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Asymmetric Synthesis of Vitamin D_3 Analogues: Organocatalytic Desymmetrization Approach toward the A-Ring Precursor of Calcifediol

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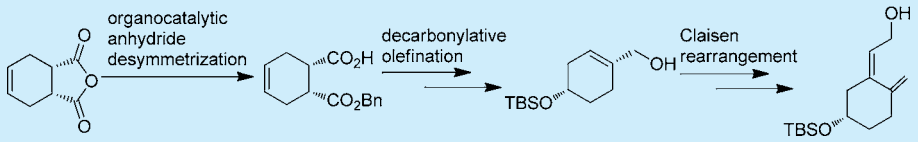
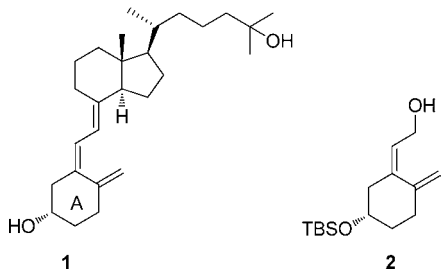
Supporting Information



ABSTRACT: A novel asymmetric synthesis has been developed for the construction of the A-ring of a chiral precursor to calcifediol. The highlights of this synthesis include (i) the introduction of the stereochemistry at the C5-position of the A-ring through the organocatalytic enantioselective desymmetrization of a prochiral cyclic anhydride using a bifunctional urea catalyst and (ii) the introduction of the *exo*-cyclic (*Z*)-dienol side chain by a tandem Claisen rearrangement/sulfoxide thermolysis of an allylic alcohol.

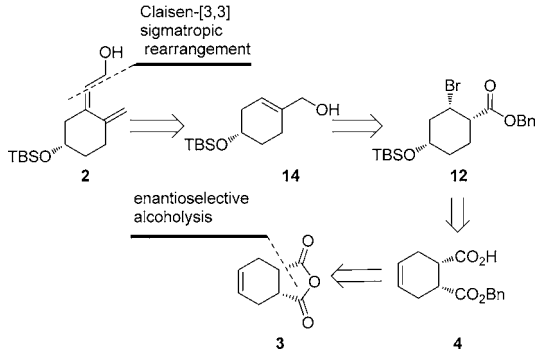
Calcifediol (25-hydroxyvitamin D_3, **1**) is a biologically active metabolite of vitamin D_3 and represents the major circulating form of vitamin D_3 present in human plasma.[1] The medicinal importance of **1** for the treatment of various metabolic diseases as well as renal failure, rickets, and osteoporosis has attracted considerable interest from researchers working in a variety of different fields, including synthetic organic chemistry.[2] The chiral dienol **2** is a precursor of the A-ring building block required for the preparation of **1** (Scheme 1). Several studies have been reported to date describing the development of elegant synthetic processes for the synthesis of **2**, including Lythgoe's partial approach starting from vitamin D_2 or vitamin D_3. Several stereoselective total syntheses have also been reported on the basis of Lythgoe's chiral pool approach and William's catalytic asymmetric strategy.[3] Despite significant progress in this area, the development of an efficient and practical process for the preparation of **2** has not yet been achieved and is still highly desired. Herein, we report a novel catalytic asymmetric synthesis of **2** from commercially available cyclic anhydride **3** using an organocatalytic anhydride desymmetrization strategy.

Scheme 1. Structures of 25-Hydroxyvitamin D_3 (1) and the A-Ring Allyl Alcohol 2



Our retrosynthetic analysis of **2** is depicted in Scheme 2. It was envisaged that the chiral dienol **2** could be assembled from the allylic alcohol **14** through a one-pot tandem Claisen [3,3]-sigmatropic rearrangement/sulfoxide thermolysis reaction followed by the reduction of the resulting ester. Compound **14** could be synthesized from **12** via the E_2 elimination and the reduction of the benzyl ester to give the required allylic alcohol **14**. In turn, compound **12** could be prepared from hemiester **4** via a series of transformations. Finally, it was envisaged that the chiral hemiester **4** could be synthesized by the organocatalytic enantioselective alcoholysis of the *meso*-cyclic anhydride **3**.

Scheme 2. Retrosynthetic Analysis



To allow for the introduction of the required stereochemical information into the key intermediate **4**, we directed our

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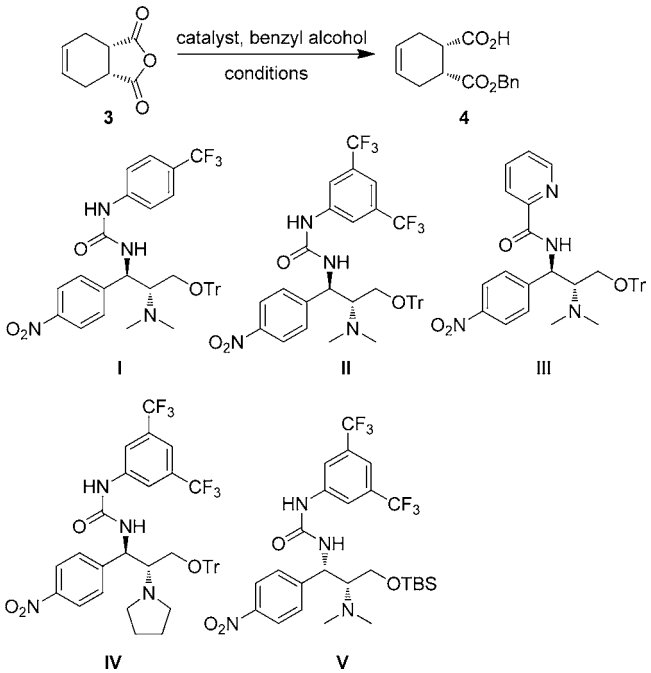
research efforts toward the development of an efficient process for the asymmetric alcoholysis of the prochiral cyclic anhydride **3**. In this way, we investigated the synthesis of (1*S*,6*R*)-hemiester **4** from **3** using a series of chiral bifunctional urea catalysts **I**–**V**, which were developed by our group (Table 1).[4]

Table 1. Conditions for the Optimization of the Enantioselective Formation of the Benzyl Hemiester 4



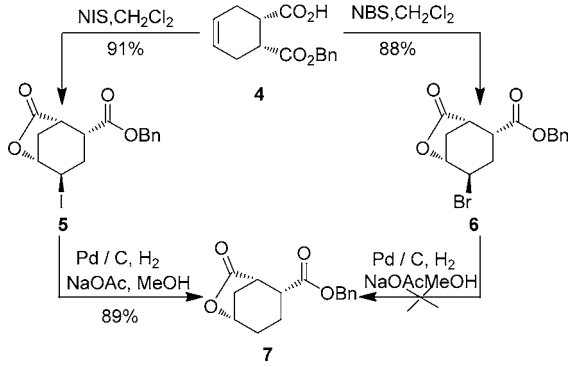
entry	cat.	solvent	concn[c]	time (h)	yield[d] (%)	ee[e] (%)
1	**I**	MTBE	0.1	40	92	69
2	**II**	MTBE	0.1	40	89	62
3	**III**	MTBE	0.1	36	93	49
4	**IV**	MTBE	0.1	40	91	56
5	**V**	MTBE	0.1	40	90	57
6	**I**	CH_2Cl_2	0.1	40	90	47
7	**I**	CH_3CN	0.1	40	93	50
8	**I**	toluene	0.1	42	90	55
9	**I**	THF	0.1	40	89	67
10	**I**	MTBE	0.05	45	92	77
11	**I**	MTBE	0.025	45	93	88
12[b]	**I**	MTBE	0.025	50	93	90

[a]Unless otherwise noted, all of the reactions were carried out with anhydride (0.5 mmol), catalyst **I**–**V** (0.025 mmol), and benzyl alcohol (2.5 mmol). [b]The catalyst loading was 10 mol %. [c]The concentration of **3** (mol/L). [d]Yield of the isolated product. [e]Enantiomeric excess was determined by chiral HPLC analysis using a chiral stationary phase.

The result of our initial experiment showed that the exposure of **3** to benzyl alcohol in the presence of catalyst **I** (5 mol %) in MTBE (0.1 M) at room temperature gave the desired hemiester **4** in 92% yield with 69% ee (Table 1, entries 1). The subsequent screening of a wide range of catalysts (i.e., catalysts **II**–**V**) and solvents, including dichloromethane, toluene, acetonitrile, and tetrahydrofuran, failed to afford any improvement in the enantioselectivity of the desymmetrization process (Table 1, entries 2–9). It is noteworthy that the reaction showed a very strong dilution effect. For example, decreasing the concentration of the anhydride from 0.1 to 0.025 mol/L in the presence of catalyst **I** (5 mol %) led to a significant increase in the enantioselectivity for the formation of the desired product **4** inform 69 to 88% ee (Table 1, entries 1,10–11). Increasing the loading of the catalyst to 10 mol % led to a significant increase in the catalytic activity, as well as the enantioselectivity (90% ee, entries 12). Pleasingly, the enantioselectivity of **4** (90% ee) was further increased to 96% ee in 87% yield by a single recrystallization from methyl *tert*-butyl ether.

The iodolactonization of **4** under the conditions established by Van Tarnelen et al. (i.e., $NaHCO_3$, I_2/KI, rt) furnished the corresponding iodolactone **5** in 86% yield, although a long reaction time (3 days) was needed.[5] Pleasingly, the treatment of **4** with NIS in dichloromethane at room temperature gave **5** in 91% yield following a much shorter reaction time (only 1 h) (Scheme 3). The absolute configuration of **5** was determined

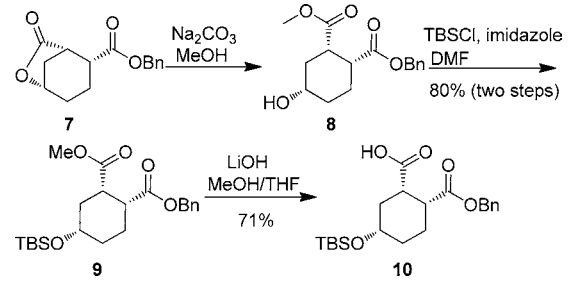
Scheme 3. Synthesis of Lactone 7



by X-ray crystallographic analysis.[6] The subsequent reductive deiodination of **5** was performed with 10% Pd/C in methanol under an atmosphere of H_2 in the presence of sodium acetate to give the corresponding lactone **7**. Bromolactone **6** was prepared in 88% yield from **4** using NBS instead of NIS under conditions similar to those used for the formation of **5**. However, the reductive debromination of **6** failed to provide **7** under the same hydrogenation conditions as those used for **5**.

The subsequent treatment of **7** with MeOH in the presence of Na_2CO_3 at room temperature gave diester **8**, which was immediately protected with TBSCl in the presence of imidazole in DMF to give *tert*-butyldimethylsilyl ether **9** in 80% yield over the two steps (Scheme 4). The hydrolysis of **9** with lithium hydroxide (1.8 equiv) in a 2 mL/2 mL/2 mL mixture of THF/MeOH/H_2O at 40 °C led to the formation of a 7:1 (m/m) mixture of hemiester **10** and the corresponding dicarboxylic acid, which was purified by silica gel chromatography to afford pure **10** in 71% yield.

Scheme 4. Synthesis of Hemiester 10



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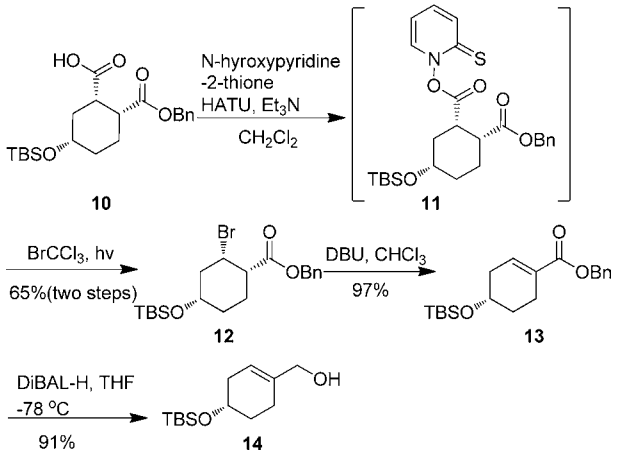
Acid **10** was then converted to the *N*-hydroxy-2-thiopyridone ester **11** (Barton ester), which was taken forward into the next step without isolation. Thus, the irradiation of **11** with a xenon lamp as irradiation source in the presence of $BrCCl_3$ at room temperature for 30 min resulted in the replacement of the carboxyl group with a bromo substituent via a Hunsdiecker radical-chain process to give **12** in 65% yield (Scheme 5).[7]

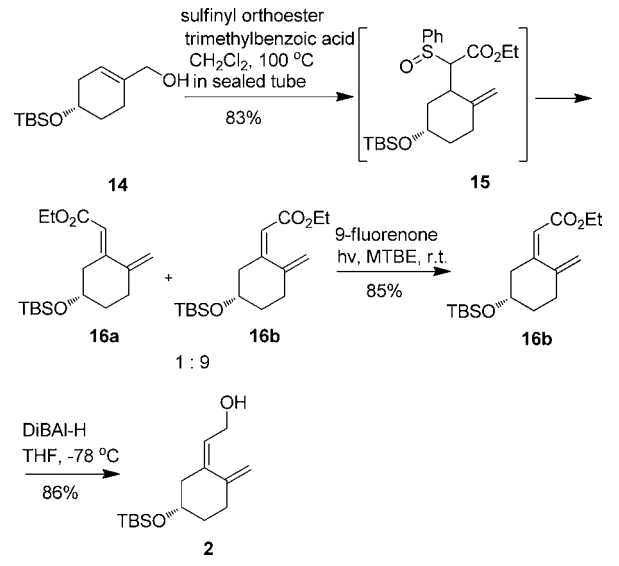
Scheme 5. Synthesis of Allylic alcohol 14



Compound **12** was then treated with DBU in $CHCl_3$ under reflux conditions to give the dehydrobromination product **13** in 97% yield. The α,β-unsaturated ester **13** was then reduced with DIBAL-H in THF at −78 °C to afford the allylic alcohol **14** in 91% yield.

Previously, Posner and co-workers achieved the synthesis of the A-ring phosphine of calciferol (1α, 25-hydroxyvitamin D_3) by taking advantage of a sulfinyl orthoester to allow for the direct conversion of the allylic alcohol into the corresponding 2-carbon-extended, conjugated dienoate ester.[8] The synthesis of allylic alcohol **2** using this process via the tandem Claisen rearrangement/sulfoxide thermolysis of **14** is shown in Scheme 6. As expected, the reaction of the allylic alcohol **14** with sulfinyl orthoester in the presence of trimethylbenzoic acid (catalyst) in methylene chloride at 100 °C in a sealed tube for 12 h afforded the conjugated dienoate esters **16a**/**16b**. Notably, the dienoate esters **16a**/**16b** were isolated after chromatography in 83% yield as a 1:9 mixture of *E*/*Z* geometrical isomers. The irradiation of the mixture with UV light in the presence of 9-fluorenone as the photosensitizer gave the pure *Z*-isomer **16b** in 85% yield.[9] The subsequent reduction of **16b** with DIBAL-H in THF at −78 °C gave the A-ring precursor of calcifediol **2**.

Scheme 6. Synthesis of the A-Ring Allylic Alcohol 2



In conclusion, we have developed an efficient new method for the enantioselective synthesis of the A-ring allylic alcohol **2** starting from the readily available prochiral cyclic anhydride **3**. The key features of this synthetic route include (i) the facile construction of the stereochemistry at the C5-position of the A-ring through an organocatalytic enantioselective desymmetrization reaction and (ii) the introduction of an *exo*-cyclic (*Z*)-dienol side chain through a tandem Claisen rearrangement/sulfoxide thermolysis reaction. Further work toward the synthesis of calcifediol is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02813.

Experimental procedures, spectroscopic and analytical data, and NMR spectra of new compounds(PDF)
X-ray data for compound **5** (CIF)

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Notes

The authors declare no competing financial interest.

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