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Efficient Asymmetric Synthesis of an A-Ring Synthon for Pd-Catalyzed Preparation of 1α-Hydroxyvitamin D Metabolites and Analogs

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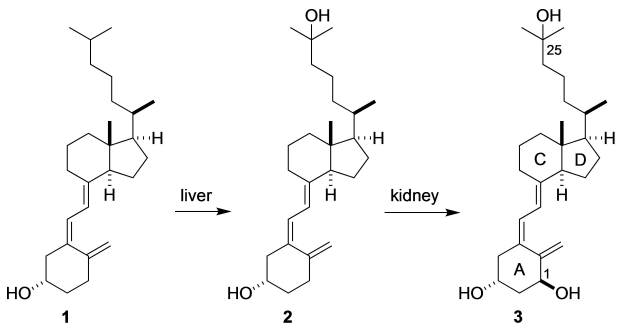
The secondary parallel hypercalcemic effects associated with the treatment of several hyperproliferative diseases with the natural hormone 1α,25-dihydroxyvitamin D_3 (calcitriol) and/or known active vitamin D metabolites and analogs, demand the development of efficient and rapid methods for the preparation of vitamin D receptor (VDR) ligands as new selective and non-calcemic agonists. Here we describe an efficient and adaptable multigram-scale synthetic sequence to access an A-ring synthon as useful precursor of the vitamin D triene system of 1α-hydroxylated vitamin D derivatives via Pd-catalyzed carbocyclization/Suzuki–Miyaura cross-coupling reactions in a protic medium. The key step is an asymmetric Lewis acid-promoted carbonyl-ene reaction to a chiral glyosylate ester to establish the 1α-hydroxyl group of 1α,25-dihydroxyvitamin D_3 and its derivatives.

Introduction

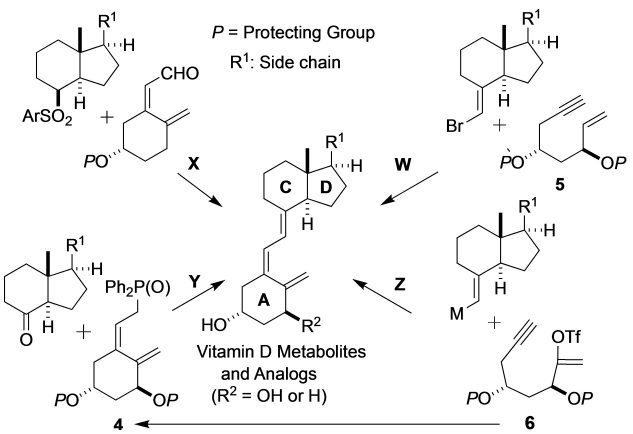
Vitamin D_3 (**1**) is a secosteroid produced in the skin by UV light or ingested in food. This prohormone undergoes two enzymatic hydroxylations, first in the liver to generate the major circulating metabolite 25-hydroxyvitamin D_3 (**2**), and then in the kidney leading to the hormonally active form 1α,25-dihydroxyvitamin D_3 (1,25D, calcitriol, **3**) (Scheme 1). The latter induces gene expression through the nuclear vitamin D receptor (VDR) to regulate calcium homeostasis and pleiotropic actions including cancer chemoprevention and modulation of the immune system.[1–3]



Scheme 1. Vitamin D_3 (**1**), 25-hydroxyvitamin D_3 (**2**), and 1α,25-dihydroxyvitamin D_3 (**3**).

Synthetic efforts[4] towards highly active and selective analogs of 1,25D for treatment of several diseases have led to the development of various convergent methods to directly assemble the vitamin D triene system (Scheme 2). These methods include the modified Julia olefination (route **X**),[5] the popular Lythgoe's Wittig-Horner approach (route **Y**),[6] based on coupling between the lithium anion of phosphine oxide **4** (A-ring fragment) and a ketone (CD-side chain fragment), and the Pd-catalyzed addition/ring-closure strategy developed by Trost (route **W**),[7] which utilizes a vinyl bromide (CD-side chain fragment) and an enyne of type **5** as precursor of the A-ring fragment.[7]

More recently, we have developed a mild Pd^0-catalyzed tandem process, which involves the ring closure of enol-triflate



Scheme 2. Methods for the direct generation of vitamin D triene system.

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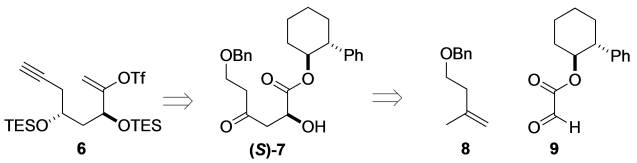
6, precursor of the A-ring[8a] followed by cross-coupling with an alkenyl-boronic ester[8b] or related alkenyl Zn[9] or Ti[10] derivatives (upper fragment) to generate the triene unit of vitamin D metabolites and analogs modified in different parts of the vitamin D skeleton (route **Z**).[11] Considerable synthetic efforts have been directed towards the vitamin D A-ring precursors such as phosphine oxide **4**[12] and enyne **5**,[13] but only one synthesis of enol-triflate **6** (P = Si*t*-BuMe$_2$) from (*R*)-carvone) has been reported.[8] The latter intermediate was also used for the preparation of phosphine oxide **4**,[8a] important intermediate in the Wittig-Horner approach (route **Y**). Drawbacks of the reported synthesis of **6** such as the lability of the triethylsilyl ether as protecting group[14] during the oxidative-cleavage of carvone epoxides and the reproducibility in the formation of the enol-triflate on a gram scale, led us to devise a new and more efficient approach to enol-triflate **6** (P = SiEt$_3$) as a valuable intermediate for the Pd-catalyzed synthesis of the A-ring fragment of the natural hormone 1,25D and its 1α-hydroxy-derivatives (route **Z**, Scheme 2).[8]

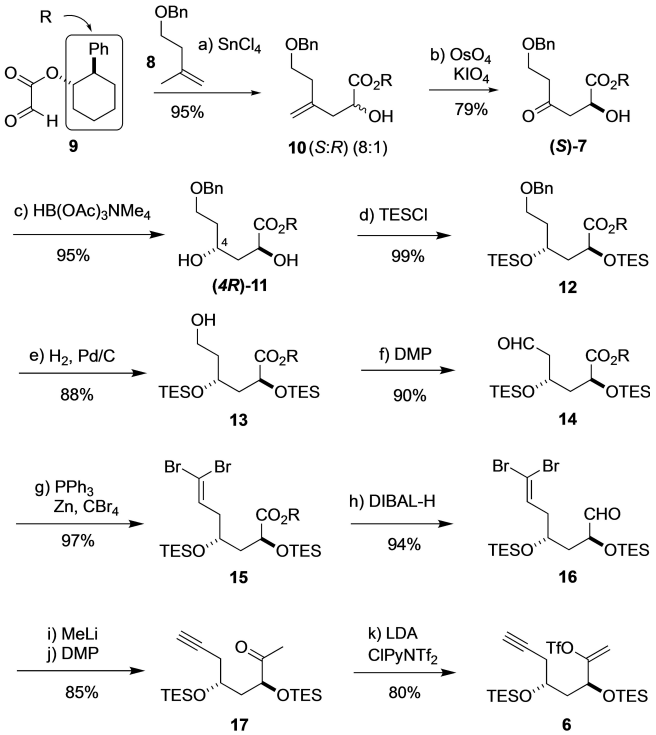
Results and Discussion

The new synthesis of enol-triflate **6** features an asymmetric glyoxylate-ene reaction between alkene **8** and the known chiral glyoxylate **9**[15] in the presence of tin tetrachloride as the Lewis-acid to access the β-hydroxy-ketone **(*S*)-7**, precursor of the A-ring[16] of 1α-hydroxy-vitamin D derivatives (Scheme 3).[17–19]

The synthesis of **6** began with chiral glyoxylate **9**[15] (Scheme 4). The diastereoselective $SnCl_4$-assisted ene reaction between **9** and olefin **8** provided a mixture of β-hydroxy esters **10** (dr 8:1 ratio),[19] which could be separated by HPLC (SI). The mixture of diastereoisomers **10** was subjected to oxidative cleavage[20] with catalytic osmium tetroxide in the presence of potassium periodate to give, after MPLC separation (VersaFlash Silica Ø 40×150 mm 20–45 μm, 7% *i*-PrOH/hexanes), pure β-hydroxy ketone **7** (79% yield). Figure 1 shows the proposed transition state for the asymmetric ene-reaction leading to **(*S*)-10**. Hydroxyl-directed reduction of **(*S*)-7** with [HB(OAc)$_3$NMe$_4$][21] provided a mixture of alcohols **(4*R*)-11** and **(4*S*)-11** (95:5, ^{1}H-NMR ratio), which upon crystallization from Et$_2$O/hexanos provided pure **(*R*)-11** as determined by ^{1}H NMR (lack of diastereomeric peak at δ 4.07). Diol **(4*R*)-11** was then converted to **12** by protective silylation (Et$_3$SiCl) (94% yield, two steps). Benzylic ether **12** was converted to aldehyde **14** by selective deprotection (H_2, Pd/C) followed by periodinane oxidation (DMP) of the resulting alcohol **13** (79% yield, two steps). Exposure of **14** to Corey-Fuchs chain extension conditions



Scheme 3. Retrosynthesis for enol-triflate **6** through intermediate **7**.



Scheme 4. Synthesis of enol-triflate **6**. Reactions and conditions: (a) $SnCl_4$ (1.1 equiv.), slow addition to **9** (>99% ee), CH_2Cl_2, −78 °C, 1 h, then **8** (1.1 equiv.), slow addition (1 h), −78 °C, 3 h (95%; (b) OsO_4 (cat), KIO_4 (2 equiv.), dioxane/H_2O (3:1), 23 °C, 12 h (79%); (c) HB(OAc)$_3$NMe$_4$ (2.5 equiv.), HOAc/MeCN (1:2), −25 °C, 4 h (95%); (d) TESCl (3 equiv.), imidazole (6 equiv.), DMAP (0.3 equiv.), DMF, 23 °C, 12 h (99%); (e) H_2, Pd/C, Et_2O, 23 °C, 12 h (88%); (f) DMP (1.1 equiv.), CH_2Cl_2, 23 °C, 20 min (90%); (g) CBr_4 (3 equiv.), Zn (3 equiv.), PPh_3 (3 equiv.), CH_2Cl_2, 0 °C to 23 °C, 1.5 h, then **14**, 23 °C, 1.5 h (97%); (h) DIBAL-H (1.1 equiv.), CH_2Cl_2, −78 °C, 30 min (94%); (i) MeLi (3.3 equiv.), Et_2O, −78 °C, 1 h; (j) DMP (1.1 equiv.), CH_2Cl_2, 23 °C, 30 min (85%, 2 steps); (k) LDA (2.2 equiv.), THF, −78 °C, 30 min,. *N*-(5-chloro-2-pyridyl)-triflimide, (1.5 equiv.), 23 °C, 1 h (80%). TESCl = chlorotriethylsilane, DMAP = 4-dimethylaminopyridine.

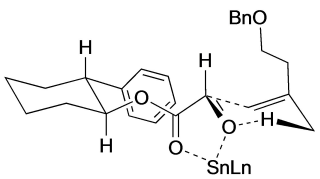


Figure 1. Proposed transition state for the Lewis acid-assisted carbonyl-ene reaction.

(Ph$_3$P=CBr$_2$)[21] led to dibromide **15**, which was reduced with DIBAL-H to remove the chiral auxiliary, leading to aldehyde **16** (91% yield, two steps). At this point, we expected that methyllithium would serve as a nucleophile to attack the carbonyl group of **16** to form the corresponding alkoxides, as well as a base to generate the triple bond. Indeed, addition of methyllithium to **16** produced a mixture of alkynols, which were oxidized with Dess-Martin periodinane to give the alkynone **17** (85% yield, two steps) as a single product as shown by its ^{13}C-NMR spectrum (two single peaks at δ 77.4 and 67.78 assigned to both CH-OTES, respectively). Notably, the methylation step

allows for isotopic labeling of the vitamin D-A-ring at C19.[16] Ketone **17** was treated with LDA and the resulting enolate was trapped with Comins' reagent [*N*-(2-pyridyl)-triflimide][22] to afford the desired enol-triflate **6** (80% yield) (34% overall yield from **9**, 11 steps), whose identity was established by comparison (^{1}H NMR, ^{13}C NMR, and $[\alpha]_D^{25}$) with an authentic sample.[9]

Conclusion

In summary, a concise asymmetric synthesis of (3*S*,5*R*)-3,5-bis [(triethylsilyl) oxy]oct-1-en-7-yn-2-yl trifluoro methanesulfonate (enol-triflate **6**), from chiral glyosylate **9**, has been achieved by an efficient approach featuring a Lewis acid-assisted asymmetric carbonyl-ene reaction (11 steps, 34% overall yield). The enyne **6** is a useful intermediate for the rapid and efficient preparation of new 1α-hydroxy-vitamin D_3 analogs of potential therapeutic potential via Pd^0-catalyzed carbocyclization/cross coupling cascades. The synthetic sequence can be used for the multigram scale generation of chiral β-hydroxy ketones.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: A-Ring synthons · Carbonyl-ene reaction · Chiral β-hydroxy ketones · 1α-Hydroxyvitamin D · Palladium

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