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An efficient method for the synthesis of versatile intermediates leading to 13-deoxy- and 9,13-dideoxyphorbols

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Abstract

An efficient method for the synthesis of versatile intermediates for biologically interesting 13-deoxy- and 9,13-dideoxyphorbol ester analogs is described. First, more efficient synthetic routes to the bicyclic ketones **7** and **8**, which are well-known intermediates for the synthesis of 13-deoxyphorbols, than the previous one were established. Second, **7** and **8** were successfully converted to the intermediates **19**, **25** and **27** for the synthesis of 9,13-dideoxyphorbols using Peterson reaction, oxymercuration and nitrile oxide cycloaddition as key steps.

Keywords: PKC; tumor promotors; structure–activity relationships.

The enzyme protein kinase C (PKC) is now thought[1] to play a major role in cellular signal transduction and as a consequence is apparently involved in cell growth regulation, including those diverse growth patterns which lead to tumor promotion and cancer. Since its first isolation, PKC has been shown to exist as several isoforms, the relative amounts and activities of which vary amongst cell populations. PKC is strongly activated in cells by endogenous 1,2-diacyl compounds such as diacylglycerol and other diverse tumor promotors, the most commonly known of which is phorbol 12-myristate-13-acetate (**1**: PMA) (Fig. 1). Computer modeling studies have shown[2] that compounds which are activators of PKC have common

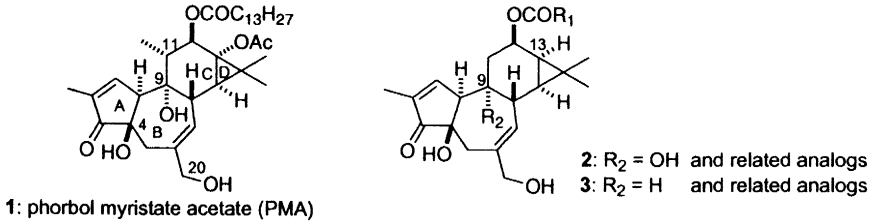

Fig. 1.

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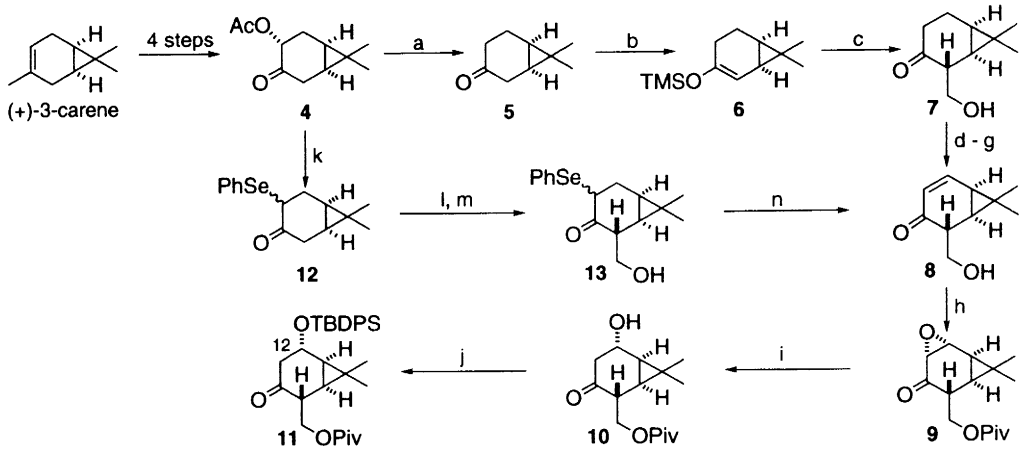
structural features. In the case of PMA (**1**), these include a carbonyl group at C-3, hydroxyl groups at C-4, C-9, and C-20, and a long-chain hydrophobic portion at C-12, indicating that an acetoxy group at C-13 is not important for the interaction of PMA (**1**) with PKC.

However, the biological evaluation of 13-deoxyphorbol esters[3] and photoaffinity labeling by 13-diazoacetyl phorbol ester derivative or 13-trifluorodiazopropionyl phorbol ester derivative[4,5] have suggested that the ester group at C-13 in phorbol esters is located in close proximity to PKC and interacts with PKC in phorbol ester-PKC-phospholipid complexes. Moreover, some recent reports on molecular modeling have supported the importance of the C-13 ester group.[6] It is of interest to assume that the C-13 acetoxy group would form a hydrogen bond with the C-9 hydroxyl group, not with PKC, based on X-ray crystallography[7] and MM calculation,[6] suggesting that these functional groups would interact with regulatory domain of PKC by hydrophobic interaction through a hydrogen bond between the C-13 acetoxy group and the C-9 hydroxyl group. Therefore, 9,13-dideoxyphorbol **3** would be quite an interesting compound, providing further information on structure–activity relationships of phorbols to propose a more precise pharmacophore model. In this communication we report an efficient method for the synthesis of versatile intermediates **7**, **8**, **19**, **25** and **27** leading to 13-deoxy- and 9,13-dideoxyphorbols **2** and **3**.

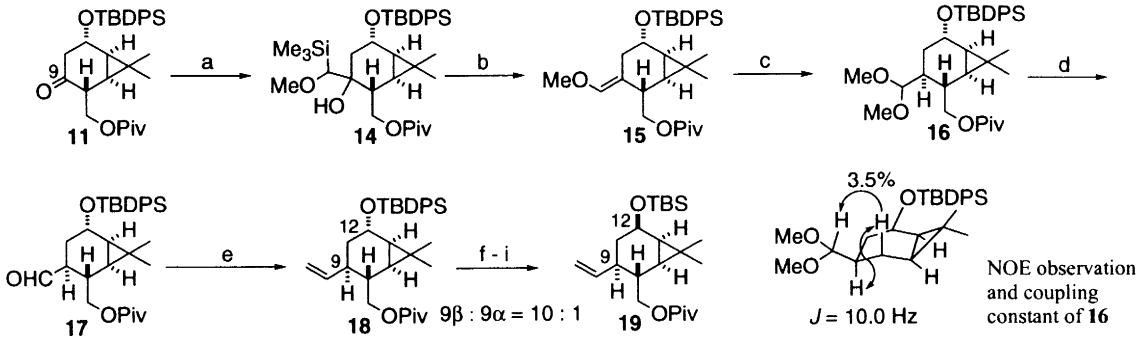


Scheme 1. Reagents and conditions: (a) Me_2CuLi (2.0 equiv.), THF, 0°C, 30 min, 98% (b) TMSCl (3.0 equiv.), LHMDS (1.2 equiv.), THF, −78°C→rt, 2 h, 78% (c) 36% HCHO aq., $Yb(OTf)_3$ (5.0 mol%) rt, 85 h, 81% (d) TBSCl (1.5 equiv.), imidazole (3.0 equiv.), DMF, rt, 2 h, 83% (e) LDA (1.3 equiv.), zirconocene dichloride (1.3 equiv.), PhSeBr (1.1 equiv.), THF, −78°C, 2 h, 84% (f) mCPBA (1.5 equiv.), CH_2Cl_2, rt, 2 h, 85% (g) *n*-Bu_4NF (1.2 equiv.), THF, 0°C, 2 h, quant. (h) (1) 30% H_2O_2 aq. (4.0 equiv.), NaOH (0.1 equiv.), THF, 0°C, 2 h, (2) pivaloyl chloride (1.5 equiv.), pyridine (3.0 equiv.), CH_2Cl_2, rt, 10 h, 81% (two steps) (i) Al–Hg, THF:EtOH:H_2O (3:2:1), −45°C, 4 days, 87% (j) TBDPSCl (2.0 equiv.), imidazole (4.0 equiv.) DMF, rt, 6 h, 60% (k) SmI_2 (2.0 equiv.), THF, −78→0°C then PhSeBr (2.0 equiv.), 0°C→rt, 15 min, 75% (l) TMSCl (3.0 equiv.), LHMDS (1.3 equiv.), THF, −78°C, 10 min, 97% (m) 36% HCHO aq., $Yb(OTf)_3$ (10 mol%), THF, rt, 5 h, 64% (n) 30% H_2O_2 aq. (10 equiv.), THF, rt, 5 min, quant.

Our strategy for synthesis of **3** basically stands on that for the synthesis of **2**.[3] However, the synthesis of the intermediate **7** was rather lengthy in our previous attempt (11 steps from (+)-3-carene, 30% overall yield).[3] Therefore, a shorter synthetic route to **7**, which is also useful for the medicinal chemistry of 13-deoxyphorbol esters **2**, was first investigated. As a result, we succeeded in synthesizing **7** with improved and shorter procedures than the previous one (seven steps from (+)-3-carene, 42% overall yield) (Scheme 1). Highly regioselective enol silylation of **5**, which is easily derived from (+)-3-carene in five steps,[8] with LHMDS and TMSCl, and subsequent aldol reaction of the enol silyl ether using 36% aqueous HCHO and 5 mol% of $Yb(OTf)_3$[9] gave **7** in 63% yield from **5**. The stereochemistry of **7** thus prepared was unequivocally determined by comparison with an authentic sample.[3] It is noteworthy that

in this route all the intermediates can be purified by simple distillation under reduced pressure. Then, according to the established procedure,[3] **7** was transformed into **8** as shown in Scheme 1. Furthermore, we were pleased to find that **8**, also a intermediate for 13-deoxyphorbols, could be synthesized in shorter steps. The acetoxy ketone **4** was treated with SmI_2[10] in THF, and the resulting samarium enolate was directly reacted with PhSeBr to give **12** in 75% yield. Compound **12** was converted to enol silyl ether in a highly regiocontrolled manner (97%), which was subjected to aldol reaction using aqueous HCHO and $Yb(OTf)_3$, affording **13** (64%) exclusively. Treatment of **13** with aqueous H_2O_2 furnished **8** in quantitative yield. The enone **8** was then converted to **11** according to the established procedure[3] (Scheme 1).

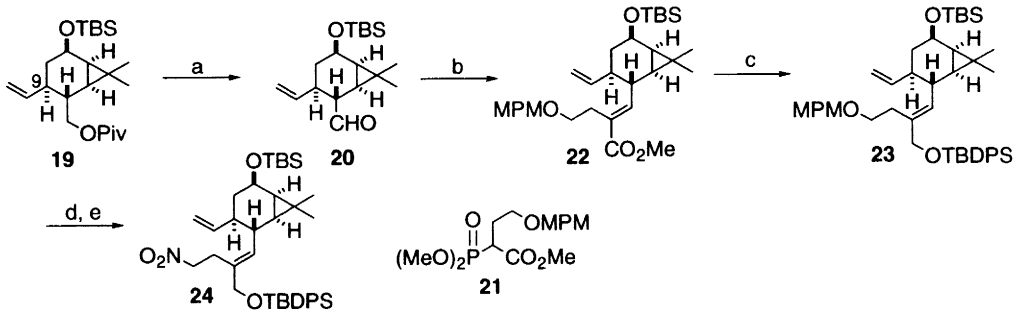
With optically pure **11** in large quantities, we then attempted crucial stereocontrolled conversion of C-9 ketone in **11** to a vinyl group. After many attempts, we finally found that the strategy using homologation of ketone to give aldehyde followed by Wittig olefination was the most effective (Scheme 2). Treatment of **11** with cerium reagent prepared from $Me_3SiCH_2OCH_3$, *sec*-BuLi and $CeCl_3$[11,12] gave **14** in 70% yield as a mixture of diastereomers. Direct conversion of **14** into aldehyde **17** with formic acid was not successful because of the sensitivity of **14** to acid. Enol methyl ether **15** obtained in a highly regiocontrolled manner from **14** on treatment with KH as single stereoisomer was also sensitive to strongly acidic conditions, such as H_2O:H_2SO_4:acetone (1:1:2), required to hydrolyze hindered trisubstituted enol methyl ether. Then, as an alternative process, oxymercuration of **15** with $Hg(OAc)_2$ and MeOH followed by $NaBH_4$ reduction was examined, giving dimethyl acetal **16** as a desired single isomer.[13] The stereochemistry of **16** was unequivocally determined by NOE experiments as shown in Scheme 2. Acetal **16** was treated with TsOH in acetone to give aldehyde **17** in quantitative yield. However, a small amount of aldehyde was epimerized to the undesired isomer in a ratio of 1:10. Finally, Wittig olefination of **17** gave vinyl compound **18**. Then, C-12 oxygen of **18** was inverted to give the desired isomer **19** exclusively by oxidation followed by reduction.



Scheme 2. Reagents and conditions: (a) $Me_3SiCH_2OCH_3$ (2.5 equiv.), *sec*-BuLi (2.0 equiv.), $CeCl_3$ (3.0 equiv.), THF, −40→0°C, 2 h, 70% (b) KH (8.0 equiv.), THF, rt, 2 h, 73% (c) $Hg(OAc)_2$ (1.1 equiv.), MeOH:CH_2Cl_2 (1:1), 0°C, 3 h then $NaBH_4$ (2.0 mol equiv.), 0°C, 10 min, 70% (d) *p*-toluenesulfonic acid (3.0 equiv.), acetone:H_2O (10:1), rt, 10 h (e) Ph_3PCH_3Br (4.0 equiv.), *n*-BuLi (3.0 equiv.), THF, 0°C, 2 h, 98% (two steps), (9β:9α, 10:1) (f) *n*-Bu_4NF (2.0 equiv.), THF, rt, 11 h, 88%, (g) SO_3·Py (10 equiv.), Et_3N (20 equiv.), DMSO, rt, 1 h, 86% (h) $NaBH_4$ (8.0 mol equiv.), MeOH, 0°C, 30 min, 86% (i) TBSCl (5.0 equiv.) imidazole (10 equiv.), DMF, rt, 22 h, 96%

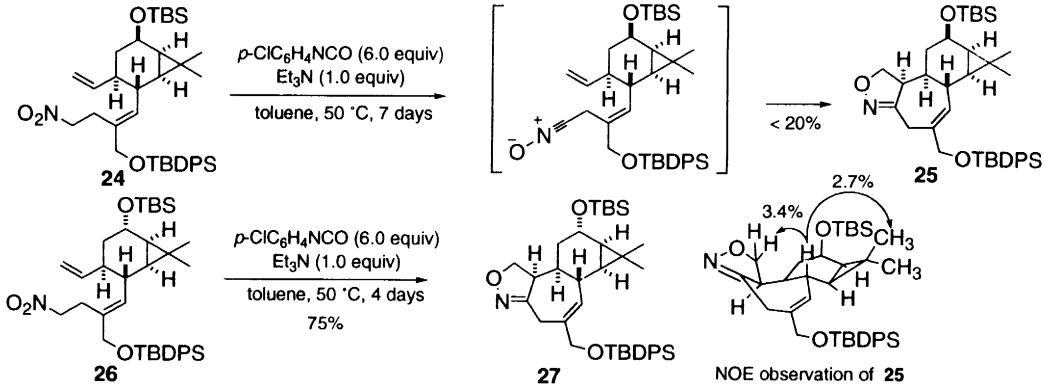
Having synthesized optically pure **19**, B-ring construction was attempted. First, as shown in Scheme 3, **19** was transformed into **24** according to the established procedure.[3]

Unfortunately, however, the intramolecular nitrile oxide cycloaddition with *p*-chlorophenyl isocyanate and triethylamine gave **25** in only poor yield, together with the recovery of the starting material **24** (80%) (Scheme 4). The stereochemistry of **25** was unequivocally determined by NOE experiments. We assumed that **24** was conformationally unfavorable for intramolecular nitrile oxide cycloaddition, and in fact this



Scheme 3. Reagents and conditions: (a) (1) $LiAlH_4$ (2.0 mol equiv.), Et_2O, 0°C, 30 min (2) $SO_3 \cdot Py$ (2.0 equiv.), Et_3N (4.0 equiv.), DMSO, rt, 2 h, 95% (b) **21** (6.0 equiv.), KHMDS (4.0 equiv.), THF, rt, 18 h, 73% (c) (1) DIBAL-H (3.0 equiv.), toluene, −78°C, 3 h (2) TBDPSCl (3.0 equiv.), imidazole (15 equiv.), DMF, rt, 5 h, 74% (two steps) (d) (1) DDQ (1.5 equiv.), CH_2Cl_2:H_2O (10:1), rt, 2 h (2) $MeSO_2Cl$ (5.0 equiv.), Et_3N (10 equiv.), CH_2Cl_2, 0°C, 30 min (3) NaI (40 equiv.), 2-butanone, 50°C, 9 h, 63%, (three steps) (e) $AgNO_2$ (5.0 equiv.), Et_2O, reflux, 48 h, 67%

appeared to be supported by our MM calculation. On the other hand, based on MM calculation, **26** was expected to give **27** more efficiently. To our delight, intramolecular nitrile oxide cycloaddition of **26** derived from **18** proceeded smoothly to give **27** in 75% yield.



Scheme 4.

In conclusion, we have succeeded in synthesizing **27** efficiently starting from optically pure (+)-3-carene. The tetracyclic isoxazolines **25** and **27** are already interesting compounds for biological evaluation. This is the first example of a synthetic approach to 9-deoxyphorbols. Therefore, the synthetic intermediates such as **19** and **27** would be quite useful for research groups working in the structure–activity relationships of phorbols. Details of all the results will be reported in due course.

References

1. (a) Nishizuka, Y. *Nature* **1984**, *308*, 693. (b) Farago, A.; Nishizuka, Y. *FEBS Lett.* **1990**, *268*, 350 and references cited therein.
2. (a) Castagna, M.; Takai, Y.; Kaibuchi, K.; Sano, K.; Kikkawa, U.; Nishizuka, Y. *J. Biol. Chem.* **1982**, *257*, 7847. (b) Jeffery, A. M.; Liskamp, R. M. *J. Proc. Natl. Acad. Sci. USA* **1986**, *83*, 241. (c) Wender, P. A.; Koehler, K. F.; Sharkey, N. A.; Dell'Aquila, M. L.; Blumberg, P. M. *J. Proc. Natl. Acad. Sci. USA* **1986**, *83*, 4214. (d) Wender, P. A.; Cribbs, C. M.; Koehler, K. F.; Sharkey, N. A.; Herald, C. L.; Kamano, Y.; Pettit, G. R.; Blumberg, P. M. *J. Proc. Natl. Acad. Sci. USA* **1988**, *85*, 7197. (e) Itai, A.; Kato, Y.; Tomioka, N.; Iitaka, N.; Endo, Y.; Hasegawa, M.; Shudo, K.; Fujiki, H.; Sakai, S. *J. Proc. Natl. Acad. Sci. USA* **1988**, *85*, 3688. (f) Nakamura, H.; Kishi, Y.; Pajares, M. A.; Rando, R. R. *J. Proc. Natl. Acad. Sci. USA* **1989**, *86*, 9672. (g) Rando, R. R.; Kishi, Y. *Biochemistry* **1992**, *31*, 2211.

3. (a) Sugita, K.; Shigeno, K.; Neville, C. F.; Sasai, H.; Shibasaki, M. *Synlett* **1994**, 325. (b) Sugita, K.; Neville, C. F.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett*. **1995**, *36*, 1067.
4. Sodeoka, M.; Uotsu, K.; Shibasaki, M. *Tetrahedron Lett.* **1995**, *36*, 8795.
5. Uotsu, K.; Sodeoka, M.; Shibasaki, M. *Bioorg. Med. Chem.* **1998**, *6*, 1117.
6. Wang, S.; Kazanietz, M. G.; Blumberg, P. M.; Marquez, V. E.; Milne, G. W. A. *J. Med. Chem.* **1996**, *39*, 2541.
7. Zhang, G.; Kazanietz, M. G.; Blumberg, P. M.; Hurley, J. H. *Cell* **1995**, *81*, 917.
8. Paquette, L. A.; Ross, R. J.; Shi, Y. J. *J. Org. Chem.* **1990**, *55*, 1589.
9. Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590.
10. Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.
11. Magnus, P.; Roy, G. *Organometallics* **1982**, *1*, 553.
12. Imamoto, T.; Kusumoto, Y.; Tawarayama, Y.; Sugiura, T.; Mita, Y.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904.
13. Radical intermediate is formed by $NaBH_4$ reduction of alkylmercury compound, and this is readily equilibrated to equatorial acetal.