H(11C)	109.4
C(113)—C(118)—H(11D)	109.5
H(11C)—C(118)—H(11D)	109.5
C(113)—C(118)—H(11E)	109.5
H(11C)—C(118)—H(11E)	109.5
H(11D)—C(118)—H(11E)	109.5
C(205)—C(210)—C(201)	110.2(6)
C(205)—C(210)—H(21Q)	109.6
C(201)—C(210)—H(21Q)	109.6
C(205)—C(210)—H(21R)	109.7
C(201)—C(210)—H(21R)	109.5
H(21Q)—C(210)—H(21R)	108.1



TABLE 3-continued

Bond lengths [Å] and angles [°].	
C(122)—C(120)—C(117)	110.0(6)
C(122)—C(120)—C(121)	108.1(6)
C(117)—C(120)—C(121)	113.4(7)
C(122)—C(120)—H(12F)	108.4
C(117)—C(120)—H(12F)	108.4
C(121)—C(120)—H(12F)	108.4
O(325)—C(325)—C(326)	109.2(8)
O(325)—C(325)—C(324)	105.3(5)
C(326)—C(325)—C(324)	114.7(8)
O(325)—C(325)—C(327)	105.7(7)
C(326)—C(325)—C(327)	113.5(11)
C(324)—C(325)—C(327)	107.7(7)
C(120)—C(117)—C(113)	120.7(6)
C(120)—C(117)—C(116)	111.2(6)
C(113)—C(117)—C(116)	103.4(6)
C(120)—C(117)—H(11F)	106.9
C(113)—C(117)—H(11F)	106.9
C(116)—C(117)—H(11F)	107.0
C(108)—C(114)—C(113)	114.7(7)
C(108)—C(114)—C(115)	119.5(7)
C(113)—C(114)—C(115)	103.6(6)
C(108)—C(114)—H(11G)	106.0
C(113)—C(114)—H(11G)	106.0
C(115)—C(114)—H(11G)	106.0
O(125)—C(125)—C(127)	109.2(8)
O(125)—C(125)—C(126)	107.4(7)
C(127)—C(125)—C(126)	110.0(8)
O(125)—C(125)—C(124)	108.7(7)
C(127)—C(125)—C(124)	111.0(7)
C(126)—C(125)—C(124)	110.5(7)
C(114)—C(115)—C(116)	102.7(7)
C(114)—C(115)—H(11H)	111.2
C(116)—C(115)—H(11H)	111.3
C(114)—C(115)—H(11I)	111.2
C(116)—C(115)—H(11I)	111.2
H(11H)—C(115)—H(11I)	109.2
C(111)—C(112)—C(113)	110.6(8)
C(111)—C(112)—H(11J)	109.5
C(113)—C(112)—H(11J)	109.5
C(111)—C(112)—H(11K)	109.5
C(113)—C(112)—H(11K)	109.5
H(11J)—C(112)—H(11K)	108.1
C(107)—C(108)—C(114)	125.1(8)
C(107)—C(108)—C(109)	125.9(8)
C(114)—C(108)—C(109)	109.1(8)
C(325)—C(327)—H(32J)	109.5
C(325)—C(327)—H(32K)	109.4
H(32J)—C(327)—H(32K)	109.5
C(325)—C(327)—H(32L)	109.5
H(32J)—C(327)—H(32L)	109.5
H(32K)—C(327)—H(32L)	109.5
O(225)—C(225)—C(224)	104.8(8)
O(225)—C(225)—C(226)	107.9(8)
C(224)—C(225)—C(226)	110.8(8)
O(225)—C(225)—C(227)	108.2(8)
C(224)—C(225)—C(227)	110.4(8)
C(226)—C(225)—C(227)	114.3(11)
C(120)—C(121)—H(12G)	109.5
C(120)—C(121)—H(12H)	109.5
H(12G)—C(121)—H(12H)	109.5
C(120)—C(121)—H(12I)	109.5
H(12G)—C(121)—H(12I)	109.5
H(12H)—C(121)—H(12I)	109.5
C(325)—C(326)—H(32M)	109.5
C(325)—C(326)—H(32N)	109.4
H(32M)—C(326)—H(32N)	109.5
C(325)—C(326)—H(32O)	109.5
H(32M)—C(326)—H(32O)	109.5
H(32N)—C(326)—H(32O)	109.5
C(105)—C(110)—C(101)	112.0(11)
C(105)—C(110)—H(11L)	109.2
C(101)—C(110)—H(11L)	109.3
C(105)—C(110)—H(11M)	109.1
C(101)—C(110)—H(11M)	109.2
H(11L)—C(110)—H(11M)	107.9
C(105)—C(106)—C(107)	129.9(11)
C(105)—C(106)—H(10C)	115.0
C(107)—C(106)—H(10C)	115.0

TABLE 3-continued

Bond lengths [Å] and angles [°].	
C(106)—C(105)—C(110)	126.2(10)
C(106)—C(105)—C(104)	120.5(12)
C(110)—C(105)—C(104)	113.3(10)
C(125)—C(126)—H(12J)	109.4
C(125)—C(126)—H(12K)	109.5
H(12J)—C(126)—H(12K)	109.5
C(125)—C(126)—H(12L)	109.6
H(12J)—C(126)—H(12L)	109.5
H(12K)—C(126)—H(12L)	109.5
C(108)—C(107)—C(106)	126.7(10)
C(108)—C(107)—H(10D)	116.6
C(106)—C(107)—H(10D)	116.6
C(225)—C(227)—H(22J)	109.5
C(225)—C(227)—H(22K)	109.4
H(22J)—C(227)—H(22K)	109.5
C(225)—C(227)—H(22L)	109.6
H(22J)—C(227)—H(22L)	109.5
H(22K)—C(227)—H(22L)	109.5
C(125)—C(127)—H(12M)	109.4
C(125)—C(127)—H(12N)	109.5
H(12M)—C(127)—H(12N)	109.5
C(125)—C(127)—H(12O)	109.5
H(12M)—C(127)—H(12O)	109.5
H(12N)—C(127)—H(12O)	109.5
C(225)—C(226)—H(22M)	109.5
C(225)—C(226)—H(22N)	109.6
H(22M)—C(226)—H(22N)	109.5
C(225)—C(226)—H(22O)	109.3
H(22M)—C(226)—H(22O)	109.5
H(22N)—C(226)—H(22O)	109.5
C(119)—C(102)—C(103)	122.4(12)
C(119)—C(102)—C(101)	125.2(15)
C(103)—C(102)—C(101)	112.3(13)
C(109)—C(111)—C(112)	113.4(9)
C(109)—C(111)—H(11N)	108.9
C(112)—C(111)—H(11N)	108.9
C(109)—C(111)—H(11O)	108.9
C(112)—C(111)—H(11O)	108.9
H(11N)—C(111)—H(11O)	107.7
C(102)—C(119)—H(11P)	120.1
C(102)—C(119)—H(11Q)	119.9
H(11P)—C(119)—H(11Q)	120.0
O(103)—C(103)—C(104)	105.7(14)
O(103)—C(103)—C(102)	116(2)
C(104)—C(103)—C(102)	114.5(10)
O(103)—C(103)—H(10E)	106.8
C(104)—C(103)—H(10E)	106.7
C(102)—C(103)—H(10E)	106.8
C(101)—O(101)—H(10J)	109.6
C(105)—C(104)—C(103)	106.8(14)
C(105)—C(104)—H(10F)	110.2
C(103)—C(104)—H(10F)	110.2
C(105)—C(104)—H(10G)	110.6
C(103)—C(104)—H(10G)	110.6
H(10F)—C(104)—H(10G)	108.6
O(101)—C(101)—C(102)	109.5(13)
O(101)—C(101)—C(110)	103.3(18)
C(102)—C(101)—C(110)	107.2(12)
O(101)—C(101)—H(10H)	112.0
C(102)—C(101)—H(10H)	112.2
C(110)—C(101)—H(10H)	112.2
C(103)—O(103)—H(10I)	109.4

TABLE 4

Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2a^{*2}U_{11} + \dots + 2hka^*b^*U_{12}]$						
	U11	U22	U33	U23	U13	U12
O(301)	42(2)	32(2)	82(3)	4(2)	32(2)	0(2)
O(303)	39(2)	44(2)	60(3)	0(2)	22(2)	3(2)
O(325)	58(3)	48(3)	69(3)	-14(2)	41(2)	-5(2)
O(203)	55(3)	47(3)	77(3)	-5(2)	34(2)	-2(2)
C(313)	29(3)	41(3)	51(3)	-3(3)	23(3)	-4(3)
O(124)	83(4)	44(3)	115(5)	-2(3)	70(3)	2(3)
C(304)	37(3)	41(3)	61(4)	-1(3)	27(3)	-2(3)
O(201)	75(3)	50(3)	77(3)	-11(3)	30(3)	-1(3)
C(307)	31(3)	32(3)	62(4)	-3(3)	24(3)	-1(2)
O(324)	41(2)	102(4)	92(4)	-49(3)	37(3)	-17(3)
C(308)	29(3)	41(3)	58(4)	-3(3)	24(3)	-2(2)
C(301)	35(3)	41(3)	55(4)	4(3)	26(3)	-1(3)
C(314)	40(3)	41(3)	59(4)	-6(3)	29(3)	-5(3)
C(305)	36(3)	46(4)	53(4)	-5(3)	22(3)	-2(3)
C(208)	45(3)	52(4)	48(4)	7(3)	22(3)	7(3)
C(322)	38(3)	40(3)	63(4)	-2(3)	32(3)	-6(3)
O(225)	99(5)	119(6)	82(4)	19(4)	54(4)	25(4)
C(318)	37(3)	44(3)	56(4)	2(3)	26(3)	1(3)
C(206)	51(4)	49(4)	51(4)	2(3)	21(3)	2(3)
C(323)	39(3)	38(3)	62(4)	-8(3)	30(3)	-8(3)
C(302)	33(3)	46(4)	50(4)	0(3)	22(3)	-6(3)
C(201)	58(4)	40(4)	74(5)	-3(3)	33(4)	1(3)
C(324)	38(3)	51(4)	56(4)	-6(3)	27(3)	5(3)
C(306)	32(3)	38(3)	61(4)	0(3)	22(3)	-1(3)
C(207)	48(3)	47(4)	52(4)	0(3)	21(3)	5(3)
C(309)	39(3)	50(4)	67(4)	10(3)	30(3)	6(3)
C(311)	41(3)	38(3)	71(4)	2(3)	31(3)	3(3)
C(214)	45(3)	42(3)	53(4)	2(3)	20(3)	3(3)
C(303)	40(3)	45(4)	49(4)	-3(3)	26(3)	-1(3)
C(312)	42(3)	41(3)	63(4)	5(3)	32(3)	1(3)
C(320)	38(3)	46(4)	54(4)	-4(3)	28(3)	-1(3)
C(116)	51(4)	58(4)	76(5)	-8(4)	32(4)	-2(3)
C(213)	45(3)	43(4)	59(4)	0(3)	25(3)	-2(3)
C(217)	47(3)	44(3)	58(4)	1(3)	27(3)	-1(3)
C(122)	75(5)	49(4)	63(5)	6(3)	34(4)	9(4)
C(310)	35(3)	45(4)	62(4)	5(3)	25(3)	-2(3)
C(218)	48(4)	46(4)	63(4)	6(3)	17(3)	-1(3)
C(215)	45(3)	55(4)	59(4)	-4(3)	24(3)	-1(3)
C(316)	48(4)	48(4)	80(5)	-13(4)	45(3)	-8(3)
C(224)	57(4)	69(5)	74(5)	5(4)	30(4)	14(4)
C(204)	59(4)	59(4)	61(5)	-3(4)	26(4)	-16(4)
C(317)	36(3)	40(3)	53(4)	-8(3)	26(3)	-3(3)
C(205)	55(4)	48(4)	60(4)	0(3)	23(3)	4(3)
O(224)	71(4)	126(6)	92(4)	6(4)	45(3)	16(4)
C(321)	50(4)	42(4)	80(5)	-10(3)	40(4)	-6(3)
C(202)	52(4)	44(4)	59(4)	5(3)	21(3)	-3(3)
C(221)	48(4)	72(5)	81(5)	-7(4)	29(4)	-5(4)
C(222)	48(4)	49(4)	76(5)	-6(4)	27(3)	-1(3)
C(211)	60(4)	54(4)	56(4)	-3(3)	25(3)	-10(3)
C(216)	48(3)	59(4)	59(4)	4(3)	29(3)	4(3)
C(203)	53(4)	51(4)	69(5)	-5(4)	29(4)	-8(3)
C(315)	57(4)	38(4)	92(5)	-12(3)	52(4)	-8(3)
O(125)	71(4)	110(5)	85(4)	14(4)	33(3)	-13(4)
C(123)	63(4)	50(4)	70(5)	9(4)	37(4)	9(4)
C(209)	50(4)	47(4)	61(4)	2(3)	28(3)	2(3)
C(219)	55(4)	58(4)	72(5)	-7(4)	21(4)	-10(4)
C(223)	56(4)	52(4)	72(5)	-4(4)	34(4)	-2(3)
C(220)	48(4)	46(4)	71(5)	-4(3)	30(3)	-3(3)
C(113)	70(4)	49(4)	61(4)	3(4)	23(4)	-7(4)
C(319)	50(4)	57(4)	65(4)	11(4)	34(3)	4(3)
C(212)	49(4)	50(4)	60(4)	-4(3)	23(3)	-1(3)
C(124)	61(4)	46(4)	79(5)	7(3)	40(4)	8(3)
C(109)	63(5)	99(7)	89(6)	6(6)	25(5)	-19(5)
C(118)	77(5)	47(4)	80(5)	1(4)	31(4)	-9(4)
C(210)	50(4)	48(4)	79(5)	-3(4)	26(4)	0(3)
C(120)	71(5)	50(4)	66(5)	8(4)	31(4)	2(4)
C(325)	76(5)	48(4)	86(5)	-13(4)	60(4)	-11(4)
C(117)	59(4)	45(4)	66(4)	11(3)	25(3)	-2(3)
C(114)	55(4)	57(4)	76(5)	11(4)	26(4)	-1(4)
C(125)	83(5)	64(5)	68(5)	2(4)	41(4)	0(4)
C(115)	62(5)	64(5)	90(6)	-12(4)	31(4)	-11(4)
C(112)	76(5)	65(5)	78(6)	17(4)	18(4)	-13(4)
C(108)	55(4)	71(5)	87(6)	12(5)	21(4)	-8(4)
C(327)	64(5)	96(7)	123(8)	-50(6)	40(5)	-24(5)
C(225)	90(6)	89(7)	76(6)	14(5)	46(5)	19(5)

TABLE 4-continued

Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U_{11} + \dots + 2hka^* b^* U_{12}]$						
	U11	U22	U33	U23	U13	U12
C(121)	86(6)	66(5)	83(6)	0(5)	38(5)	-6(5)
C(326)	390(30)	47(5)	125(10)	-17(6)	176(15)	-8(9)
C(110)	67(5)	115(8)	117(8)	8(7)	46(6)	-17(6)
C(106)	82(7)	130(10)	122(10)	-23(8)	33(7)	-43(7)
C(105)	81(6)	109(8)	86(7)	6(6)	44(5)	-11(6)
C(126)	100(7)	82(6)	99(7)	-29(6)	51(6)	0(6)
C(107)	64(5)	78(6)	98(7)	3(5)	40(5)	-13(4)
C(227)	156(11)	98(8)	75(7)	-22(6)	41(7)	-17(8)
C(127)	137(9)	68(6)	113(8)	-14(5)	75(7)	-33(6)
C(226)	81(6)	172(13)	87(7)	3(7)	38(6)	35(8)
C(102)	79(6)	101(8)	132(10)	52(7)	46(7)	17(6)
C(111)	90(7)	103(8)	80(6)	12(6)	-7(5)	-41(6)
C(119)	94(8)	95(8)	151(12)	31(8)	59(8)	7(6)
C(103)	56(6)	370(30)	98(9)	59(15)	37(6)	-12(12)
O(101)	530(40)	430(30)	520(30)	-380(30)	460(30)	-380(30)
C(104)	123(10)	195(16)	122(10)	-25(10)	71(9)	-76(11)
C(101)	150(13)	134(12)	229(19)	-24(13)	149(14)	-14(10)
O(103)	107(7)	840(60)	131(9)	200(19)	70(7)	168(17)
O(2)	300(30)	990(120)	400(50)	-240(70)	-180(40)	-70(50)
O(1)	153(8)	198(11)	101(6)	-15(6)	63(6)	33(8)
O(3)	350(50)	2000(300)	460(60)	-400(120)	300(50)	-400(110)
O(4)	500(60)	2000(300)	210(20)	480(80)	-140(30)	-160(110)

TABLE 5

Hydrogen coordinates ( $\text{\AA} \times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ).				
	x	y	z	U(eq)
H(30A)	6176	2121	325	73
H(30B)	4245	6222	-201	69
H(32A)	11486	4676	-2293	80
H(20A)	10549	12997	-2770	85
H(12A)	11774	6665	-2750	107
H(30C)	5436	7553	489	53
H(30D)	5985	6717	1011	53
H(20B)	11722	8900	-3254	99
H(30E)	7615	6690	-159	47
H(32B)	12682	7487	-1182	112
H(30F)	5822	4048	-93	49
H(31A)	7833	8669	-1092	53
H(32C)	10358	9105	-1690	52
H(22A)	18172	13343	-4632	141
H(31B)	9800	8250	51	65
H(31C)	10060	9792	117	65
H(31D)	9257	9266	287	65
H(20C)	13271	13226	-1743	59
H(32D)	11581	7724	-875	52
H(20D)	11669	11530	-3200	66
H(32E)	11321	7887	-2018	55
H(30G)	6429	8359	142	50
H(20E)	14031	12311	-2525	57
H(30H)	6938	10034	-130	59
H(30I)	6837	10129	-761	59
H(31E)	7719	11904	-335	56
H(31F)	8326	10956	127	56
H(21A)	15329	14837	-2412	55
H(30J)	4622	5693	656	50
H(31G)	8285	11030	-984	54
H(31H)	9085	11481	-470	54
H(32F)	10733	9154	-530	51
H(11A)	14998	5863	-3433	71
H(11B)	14640	7225	-3751	71
H(21B)	16826	14943	-2362	57
H(12B)	14256	6735	-2530	71
H(31I)	7203	5010	822	54
H(31J)	7187	5016	205	54
H(21C)	16353	11655	-2001	78
H(21D)	17046	12167	-1447	78
H(21E)	16042	12066	-1500	78
H(21F)	14882	13442	-3125	62

TABLE 5-continued

Hydrogen coordinates ( $\text{\AA} \times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ).				
	x	y	z	U(eq)
H(21G)	15237	12143	-2756	62
H(31K)	9194	7144	-1361	64
H(31L)	9887	7054	-760	64
H(22B)	18593	14635	-3398	78
H(20F)	12101	12250	-1617	70
H(20G)	12091	10667	-1692	70
H(31M)	9046	9350	-1328	48
H(22C)	19861	13609	-3036	138
H(32G)	10238	11397	-635	79
H(32H)	11040	11220	-855	79
H(32I)	10074	11307	-1274	79
H(22D)	18173	13754	-1333	98
H(22E)	18970	13676	-1563	98
H(22F)	18397	15002	-1646	98
H(22G)	18062	14821	-2699	67
H(21H)	15853	15294	-885	66
H(21I)	15857	13714	-961	66
H(21J)	16213	13940	-3151	63
H(21K)	16503	12479	-2909	63
H(20H)	10683	11442	-2125	66
H(31N)	8176	6510	-1004	67
H(31O)	8835	6690	-395	67
H(12C)	12249	6619	-4146	130
H(12D)	13100	7957	-3423	69
H(20I)	14418	14390	-1361	60
H(20J)	14692	15561	-1689	60
H(21L)	10346	9104	-3160	93
H(21M)	9965	9750	-2703	93
H(22H)	18508	12210	-2828	68
H(22I)	17797	12496	-2138	63
H(31P)	4865	3604	1087	80
H(31Q)	5594	2569	1005	80
H(21O)	16427	15630	-1592	62
H(21P)	17039	14587	-1176	62
H(12E)	12901	5800	-2760	70
H(10A)	18388	7351	-2666	100
H(10B)	18660	8528	-2990	100
H(11C)	15758	10201	-3197	100
H(11D)	16491	9929	-3470	100
H(11E)	15551	9271	-3723	100
H(21Q)	12741	9706	-2416	69
H(21R)	13079	10761	-2763	69

TABLE 5-continued

Hydrogen coordinates ( $\text{\AA} \times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ).				
	x	y	z	U(eq)
H(12F)	14524	8977	-3133	72
H(11F)	15745	6896	-2665	67
H(11G)	16871	6501	-3032	74
H(11H)	15990	5824	-3870	84
H(11I)	15759	7329	-4083	84
H(11J)	16801	9437	-2305	89
H(11K)	17143	7931	-2232	89
H(32J)	9908	6342	-1943	138
H(32K)	10168	6622	-2475	138
H(32L)	10033	5125	-2307	138
H(12G)	15550	9726	-2294	114
H(12H)	14605	9584	-2239	114
H(12I)	15324	8466	-1989	114
H(32M)	11108	5369	-1107	250
H(32N)	11194	4146	-1479	250
H(32O)	12031	5007	-1163	250
H(11L)	17781	7726	-5286	115
H(11M)	17564	6696	-4879	115
H(10C)	18730	8635	-3772	134
H(12J)	13278	4095	-3364	134
H(12K)	12757	4080	-4001	134
H(12L)	13413	5271	-3743	134
H(10D)	17120	7265	-4191	92
H(22J)	17851	11224	-3670	163
H(22K)	17803	11227	-4294	163
H(22L)	18724	11272	-3824	163
H(12M)	11870	3937	-3176	146
H(12N)	11118	4989	-3451	146
H(12O)	11383	3901	-3818	146
H(22M)	16896	13354	-3835	166
H(22N)	17213	14637	-4082	166
H(22O)	16845	13368	-4459	166
H(11N)	17725	9989	-2791	119
H(11O)	18295	9307	-2234	119
H(11P)	20148	7348	-5603	162
H(11Q)	19417	6187	-5860	162
H(10E)	20268	8376	-4813	206
H(10F)	18421	4963	-5709	638
H(10G)	19496	9369	-4271	167
H(10H)	18961	9424	-4910	167
H(10I)	18859	5427	-4794	180
H(10J)	20735	6854	-4210	530

TABLE 6

Torsion angles [ $^\circ$ ].	
C(306)—C(307)—C(308)—C(309)	1.2(11)
C(306)—C(307)—C(308)—C(314)	-172.7(6)
C(307)—C(308)—C(314)—C(315)	-5.4(10)
C(309)—C(308)—C(314)—C(315)	179.9(6)
C(307)—C(308)—C(314)—C(313)	-130.1(6)
C(309)—C(308)—C(314)—C(313)	55.3(7)
C(312)—C(313)—C(314)—C(315)	169.1(6)
C(318)—C(313)—C(314)—C(315)	-68.2(6)
C(317)—C(313)—C(314)—C(315)	47.2(6)
C(312)—C(313)—C(314)—C(308)	-57.6(7)
C(318)—C(313)—C(314)—C(308)	65.1(7)
C(317)—C(313)—C(314)—C(308)	-179.5(5)
C(303)—C(304)—C(305)—C(306)	134.1(6)
C(303)—C(304)—C(305)—C(310)	-48.6(8)
C(320)—C(322)—C(323)—C(324)	178.5(6)
O(301)—C(301)—C(302)—C(319)	0.1(9)
C(310)—C(301)—C(302)—C(319)	-123.7(7)
O(301)—C(301)—C(302)—C(303)	-178.4(5)
C(310)—C(301)—C(302)—C(303)	57.8(7)
C(322)—C(323)—C(324)—O(324)	134.3(6)
C(322)—C(323)—C(324)—C(325)	-102.2(8)
C(304)—C(305)—C(306)—C(307)	-177.2(6)
C(310)—C(305)—C(306)—C(307)	5.8(11)
C(308)—C(307)—C(306)—C(305)	179.8(7)
C(214)—C(208)—C(207)—C(206)	-178.5(6)

TABLE 6-continued

Torsion angles [ $^\circ$ ].	
C(209)—C(208)—C(207)—C(206)	1.4(11)
C(205)—C(206)—C(207)—C(208)	-171.5(7)
C(307)—C(308)—C(309)—C(311)	135.4(7)
C(314)—C(308)—C(309)—C(311)	-50.2(8)
C(308)—C(309)—C(311)—C(312)	50.3(8)
C(207)—C(208)—C(214)—C(215)	2.2(10)
C(209)—C(208)—C(214)—C(215)	-177.7(6)
C(207)—C(208)—C(214)—C(213)	-124.7(7)
C(209)—C(208)—C(214)—C(213)	55.4(7)
C(319)—C(302)—C(303)—O(303)	-116.4(7)
C(301)—C(302)—C(303)—O(303)	62.1(6)
C(319)—C(302)—C(303)—C(304)	122.0(7)
C(301)—C(302)—C(303)—C(304)	-59.5(7)
C(305)—C(304)—C(303)—O(303)	-64.5(7)
C(305)—C(304)—C(303)—C(302)	54.4(7)
C(318)—C(313)—C(312)—C(311)	-67.7(7)
C(317)—C(313)—C(312)—C(311)	165.7(5)
C(314)—C(313)—C(312)—C(311)	55.2(7)
C(309)—C(311)—C(312)—C(313)	-53.4(8)
C(323)—C(322)—C(320)—C(321)	121.7(7)
C(323)—C(322)—C(320)—C(317)	-114.2(7)
C(208)—C(214)—C(213)—C(212)	-58.0(7)
C(215)—C(214)—C(213)—C(212)	167.2(6)
C(208)—C(214)—C(213)—C(218)	64.5(8)
C(215)—C(214)—C(213)—C(218)	-70.3(7)
C(208)—C(214)—C(213)—C(217)	-179.5(6)
C(215)—C(214)—C(213)—C(217)	45.7(6)
C(212)—C(213)—C(217)—C(216)	-151.8(6)
C(218)—C(213)—C(217)—C(216)	79.8(6)
C(214)—C(213)—C(217)—C(216)	-36.1(6)
C(212)—C(213)—C(217)—C(220)	82.9(8)
C(218)—C(213)—C(217)—C(220)	-45.5(8)
C(214)—C(213)—C(217)—C(220)	-161.4(6)
C(306)—C(305)—C(310)—C(301)	-136.2(7)
C(304)—C(305)—C(310)—C(301)	46.6(8)
O(301)—C(301)—C(310)—C(305)	-175.3(5)
C(302)—C(301)—C(310)—C(305)	-49.9(7)
C(208)—C(214)—C(215)—C(216)	-167.4(6)
C(213)—C(214)—C(215)—C(216)	-36.2(7)
C(322)—C(320)—C(317)—C(316)	53.9(7)
C(321)—C(320)—C(317)—C(316)	175.7(6)
C(322)—C(320)—C(317)—C(313)	175.5(5)
C(321)—C(320)—C(317)—C(313)	-62.7(8)
C(315)—C(316)—C(317)—C(320)	150.4(6)
C(315)—C(316)—C(317)—C(313)	19.6(7)
C(312)—C(313)—C(317)—C(320)	78.8(7)
C(318)—C(313)—C(317)—C(320)	-48.5(7)
C(314)—C(313)—C(317)—C(320)	-165.4(6)
C(312)—C(313)—C(317)—C(316)	-155.4(6)
C(318)—C(313)—C(317)—C(316)	77.3(6)
C(314)—C(313)—C(317)—C(316)	-39.6(6)
C(207)—C(206)—C(205)—C(204)	179.1(7)
C(207)—C(206)—C(205)—C(210)	-3.3(12)
C(203)—C(204)—C(205)—C(206)	120.9(7)
C(203)—C(204)—C(205)—C(210)	-57.0(8)
O(201)—C(201)—C(202)—C(219)	-1.9(10)
C(210)—C(201)—C(202)—C(219)	-127.0(8)
O(201)—C(201)—C(202)—C(203)	177.3(6)
C(210)—C(201)—C(202)—C(203)	52.2(8)
C(214)—C(215)—C(216)—C(217)	12.7(7)
C(213)—C(217)—C(216)—C(215)	15.3(7)
C(220)—C(217)—C(216)—C(215)	146.5(6)
C(219)—C(202)—C(203)—O(203)	-115.1(8)
C(201)—C(202)—C(203)—O(203)	65.7(8)
C(219)—C(202)—C(203)—C(204)	126.1(8)
C(201)—C(202)—C(203)—C(204)	-53.1(8)
C(205)—C(204)—C(203)—O(203)	-67.2(8)
C(205)—C(204)—C(203)—C(202)	53.9(8)
C(308)—C(314)—C(315)—C(316)	-164.8(6)
C(313)—C(314)—C(315)—C(316)	-35.7(7)
C(317)—C(316)—C(315)—C(314)	9.9(8)
C(120)—C(122)—C(123)—C(124)	-179.3(7)
C(207)—C(208)—C(209)—C(211)	130.6(7)
C(214)—C(208)—C(209)—C(211)	-49.5(8)
C(212)—C(211)—C(209)—C(208)	49.5(8)
C(220)—C(222)—C(223)—C(224)	175.5(7)
O(224)—C(224)—C(223)—C(222)	125.8(8)
C(225)—C(224)—C(223)—C(222)	-113.7(9)

TABLE 6-continued

Torsion angles [°].	
C(223)—C(222)—C(220)—C(221)	112.0(8)
C(223)—C(222)—C(220)—C(217)	-122.9(8)
C(213)—C(217)—C(220)—C(222)	-179.2(6)
C(216)—C(217)—C(220)—C(222)	59.0(7)
C(213)—C(217)—C(220)—C(221)	-56.6(9)
C(216)—C(217)—C(220)—C(221)	178.4(6)
C(218)—C(213)—C(212)—C(211)	-65.7(8)
C(217)—C(213)—C(212)—C(211)	166.8(6)
C(214)—C(213)—C(212)—C(211)	55.6(7)
C(209)—C(211)—C(212)—C(213)	-53.7(8)
C(122)—C(123)—C(124)—O(124)	118.6(8)
C(122)—C(123)—C(124)—C(125)	-117.7(9)
C(206)—C(205)—C(210)—C(201)	-122.8(8)
C(204)—C(205)—C(210)—C(201)	54.9(8)
O(201)—C(201)—C(210)—C(205)	-177.8(6)
C(202)—C(201)—C(210)—C(205)	-51.2(8)
C(123)—C(122)—C(120)—C(117)	-115.6(9)
C(123)—C(122)—C(120)—C(121)	120.0(9)
O(324)—C(324)—C(325)—O(325)	-49.3(8)
C(323)—C(324)—C(325)—O(325)	-171.4(6)
O(324)—C(324)—C(325)—C(326)	70.8(11)
C(323)—C(324)—C(325)—C(326)	-51.3(12)
O(324)—C(324)—C(325)—C(327)	-161.7(7)
C(323)—C(324)—C(325)—C(327)	76.2(8)
C(122)—C(120)—C(117)—C(113)	178.5(7)
C(121)—C(120)—C(117)—C(113)	-60.3(9)
C(122)—C(120)—C(117)—C(116)	57.2(8)
C(121)—C(120)—C(117)—C(116)	178.4(6)
C(114)—C(113)—C(117)—C(120)	-164.4(7)
C(118)—C(113)—C(117)—C(120)	-46.7(9)
C(112)—C(113)—C(117)—C(120)	79.9(9)
C(114)—C(113)—C(117)—C(116)	-39.4(7)
C(118)—C(113)—C(117)—C(116)	78.3(7)
C(112)—C(113)—C(117)—C(116)	-155.1(7)
C(115)—C(116)—C(117)—C(120)	148.5(7)
C(115)—C(116)—C(117)—C(113)	17.5(8)
C(118)—C(113)—C(114)—C(108)	63.2(9)
C(112)—C(113)—C(114)—C(108)	-58.8(8)
C(117)—C(113)—C(114)—C(108)	179.7(7)
C(118)—C(113)—C(114)—C(115)	-68.8(8)
C(112)—C(113)—C(114)—C(115)	169.2(6)
C(117)—C(113)—C(114)—C(115)	47.7(7)
O(124)—C(124)—C(125)—O(125)	63.8(8)
C(123)—C(124)—C(125)—O(125)	-59.9(9)
O(124)—C(124)—C(125)—C(127)	-56.3(9)
C(123)—C(124)—C(125)—C(127)	180.0(8)
O(124)—C(124)—C(125)—C(126)	-178.6(7)
C(123)—C(124)—C(125)—C(126)	57.7(9)
C(108)—C(114)—C(115)—C(116)	-165.5(7)
C(113)—C(114)—C(115)—C(116)	-36.4(8)
C(117)—C(116)—C(115)—C(114)	11.3(8)
C(114)—C(113)—C(112)—C(111)	55.2(10)
C(118)—C(113)—C(112)—C(111)	-67.0(10)
C(117)—C(113)—C(112)—C(111)	167.0(8)
C(113)—C(114)—C(108)—C(107)	-124.0(10)
C(115)—C(114)—C(108)—C(107)	-0.1(13)
C(113)—C(114)—C(108)—C(109)	56.0(10)
C(115)—C(114)—C(108)—C(109)	179.8(8)
C(111)—C(109)—C(108)—C(107)	129.2(11)
C(111)—C(109)—C(108)—C(114)	-50.8(11)
O(224)—C(224)—C(225)—O(225)	-50.2(9)
C(223)—C(224)—C(225)—O(225)	-172.6(7)
O(224)—C(224)—C(225)—C(226)	-166.3(9)
C(223)—C(224)—C(225)—C(226)	71.3(11)
O(224)—C(224)—C(225)—C(227)	66.1(10)
C(223)—C(224)—C(225)—C(227)	-56.3(10)
C(107)—C(106)—C(105)—C(110)	-9(2)
C(107)—C(106)—C(105)—C(104)	168.6(14)
C(101)—C(110)—C(105)—C(106)	-120.2(15)
C(101)—C(110)—C(105)—C(104)	61.6(15)
C(114)—C(108)—C(107)—C(106)	174.8(10)
C(109)—C(108)—C(107)—C(106)	-5.2(18)
C(105)—C(106)—C(107)—C(108)	171.5(14)
C(108)—C(109)—C(111)—C(112)	51.9(12)
C(113)—C(112)—C(111)—C(109)	-53.9(11)
C(119)—C(102)—C(103)—O(103)	-114.4(13)
C(101)—C(102)—C(103)—O(103)	68.6(15)
C(119)—C(102)—C(103)—C(104)	122.2(13)

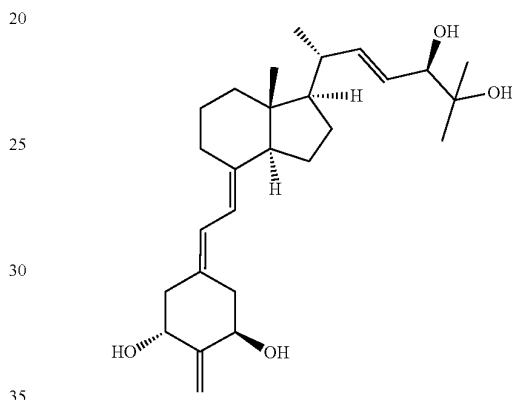
TABLE 6-continued

Torsion angles [°].	
C(101)—C(102)—C(103)—C(104)	-54.8(18)
C(106)—C(105)—C(104)—C(103)	123.0(14)
C(110)—C(105)—C(104)—C(103)	-58.7(15)
O(103)—C(103)—C(104)—C(105)	-73.2(19)
C(102)—C(103)—C(104)—C(105)	55.4(16)
C(119)—C(102)—C(101)—O(101)	-15(2)
C(103)—C(102)—C(101)—O(101)	162.2(19)
C(119)—C(102)—C(101)—C(110)	-126.2(14)
C(103)—C(102)—C(101)—C(110)	50.7(19)
C(105)—C(110)—C(101)—O(101)	-170.0(13)
C(105)—C(110)—C(101)—C(102)	-54.4(17)

15 Symmetry Transformations Used to Generate Equivalent Atoms:

We claim:

1. A compound having the formula



in a crystalline form and named (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub>, wherein the crystalline form has molecular packing arrangement defined by space group P2<sub>1</sub> and unit cell dimensions: a=16.3058(9) Å; b=10.0461(6) Å; c=26.0527(15) Å;  $\alpha$ =90°;  $\beta$ =109.001(3)°; and  $\gamma$ =90°.

2. A three dimensional structure for (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub> as defined by the molecular packing arrangement set forth in claim 1.

3. A method of purifying (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub>, comprising the steps of:

- 50 (a) dissolving (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub> in a volume of ethyl acetate as solvent to prepare a solution of (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub>,
- 55 (b) adding a volume of hexane dropwise to the solution, to reach a saturation point, to form a solution of (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub> in a mixture of ethyl acetate and hexane as solvent wherein crystals of (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub> form and precipitate from the solution; and
- 60 (c) separating the (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub> crystals from the solution, wherein the (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub> crystals have a crystalline form that has molecular packing arrangement defined by space group P2<sub>1</sub> and unit cell

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dimensions:  $a=16.3058(9)$  Å;  $b=10.0461(6)$  Å;  $c=26.0527(15)$  Å;  $\alpha=90^\circ$ ;  $\beta=109.001(3)^\circ$ ; and  $\gamma=90^\circ$ .

4. The method of claim 3, wherein the solution of (22E)-(24R)-2-methylene-22-dehydro- $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub> in the mixture of ethyl acetate and hexane as solvent is placed at room temperature, wherein crystals of (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub> form and precipitate from the solution.

5. The method of claim 3, wherein the step of separating comprises filtering the mixture and precipitate to obtain the crystals.

6. The method of claim 3 including a further step (d) comprising repeating steps (a) through (c) using the recovered crystals of (22E)-(24R)-2-methylene-22-dehydro-1 $\alpha$ ,24,25-trihydroxy-19-nor-vitamin D<sub>3</sub> from step (c) in step (a).

7. The method of claim 3 wherein the mixture of ethyl acetate and hexane comprises about 20-30% ethyl acetate and about 70-80% hexane by volume.

8. A pharmaceutical composition containing an effective amount of the compound of claim 1 in crystalline form and a pharmaceutically acceptable excipient.

9. A method of treating or preventing a skin disease, disorder, or condition in a subject in need thereof, the method comprising administering to the subject an effective amount of the compound of claim 1 in crystalline form.

10. The method of claim 9, wherein the skin disease, disorder, or condition is psoriasis.

11. A method of treating or preventing a cell proliferative disease or disorder in a subject in need thereof, the method

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comprising administering to the subject an effective amount of the compound of claim 1 in crystalline form.

12. The method of claim 11, wherein the cell proliferative disease or disorder is selected from the group consisting of leukemia, neuroblastoma, retinoblastoma, melanoma, colon cancer, breast cancer, and prostate cancer.

13. A method of treating or preventing a disease or disorder in a subject in need thereof, the disease or disorder selected from the group consisting of multiple sclerosis, diabetes mellitus, lupus, host versus graft reaction, and rejection of transplants, the method comprising administering to the subject an effective amount of the compound of claim 1 in crystalline form.

14. A method of treating or preventing an inflammatory disease or disorder in a subject in need thereof, the method comprising administering to the subject an effective amount of the compound of claim 1 in crystalline form.

15. The method of claim 14, wherein the inflammatory disease or disorder is selected from the group consisting of rheumatoid arthritis, asthmas, and inflammatory bowel diseases.

16. The method of claim 14, wherein the inflammatory disease or disorder is selected from the group consisting of Crohn's disease and ulcerative colitis.

17. A method of treating or preventing obesity, inhibiting adipocyte differentiation, inhibiting SCD-1 gene transcription, and/or reducing body fat in a subject in need thereof, the method comprising administering to the subject an effective amount of the compound of claim 1 in crystalline form.

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