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**PAPER**

# Combined coinage metal catalysis in natural product synthesis: total synthesis of (+)-varitriol and seven analogs†‡

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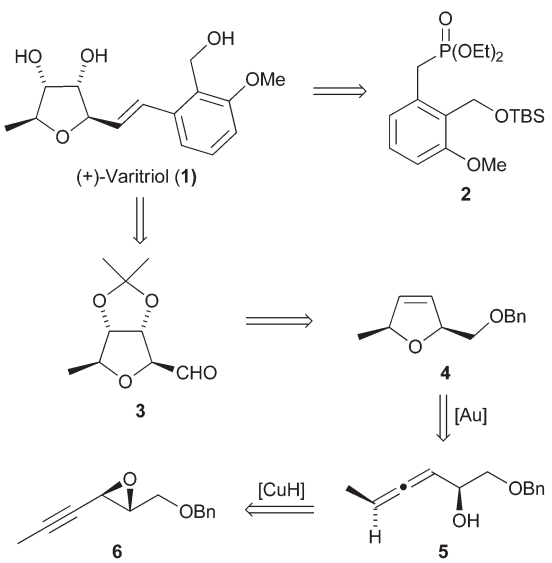
A modular total synthesis of the natural product (+)-varitriol (**1**) and seven analogs was achieved by using *combined coinage metal catalysis*. Starting from enynol **13**, reagent-controlled introduction of stereogenic centers and efficient *center-to-axis-to-center chirality transfer via* α-hydroxyallene **5** afforded (+)-varitriol with 6.4% yield over 10 steps.

## Introduction

Natural products derived from marine sources continue to fascinate due to their intriguing biological activities and their challenging structures.[1] The fungus *Emericella variecolor* was isolated from a sponge collected in Venezuelan waters of the Caribbean Sea.[2] In 2002, Barrero and co-workers isolated (+)-varitriol (**1**) from this fungus and disclosed its structure, including the relative configuration of the tetrahydrofuran ring.[3] Varitriol shows a more than 100-fold increased potency (over the mean toxicity) toward RXF 393 (renal cancer), T-47D (breast cancer) and SNB-75 (CNS cancer) cell lines and lower potency against prostate cancer, leukemia, ovarian cancer, and colon cancer cell lines.[3] This is a remarkable activity for such a small molecule, even though the mode of action remains to be elucidated.[4]

Notwithstanding the trisubstituted aromatic ring, the real synthetic challenge of varitriol is the richly substituted tetrahydrofuran bearing four stereogenic centers. Previous syntheses of (+)-varitriol,[5–7] its enantiomer,[7–9] and analogs thereof[7,10] used starting materials from the chiral pool (mannitol, dimethyl tartrate) and employed various olefination methods for attaching the aromatic side chain. Even though these approaches were successful, they render structural variations at the tetrahydrofuran ring (*e.g.*, different relative and/or absolute configuration at the four chirality centers) difficult. Based on our interest in combined coinage metal catalysis using functionalized allenes,[11] we now disclose a highly modular synthesis of (+)-varitriol, as well as of seven analogs of this natural product. Important features of our approach are the reagent-controlled introduction of all stereogenic centers and an efficient *center-to-axis-to-center chirality transfer* using *combined coinage metal catalysis*.[11,12]

The retrosynthetic analysis of (+)-varitriol (**1**) is delineated in Scheme 1. We envisaged that (+)-**1** can be derived from the aromatic phosphonate **2** and the chiral aldehyde **3** utilizing a Horner–Wadsworth–Emmons (HWE) olefination. The phosphonate **2** should be prepared from 3-methoxybenzoic acid by Kamikawa's procedure.[13] The aldehyde **3**, in which all four chiral centers are present, should be synthesized from 2,5-dihydrofuran **4**, which should be accessible by a gold-catalyzed cycloisomerization of the α-hydroxyallene **5**.[11,14] A copper hydride-catalyzed reduction of propargyl oxirane **6**[11,15] should provide the key intermediate **5**.




**Scheme 1**

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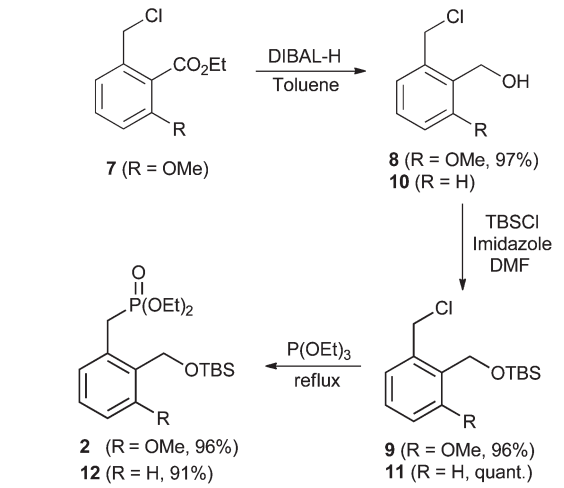
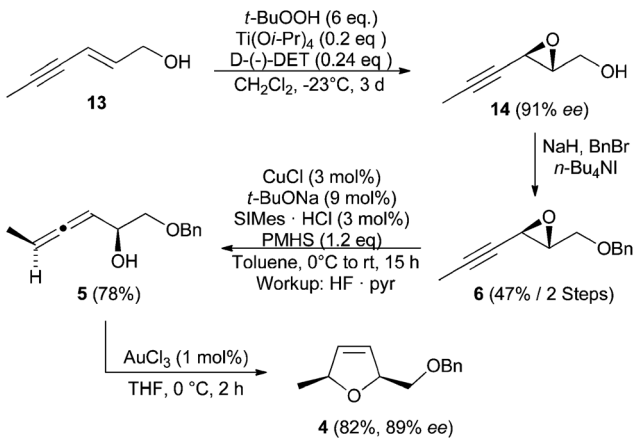
‡ Electronic supplementary information (ESI) available: Experimental procedures and copies of NMR spectra. See DOI: 10.1039/c2ob25069a




**Scheme 2**




**Scheme 3**

## Results and discussion

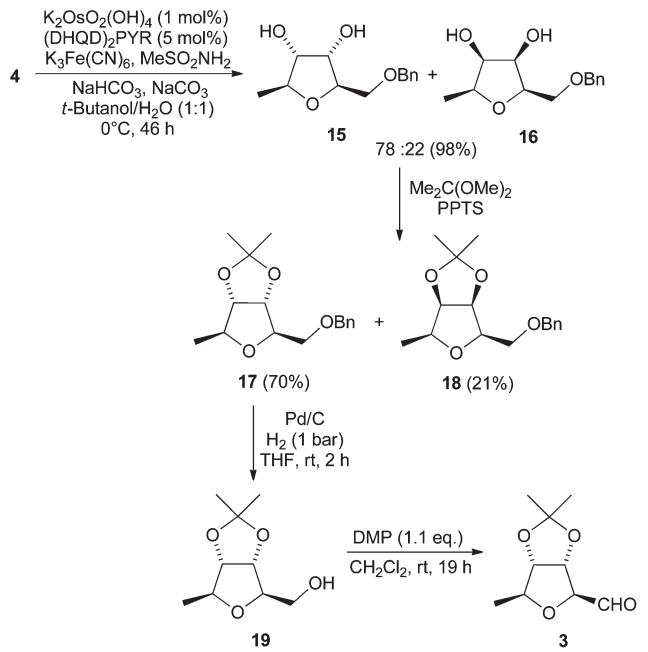
The synthesis of the aromatic phosphonate **2** and its simpler counterpart **12** is shown in Scheme 2. Reduction of ethyl 6-chloromethyl-2-methoxybenzoate (**7**), which was prepared from 3-methoxybenzoic acid according to Kamikawa's route,[13] with DIBAL-H followed by protection of **8** with TBSCl provided the substituted benzyl chloride **9**. This was treated with triethylphosphite in an Arbuzov reaction to give the corresponding HWE agent **2**. The aromatic phosphonate **12**, which is required for the synthesis of analogs of varitriol, was obtained in the same way (Scheme 2) starting from 2-hydroxymethylbenzyl chloride (**10**) which was prepared from 1,2-phenylenedimethanol with high yield (93%).[16]

The synthesis of **6** (Scheme 3) commenced with enyne **13**.[17] Catalytic Katsuki–Sharpless epoxidation[18] with D-(−)-DET provided the oxirane **14** with 91% ee after 3 days at −23 °C. Instead of the usual basic work up with aqueous NaOH,[18b] which destroyed the product, the reaction mixture was worked up only with ferrous sulfate and tartaric acid and the crude product was directly used in the following benzylation which afforded the desired propargyl oxirane **6** with 47% yield over 2 steps. Use of L-(+)-DIPT instead of D-(−)-DET afforded *ent*-**14** with 92% ee. Thus, the precursors for both enantiomers of varitriol were at hand with high enantioselectivity.

In the first of two consecutive coinage metal-catalyzed steps, the propargyl oxirane **6** was converted into α-hydroxyallene **5** by *anti*-stereoselective $S_N2'$-reduction using an NHC-stabilized copper hydride catalyst (Scheme 3).[15,19] This was formed *in situ* from copper(I) chloride, an imidazolium salt and sodium *tert*-butoxide in the presence of polymethylhydridosiloxane (PMHS) as stoichiometric hydride source. Among different NHC precursors used in this reaction, IBiox12·HOTf[20] and SIMes·HCl[21] gave similar results, but the latter is more readily available. In the presence of 3 mol% NHC–CuH and 1.2 eq. PMHS, allene **5** was obtained with 78% yield and complete *center-to-axis chirality transfer*.

Based on our continued interest in the stereoselective synthesis and transformation of functionalized allenes, we had developed the gold-catalyzed cycloisomerization of allenes bearing a hydroxy, amino, or thiol group in the α- or β-position, to the corresponding five- or six-membered heterocycles, a method that combines high reactivity and excellent *axis-to-center chirality transfer* with a tolerance towards many functional groups.[11,12,14,22] With this method the α-hydroxyallene **5** was conveniently transformed into the desired 2,5-dihydofuran **4** (Scheme 3). The chirality transfer was virtually complete when the reaction was catalyzed by 1 mol% gold(III)-chloride in THF at 0 °C, giving **4** with 89% ee and 82% yield. At room temperature, partial epimerization[22a] was observed. Gold(I)-chloride in the presence of pyridine or 2,2′-bipyridine[22a] can also be used, but the reaction was much slower.

After successful introduction of two stereogenic centers under reagent control, our intention was to install the remaining two chirality centers of varitriol by reagent control as well. Here, the




**Scheme 4**

Sharpless dihydroxylation[23] is the method of choice, even though (cyclic or acyclic) *cis*-1,2-disubstituted olefins are not the best substrates for this transformation.[24] Therefore, a ligand screening with dihydrofuran **4** was carried out (Scheme 4). Whereas $(DHQD)_2PHAL$ and $(DHQD)_2AQN$ were almost unselective, affording ratios of diastereomeric diols **15** and **16** of 55 : 45 and 57 : 43, respectively, the ligand $(DHQD)_2PYR$ led to a ratio of 78 : 22, a diastereoselectivity that we consider satisfactory for this type of substrate. The dihydroxylation was carried out with a loading of 1 mol% potassium osmate(VI) dihydrate and 5 mol% $(DHQD)_2PYR$ and gave an almost quantitative yield after 2 days at 0 °C.[25]

The mixture of **15** and **16** was treated with 2,2-methoxypropane and PPTS to give the bicyclic acetals **17** and **18** (Scheme 4) which could be separated chromatographically. The relative configuration of **17** was determined by an NOESY experiment which shows cross peaks between $H^2/H^3$ and the methyl group at the tetrahydrofuran ring, as well as a cross peak between $H^3$ and $H^2$ (Fig. 1). Due to overlapping signals in the $^1H$ NMR spectrum of diastereomer **18**, we conducted the NOESY experiment with the debenzylated product **20** (Fig. 1), Cross peaks between $H^1$ and $H^2$, between $H^2$ and $H^3$, and between $H^3$ and $H^4$ confirm the *all-cis*-configuration.

Hydrogenative debenzylation[26] of **17** provided the alcohol **19** which was sufficiently pure for the subsequent oxidation (Scheme 4). Whereas Swern, Parikh–Doering, and IBX oxidation failed, clean conversion of **19** to the desired aldehyde **3** was achieved with Dess–Martin periodinane (DMP).[27] Gratifyingly, no epimerization of **3** was observed. Likewise, the *all-cis*-substituted diastereomer **18** was converted into the corresponding aldehyde **21** which was used for the synthesis of analogs of (+)-varitriol.

The aldehyde **3** was used in the subsequent HWE-olefination[28] without purification. Deprotonation of phosphonate **2** with *n*-BuLi and addition of aldehyde **3** resulted in no reaction at 0 °C and only sluggish conversion at ambient temperature. However, heating to 50 °C for 15 hours afforded the desired coupling product **22** with 40% yield over 3 steps (debenzylation, oxidation and HWE-reaction). Running the olefination in a microwave[29] at 80 °C for 1 hour gave a similar result (37% yield of **22**). In both cases, the *E*-isomer was formed exclusively.

Global deprotection of the olefin **22** with a standard procedure[5,9,10] furnished the enantiomerically pure natural product (+)-varitriol (**1**) as colorless needles after recrystallization from cyclohexane–ethyl acetate (Scheme 5). All spectroscopic data agree with those reported for the isolated product.[3] The optical rotation of $[\alpha]_D^{20}$ = +40.3 (*c* = 2.7, MeOH) measured for our product matches well with the values reported by Gracza *et al.*,[6]

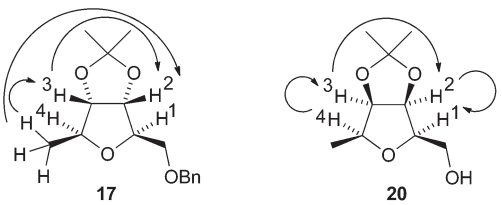
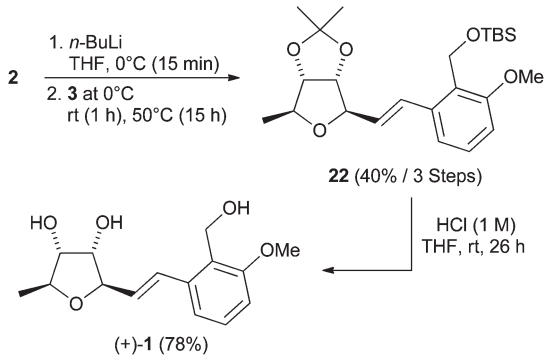



**Fig. 1** NOESY experiments of **17** and **20**.




**Scheme 5**

**Table 1** Specific rotation reported for varitriol (**1**)

| Enantiomer | Specific rotation $[\alpha]_D^{20}$ | Reference |
|---|---|---|
| (+)-**1** | +40.3 (*c* 2.7, MeOH) | Our value |
| (+)-**1** | +18.5 (*c* 2.3, MeOH) | 3 |
| (+)-**1** | +19.4 (*c* 2.7, MeOH) | 5 |
| (+)-**1** | +43.4 (*c* 0.53, MeOH) | 6 |
| (+)-**1** | +40.0 (*c* 0.21, MeOH) | 7 |
| (−)-**1** | −42.2 (*c* 0.135, MeOH) | 7 |
| (−)-**1** | −18.2 (*c* 0.0033, MeOH) | 8 |
| (−)-**1** | −40.6 (*c* 1.6, MeOH) | 9 |

Ghosh and Pradhan,[7] and Taylor *et al.*,[9] but not with other literature values[3,5,8] (Table 1). Thus, it seems that previously varitriol was not always obtained in pure form.

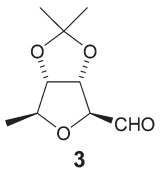
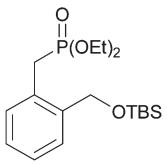
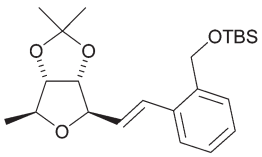
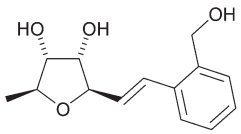
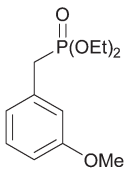
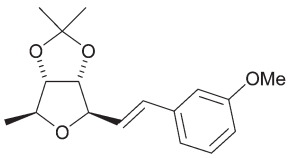
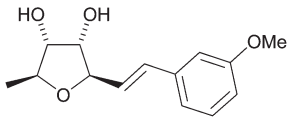
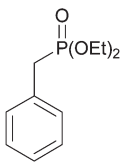
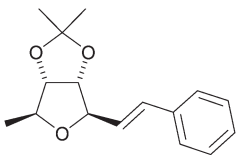
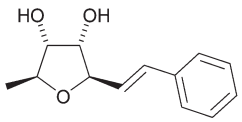
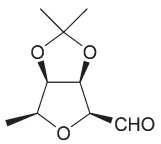
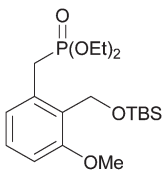
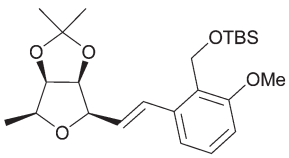
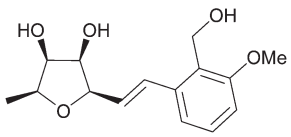
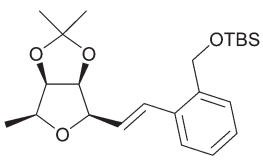
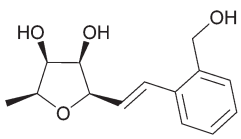
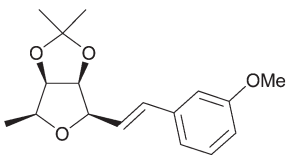
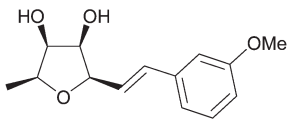
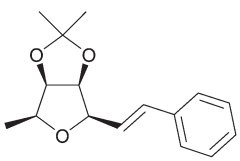
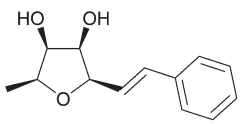
With the natural product (+)-varitriol (**1**) and an optimized procedure for the HWE-reaction in hand, we synthesized seven analogs of the natural product[7,10] using aldehydes **3** or **21** and phosphonates **2**, **12**, **23**, or **24** (Table 2). Whereas the latter is commercially available, phosphonate **23** was obtained by Arbuzov reaction from 3-methoxybenzyl chloride and triethylphosphite. The HWE-olefination proceeded smoothly under the conditions used for the synthesis of **22** and afforded the desired products **25–31** with 31–49% yield over 3 steps (starting from **17** or **18**). In all cases, the *E*-olefin was obtained exclusively. The deprotection under the acidic conditions used for the synthesis of (+)-**1** was successful as well to furnish the varitriol analogs **32–38** with 45–91% yield. Among these is the *all-cis*-diastereomer **35** of the natural product. It was remarkable that deprotection of compounds **28–31** which bear an *all-cis*-substituted tetrahydrofuran ring required a larger excess of HCl (1 M, 72–120 eq.) and longer reactions times (18–52 h) than substrates **25–27** (1 M HCl, 18 eq; 18–28 h).

## Conclusions

A modular total synthesis of the marine-derived natural product (+)-varitriol (**1**) was achieved from enynol **13** with 6.4% yield over 10 steps. Key steps are the copper hydride-catalyzed $S_N2'$-reduction of propargyl oxirane **6** and the subsequent gold-catalyzed cycloisomerization of α-hydroxyallene **5** to 2,5-dihydrofuran **4**. This *combined coinage metal catalysis* enables an efficient *center-to-axis-to-center chirality transfer*. In contrast to

**Table 2** Varitriol analogs **32–38** and their precursors **25–31**

Phosphonate —(1. *n*-BuLi, 2. Aldehyde)→ HWE-Product —(HCl, THF)→ Analog

| Aldehyde | Phosphonate | HWE-Product | Analog of Varitriol |
|---|---|---|---|
|  **3** |  **12** |  **25** |  **32** |
| **3** |  **23** |  **26** |  **33** |
| **3** |  **24** |  **27** |  **34** |
|  **21** |  **2** |  **28** |  **35** |
| **21** | **12** |  **29** |  **36** |
| **21** | **23** |  **30** |  **37** |
| **21** | **24** |  **31** |  **38** |

previous ex-chiral-pool syntheses, the modularity and the reagent-controlled introduction of all stereogenic centers renders our approach particularly useful for the synthesis of analogs of the natural product and hence for structure–activity studies. This was demonstrated by the rapid and efficient preparation of derivatives **32–38**, including diastereomer **35** of varitriol. Likewise, the unnatural enantiomer (−)-**1** and analogs thereof are accessible from readily available oxirane *ent*-**14**. We are continuing to expand the repertoire of coinage metal catalysis and to apply these methods to target-oriented synthesis.



## Experimental section

### (2*S*,4*S*)-1-(Benzyloxy)hexa-3,4-dien-2-ol (5)

A mixture of CuCl (13 mg, 0.131 mmol), NaO*t*-Bu (38 mg, 0.392 mmol) and SIMes·HCl (45 mg, 0.131 mmol) in degassed toluene (18 mL) was briefly heated in a hot water bath to 100 °C and then allowed to cool to room temperature (*ca*. 40 min). To this solution was added dropwise PMHS (315 mg, 5.24 mmol). After stirring at room temperature for 5 min, the yellow solution was cooled to 0 °C and **15** (880 mg, 4.36 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 3 h and further at room temperature for 19 h. To the solution was added a solution of HF·Pyr (65% in pyridine, 2.65 g, 17.4 mmol) in THF (400 mL) at 0 °C. After stirring at this temperature for 2 h, the reaction was quenched with aq. saturated $NaHCO_3$ solution (120 mL). The aqueous phase was extracted with $Et_2O$ (4 × 60 mL), the combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane–AcOEt (5 : 1) to give **5** (693 mg, 3.39 mmol, 78%) as a yellow oil. $[\alpha]_D^{20}$ = +42.2 (*c* 1.2, $CHCl_3$). IR ($\nu$ $cm^{-1}$): 3430 (OH), 3030, 2859, 1968 (C═C═C), 1454, 1110, 737. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.27–7.39 (5H, m), 5.22–5.30 (1H, m), 5.15–5.22 (1H, m), 4.58 (2H, s), 4.36 (1H, m), 3.56 (1H, dd, *J* 9.6, 3.6), 3.45 (1H, dd, *J* 9.6, 7.6), 2.56 (OH, brs), 1.70 (3H, dd, *J* 7.0, 3.3). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 203.9 (C═C═C), 137.8 (C), 128.4, 127.7 (5 CH), 91.0, 88.6 (2 CH, C═C═C), 74.1, 73.3 (2 $CH_2$), 68.6 (CH), 14.1 ($CH_3$). EI-HRMS *m*/*z*: found 227.1044, calcd for $C_{13}H_{16}O_2Na$ $(M + Na)^+$: 227.1043.

### (2*S*,5*S*)-2-(Benzyloxymethyl)-5-methyl-2,5-dihydrofuran (4)

To a solution of **5** (681 mg, 3.33 mmol) in THF (33 mL) was added $AuCl_3$ (10.1 mg, 0.0333 mmol) at 0 °C. After being stirred at 0 °C for 2 h, the reaction mixture was filtered through silica gel and the residue was washed with $Et_2O$–isohexane (3 : 1, 110 mL). After being concentrated under vacuum, the residue was purified by column chromatography using cyclohexane–AcOEt (20 : 1) to give **4** (555 mg, 2.72 mmol, 82%) as a light yellow oil. $[\alpha]_D^{20}$ = −48.9 (*c* 1.6, $CHCl_3$). IR ($\nu$ $cm^{-1}$): 3030, 2857, 1453, 1366, 1094, 737. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.25–7.38 (5H, m), 5.85 (1H, d, *J* 5.9), 5.79 (1H, d, *J* 6.1), 4.91–4.99 (2H, m), 4.63 (1H, d, *J* 12.2), 4.58 (1H, d, *J* 12.2) (AB-system with doublet by 4.63), 3.50–3.53 (2H, m), 1.30 (3H, d, *J* 6.2). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 138.2 (C), 132.8 (CH), 128.2 (2CH), 127.5 (2CH), 127.4, 126.8 (2 CH), 85.2, 82.2 (2 CH), 73.8, 73.2 (2 $CH_2$), 22.7 ($CH_3$). EI-HRMS *m*/*z*: found 204.1137, calcd for $C_{13}H_{16}O_2$ ($M^+$): 204.1145.

### General procedure for HWE-olefinations

To a solution of the phosphonate (1 mmol) in THF (3 mL) was added dropwise at 0 °C *n*-BuLi (2.24 M in hexane, 0.45 mL, 1 mmol). After stirring at 0 °C for 15 min, a solution of the crude aldehyde (0.455 mmol) in THF (1.5 mL) was added. The mixture was stirred at 0 °C for 30 min, at room temperature for 1 h, and at 50 °C for 8–21 h. After cooling to room temperature, $H_2O$ (3 mL) and aq. saturated NaCl (3 mL) solution were added. After extraction with $Et_2O$ (4 × 6 mL), the organic layer was dried with $MgSO_4$ and concentrated under vacuum. The crude was purified by column chromatography using cyclohexane–AcOEt (20 : 1).

### *tert*-Butyl(2-methoxy-6-((*E*)-2-((3a*R*,4*R*,6*S*,6a*S*)-2,2,6-trimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)vinyl)benzyloxy) dimethylsilane (22)

HWE-reaction according to the general procedure (reaction time: 15 h) of **2** (285 mg, 0.708 mmol) and **3** (crude product, 60 mg) gave **22** (58 mg, 0.133 mmol, 40% for 3 steps) as a light yellow oil. $[\alpha]_D^{20}$ = +19.9 (*c* 1.4, $CHCl_3$). IR ($\nu$ $cm^{-1}$): 2930, 2856, 1579, 1472, 1381, 1252, 1080, 837. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.08–7.22 (3H, m), 6.78 (1H, d, *J* 8.1), 6.19 (1H, dd, *J* 15.9, 6.5, HC═C), 4.81 (2H, s), 4.55 (1H, dq, *J* 6.8, 5.0), 4.44–4.49 (1H, m), 4.33 (1H, dd, *J* 6.8, 4.8), 4.01–4.08 (1H, m), 3.81 (3H, s), 1.57 (3H, s), 1.36 (3H, d, *J* 6.7), 1.35 (3H, s), 0.89 (9H, s), 0.06 (6H, s). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 157.4, 138.5 (2 C), 130.2, 129.3, 128.5 (3 CH), 126.5 (C), 118.7 (CH), 114.9 (C), 110.0 (CH), 86.2, 85.6, 84.8, 80.2 (4 CH), 55.9 ($CH_2$), 55.6 ($OCH_3$), 27.4 ($CH_3$), 26.0 ($C(CH_3)_3$), 25.5, 19.1 (2 $CH_3$), 18.4 ($C(CH_3)_3$), −5.3 ($2CH_3$). ESI-HRMS *m*/*z*: found 452.2825, calcd for $C_{24}H_{42}O_5NSi$ $(M + NH_4)^+$: 452.2827.

### General procedure for deprotection of the HWE-product

To a solution of the HWE-product. (1 mmol) in THF (3.5 mL) was added at room temperature HCl (1 M, 18–120 eq). After stirring at room temperature for 18–52 h, the reaction mixture was neutralized with aq. saturated $NaHCO_3$ solution After extraction with $CH_2Cl_2$, the organic layer was dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography using $CH_2Cl_2$–acetone (for triols) or cyclohexane–AcOEt (for diols).

### (+)-Varitriol ((+)-1)

Deprotection of **22** (126 mg, 0.290 mmol) according to the general procedure (5.4 mL 1 M HCl, 18 eq, 26 h) and column chromatography using $CH_2Cl_2$–acetone (2 : 1) gave (+)-**1** (63 mg, 0.225 mmol, 78%) as a colorless solid which became colorless needles after recrystallization from cyclohexane–ethyl acetate (1 : 1). Mp 108–110 °C. $[\alpha]_D^{20}$ = +40.3 (*c* 2.7, $CH_3OH$). IR ($\nu$ $cm^{-1}$): 3383 (OH), 2969, 2928, 1578, 1472, 1384, 1264, 1093, 1003, 786, 746. $^1$H NMR (400 MHz, acetone-$d_6$) $\delta$: 7.22 (1H, t, *J* 8.0), 7.08–7.16 (2H, m), 6.89 (1H, d, *J* 8.1), 6.20 (1H, dd, *J* 15.8, 6.7, HC═C), 4.71 (2H, s), 4.26–4.32 (1H, m), 3.90 (1H, t, *J* 5.5), 3.78–3.87 (1H, m), 3.81 (3H, s, $OCH_3$), 3.69 (1H, t, *J* 5.7), 3.01 (1H, brs, OH), 1.27 (3H, d, *J* 6.4). $^{13}$C NMR (100 MHz, acetone-$d_6$) $\delta$: 158.9, 139.0 (2 C), 132.4, 129.3, 129.3 (3 CH), 127.9 (C), 119.3, 110.6 (2 CH), 85.3, 80.0, 77.1, 76.4 (4 CH), 56.0 ($OCH_3$), 55.4 ($CH_2$), 19.5 ($CH_3$). ESI-HRMS *m*/*z*: found 561.2688, calcd for $C_{30}H_{41}O_{10}$ $(2M + H)^+$: 561.2694.

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