Pergamon

Tetrahedron Letters, Vol. 37, No. 14, pp. 2449-2452, 1996
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0040-4039/96 $15.00 + 0.00

S0040-4039(96)00315-2

Catalytic Asymmetric Intramolecular Cyclopropanation of Enol Silyl Ether. Synthesis of the Phorbol CD-ring Skeleton

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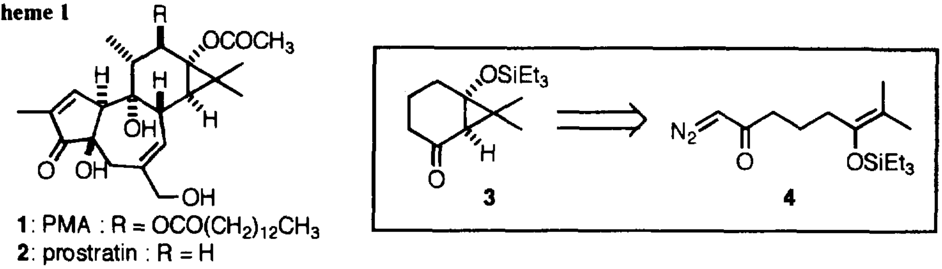
Abstract : The optically active phorbol CD-ring skeleton was constructed using the catalytic asymmetric intramolecular cyclopropanation of enol silyl ether as a key step. Up to 92% ee was achieved using a newly modified bisoxazoline ligand. Copyright © 1996 Elsevier Science Ltd

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] Recently, prostratin (**2**) has also attracted attention because of its anti-HIV activity.[2] Although many synthetic approaches to phorbol skeletons have been reported so far,[3] 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 the likely synthetic intermediate **3** (up to 92% ee) for many kinds of phorbol analogs. This synthesis features the catalytic asymmetric intramolecular cyclopropanation of enol silyl ether using a newly modified bisoxazoline ligand.

Our basic strategy for constructing the optically active CD-ring skeleton **3** is the catalytic asymmetric intramolecular cyclopropanation of the enol silyl ether **4** (Scheme 1). There have been several reports of asymmetric intramolecular cyclopropanations catalyzed by Cu or Rh complexes.[4] To the best of our knowledge, however, the intramolecular cyclopropanation of an enol silyl ether has not been reported,[5] probably because of the difficulty in preparing the substrates, i.e., α-diazo-carbonyl compounds with chemically unstable enol silyl ether moieties. We have solved this problem by the following two synthetic routes.

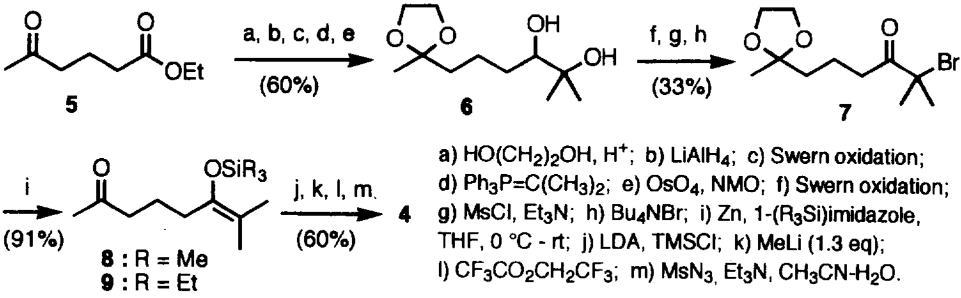
Scheme 1



1: PMA : R = $OCO(CH_2)_{12}CH_3$
2: prostratin : R = H

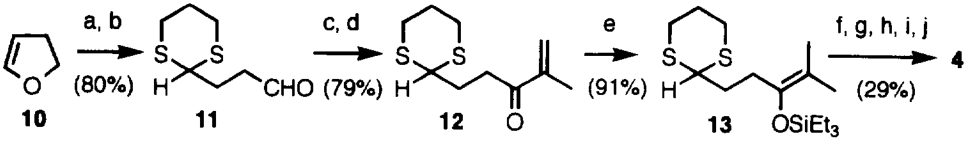
The first route begins with commercially available ethyl 5-oxohexanoate (**5**) (Scheme 2). Since all attempts to regenerate the methyl-ketone moiety from the protected form in the presence of the tetrasubstituted enol silyl ether were unsuccessful, the challenging step in this synthesis was the selective construction of the tetrasubstituted enol silyl ether in the presence of another carbonyl group. We planned to use the reductive formation of enol silyl ether from the α-bromo-ketone **7** which could be obtained from **5** in an 8-step sequence of reactions. However, the reductive formation of enol silyl ether using previously reported conditions (Zn, trimethylsilyl chloride, THF, room temperature)[6] was unsuccessful because of the competitive intramolecular aldol reaction, which gave 3-hydroxy-2,2,3-trimethylcyclohexanone. After examining several reaction conditions, we were pleased to find that the use of 1-(trimethylsilyl)imidazole instead of trimethylsilyl chloride completely suppressed the side reaction to give the desired enol trimethylsilyl ether **8**. 1-(Triethylsilyl) imidazole[7] is less reactive, but the reaction still proceeded smoothly to give the more stable enol triethylsilyl ether **9** in 91% yield. The target substrate **4** was then prepared by introducing a diazo group using Danheiser's procedure.[8]

Scheme 2



a) $HO(CH_2)_2OH$, H^+; b) $LiAlH_4$; c) Swern oxidation; d) $Ph_3P{=}C(CH_3)_2$; e) OsO_4, NMO; f) Swern oxidation; g) MsCl, Et_3N; h) Bu_4NBr; i) Zn, 1-(R_3Si)imidazole, THF, 0 °C - rt; j) LDA, TMSCl; k) MeLi (1.3 eq); l) $CF_3CO_2CH_2CF_3$; m) MsN_3, Et_3N, CH_3CN-H_2O.

Scheme 3



a) $HS(CH_2)_3SH$, cat. BF_3-Et_2O, CH_2Cl_2, 0 °C - rt; b) SO_3•Py, *i*-Pr_2NEt, DMSO, 0 °C - rt; c) 2-propenylmagnesium bromide, THF, 0 °C - rt; d) SO_3•Py, *i*-Pr_2NEt, DMSO, 0 °C - rt; e) Et_3SiH, $RhCl(PPh_3)_3$ (2 mol %), 90 °C; f) *n*-BuLi, THF, -20 °C (3.5 h); g) CO_2 (dry-ice); h) Raney Ni (W-2), EtOH, (2 h); i) $ClCO_2Et$, Et_3N, CH_2Cl_2, 0 °C - rt; j) CH_2N_2.

Since ethyl 5-oxohexanoate is rather expensive, we developed another synthetic route to **4** starting from dihydrofuran for large-scale preparation, in which the α-diazo-ketone group was introduced after construction of the enol silyl ether (Scheme 3). Key steps in this route are the selective 1,4-hydrosilylation of enone **12** using Wilkinson's catalyst,[9] and the introduction of a diazoacetyl group, which was achieved by the following sequential reactions without purification. The dithiane **13** was first lithiated at -20 °C (3.5 h), and the resulting carbanion was treated with dry-ice to give the lithium carboxylate.[10] The sulfur group was then removed by reduction using Raney Ni W-2 in ethanol (reflux, 2 h).[11] Treatment of the resulting lithium salt with ethyl chloroformate and triethylamine in methylene chloride (0 - 23 °C) followed by reaction with diazomethane in ether at 23 °C gave the desired product **4** in 29% yield (from **13**) via the mixed anhydride.[12]

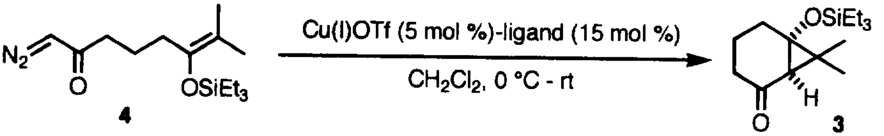
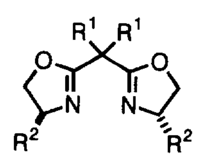


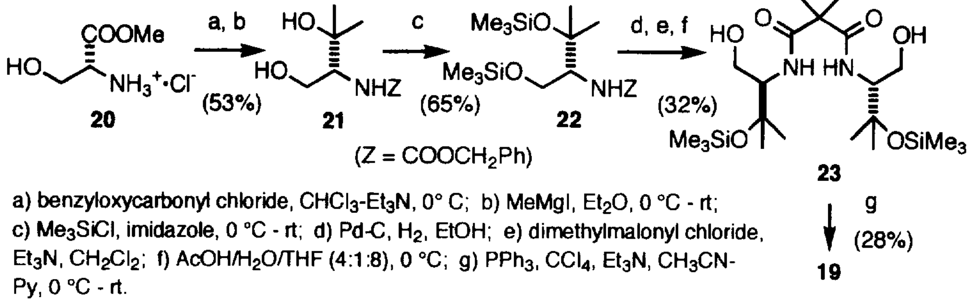
Table 1. Catalytic Asymmetric Cyclization of **4** to **3** Promoted by Cu(I)OTf-Bisoxazoline Ligand

entry	ligand	R^1	R^2	time (h)	yield (%)	ee (%)
1	**14**	H	$CH_2CH(CH_3)_2$	12	96	33
2	**15**	H	$C(CH_3)_3$	12	85	77
3	**16**	CH_3	C_6H_5	2	38	13
4	**17**	CH_3	$CH_2CH(CH_3)_2$	12	55	36
5	**18**	CH_3	$C(CH_3)_3$	19	82	78
6	**19**	CH_3	$C(CH_3)_2OSiMe_3$	19	70	92



With a large amount of the key substrate **4** in hand, asymmetric cyclization was examined using the combination of CuOTf and the known bisoxazoline ligands **14** - **18**[13] as asymmetric catalysts (Table 1, entries 1-5). After several attempts, we found that the desired cyclized product **3** was obtained in 78% ee and in 82% yield using ligand **18**. Asymmetric ligands with bulky substituents such as a *tert*-butyl group (**15** and **18**) were revealed to give higher asymmetric induction than those with smaller substituents (**14**, **16** and **17**). Thus, to further improve the ee of the product, the newly modified bisoxazoline ligand **19** was synthesized as shown in Scheme 4.

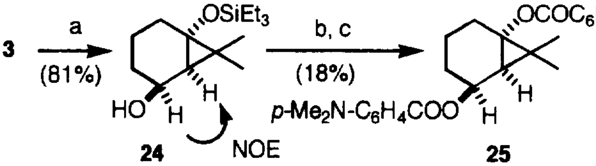
Scheme 4



a) benzyloxycarbonyl chloride, $CHCl_3$-Et_3N, 0° C; b) MeMgI, Et_2O, 0 °C - rt; c) Me_3SiCl, imidazole, 0 °C - rt; d) Pd-C, H_2, EtOH; e) dimethylmalonyl chloride, Et_3N, CH_2Cl_2; f) $AcOH/H_2O/THF$ (4:1:8), 0 °C; g) PPh_3, CCl_4, Et_3N, CH_3CN-Py, 0 °C - rt.

N-Benzyloxycarbonyl-D-serine methyl ester[14] was first treated with methylmagnesium iodide to give diol **21** in 53% yield, and the alcohol functionalities were then protected with a trimethylsilyl group. After the benzyloxycarbonyl group was removed by hydrogenolysis, the resulting amine was treated with dimethylmalonyl chloride and then with acetic acid to give the amide **23** in 32% yield (3 steps). Finally, the desired bisoxazoline **19** ($[\alpha]_D^{24}$ -59.3° (*c* 1.9, $CHCl_3$)) was obtained in 28% yield by treatment with triphenylphosphine, carbon tetrachloride and triethylamine in CH_3CN-pyridine.[15] Using this new ligand **19**, the intramolecular cyclopropanation of **4** proceeded smoothly, and, as expected, the *enantiomeric excess was increased to 92%* ($[\alpha]_D^{24}$ -59.1° (*c* 0.3, $CHCl_3$)).[16] The enantiomeric excess (ee) of **3** was determined by GC analysis using a chiral phase column (Chiraldex™ G-TA), and the absolute configuration of the product was determined by application of the CD exciton chirality method to **25** prepared from **3**, as shown in Scheme 5.

Scheme 5



a) K-Selectride, -20 °C - -5 °C, then separation; b) K_2CO_3 / 1N NaOH, rt; c) *p*-dimethylaminobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2.

In summary, two synthetic routes to the α-diazo-ketone **4** with a enol silyl ether moiety have been established for the first time, and the catalytic asymmetric intramolecular cyclopropanation of this substrate has been achieved, giving **3** with excellent asymmetric induction (up to 92% ee), by the use of the newly modified bisoxazoline ligand **19**. These results are useful not only for the catalytic asymmetric synthesis of the phorbol CD-ring skeleton but also for the catalytic asymmetric synthesis of various other compounds.

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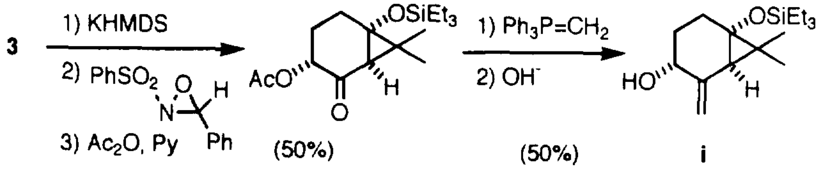
(16) Compound **3** has already been converted to **i** as follows.



(*Received in Japan* 16 *January* 1996; *accepted* 15 *February* 1996)