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Studies on the regio- and diastereo-selective epoxidation of daphnanes and tiglianes

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Abstract

Daphnanes and tiglianes are diterpenes with a shared tricyclic 5-7-6 ring system. Many members exhibit significant biological activities often associated with protein kinase C signaling. Many of these natural products (~100) have a C6-C7 α -epoxide whose influence on biological activity is little studied. Using the more readily available phorbol ester PDBu as a test substrate, we report an efficient, and potentially general, α -epoxidation method based on a vanadium-catalyzed asymmetric epoxidation with bishydroxamic acid (BHA) ligands.

Keywords

Protein kinase C; Daphnane; Tiglane; Epoxidation

1. Introduction

The daphnane and tigliane diterpenes are large families of structurally complex and densely functionalized natural products that share a common 5-7-6 tricyclic ring system.¹ Plant extracts of the Euphorbiaceae and Thymelaeaceae families, from which these diterpenes are derived, have been used for medicinal purposes for millennia.² Only recently, however, have scientists begun to structurally characterize the active compounds and elucidate their molecular modes of action. Representative members of these families (Figure 1) include the phorbol esters, yuanhuapin,^{3,4} gnidimacrin,⁵ and rediocide A⁶ which, along with many other family members, have emerged as significant therapeutic leads and research tools.¹ The phorbol esters, for example, are the most studied and potent tumor promoters known⁷ while prostratin, 12-deoxy-phorbol 13-acetate, is a preclinical lead in studies directed at an as yet

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Dedication

This manuscript is dedicated to the memory of Harry Wasserman, an inspiring scientist, teacher, artist, and friend.

Supplementary data

Supplementary data (experimental conditions, spectroscopic data (1H and 13C NMR spectra) and HRMS) associated with this article can be found, in the online version.

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unattained but hugely important goal, the eradication of HIV/AIDS.^{8,9} Other members of these families have shown promising activity as antiviral, anti-cancer, neurotropic and insecticidal agents.^{10,11,1}

The biological activities exhibited by many of these diterpenes are associated with their modulation of one or more protein kinase C (PKC) isoforms.^{7,12} These isoforms play important roles in several signal transduction cascades and respond to many stimulators including hormones, growth factors and other ligands related to membrane receptors. Separately or in combination, PKC isoforms are implicated in numerous clinical indications including cancer,¹³ Alzheimer's disease,¹⁴ cardiovascular disease,¹⁵ immune and inflammatory diseases,¹⁶ metabolic disorders,¹⁷ stroke,¹⁸ and atherosclerosis.¹⁹ While relatively little is known about the PKC isoform selectivities of the PKC active diterpenes, some agents have shown promising PKC selective activity and therapeutic potential. Gnidimacrin (NSC 252940),²⁰ for example, is a member of the daphnane family and shows potent antitumor activity against murine tumors *in vivo* and several human tumor cell lines *in vitro*.²¹ Importantly, gnidimacrin is proposed to operate by activation of PKC β II, arresting the cell cycle at the G1 phase through inhibition of cyclin-dependent kinase-2 (cdk2) activity in human K562 leukemia cells.

Studies on the modes of action and therapeutic potential of tigliane and daphnane diterpenes have been hampered by their scarce and often variable supply, high cost (generally >\$50/mg), difficulty in accessing sources due to geopolitical issues, and challenges associated with their synthesis and chemical modification. To date, phorbol²² is the only tigliane and resiniferatoxin²³ is the only daphnane for which total syntheses have been reported. A semi-synthesis of prostratin from phorbol has also been reported,²⁴ enabling synthetic access to more potent analogs now being studied as latency reversing agents in strategies to eradicate HIV.²⁵ In 2011, we also reported a study directed at producing an advanced daphnane precursor that could be used to synthetically access most members of the large daphnane diterpene family. This "gateway strategy" resulted in the synthesis of a general precursor to potentially >70 daphnanes and led to the synthesis of *des*-epoxy-yuanhuapin.⁴ This study also led to the identification of PKC as a target for yuanhuapin and the additional finding that *des*-epoxy-yuanhuapin is a potent PKC modulator with a K_i of 1.6 nM.

In the course of our studies on yuanhuapin,⁴ we found that epoxidation of *des*-epoxy-yuanhuapin resulted in exclusive formation of C6,C7-*epi*-yuanhuapin. In other words, epoxidation of the C6,C7 double bond occurred exclusively on the β -face. Notwithstanding the presence of the α -epoxide in most daphnanes, this epoxidation problem and stereochemistry have received little attention. Tyler and Howden have reported that under conditions similar to the ones used with *des*-epoxy-yuanhuapin to make the β -epoxide, phorbol 12,13-dibenzoate was converted to the α -epoxide.²⁶ This stands in contrast to the yuanhuapin study⁴ and an earlier report by Hecker and Schmidt that epoxidation of phorbol 12,13,20-triacetate proceeds on the β -face of the C6,C7 double bond (Scheme 1).²⁷ Given that over 90 members of the daphnane family possess an α -epoxide and that epoxidation would preferably be done as a final synthetic step when most delicate functionalities would be in place, we sought, as described herein, to determine the intrinsic facial selectivity for

direct epoxidations of such complex targets and to develop mild strategies to selectively access either epoxide as needed for synthesis and structure-function studies.

To establish a reliable protocol for stereoselective epoxidation of tiglanes and daphnanes, the readily available phorbol 12,13-dibutyrate (PDBu, **5**) was selected as our test system. Phorbol (**1**) itself was obtained from abundantly available croton oil by first hydrolyzing various naturally occurring ester derivatives in the oil and extracting the resultant free phorbol in 1.6% yield after flash chromatography (see supporting information). Phorbol was then converted to PDBu (**5**) by a standard three-step procedure (Scheme 2). Direct epoxidation of PDBu or a C20 protected derivative led to β -face epoxidation, consistent with our yuanhuapin (daphnane) study and the earlier report of Hecker and Schmidt on the tiglane phorbol triacetate (Scheme 1). This is consistent with the phorbol B-ring assuming a conformation with a fold between C4 and C8 and thus a more accessible convex β -face. In cases where a direct epoxidation gives the undesired stereoisomer, one can often produce the desired epoxide isomer by using a two-step procedure in which a bromine is delivered to the more accessible substrate face to form a bromonium ion which with water would give a halohydrin whose closure in base would give the complementary epoxide stereochemistry.²⁸ However, when PDBu **5** is treated with Br₂ in a mixture of acetone and water (1:1), it undergoes preferential oxidation to the C20 aldehyde with only a small amount of the desired bromohydrin (<5%) being formed. The same results were observed using NBS instead of Br₂ on the same substrate. It was expected that the C20 butyric acid ester **2** could prevent this oxidation. However, the reaction with PTBu **2** and 1.3 eq. of NBS was very slow and again when heated led to aldehyde formation presumably by hydrolysis of the primary ester and subsequent allylic alcohol oxidation.

Another useful reagent for bromonium ion formation is N-bromoacetamide (NBA).²⁹ NBA has been used in steroid syntheses to produce epoxides complementary in stereochemistry to those obtained with peroxyacids such as mCPBA.³⁰ In our case, the same conditions (NBA in dioxane/water and a catalytic amount of HClO₄) led again to the C20 aldehyde and many other unidentified products, likely resulting from acid-catalyzed opening of the cyclopropane (D) ring. In 2002, White reported the formation of bromohydrins from silyl ether protected allylic alcohols using NBS/H₂O in THF.³¹ This procedure proceeds without deprotection and oxidation of the alcohol. To test this method, we prepared the C20-TBDPS PDBu **6** from phorbol in 4 steps (Scheme 2). Unfortunately, the reported conditions also led to oxidation of **6** to the C20 aldehyde, proceeding in 6 h at 0°C and in nearly quantitative yield. The same results were observed with a trityl protecting group (Table 1).

Due to competitive oxidation at C20 in procedures directed at halohydrin formation, we next decided to explore a different strategy involving reagent-controlled epoxidation. Dioxiranes from chiral alcohols are known to react with a variety of alkenes to produce epoxides in a highly enantioselective fashion.³² For our studies, the Shi D-fructose ligand **8** was synthesized in 2 steps from the commercially available D-fructose. Reaction of C20-trityl PDBu **4** with this ketone in the presence of oxone and K₂CO₃ under reported conditions cleanly produced an epoxide **7** in nearly quantitative yield (Scheme 3). Unfortunately, this proved to be the β -epoxide. The enantiomeric ketone (ent-**8**) was then prepared in 8 steps

from L-sorbose.³³ Unfortunately, this system did not react with C20-trityl PDBu **4** at room temperature and at higher temperature decomposed.

The Sharpless asymmetric epoxidation represents another procedure for controlling facial selectivity in epoxidations of allylic alcohols and thus for overcoming intrinsic substrate facial selectivity through catalyst control.³⁴ However, with PDBu **5** this epoxidation was especially slow and variable and led to only trace amounts of the α -epoxide. In the best case, a 1.5:1 mixture in favor of the β -epoxide was obtained using 10 eq. of $\text{Ti}(\text{OiPr})_4$, 12 eq. of (+)-DIPT and 2 eq. of TBHP after 7 days of reaction in dichloromethane at -20°C . While not optimal, the formation of some of the α -epoxide provided encouragement that the intrinsic facial barrier presented by the substrate could be overcome through reagent control.

Yamamoto and co-workers reported a method for the facially selective epoxidation of a variety of allylic alcohols using $\text{VO}(\text{OiPr})_3$ modified with a chiral (1*S*,2*S*)-*N,N'*-Dihydroxy-*N,N'*-bis(diphenylacetyl)-1,2-cyclohexane-diamine (BHA) ligand. With 2 mol% of the BHA ligand and 1 mol% of $\text{VO}(\text{OiPr})_3$ and *tert*-butyl hydroperoxide (TBHP) in air at temperatures between 0°C and -20°C , many allylic alcohols are efficiently converted to epoxy alcohols with high enantioselectivities.³⁵ Significantly, in our studies, using 10% of $\text{VO}(\text{acac})_2$ and Yamamoto ligand **A** for 12h at room temperature in dichloromethane, we observed the conversion of PDBu **5** to a 50:50 mixture of epoxides in 80% isolated yield (Scheme 4). The use of $\text{VO}(\text{OiPr})_3$ was subsequently found to be more reproducible. Using our preferred conditions (10% of $\text{VO}(\text{OiPr})_3$, 20% of ligand **A**, and 2 eq. of aqueous *t*-butylhydroperoxide), a screen of different solvents was then performed at different temperatures (Table 2). As previously shown, when no ligand was added, only β -epoxide was observed. No difference in selectivity was observed using dichloromethane, toluene, or chloroform. Running the reaction in benzene led to a ratio of 55 to 45 in favor of the α -epoxide in less than 12h. Progress was being made.

The effect of the peroxide source was also investigated (Table 3). The selectivity is slightly better with *tert*-butyl hydroperoxide in decane and the reaction proceeds in approximately the same yield. Aqueous *t*-butyl hydroperoxide (TBHP) and cumene hydroperoxide gave slightly decreased selectivities and increased reaction times. As expected, the temperature of the reaction also affects the selectivity. Selectivity is slightly increased at 4°C relative to room temperature without any effect on conversion. However, the time of the reaction is much longer. At -20° , the reaction is very slow and incomplete after 3 weeks.

Finally, Yamamoto also demonstrated that the ligand can modulate diastereoselectivity. Using the best conditions developed so far, epoxidation of PDBu **5** using ligand **C** led to a ratio of 80:20 in favor of the α -epoxide in very good yield in about 12 h at room temperature. Decreasing the reaction temperature to 4°C increases the selectivity to produce the α -epoxide in an 89:11 ratio. Moreover, with ligand **C**, the reaction time was considerably decreased compared to ligand **A** and **B** while still providing an excellent yield (90%) of product (Table 4).

In summary, we have established that epoxidation of phorbol (tiglane) and *des*-epoxy-yuanhuapin (daphnane) derivatives, and thus by analogy structurally related tiglianes and

daphnanes, with peracids occurs preferentially from the convex β -face of the Bring and is not assisted by directed delivery of the C9-OH. Direct epoxidation leads to formation of the β -epoxide with high selectivity. This would be expected for most daphnanes and tiglianes that share a similar B-ring conformation and thus preferred convex face accessibility. While there are many methods that have been developed with simple substrates to reverse such a preference using reagent-based facial control, many of these methods encounter problems as found here with the more complex, densely functionalized and labile structures represented by phorbol derivatives. Moreover, many of these compounds undergo competitive, if not exclusive, oxidation of the allylic alcohol functionality. Many members of these families are also sensitive to acid and base, thus limiting reagent selection. Importantly, however, with respect to syntheses and structure-function studies in the tigliane and daphnane series, we have now established a procedure, based on elegant studies by the Yamamoto group, for the selective formation of the naturally occurring α -epoxide. This study produces the first α -epoxide in the phorbol series and the opportunity to begin to explore the role of this functionality in the many activities associated with phorbol derivatives and the large tigliane and daphnane families. This study also provides a more exacting synthetic reference point for testing existing or emerging epoxidation strategies and reagents and now opens the way for synthesis and structure function studies related to biologically promising tigliane and daphnane diterpenes. Studies on the application of this methodology to the less readily available alkene precursors of tigliane and daphnane epoxides will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Representative members of the daphnane and tiglane families

Scheme 1.
Hecker's β -face epoxidation of phorbol-triacetate ²⁷

Scheme 2. Synthesis of PTBu **3**, C20-Trityl PDBu **4** and C20-TBDPS PDBu **6**

Scheme 3. Reaction under Shi epoxidation conditions with catalyst **8** and ent-**8**

Scheme 4.
Vanadium epoxidation with Yamamoto ligand A

Table 1

Halohydrin formation attempts from PDBu derivatives

Entry	R	Conditions	Results
1	H	1.3 eq. NBS, Acetone/H ₂ O, rt	Mixture, C20 Aldehyde
2	COC ₃ H ₇	1.1 eq. NBS, DME/H ₂ O (16:1), 0°C to rt	No Rxn
3	COC ₃ H ₇	NBA, HClO ₄ , Dioxane/H ₂ O, rt	No Rxn
4	COC ₃ H ₇	NBA, HClO ₄ , Dioxane/H ₂ O, 50°C	Mixture, C20 Aldehyde
5	Trityl	NBS, DME/H ₂ O, rt, 3h	> 75% of C20 aldehyde
6	Trityl	NBS, CaCO ₃ , DME/H ₂ O, 0°C to rt	No Rxn
7	Trityl	NBS, H ₂ O, DMSO/THF (4:1), 0°C to rt	C20 aldehyde
8	Trityl	I ₂ , Cu(OAc) ₂ , Dioxane/H ₂ O, 0 to 60°C, 36h	No Rxn
9	TBDPS	1.1 eq. NBS, H ₂ O/THF, 0°C	C20 Aldehyde
10	TBDPS	1.1 eq. NBS, H ₂ O/THF, NaOAc, rt	No Rxn
11	TBDPS	4 eq. NBS, H ₂ O/THF, NaOAc, rt	Dibrominated

Table 2

Solvent effect on Yamamoto epoxidation with PDBu and ligand A

Entry	Solvent	Time (h)	Conversion (%)	Yield (%)	$\alpha:\beta^a$
1	CH ₂ Cl ₂	24	100	81	1:1
2	PhMe	24	100	84	1:1
3	Benzene	12	100	84	55:45
4	Acetone	24	48	44	22:78
5	THF	24	65	62	β major
6	CHCl ₃	24	91	81	1:1

^aThe ratios of α to β were determined by ¹H NMR of the crude mixture using the C18 ¹H-NMR signal

Table 3

Peroxide effect on Yamamoto epoxidation with PDBu and ligand **A**

Entry	Peroxide	Time (h)	Conversion (%)	Yield (%)	(α:β)
1	Aq. TBHP	24	100	84	55:45
2	TBHP (5.5M in decane)	24	100	79	60:40
3	Cumene hydroperoxide	48	80	82	55:45

Table 4

Ligand effect on Yamamoto epoxidation with PDBu

Entry	Ligand ^a	Temp	Time (h)	Conv. (%)	Yield (%)	(α : β)
1	A	0°C to r.t.	12	100	84	60:40
2	A	4°C	96	100	78	63:37
3	B	0°C to r.t.	36–48	100	85	75:25
4	B	4°C	120	100	73	79:19
5	C	0°C to r.t.	>12	100	89	80:20
6	C	4°C	24	100	90	89:11

^a Ligands A–C shown in Scheme 4