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# A Catalytic Asymmetric Synthesis of a Versatile Intermediate for Phorbol Derivatives

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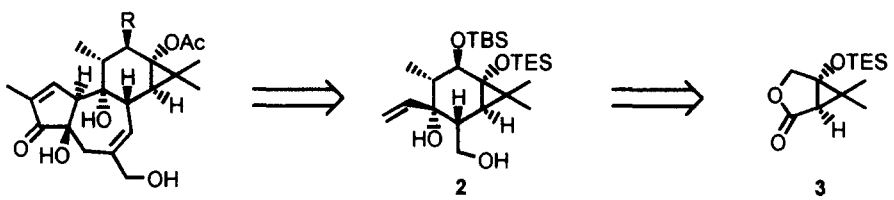
**Abstract:** A catalytic asymmetric cyclopropanation of enol silyl ether **9** gave the lactone **3** in up to 78% ee. The lactone **3** was then transformed into **2**, potentially a very versatile intermediate for phorbol analogs, using an intramolecular nitrile oxide cycloaddition as a key step. 

*Keywords:* cyclopropanation ; asymmetric addition ; nitrile oxide cycloaddition.

Phorbol derivatives such as PMA [phorbol myristate acetate (**1**)] are recognized as important compounds which control intracellular signal transduction through protein kinase C (PKC) [1]. Although many synthetic approaches to phorbol skeletons, including elegant total syntheses, have been reported so far [2], an efficient and flexible synthetic route leading to a variety of optically active phorbol derivatives is still required to clarify the structure-activity relationships of phorbol derivatives. In this paper, we describe the catalytic asymmetric synthesis of **2** (in up to 78% ee), which, based on our synthetic studies in this field [3], is a potentially versatile intermediate for many kinds of phorbol analogs. Our synthesis features the catalytic asymmetric intramolecular cyclopropanation of an enol silyl ether using a chiral Rh complex.

**Scheme 1**




**1**:PMA:R=$OCO(CH_2)_{12}CH_3$
& related compounds

**2**

**3**

Previously, we succeeded in the catalytic asymmetric synthesis of **10** (in up to 92% ee) [4], however, this compound proved to be ineffective for the synthesis of many phorbol analogs. Consequently, we designed the 5-membered lactone **3** as a key intermediate for **2**, potentially leading to many analogs [3]. First of all, the synthesis of (±)-**3** was undertaken. As shown in Scheme 2, prenol (**4**) was converted to the diol **6**, via the epoxide **5**, and was then acetylated to give **7**. Oxidation of **7** followed by 1,4-hydrosilylation [5] provided the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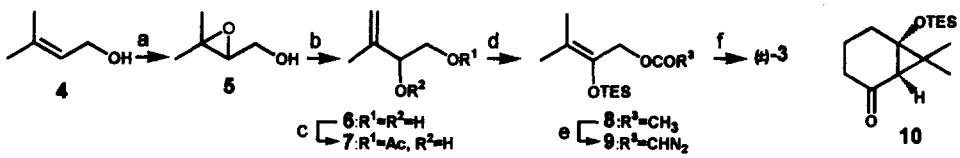
enol silyl ether **8**, which was then transformed into the requisite diazoacetate **9** [6]. With large quantities of **9** in hand, a catalytic cyclopropanation of **9** was carefully examined [7]. Although the use of $Rh_2(OAc)_4$ or $Rh_2(PTPA)_4$ [8], in $CH_2Cl_2$, resulted in the formation of the desired lactone **3** in low yield (together with many by-products), we were pleased to find that treatment of **9** with 5 mol % of $Cu(acac)_2$, in benzene at reflux temperature for 35 min, afforded **3** in 73% yield [9].

**Scheme 2**



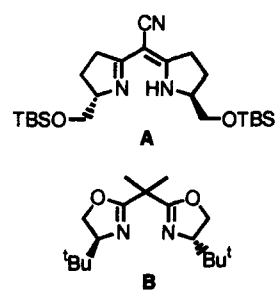

**Reagents and Conditions:** a) TBHP (1.2 equiv), $VO(acac)_2$ (1 mol %), toluene, 60 °C, 2.5 hr. b) 1) $Ac_2O$ (1.5 equiv), $Et_3N$ (2 equiv), rt., 12 hr, 2) $Ti(O^iPr)_4$ (2.1 molar equiv), rt., 5 days, 58% (from 4). c) 1) $Ac_2O$ (1.4 molar equiv), $Et_3N$ (1.6 molar equiv), $CH_2Cl_2$, 0 °C, 7 hr, 77%. d)$SO_3$· py (2 equiv), $Et_3N$ (3 equiv), DMSO, rt., 2 hr, 75%, 2) $Et_3SiH$ (1.2 equiv), $(Ph_3P)_3RhCl$ (0.2 mol %), 80 °C, 30 min, 70%. e) 1) LiHMDS (1.5 equiv), THF, -78 °C, 20 min, 2) $CF_3CO_2CH_2CF_3$ (1.7 equiv), -78 °C→-30 °C , 1 hr, 3) $Et_3N$ (7 equiv); $H_2O$ (1.5 equiv); $MsN_3$ (5 equiv), -30°C→rt., 83 hr, 60%. f) $Cu(acac)_2$ (5 mol %), benzene (finally 0.02M), refl., 35 min ( **9** was added dropwise over 30 min.), 73%.

Having developed an efficient synthesis of (±)-**3**, we then turned our attention to a catalytic asymmetric synthesis of **3**. The results are summarized in Table 1. Initially, it was found that the use of chiral Cu complexes resulted in the formation of **3** with modest ees (entry 1 and 2). However, in contrast to the synthesis of (±)-**3**, the use of chiral Rh complexes gave **3** in good chemical yields and in good ees. As shown in entry 4 (Table 2), treatment of **9** with 1 mol % of Doyle's catalyst [$Rh_2(5R\text{-MEPY})_4$] [10], in 1,2-dichloroethane at reflux temperature for 0.5 h, furnished **3** in 73% chemical yield and 77% ee. The enantiomeric excess of **3** was determined by chiral HPLC analysis (Daicel CHIRALCEL OD, 0.5% $^i$PrOH in hexane, flow rate: 0.7 mL/min), and the absolute configuration of **3** was unequivocally determined by the following transformation (Scheme 3). The optically active lactone **3** (78% ee) was first converted to the benzoate **13** in a 9-step sequence of reactions. Alternatively, benzoate **13** was also prepared from the known lactone **14** (99% ee) [11] in 4-step sequence of reactions. Thus, the absolute configuration of **13**, derived from **3** [12], was determined by comparison with **13**, from **14**, using chiral HPLC (Daicel CHIRALPAK AD, 0.2% $^i$PrOH in hexane, flow rate: 0.6 mL/min, retention time = 12.2 min and 15 min).

**Table 1.** Catalytic Asymmetric Cyclopropanation.

| entry | catalyst (mol %) | solvent | yield of 3 (%) | ee of 3 (%) |
|---|---|---|---|---|
| 1 | $Cu(OAc)_2$/A (5) [13] | $C_6H_6$ | 21 | 48 |
| 2 | Cu(OTf)/B (5) [14] | $ClCH_2CH_2Cl$ | 86 | 39 |
| 3 | $Rh_2(5R\text{-MEPY})_4$ (1) | $ClCH_2CH_2Cl$ | 80 | 62 |
| 4 | $Rh_2(5R\text{-MEPY})_4$ (1) | $CH_2Cl_2$ | 73 | 77 |
| 5 | $Rh_2(5R\text{-MEPY})_4$ (1) | $C_6H_{12}$ | 56 | 61 |
| 6 | $Rh_2(4R\text{-MEOX})_4$ (1) [15] | $CH_2Cl_2$ | 59 | 78 |

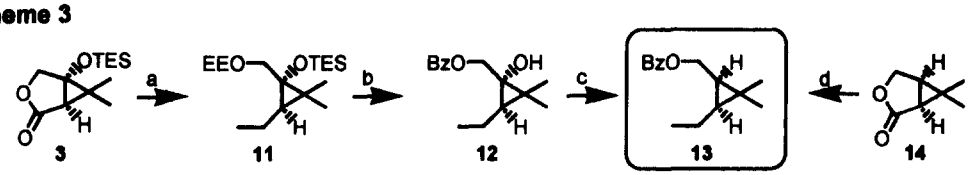
1) All reactions were carried out at reflux temperature.
2) All reactions were finished within 0.5 hr except for entry 1 (4 hr).




With optically active **3** in hand, transformation to the versatile synthetic intermediate **2** was pursued.

First of all, we were very surprised to see that the reaction of **3** with diisobutylaluminium hyride (DIBAH) in $CH_2Cl_2$, even at –78 °C, gave rise to **27** exclusively. However, the Weinreb amide **15** [16] was cleanly formed and oxidation of a primary alcohol furnished the aldehyde **16**.

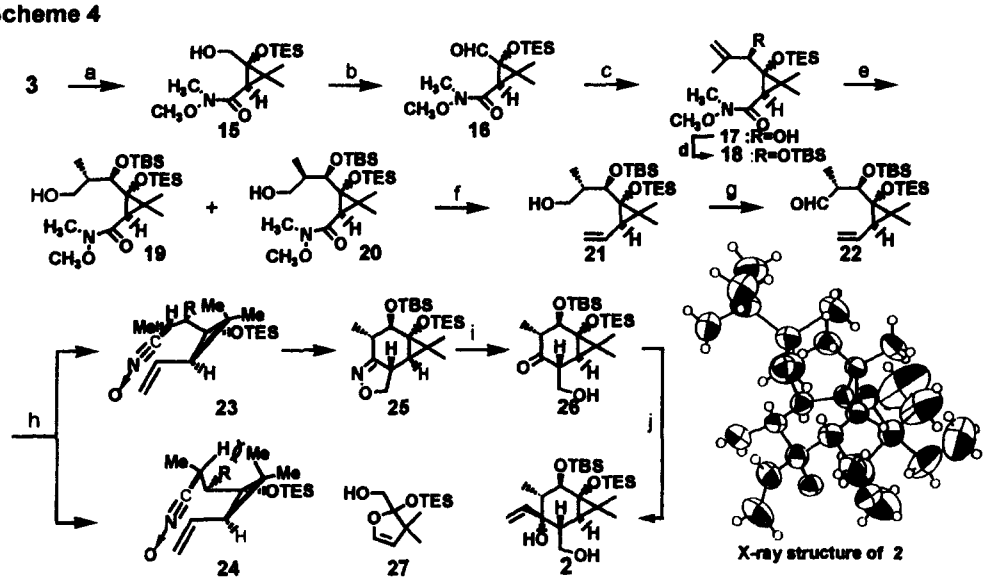
**Scheme 3**




**Reagents and Conditions:** a) MeAlCl(N(Me)OMe (2.5 equiv), toluene, -78 °C→rt., 2 hr, 2) ethyl vinyl ether (2 equiv), PPTS (5 mol %), $CH_2Cl_2$, rt., 1 hr, 3) DIBAH (1.4 equiv), toluene, -78 °C, 4 hr, 4) $Ph_3PCH_2$ (1.5 equiv), THF, -78 °C→+30 °C, 30 min, 5) $KO_2CN{=}NCO_2K$ (6 equiv), AcOH (13 equiv), MeOH, rt., 2 hr, 55% (5 steps). b) 1) PPTS (3 mol %), MeOH, rt., 30 min, 2) benzoyltetrazole (1.1 equiv), $Et_3N$ (10 mol %), dioxane, rt., 1 hr, 61% (2 steps). c) 1,1'-thiocarbonyldiimidazole (2 equiv), DMAP (20 mol %), THF, refl., 6 hr, 2) $Bu_3SnH$ (1.2 equiv), AIBN (23 mol %), benzene, 80 °C, 4 hr, 53% (2 steps). d) 1) DIBAH (1.1 equiv), $CH_2Cl_2$, -78 °C, 3 hr, 2) $Ph_3PCH_2$ (2 equiv), THF, -78 °C→rt., 30 min, 3) $KO_2CN{=}NCO_2K$ (6 equiv), AcOH (13 equiv), MeOH, rt., 2 hr, 4) benzoyltetrazole (2 equiv), $Et_3N$ (10 mol %), dioxane, rt., 1 hr, 43% (4 steps).

Treatment of **16** with isopropenylmagnesium bromide (at –60 °C) gave the allylic alcohol **17** in a highly stereocontrolled manner [17], which was then protected as a TBS ether to give **18**. Hydroboration of **18** with 9-BBN followed by oxidative work-up afforded only the undesired stereoisomer **20** [17]. Upon treatment of **18** with $BH_3$·THF, in toluene/THF(4:1) at -30~-35 °C, followed by oxidative work-up, gave the desired product **19** [17] in a ratio of 6:1. DIBAH reduction of **19** to the corresponding aldehyde, followed by a Wittig reaction furnished **21** in 50% overall yield. Oxidation of a primary alcohol in **21** gave the aldehyde **22**, which was then treated with $H_2NOH$·HCl and NaOAc, followed by 5% aqueous NaOCl, to give the desired isoxazoline **25** in a highly stereoselective manner [17]. The exclusive formation of **25**, as expected, can be easily understood by considering two possible transition states **23** and **24**. The reaction of **25** with Raney Ni and $H_3BO_3$, in an atmosphere of $H_2$, provided the hydroxy-ketone **26**, which was then treated with vinylmagnesium bromide to give **2** in a highly stereoselective manner. The structure of the versatile synthetic intermediate **2** was unequivocally determined by X-ray crystallography (R=0.107, $R_w$=0.105).

**Scheme 4**



**Reagents and Conditions:** a) MeAlClN(Me)OMe (2.5 equiv), toluene, -78 °C→rt., 3 hr, 92%. b) PDC (2 equiv), MS4A, $CH_2Cl_2$, rt., 2.5 hr, 92%. c) isopropenylmagnesium bromide (1.5 equiv), THF, -78 °C→-60 °C, 1.5 hr, 88%. d) TBSOTf (1.5 equiv), $^iPr_2NEt$ (2 equiv), $CH_2Cl_2$, -78 °C→-10~-5 °C, 1.5 hr, 88%.e) $BH_3$·THF (7 molar equiv), toluene/THF (4:1), -78 °C→-35~-30 °C, 228 hr, 73% (19:20=6:1). f) 1) DIBAH (3.5 molar equiv), toluene, -40 °C, 30 min, 2) $Ph_3PCH_2$ (3 molar equiv), THF, -78 °C→0 °C, 20 min, 66% (2steps). g) PDC (2 equiv), MS4A, $CH_2Cl_2$, rt., 1 hr, 93%. h) 1) $NH_2OH$·HCl (1.5 equiv), NaOAc (3 equiv), $H_2O$, EtOH, rt., 5 min, 2) 5% NaOClaq, $CH_2Cl_2$, 0 °C, 14 hr, 78% (2 steps). i ) $H_2$, Raney-Ni (W-2), $H_3BO_3$ (30 molar equiv), EtOH/MeOH/$H_2O$ (5:1:1), rt., 30 min, 88%. j) vinylmagnesium bromide (10 molar equiv), THF, -30 °C, 20 min ( **26** was added dropwise over 10 min.), 69%.

In conclusion, we have succeeded in the synthesis of **2** in a catalytic asymmetric manner (in up to 78% ee). This intermediate **2** is potentially very versatile for the synthesis of many phorbol analogs, including PMA (**1**) itself, leading to the clarification of the structure-activity relationships of phorbol derivatives. Further studies are currently under investigation.

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