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New A-ring analogs of the hormone 1α,25-dihydroxyvitamin D_3: (2′-hydroxymethyl)tetrahydrofuro[1,2-*a*]-25-hydroxyvitamin D_3

Heung Bae Jeon [a,b], Gary H. Posner [a,*]

[a] *Department of Chemistry, The Johns Hopkins University, Baltimore, MD 21218, USA*
[b] *Department of Chemistry, Kwangwoon University, Seoul 139-701, Republic of Korea*

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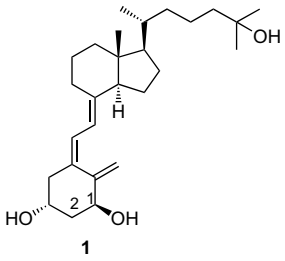
ABSTRACT

Conceptually new, enantiomerically pure bicyclic tetrahydrofuro[1,2-*a*]-A-ring phosphine oxides (+)-**4** and (−)-**4** were successfully prepared from methyl 2-pyrone-3-carboxylate and (*S*)- or (*R*)-2-(*tert*-butyldimethylsilyloxy)methyl-2,3-dihydrofuran, respectively. In addition, (2′-hydroxymethyl)tetrahydrofuro[1,2-*a*]-25-hydroxyvitamin D_3 **3a** and **3b** as new A-ring-modified analogs of the natural hormone 1α,25-dihydroxyvitamin D_3 were readily synthesized by using Lythgoe-type coupling of the A-ring phosphine oxides (+)-**4** and (−)-**4** with C,D-ring ketone (+)-**5**.

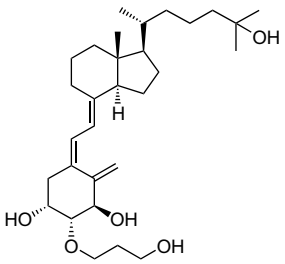
1. Introduction

The natural hormone 1α,25-dihydroxyvitamin D_3 (**1**, calcitriol), regulates diverse biochemical functions, such as immunomodulation, control of hormonal systems, inhibition of cell growth, and induction of cell differentiation.[1–3] This hormone and some of its synthetic analogs are currently used as efficacious drugs for chemotherapy of patients having secondary hyperthyroidism, osteoporosis, and psoriasis.[3,4] Currently, more than six analogs are regularly used as drugs that promote healthier living.[4] Although most synthetic analogs feature changes in the side chain of the molecule,[3,5] some A-ring-modified analogs have potent biological activities and potential for chemotherapy of cancer.[6]

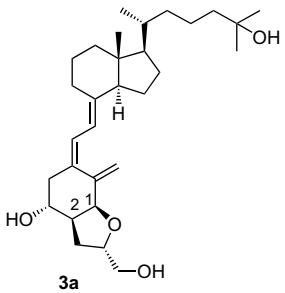
Crystallizing the modified vitamin D receptor (VDR) containing calcitriol (**1**) has allowed X-ray determination to show that the relatively large ligand-binding pocket can accommodate much structural variation in potential calcitriol analog ligands.[7] On this basis and on some structural similarity to 2β-(3-hydroxypropoxy)-1α,25-dihydroxyvitamin D_3 (**2**, ED-71), which was developed from the Chugai Pharmaceutical Co. as a promising candidate for the treatment of osteoporosis,[8] enantiomerically pure analogs **3a** and **3b** having the bicyclic A-ring moiety attached with a 2-hydroxymethyltetrahydrofuran ring at C1 and C2 of natural A-ring were designed to mimic the terminal –OH in the 3-hydroxypropoxy group at C2 of ED-71 (**2**). As far as we know, the bicyclic A-ring moiety in 1α,25-dihydroxyvitamin D_3 analog was never introduced until now. Herein, we describe the stereoselective synthesis of the conceptually new analogs **3a** and **3b**.



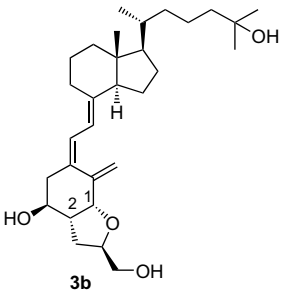
1
1α,25-Dihydroxyvitamin D_3
(calcitriol)



2
ED-71



3a
1,2-α-THF-β-CH_2OH



3b
1,2-β-THF-α–CH_2OH

* Corresponding author. Tel.: +1 410 516 4670; fax: +1 410 516 8420.
E-mail address: ghp@jhu.edu (G.H. Posner).

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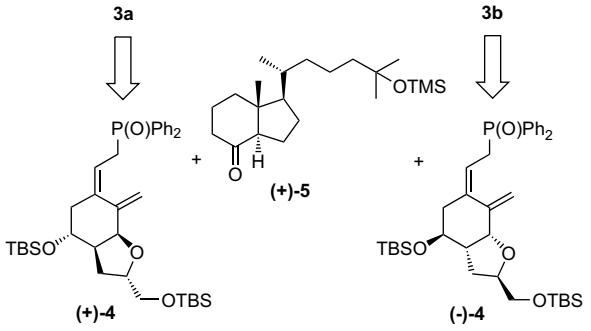
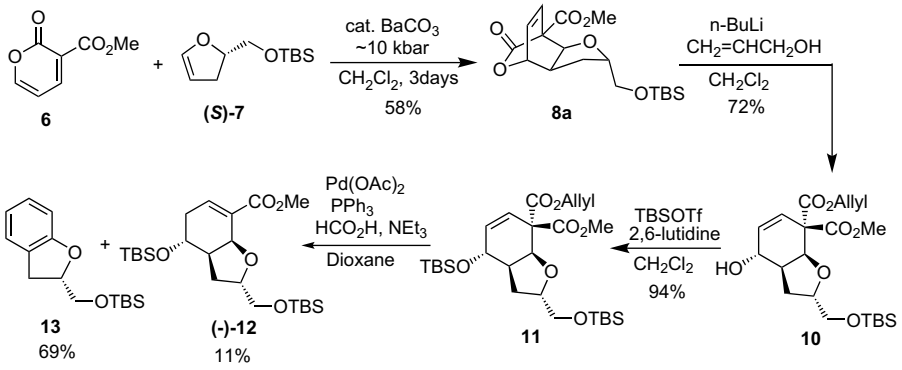


Scheme 1.

2. Results and discussion

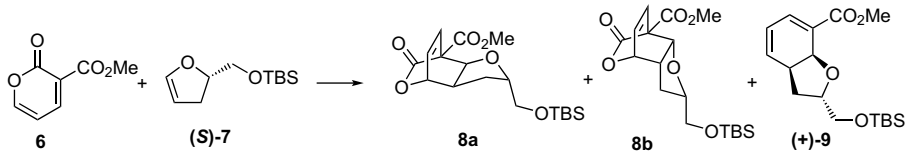
Synthesis of the tetrahydrofuro[1,2-*a*] (THF) attached hybrid analogs **3a** and **3b** can be envisioned retrosynthetically through the disconnections shown in Scheme 1. Analogs **3a** and **3b** can be prepared through Horner–Wadsworth–Emmons coupling of C,D-ring ketone (+)-**5**[9] and bicyclic tetrahydrofuro[1,2-*a*]-A-ring phosphine oxide (+)-**4** and (−)-**4**.

Our approach to the tetrahydrofuro[1,2-*a*] (THF)-attached bicyclic A-ring phosphine oxide (+)-**4** commenced with commercially available methyl 2-pyrone-3-carboxylate (**6**) and *tert*-butyldimethylsilyl (TBS)-protected (*S*)-2-hydroxymethyl-2,3-dihydrofuran (*S*)-**7**, which was prepared according to a previously reported procedure,[10] as shown in Scheme 2. Inverse-electron-demand Diels–Alder cycloaddition of 2-pyrone-3-carboxylate **6** with 2 equiv of dihydrofuran (*S*)-**7** to allow isolation of the bridged tricyclic adduct **8a** without loss of CO_2 by cycloreversion was accomplished by various different reaction conditions with various solvents, catalysts, temperatures, times, and pressures. The results are shown in Table 1. Thus, the desired tricyclic adduct **8a** was obtained in good yield via high pressure (~10 kbar) cycloaddition with a catalytic amount of $BaCO_3$ at room temperature, although the reaction gave a mixture of *endo* and *exo* isomers as 4:1 ratio (entry 17 in Table 1). Chemospecific allyloxide opening of the lactone ring in tricyclic lactone ester **8a** and subsequent protection of the resultant alcohol **10** with *tert*-butyldimethylsilyl triflate



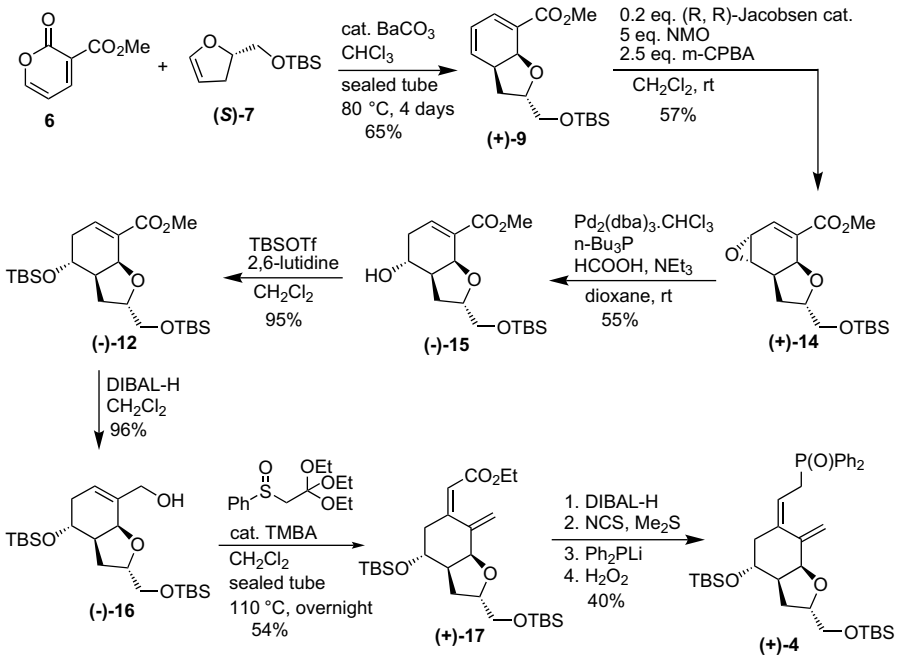
Scheme 2.

Table 1
Diels–Alder cycloaddition of **6** and (*S*)-**7** in various conditions[a]



Entry	Solvent	Catalyst	Temp	Time	Yield [**8a**/**8b**/(+)-**9**][b]
1	CH_2Cl_2	$ZnBr_2$	rt	24 h	20% (only **8a**)
2	THF	$ZnBr_2$	rt	24 h	No reaction
3	THF	$ZnBr_2$	Reflux	24 h	No reaction
4	CH_2Cl_2	$BaCO_3$	Sealed tube (80–85 °C)	24 h	12% (9:2:2)
5	Benzene		Reflux	24 h	<5% (2:1:1)
6	$ClCH_2CH_2Cl$	$BaCO_3$	Sealed tube (85–90 °C)	24 h	15% (1:1:2)
7	DMSO		Sealed tube (85–90 °C)	24 h	15% (1:1:2)
8	$CHCl_3$	$BaCO_3$	Sealed tube (80–85 °C)	24 h	32% (2:1:1)
9	Benzene	$BaCO_3$	Sealed tube (80–85 °C)	24 h	12% (2:1:1)
10	CH_2Cl_2	$Yb(OTf)_3$	rt	3 h	<5% (only **8a**)
11	CH_2Cl_2	$BaCO_3$	Sealed tube (80–85 °C)	4 days	91% (1:3:10)
12	$CHCl_3$	$BaCO_3$	Sealed tube (80–85 °C)	4 days	89% (1:7:25)
13	CH_2Cl_2	$BaCO_3$	Sealed tube (40–45 °C)	4 days	11% (4:1:0)
14	CH_2Cl_2	$BaCO_3$	Sealed tube (55–60 °C)	4 days	26% (4:1:2)
15	CH_2Cl_2		Sealed tube (55–60 °C)	4 days	27% (3:1:1)
16	CH_2Cl_2	$ZnBr_2$	High pressure	3 days	43% (10:1:0)
17	CH_2Cl_2	$BaCO_3$	High pressure	3 days	63% (4:1:0)
18	CH_2Cl_2		High pressure	3 days	61% (4:1:0)

[a] Compound **6** (1 equiv) and 2 equiv of (*S*)-**7** were used for all reactions.
[b] The yield and the ratio of **8a**, **8b**, and (+)-**9** were measured by ^1H NMR, compared to the remaining starting material **6**.



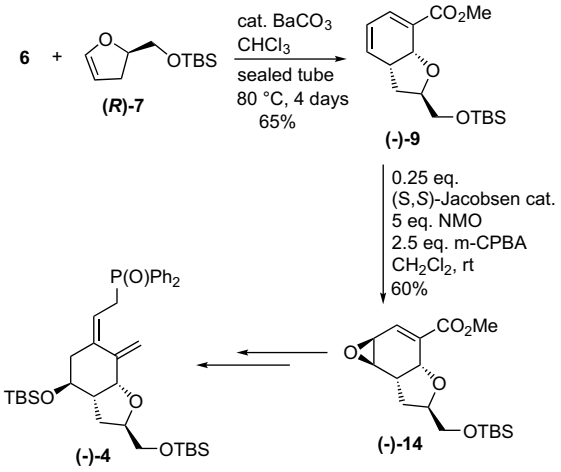
Scheme 3.

(TBSOTf) afforded bicyclic allyl methyl malonate **11** in good yield (Scheme 2). Deallyloxycarbonylation of allyl ester **11** under reflux in dioxane using formic acid and a catalytic amount of palladium acetate,[11] however, provided the desired conjugated enoate ester (−)-**12**[12] in only 10% yield, along with undesired dihydrobenzofuran **13** in 69% yield as a major product.

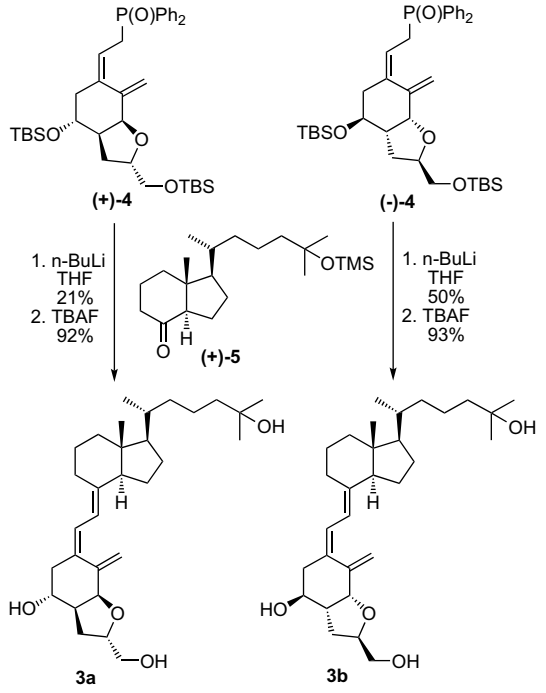
The low yield in the deallyloxycarbonylation of **11** led us to examine other synthetic routes to intermediate (−)-**12**. We envisaged that the decarboxylated bicyclic adduct (+)-**9** of **8a** would give the enoate ester (−)-**12** by introducing a hydroxyl group stereoselectively at C3. Thus, heating 2-pyrone-3-carboxylate **6** and dihydrofuran (*S*)-**7** along with a catalytic amount of $BaCO_3$ in a sealed tube at 80–85 °C for 4 days afforded the desired bicyclic adduct (+)-**9** in 65% yield (entry 12 in Table 1 and Scheme 3). Reaction of (+)-**9** with *m*-chloroperoxybenzoic acid (*m*-CPBA) in the presence of a catalytic amount of the (*R*,*R*)-Jacobsen catalyst and excess *N*-methylmorpholine-*N*-oxide (NMO) gave epoxide (+)-**14** stereoselectively in 57% yield.[13] Epoxide ring opening of (+)-**14** using formic acid and a catalytic amount of tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$][14] followed by O-silylation of the resulting alcohol (−)-**15** provided the desired enoate ester (−)-**12** in good yield. Reduction of the conjugated methyl ester functionality in (−)-**12** by diisobutylaluminum hydride (DIBAL-H) produced allylic alcohol (−)-**16** in 96% yield. The [3,3]-sigmatropic Claisen rearrangement using 1-(phenylsulfinyl)-2,2,2-triethoxyethane in the presence of a catalytic amount of 2,4,6-trimethylbenzoic acid (TMBA) allowed allyl alcohol (−)-**16** to undergo efficient, regiospecific formation of two-carbon-extended conjugated dienoate ester (+)-**17** as the desired *Z*-isomer in 54% yield, along with the *E*-isomer as a side product in 10% yield.[15] On the basis of the literature precedent[9] and our own experience, dienoate ester (+)-**17** was reduced by DIBAL-H, chlorinated by *N*-chlorosuccimide (NCS), converted into the corresponding phosphine by lithium diphenylphosphide (Ph_2PLi), generated from diphenylphosphine (Ph_2PH) and *n*-BuLi, and finally oxidized by H_2O_2 to give tetrahydrofuro[1,2-*a*]-A-ring phosphine oxide (+)-**4** in good yield.

For the synthesis of enantiomerically pure A-ring phosphine oxide (−)-**4**, the enantiomer of (+)-**4**, Diels–Alder reaction of methyl 2-pyrone-3-carboxylate (**6**), and dihydrofuran (*R*)-**7** was accomplished by heating in a sealed tube to give bicyclic adduct (−)-**9** in 65% yield (Scheme 4). Stereoselective epoxidation of (−)-**9** with *m*-CPBA in the presence of a catalytic amount of (*S*,*S*)-Jacobsen catalyst and excess NMO gave epoxide (−)-**14** in 60% yield. Then, the A-ring phosphine oxide (−)-**4** was readily obtained from epoxide (−)-**14** in several steps in similar yields according to the same procedure to (+)-**4** from (+)-**14** as shown in Scheme 3.

Finally, Lythgoe-type coupling[16] of the bicyclic A-ring phosphine oxides (+)-**4** and (−)-**4** with enantiomerically pure C,D-ring ketone (+)-**5** was followed by fluoride-promoted desilylation using tetrabutylammonium fluoride (TBAF) to afford diastereomerically pure 1α,25-dihydroxyvitamin D_3 analogs **3a** and **3b**, respectively (Scheme 5). The lack of any significant in vitro antiproliferative activity of new analogs **3a** and **3b**, however, was disappointing.



Scheme 4.



Scheme 5.

3. Conclusion

In conclusion, the diastereomerically pure (2′-hydroxymethyl)tetrahydrofuro[1,2-*a*]-25-hydroxyvitamin D_3 **3a** and **3b** as new A-ring-modified analogs of the hormone 1α,25-dihydroxyvitamin D_3 have been successfully synthesized by Lythgoe-type coupling of the conceptually new bicyclic (2′-hydroxymethyl)tetrahydrofuro[1,2-*a*]-A-ring phosphine oxides (+)-**4** and (−)-**4** with enantiomerically pure C,D-ring ketone (+)-**5**.

4. Experimental

4.1. General

All reactions were conducted under a positive pressure of dry argon with dry, freshly distilled solvents unless otherwise noted. All reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. Flash column chromatography was performed by employing 230–400 mesh silica gel. Thin-layer chromatography was performed using silica gel 60 F_{254} precoated plates (0.25 mm thickness) with a fluorescent indicator. Infrared spectra were recorded on a Perkin–Elmer 1600 FT-IR spectrometer using NaCl plates. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ solution and were referenced to $CHCl_3$ (7.26 and 77.0 ppm, respectively) using a Varian XL 400 MHz NMR spectrometer. Optical rotations were measured with a JASCO, P-100 model polarimeter.

4.2. Methyl 2,3,3a(*S*),7a(*S*)-tetrahydro-2(*S*)-(*tert*-butyldimethylsilyloxymethyl)benzofuran-7-carboxylate [(+)-9]

In a sealed tube, a solution of methyl-2-oxo-2*H*-pyran-3-carboxylate (**6**, 1.08 g, 7.01 mmol), dihydrofuran (*S*)-**7** (2.74 g, 12.8 mmol), and catalytic amount (0.10 g) of $BaCO_3$ in $CHCl_3$ (14 mL) was heated to 80 °C for 4 days. The reaction mixture was concentrated. The residue was subjected to column chromatography with EtOAc–hexanes (1:7) as eluent to give the desired cycloadduct (+)-**9** (1.48 g, 65%). $[\alpha]_D^{22}$ +35.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J*=6.0 Hz, 1H), 6.10 (ddd, *J*=9.6, 6.0, 2.4 Hz, 1H), 5.98 (dd, *J*=9.6, 7.8 Hz, 1H), 4.85 (d, *J*=8.0 Hz, 1H), 3.84 (m, 1H), 3.77 (s, 3H), 3.71 (dd, *J*=10.8, 4.0 Hz, 1H), 3.65 (dd, *J*=10.8, 5.6 Hz, 1H), 3.19 (m, 1H), 2.34 (dt, J_d=12.4 Hz, J_t=8.4 Hz, 1H), 2.12 (ddd, *J*=12.4, 6.4, 2.0 Hz, 1H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 137.6, 134.3, 126.1, 121.9, 77.2, 71.2, 65.4, 51.7, 39.8, 35.3, 25.9, 18.3, −5.39, −5.42. HRMS ($[M+Na]^+$) calcd 324.1757, found 324.1750.

4.3. Methyl 1a,3a,5,6,6a(*S*),6b(*S*)-hexahydro-5(*S*)-(*tert*-butyldimethylsilyloxy)methyl-7-oxa-bicyclo[4.1.0]hepta-1(6),2-dieno[4,5-*b*]furan-3-carboxylate [(+)-14]

To a solution of cycloadduct (+)-**9** (0.80 g, 2.47 mmol), (*R*,*R*)-Jacobsen catalyst (0.34 g, 0.50 mmol), NMO (1.44 g, 12.3 mmol) in CH_2Cl_2 (25 mL) was added *m*-CPBA (0.85 g, 4.94 mmol) at rt. After stirring for overnight at rt, the reaction mixture was quenched with water. After addition of CH_2Cl_2 (60 mL), the organic layer was washed with water, saturated aqueous Na_2SO_3, and saturated aqueous $NaHCO_3$, then dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography with EtOAc–hexanes (1:5) as eluent to give the desired α-epoxide (+)-**14** (0.48 g, 57%) and the β-epoxide diastereomer (0.10 g, 12%). Compound (+)-**14**: $[\alpha]_D^{22}$ +52.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, *J*=4.0 Hz, 1H), 4.74 (d, *J*=8.8 Hz, 1H), 4.03 (ddd, *J*=9.6, 8.8, 4.0 Hz, 1H), 3.76 (s, 3H), 3.62 (dd, *J*=10.4, 4.0 Hz, 1H), 3.56 (dd, *J*=10.4, 5.2 Hz, 1H), 3.47 (dd, *J*=3.6, 2.0 Hz, 1H), 3.40 (t, *J*=4.0 Hz, 1H), 3.25 (qd, J_q=9.2 Hz, J_d=1.6 Hz, 1H), 2.13 (ddd, *J*=12.8, 9.2, 4.0 Hz, 1H), 1.80 (m, 1H), 0.88 (s, 9H), 0.046 (s, 3H), 0.040 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 135.8, 133.0, 78.6, 72.0, 65.3, 52.8, 52.0, 45.4, 36.2, 31.1, 25.8, 18.2, −5.37, −5.43. IR (neat, cm^{-1}) 2952, 2929, 2856, 1726, 1472, 1435, 1256, 1114, 1090, 837, 778. HRMS ($[M+Na]^+$) calcd 363.1598, found 363.1594.

4.4. Methyl 2,3,3a(*S*),4,5,7a(*S*)-hexahydro-4(*R*)-hydroxy-2(*S*)-(*tert*-butyldimethylsilyloxymethyl)benzofuran-7-carboxylate [(−)-15]

To a solution of $Pd_2(dba)_3CHCl_3$ (62 mg, 0.06 mmol) and *n*-Bu_3P (30 μL, 0.12 mmol) in dioxane (6 mL) was added a solution of formic acid (0.6 mL, 12.5 mmol) and NEt_3 (0.69 mL) in dioxane (5 mL). After the resulting solution stirring for 10 min at rt, a solution of epoxide (+)-**14** (0.71 g, 2.09 mmol) in dioxane (5 mL) was added. The mixture solution was stirred for overnight at rt, and then quenched with water. The solution was extracted ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography with EtOAc–hexanes (2:3) as eluent to give the desired alcohol (−)-**15** (0.39 g, 55%). $[\alpha]_D^{25}$ −50.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (dd, *J*=6.0, 2.8 Hz, 1H), 4.76 (d, *J*=4.8 Hz, 1H), 4.15 (ddd, *J*=12.0, 7.6, 4.4 Hz, 1H), 3.76 (s, 3H), 3.66–3.76 (m, 3H), 2.64 (dt, J_d=18.8 Hz, J_t=5.6 Hz, 1H), 2.13–2.25 (m, 3H), 2.04 (dt, J_d=13.6 Hz, J_t=7.6 Hz, 1H), 1.69 (br s, 1H), 0.90 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 140.1, 130.1, 77.5, 74.4, 66.5, 65.8, 51.8, 45.5, 34.2, 30.0, 25.9, 18.3, −5.4. IR (neat, cm^{-1}) 3437, 2952, 2928, 2856, 1723, 1652, 1472, 1436, 1252, 1134, 1090, 1033, 1005, 837, 779. HRMS ($[M+Na]^+$) calcd 365.1755, found 365.1767.

4.5. Methyl 2,3,3a(*S*),4,5,7a(*S*)-hexahydro-4(*R*)-(*tert*-butyldimethylsilyloxy)-2(*S*)-(*tert*-butyldimethylsilyloxymethyl)-benzofuran-7-carboxylate [(−)-12]

To a solution of alcohol (−)-**15** (0.14 g, 0.41 mmol) and 2,6-lutidine (0.14 mL, 1.23 mmol) in CH_2Cl_2 (20 mL) was added TBSOTf (0.19 mL, 0.82 mmol) at −78 °C. After stirring for 1 h at −78 °C, the reaction mixture was warmed to rt. The solution was quenched

with aqueous 1 N HCl (1 mL) and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography with EtOAc–hexanes (1:7) as eluent to give the desired TBS-protected alcohol (−)-**12** (0.18 g, 95%). $[\alpha]_D^{25}$ −42.6 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (dd, J=5.6, 2.4 Hz, 1H), 4.72 (d, J=4.8 Hz, 1H), 4.10 (ddd, J=12.4, 8.4, 4.4 Hz, 1H), 3.74 (s, 3H), 3.66–3.72 (m, 3H), 2.51 (dt, J_d=18.8 Hz, J_t=5.2 Hz, 1H), 2.10–2.21 (m, 3H), 1.93 (dt, J_d=13.6 Hz, J_t=7.6 Hz, 1H), 0.894 (s, 9H), 0.888 (s, 9H), 0.08 (s, 3H), 0.07 (s, 6H), 0.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 140.6, 129.9, 77.5, 74.5, 66.8, 65.9, 51.7, 46.0, 34.8, 30.1, 25.9, 25.8, 18.3, 17.9, −4.2, −4.8, −5.4. IR (neat, cm^{-1}) 2953, 2929, 2857, 1725, 1654, 1472, 1463, 1436, 1386, 1361, 1311, 1251, 1102, 1034, 1006, 921, 836, 776. HRMS ($[M+Na]^+$) calcd 479.2619, found 479.2613.

4.6. 2,3,3a(*S*),4,5,7a(*S*)-Hexahydro-4(*R*)-(*tert*-butyldimethylsilyloxy)-2(*S*)-(*tert*-butyldimethylsilyloxymethyl)-7-(hydroxymethyl)benzofuran [(−)-16]

To a solution of ester (−)-**12** (0.18 g, 0.39 mmol) in CH_2Cl_2 (25 mL) was added DIBAL-H (1.5 M in Tol., 0.66 mL, 0.99 mmol) at −78 °C. After stirring for 1 h at −78 °C, the reaction mixture was quenched with aqueous 1 N HCl (2 mL). The solution was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography with EtOAc–hexanes (1:4) as eluent to give the desired alcohol (−)-**16** (0.16 g, 96%). $[\alpha]_D^{24}$ −38.4 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 5.72 (m, 1H), 4.43 (d, J=12.4 Hz, 1H), 4.10 (m, 1H), 4.05 (d, J=12.4 Hz, 1H), 3.59–3.66 (m, 3H), 2.52 (s, 1H), 2.31 (dt, J_d=17.2 Hz, J_t=5.6 Hz, 1H), 2.22 (m, 1H), 2.10 (ddd, J=13.2, 6.8, 2.0 Hz, 1H), 1.99 (m, 1H), 1.84 (dt, J_d=13.2 Hz, J_t=7.6 Hz, 1H), 0.883 (s, 9H), 0.879 (s, 9H), 0.056 (s), 0.047 (s)—total 12H. ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 124.7, 78.1, 77.8, 68.0, 66.1, 65.9, 46.2, 33.9, 30.2, 25.83, 25.77, 18.2, 18.0, −4.2, −4.8, −5.3. IR (neat, cm^{-1}) 3389, 2955, 2929, 2857, 1472, 1461, 1349, 1255, 1102, 1002, 838, 773. HRMS ($[M+Na]^+$) calcd 451.2670, found 451.2664.

4.7. (*Z*)-Ethyl 2-[hexahydro-4(*R*)-(*tert*-butyldimethylsilyloxy)-2(*S*)-(*tert*-butyldimethylsilyloxymethyl)-7-methylenebenzofuran-6(2*H*)-ylidene]acetate [(+)-17]

A sealed tube, equipped with a stirring bar, was charged with allyl alcohol (−)-**16** (0.16 g, 0.35 mmol), 2,4,6-trimethylbenzoic acid (5 mg), 1-(phenylsulfinyl)-2,2,2-triethoxyethane (0.20 g, 0.70 mmol), and CH_2Cl_2 (5 mL). The mixture was sealed with argon and heated to 110 °C overnight. The reaction mixture was cooled to rt and concentrated. The residue was subjected to column chromatography with EtOAc–hexanes (1:15) as eluent to give desired dienoate (+)-**17** (94 mg, 54%). $[\alpha]_D^{25}$ +2.97 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 5.68 (s, 1H), 5.32 (t, J=1.6 Hz, 1H), 5.24 (t, J=1.2 Hz, 1H), 4.55 (d, J=5.2 Hz, 1H), 4.08–4.15 (m, 3H), 3.83 (ddd, J=8.0, 6.8, 3.6 Hz, 1H), 3.60–3.67 (m, 2H), 2.50 (m, 1H), 2.23–2.35 (m, 2H), 1.91 (t, J=6.8 Hz, 2H), 1.23 (t, J=7.2 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.057 (s), 0.051 (s), 0.048 (s)—total 12H. ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 152.0, 142.0, 118.0, 116.5, 81.5, 77.5, 70.3, 65.7, 59.9, 49.2, 43.9, 30.4, 25.9, 25.7, 18.3, 17.9, 14.0, −4.37, −4.82, −5.31, −5.35. IR (neat, cm^{-1}) 2954, 2929, 2857, 1729, 1641, 1472, 1361, 1255, 1178, 1092, 1038, 836, 776. HRMS ($[M+Na]^+$) calcd 519.2932, found 519.2952.

4.8. (2′-*tert*-Butyldimethylsilyloxymethyl)tetrahydrofuro-[1,2-*a*]-A-ring phosphine oxide (+)-4

To a solution of dienoate (+)-**17** (0.38 g, 0.76 mmol) in toluene (10 mL) was added DIBAL-H (1.5 M in Tol., 1.27 mL, 1.91 mmol) at −78 °C. After stirring for 1 h at −78 °C, the reaction mixture was quenched with aqueous 2 N potassium, sodium-tartrate (2 mL), and aqueous 1 N HCl (3 mL). The solution was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography with EtOAc–hexanes (1:3) as eluent to give the desired allyl alcohol (0.19 g, 55%).

To a solution of *N*-chlorosuccinimide (0.17 g, 1.27 mmol) in CH_2Cl_2 (15 mL) was added dimethylsulfide (95 mL, 1.29 mmol) at 0 °C. After stirring for 15 min at 0 °C, and then 10 min −20 °C, the resulting allyl alcohol (0.17 g, 0.37 mmol) in CH_2Cl_2 (5 mL) was added dropwise via cannula. After stirring for 1.5 h at −20 °C, the reaction mixture was quenched with water, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated. The residue was passed over a plug of silica gel (60% hexanes, 40% EtOAc), concentrated, and azeotropically dried with benzene. The resulting allyl chloride was immediately carried on to the next step.

To the allyl chloride in THF (10 mL) at −78 °C was added a solution of lithium diphenylphosphide, prepared by the addition of *n*-butyllithium (1.6 M in hexanes, 1.37 mL, 2.2 mmol) to a solution of diphenylphosphine (0.38 mL, 2.2 mmol) in THF (8 mL) at 0 °C, via cannula and the orange solution was stirred for 1.5 h at −78 °C. The mixture was slowly diluted with 5 mL of water and evaporated. The residue was diluted with CH_2Cl_2 (15 mL) and water (10 mL) and the vigorously stirred mixture was treated with hydrogen peroxide (30%, 4.0 mL) and stirring was continued overnight. The reaction mixture was extracted with CH_2Cl_2 and water, dried over $MgSO_4$, and concentrated. The residue was subjected to silica gel column chromatography with EtOAc–hexanes (2:1) as eluent to give the pure phosphine oxide (+)-**4** (0.15 g, 63%). $[\alpha]_D^{23}$ +16.5 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.78 (m, 4H), 7.40–7.53 (m, 6H), 5.49 (q, J=7.2 Hz, 1H), 5.29 (d, J=2.0 Hz, 1H), 5.08 (d, J=2.0 Hz, 1H), 4.31 (d, J=4.8 Hz, 1H), 4.06 (m, 1H), 3.65 (d, J=4.4 Hz, 2H), 3.48 (ddd, J=10.0, 8.4, 4.0 Hz, 1H), 3.27–3.34 (m, 2H), 2.37 (dd, J=12.8, 4.0 Hz, 1H), 2.12–2.22 (m, 2H), 1.98 (ddd, J=12.8, 7.6, 3.2 Hz, 1H), 1.84 (m, 1H), 0.90 (s, 9H), 0.83 (s, 9H), 0.075 (s, 3H), 0.070 (s, 3H), −0.014 (s, 3H), −0.028 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1 (d, J=2.3 Hz), 140.1 (d, J=12.2 Hz), 131.7 (d, J=3.0 Hz), 131.6 (d, J=2.3 Hz), 131.6 (d, J=74.3 Hz), 131.5 (d, J=75.1 Hz), 131.4 (d, J=9.1 Hz), 130.8 (d, J=9.1 Hz), 128.6 (d, J=1.5 Hz), 128.5 (d, J=1.5 Hz), 117.5, 116.2 (d, J=7.6 Hz), 82.2, 77.7, 70.7 (d, J=1.2 Hz), 66.0, 49.7, 44.3, 31.5 (d, J=69.8 Hz), 31.1, 25.9, 25.8, 18.3, 17.9, −4.2, −4.8, −5.2, −5.3. IR (neat, cm^{-1}) 2955, 2931, 2856, 1472, 1438, 1254, 1192, 1120, 1102, 1073, 836, 775, 744, 718, 695. HRMS ($[M+Na]^+$) calcd 638.3376, found 638.3368.

4.9. (2′-Hydroxymethyl)tetrahydrofuro[1,2-*a*]-25-hydroxyvitamin D_3 3a (1,2-α-THF-β-CH_2OH)

A solution of 35 mg (0.055 mmol) of A-ring phosphine oxide (+)-**4** in 1.5 mL of anhydrous THF was cooled to −78 °C and treated with 34 μL (0.055 mmol, 1.6 M in hexanes) of *n*-BuLi under argon atmosphere. The mixture turned deep reddish and was stirred for 15 min at −78 °C. To the solution was added dropwise a precooled (−78 °C) solution of 12 mg (0.034 mmol) of the C,D-ring ketone (+)-**5** in 1.5 mL of anhydrous THF via cannula. The reaction kept going until the reddish orange color faded to yellow (about 6.5 h). The reaction was quenched by adding 1.0 mL of pH 7 buffer (commercially available from ALDRICH) at −78 °C, then warmed to room temperature, extracted with EtOAc (20 mL×2), washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography with EtOAc–hexanes (1:15) as eluent to afford 5.5 mg (21%) of the coupled product as a colorless oil.

The coupled product (5.5 mg, 0.0071 mmol) was dissolved in 2 mL of anhydrous THF, and to the solution was added 78 μL (0.078 mmol) of a 1.0 M solution of TBAF in THF. The resulting mixture was stirred in darkness overnight at room temperature, then quenched with 2 mL of water. The solution was extracted with EtOAc (20 mL×3), washed with brine, dried over $MgSO_4$, and

concentrated. The residue was subjected to column chromatography with EtOAc as eluent to give 3.4 mg (92%) of the desired product **3a**. $[\alpha]_D^{24}$ +11.9 (*c* 0.072, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 6.38 (d, *J*=10.8 Hz, 1H), 6.04 (d, *J*=11.2 Hz, 1H), 5.41 (s, 1H), 5.15 (s, 1H), 4.49 (d, *J*=5.6 Hz, 1H), 4.25 (m, 1H), 3.82 (m, 1H), 3.67 (m, 1H), 3.54 (m, 1H), 2.82 (dd, *J*=12.3, 2.6 Hz, 1H), 2.64 (dd, *J*=13.2, 3.0 Hz, 1H), 1.22 (s, 6H), 0.87 (d, *J*=7.3 Hz, 3H), 0.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 142.5, 131.9, 125.1, 117.4, 116.7, 81.3, 71.1, 69.9, 65.4, 56.5, 56.4, 48.9, 45.9, 44.4, 42.7, 40.5, 36.4, 36.1, 30.4, 29.4, 29.2, 29.1, 27.6, 23.6, 22.3, 20.8, 18.8, 12.1. IR (neat, cm^{-1}) 3389, 2928, 2872, 1655, 1455, 1378, 1261, 1214, 1096, 1044, 914, 797, 761. UV (MeOH) λ_{max} 270 (ε 1831). HRMS ($[M+Na]^+$) calcd 495.3445, found 495.3433.

4.10. (2′-Hydroxymethyl)tetrahydrofuro[1,2-*a*]-25-hydroxyvitamin D_3 3b (1,2-β-THF-α-CH_2OH)

A solution of 70 mg (0.11 mmol) of A-ring phosphine oxide (−)-**4** in 1.5 mL of anhydrous THF was cooled to −78 °C and treated with 68 μL (0.11 mmol, 1.6 M in hexanes) of *n*-BuLi under argon atmosphere. The mixture turned deep reddish and was stirred for 15 min at −78 °C. To the solution was added dropwise a precooled (−78 °C) solution of 18 mg (0.055 mmol) of the C,D-ring ketone (+)-**5** in 1.5 mL of anhydrous THF via cannula. The reaction kept going for 7 h with the reddish orange color at −78 °C, and then kept going at −55 °C for overnight (changed to colorless). The reaction was quenched by adding 1.0 mL of pH 7 buffer (commercially available from ALDRICH) at −78 °C, then warmed to room temperature, extracted with EtOAc (25 mL×2), washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography with EtOAc–hexanes (1:15) as eluent to afford 20 mg (50%) of the coupled product as a colorless oil.

The coupled product (20 mg, 0.026 mmol) was dissolved in 2 mL of anhydrous THF, and to the solution was added 0.31 mL (0.31 mmol) of a 1.0 M solution of TBAF in THF. The resulting mixture was stirred in darkness overnight at room temperature, then quenched with 2 mL of water. The solution was extracted with EtOAc (20 mL×3), washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography with EtOAc as eluent to give 11 mg (93%) of the desired product **3b**. $[\alpha]_D^{25}$ −3.88 (*c* 0.35, MeOH). ^1H NMR (400 MHz, $CDCl_3$) δ 6.39 (d, *J*=10.8 Hz, 1H), 6.07 (d, *J*=11.2 Hz, 1H), 5.42 (d, *J*=1.6 Hz, 1H), 5.20 (d, *J*=2.0 Hz, 1H), 4.44 (d, *J*=4.8 Hz, 1H), 4.23 (m, 1H), 3.66–3.76 (m, 2H), 3.53 (dd, *J*=11.6, 6.0 Hz, 1H), 2.82 (dd, *J*=12.4, 4.0 Hz, 1H), 2.61 (dd, *J*=13.6, 4.0 Hz, 1H), 1.21 (s, 6H), 0.93 (d, *J*=6.4 Hz, 3H), 0.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 142.2, 132.1, 124.9, 117.9, 117.3, 81.9, 71.1, 70.2, 65.2, 56.5, 56.4, 49.1, 45.9, 44.3, 43.6, 40.4, 36.3, 36.1, 30.7, 29.3, 29.2, 29.0, 27.6, 23.6, 22.3, 20.8, 18.8, 12.0. IR (neat, cm^{-1}) 3389, 2928, 2872, 1655, 1455, 1378, 1261, 1214, 1096, 1044, 914, 797, 761. UV (MeOH) λ_{max} 270 (ε 6629). HRMS ($[M+Na]^+$) calcd 495.3445, found 495.3422.

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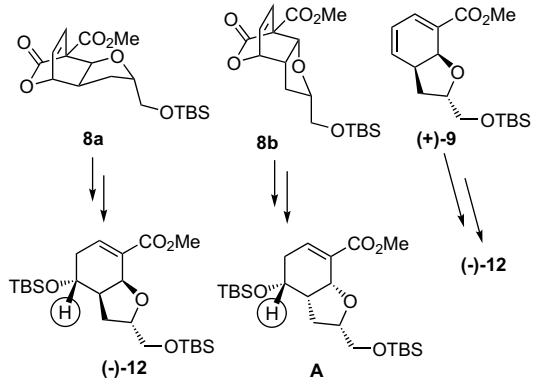
12. The structure of (−)-**12** can be explained as following: due to the steric issue of the large group, –CH_2OTBS, in dienophile (*S*)-**7**, only two possible cycloadducts, *endo*-**8a** and *exo*-**8b**, can be obtained from the lower approach of (*S*)-**7** to diene **6** in Diels–Alder cycloaddition. Under high pressure, that the major product is *endo*-cycloadduct **8a** can be explained by the various products generated from the following reaction steps as shown in Scheme 2. For example, after several reaction steps with the major cycloadduct, deallyloxycarbonylation afforded a conjugated enoate ester product. If this product was generated from **8a**, it should be (−)-**12**. Or, if this product was generated from **8b**, it should be compound **A**. Herein, the coupling constant of H at C3 (see the circled H below in structures (−)-**12** and **A**) in ^1H NMR showed a trans, trans, cis coupling constant of ddd (*J*=12.4, 8.4, 4.4 Hz) pattern. From this fact, it was concluded that product (−)-**12** was generated from the cycloadduct **8a**. In addition, the other intermediates shown in Schemes 2 and 3 also showed that the coupling constant of H at C3 matched with the trans, trans, cis type. In case of (+)-**9**, although its stereochemistry was not clear at first, the same compound (−)-**12** with the same physical data after several reaction steps was obtained.



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