The liberation of phosphine ligand during syntheses occurs probably due to the fact the volume of the ligand **I** is too big to be accommodated by the small vanadium. It is worth noting that the size of the phosphine ligand exerts an influence on the geometry around the vanadium metal center. NMR studies of **II** and **III**[6,7] indicate the difference in the symmetries around the vanadium metal. Complex **III**, which has PMe_3, shows four types of carbon atoms of the benzene ring on its ^{13}C-NMR spectra and three types of hydrogen atoms on its ^{1}H-NMR spectra, indicating that the two phenyl groups are in the same environment. Therefore the coordination sphere of vanadium in **III** can be described as a pseudotetrahedron. On the other hand, Complex **II** (a PEt_3 analog) exhibits complicated NMR peak-splittings. ^{13}C-NMR spectra of **II** exhibit twelve different carbon peaks of the phenyl groups and ^{1}H-NMR spectra also indicate the existence of two different benzene rings. One carbon atom of the benzene ring even appears as a doublet (δ 123.19) with a coupling constant $J_{C\text{-}P}$=16.2 Hz. Although at this time we cannot explain clearly why one carbon atom of the benzene ring on the tetrazene ligand backbone couples with the phosphorous atom, the results maybe imply that a larger phosphine (PEt_3) induces a more geometrically distorted tetrahedron. Reactivities and other chemistries of these complexes are under study.

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References

1. (a) M. Dekker and G. R. Knox, *J.C.S. Chem. Commun.*, 1243 (1967); (b) R. J. Doedens, *J.C.S. Chem. Commun.*, 1271 (1968); (c) F. W. B. Einstein and D. Sutton, *Inorg. Chem.*, **11**, 2827 (1972); (d) G. La Monica, P. Sondrinic, F. Zingales, and S. Cenini, *J. Organomet. Chem.*, **50**, 287 (1973); (e) S. Cenini, P. Fantucci, and G. La Monica, *Inorg. Chim. Acta.*, **13**, 243 (1975); (f) P. Overbosch, G. van Koten, and O. Overbeek, *J. Am. Chem. Soc.*, **102**, 2091 (1980); (g) M. E. Gross, W. C. Trogler, and J. A. Ibers, *J. Am. Chem. Soc.*, **103**, 192 (1981); (h) W. C. Trogler, C. E. Jhonson, and D. E. Ellis, *Inorg. Chem.*, **20**, 980 (1981); (i) P. Overbosch, G. van Koten, A. L. Speck, and A. J. M. Duinsenberg, *Inorg. Chem.*, **21**, 3253 (1982); (j) J. Geisenberger, V. Nagel, A. Sebald, and W. Beck, *Chem. Ber.*, **116**, 911 (1983); (k) M. J. Moroney and W. C. Trogler, *J. Am. Chem. Soc.*, **106**, 4144 (1984).
2. (a) S. W. Lee, G. A. Miller, C. F. Campana, M. L. Maciejewski, and W. C. Trogler, *J. Am. Chem. Soc.*, **109**, 5050 (1987); (b) S. W. Lee, G. A. Miller, C. F. Campana, and W. C. Trogler, *Inorg. Chem.*, **27**, 1215 (1988); (c) S. W. Lee and W. C. Trogler, *Organomet.*, **9**, 1470 (1990); (d) G. A. Miller, S. W. Lee, and W. C. Trogler, *Organomet.*, **8**, 738 (1989).
3. M. E. Gross, C. E. Jhonson, and W. C. Trogler, *Inorg. Chem.*, **23**, 2968 (1984).
4. (a) J. Nieman and J. C. Huffman, *J. Organomet. Chem.*, **255**, 193 (1983); (b) Von K. Issleib and G. Bohn, *Anorg. Allgem. Chem.*, **301**, 188 (1959).
5. A radius of V^{3+} with coordination number 6 is 0.78 Å. For additional informations, see; R. D. Shannon, *Acta Cryst.*, **A32**, 751 (1976).
6. Complex **II**. ^{1}H-NMR (C_6D_6, 500 MHz): δ 7.32 (t, 2H, C_6H_5, J=7.4 Hz), 7.13 (t, 2H, C_6H_5, J=7.1 Hz), 7.06 (d, 2H, C_6H_5, J=7.23 Hz), 6.90 (t, 1H, C_6H_5, J=7.1 Hz), 6.77 (t, 1H, C_6H_5, J=7.1 Hz), 6.48 (d, 2H, C_6H_5, J=7.23 Hz), 1.35 (m, 6H, $PC\underline{H_2}CH_3$), 0.87 (m, 9H, $PCH_2\underline{CH_3}$); ^{13}C-NMR (C_6D_5, 500 MHz): δ 153.78-114.42 (C_6H_5), 18.98 (td, $PC\underline{H_2}CH_3$, $J_{C\text{-}H}$ =128, $J_{C\text{-}P}$=63.2 Hz), 6.18 (qd, $PCH_2\underline{CH_3}$, $J_{C\text{-}H}$=128, $^2J_{C\text{-}P}$ =4.2 Hz); ^{13}C{H} NMR (C_6D_6, 500 MHz): δ 115.03, 116.71, 118.13, 129.13, 129.34, 147.31, 153.74 (s, C_6H_5), 123.19 (d, C_6H_5, $J_{C\text{-}P}$=16.2 Hz). MS (EI): 412.27 (M^+-2, 2), 379.49 (M^+-Cl, 11), 365.47 ($V(PEt^2)N_3Ph_2$, 8), 351.45 ($V(PEt_3)N_2Ph_2$, 6), 337.41 ($V(PEt_3)ClN_4Ph$, 5), 235.19 ($V(NHPh)_2$, 33), 225.17 ($VN_4(PEt_3)$, 67), 212.16 ($N_4H_2Ph_2$, 24), 119.06 (PhN_3, 20), 105.09 (PhN_2, 18) 93.09 (NH_2Ph, 100).
7. Complex **III**. ^{1}H-NMR (C_6D_6, 500 MHz): δ 6.43 (d, 4H, C_6H_5, J=7.5 Hz), 6.78 (t, 4H, C_6H_5, J=7.5 Hz), 7.14 (t, 2H, C_6H_5, J=7.5 Hz), 0.925 (m, 9H, CH_3); ^{13}C-NMR (C_6D_6, 500 MHz): δ 129.37 (dd, C_6H_5, $J_{C\text{-}H}$=156, $^3J_{C\text{-}H}$=8.2 Hz), 118.23 (dt, C_6H_5, $J_{C\text{-}H}$=160, $^3J_{C\text{-}H}$=7.4 Hz), 114.97 (dt, C_6H_5, $J_{C\text{-}H}$=155, $^3J_{C\text{-}H}$=6.4 Hz), 1.32 (q, CH_3, $J_{C\text{-}H}$=118 Hz); ^{13}C{H} NMR (C_6D_6, 500 MHz): 147.16 (s, C_6H_5), δ 129.37 (s, C_6H_5), 118.23 (s, C_6H_5), 114.97 (s, C_6H_5), 1.31 (s, CH_3). MS (EI): 372.22 (M^+, 4), 336.24 (M^+-Cl, 6), 323.32 ($V(PMe_3)N_3Ph_2$, 15), 296.19 (M^+-PMe_3, 6), 212.11 ($N_4H_2Ph_2$, 5), 105.08 (PhN_2, 35), 93.09 (NH_2Ph, 100), 77.06 (Ph, 59).

Synthesis of Prostaglandins II[1]. Convenient Synthesis of Misoprostol

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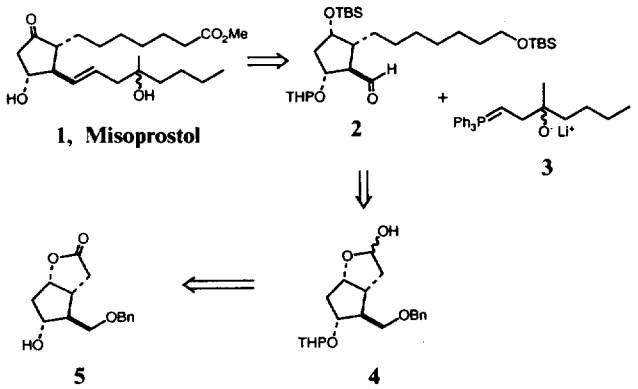
It is well known that naturally occurring prostaglandins of E-series exhibit powerful gastric antisecretory activity and cytoprotection.[2] However, their numerous side effects, rapid metabolism, and chemical instability limit their application as a therapeutic agent for the treatment of peptic ulcer disease. Misoprostol **1**, the 15-deoxy-16-hydroxy-16-methylprostaglandin E_1 is a potent anti-ulcer agent which reduced the critical drawbacks of the natural prostaglandins.[3] Since its development, a number of synthetic methods for **1** have been reported. In most cases, the synthetic routes to **1** involve, for the introduction of ω-side chain, a 1,4-conjugate addition of an appropriate 16-hydroxy-16-methyl vinyl copper species to the cyclopentenone ring which already has the α-side chain.[4] Here we describe a new efficient synthetic approach to **1**.

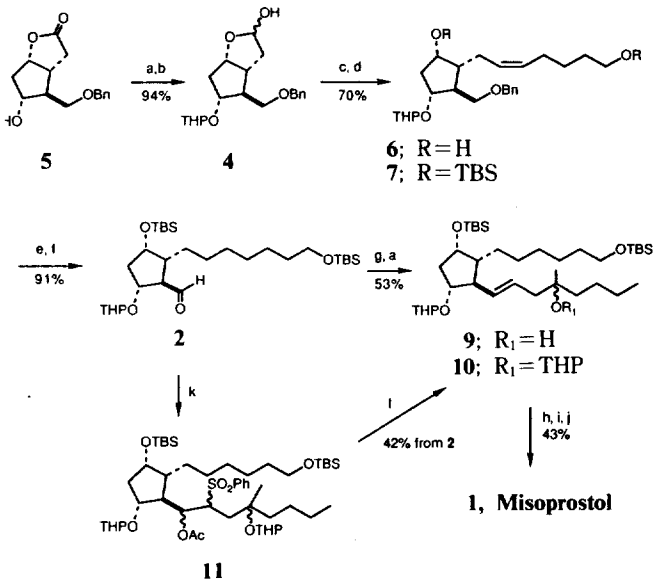
Since the highly efficient method to construct the upper side chain had been available,[5] our attention was focused upon the introduction of the lower side chain bearing *trans*-



1, Misoprostol **2** **3**

5 **4**

Scheme 1



5 **4** **6**; R=H **7**; R=TBS

2 **9**; R_1=H **10**; R_1=THP

11 **1, Misoprostol**

(a) DHP/PPTS, CH_2Cl_2; (b) DIBAH, $PhCH_3$; (c) *n*-BuLi, $PhP^+CH_2(CH_2)_3CH_2OH$, Br^-; (d) TBSCl, Imidazole, DMF; (e) H_2, 5% Pd/C, 5% AcOH in EtOH; (f) Collins reagent, CH_2Cl_2; (g) *n*-BuLi, **8**, $Ph_3P^+CH_2CH_2C(CH_3)(OH)CH_2(CH_2)_2CH_3$, I^-; (h) TBAF, THP; (i) PDC, DMF; CH_2N_2, Et_2O; (j) AcOH/H_2O/THF (20 : 10 : 3); (k) *n*-BuLi, $PhSO_2CH_2CH_2C(CH_3)(OTHP)CH_2(CH_2)_2CH_3$; then Ac_2O; (l) 5%-Na(Hg)/Na_2HPO_4, MeOH

Scheme 2

homoallylic alcohol unit. As outlined in Scheme 1, a key feature of our approach to **1** involves the *trans*-stereoselective Wittig coupling of the optically active aldehyde **2**, with γ-oxide ylide **3**.

Although non-stabilized phosphonium ylides react with aldehydes to afford largely *cis* olefin, γ-oxido ylides exhibit unexpectedly high *trans* stereoselectivity by intramolecular base (β- or γ-alkoxide)[6] or intermolecular base induced (Schlosser method)[7] equilibration of a Wittig intermediate. Accordingly, we anticipated that misoprostol could be synthesized efficiently by employing *trans*-stereoselective Wittig coupling strategy.

As shown in Scheme 2, aldehyde **2** was prepared as follows. Protection of Corey lactone benzyl ether **5** as its THP ether, followed by DIBAH reduction delivered the lactol **4** in 94% yield. Subsequent construction of α-side chain was carried out by the Wittig reaction of the lactol **4**, with the ylide derived from (5-hydroxypentyl)triphenylphosphonium bromide and *n*-BuLi to afford the diol **6**, in 74% yield. The diol **6** was converted into the aldehyde **2** by a three step sequence; protection of the diol **6** as di-*t*-butyldimethylsilyl ethers (TBS), concomitant hydrogenolysis and debenzylation by treatment with H_2 in the presence of 5% Pd/C, and Collins oxidation of the corresponding alcohol. With the aldehyde **2** in hand, the next step is the installation of ω-side chain by the *trans*-selective Wittig coupling of the aldehyde **2** with the γ-oxido ylide **3**, generated by treatment of (3-hydroxy-3-methyl)heptyltriphenylphosphonium iodide **8** with *n*-BuLi.

Reaction of (3-hydroxy-3-methyl)heptyltriphenylphosphonium iodide (**8**, 80 mg, 0.15 mmol) with *n*- BuLi (0.336 mmol) in THF (1 m*l*) at room temperature for 30 min afforded the deep red γ-oxido ylide solution. The solution was cooled to −78℃ and treated with a solution of aldehyde (**2**, 43 mg, 0.077 mmol) in THF (0.4 m*l*) at that temperature. The mixture was allowed to warm to room temperature over 1 h. The mixture was poured into ice-water and extracted with ether. The ether solution was dried and purified by flash column chromatography (EtOAc/hexane=1 : 3) to afford **9** (33 mg, 64%) exclusively. ^{1}H-NMR (200 MHz $CDCl_3$); δ 5.45 (m, 1H, C_{14}), 5.36 (dd, J=14.8 Hz, 8.9 Hz, 1H, C_{13}), 4.51 and 4.69 (two br. s, 1H, -OTHP) 4.05 (m, 1H), 3.82 (m, 2H, -OTHP), 3.54 (t, J=6.6 Hz, 2H, C_1), 3.39 (m, 1H), 0.84 (s, 21H), 0.00 (s, 12H). IR (neat); 3459, 2930, 2857, 1466, 1253, 1100 cm^{-1}.

The stereochemistry of the double bond was confirmed as *trans* by the coupling constant (14.8 Hz) in the ^{1}H-NMR spectrum. From this point of view, it should be noted that the presence of the hydroxy group in phosphonium salt **8** is critical for the *trans*-selective Wittig reaction, wherein deprotonation/equlibriation of the intermediate betaine is effected by the basic alkoxide.[6,7]

16-Hydroxy group of **9** was protected as THP ethers to give **10**. The *trans* stereochemistry of double bond in **10** was again proved by unambiguous synthesis of **11**, and then **10** (overall 42% from the aldehyde **2**) employing Julia olefination[8] as shown in Scheme 2.

Deprotection of the silyl ether and subsequent oxidation of the diol **6** with pyridinium dichromate (PDC) followed by methylation with diazomethane gave the 9-keto-ester. Finally, the THP groups were removed by treatment with acetic acid in aqueous THF to afford misoprostol **1**. The spectral data of misoprostol, thus obtained, were in complete agreement with those reported earlier.[4a,c]

In summary, we have developed a new synthetic route to misoprostol using a *trans*-stereoselective Wittig reaction as a key step. The whole synthesis comprises 11 steps from Corey lactone benzyl ether and proceeds in ~13% overall yield. This synthetic route may also provide substantial flexibility for the synthesis of 15-deoxy-16-hydroxy prostaglandin analogues.

References

1. H. Park, Y. S. Lee, S. C. Sim, and S. H. Jung, *Syn. Commun.*, **22**, 1445 (1992).
2. E. Z. Dajani, D. R. Driskill, R. G. Bianchi, P. W. Collins,

and R. Pappo, *Prostaglandins*, **10**, 733 (1975).
3. P. W. Collins, *J. Med. Chem.*, **29**, 437 (1986).
4. (a) P. F. Corey, *Eur. Pat.*, 0,133,450; (b) P. W. Collins, C. J. Jung, and R. Pappo, *Tetrahedron Lett.*, **19**, 3187 (1978); (c) T. Tanaka, A. Hazato, N. Okamura, S. Sugiura, K. Toru, and S. Kurozumi, *Tetrahedron*, **43**, 813 (1987).
5. E. J. Corey, Ned M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969).
6. (a) W. G. Salmond, M. A. Barta, and J. A. Havens, *J. Org. Chem.*, **43**, 790 (1978); (b) A. P. Kozikowski, R. J. Schmiesing, and K. L. Sorgi, *J. Am. Chem. Soc.*, **102**, 6580 (1980); (c) A. P. Kozikowski, H. Ishida, and Y. Chen, *J. Org. Chem.*, **45**, 3350 (1980); (d) E. J. Corey, H. Niwa, and J. Knolle, *J. Am. Chem. Soc.*, **100**, 1942 (1978).
7. M. Schlosser, H. B. Tuong, and B. Schaub, *Tetrahedron Lett.*, **26**, 311 (1985).
8. (a) P. J. Kocienski, B. Lythgoe, and I. Waterhouse, *J.C.S. Perkin I*, 1045 (1980); (b) P. J. Kocienski, *Phosphorus and Sulfur*, **24**, 97 (1985).

Mixed Amplitude and Phase Grating Effect in Forced Rayleigh Scattering

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Although the forced Rayleigh scattering (FRS) has recently emerged as a powerful tool for the study of mass diffusion in various media,[1-9] there still remain some aspects of the technique which seem to deserve further attention. The technique utilizes the diffraction from a transient concentration fringe pattern created by a photo-reaction of appropriate photoprobe. In order for the concentration fringe to diffract the light, the product of the photo-reaction (shifted state) should possess a different optical properties from the unshifted state either in absorptivity (amplitude grating) or in refractive index (phase grating).[10-12] If the transient sinusoidal concentration fringe decays by the Fickian diffusion process, the diffracted optical filed decays exponentially following the functional form, $E_d = A \exp(-t/\tau)$.

However, deviations from the single exponential type decay of diffracted signal have often been observed and the deviation is ascribed to the difference in the decay time constants of a pair of complementary gratings which consist of excess optically shifted and unshifted state of the photoprobe.[5,6,9,12,13] Under this circumstance, the time-varying diffracted intensity has been analyzed by the following model function.

$$I_d(t) = [A_1 \exp(-t/\tau_1) - A_2 \exp(-t/\tau_2)]^2 + B \quad (1)$$

where τ_1 and τ_2 are the respective decay time constants of two complementary gratings, B is the baseline, and A_1 and A_2 represent the amplitude of optical fields diffracted from each complementary grating. The negative sign arises from the fact that two gratings are 180° out of phase, but it is only valid for either pure phase (contrast in refractive index) or amplitude (contrast in absorptivity) grating.[11,12] Otherwise, it is necessary to include one more parameter, *i.e.*, the phase difference between two diffracted optical fields from each grating in order to describe the FRS decay profile.[3,9,11,12] The amplitude and phase grating contribution to the diffraction was well demonstrated previously in the other type of transient optical grating experiment,[10] however, the mixed grating effect exhibits itself in a somewhat different fashion in FRS.

For an unslanted grating, the coupled-wave theory gives the diffracted optical field, E_d from a weak diffraction grating,[3,10,11]

$$E_d \propto [-i(\Delta n) + (\Delta k)] \quad (2)$$

where Δn and Δk are the gratings peak-null differences in real and imaginary part of complex refractive index, respectively. Eq. (2) shows that a pure amplitude grating ($\Delta n = 0$) introduces no phase shift while light diffracted from a pure phase grating ($\Delta k = 0$) is shifted by $-\pi/2$. For an arbitrary grating in the weak grating limit, the phase shift is given by

$$\varphi = \sin^{-1}\{-\Delta n/[(\Delta n)^2 + (\Delta k)^2]^{1/2}\} \quad (3)$$

This phase information is lost in the detection of diffracted light from a *single* grating by a square-law detector such as a photomultiplier. However, the phase shift leads to a distinct departure from a simple exponential decay when the complementary grating effect is visible. For a mixed amplitude and phase grating, Eq. (1) should be written as

$$\begin{aligned} I_d(t) &= |E_d(t)|^2 \\ &= [A_1 \exp(-t/\tau_1) + A_2 \exp(-t/\tau_2) \exp(i\,\Delta\varphi)] \times \\ &\quad [A_1 \exp(-t/\tau_1) + A_2 \exp(-t/\tau_2) \exp(-i\,\Delta\varphi)] + B \end{aligned} \quad (4)$$

where $\Delta\varphi$ is the phase difference between the diffracted optical fields from two complementary gratings, *i.e.* $\Delta\varphi = \pi + (\varphi_1 - \varphi_2)$. The analysis according to Eq. (4) is not trivial and thus it seems advantageous to choose a photoprobe exhibiting either a pure amplitude or phase grating behavior at the reading beam wavelength. In this case, $\Delta\varphi = \pi$, which reduces Eq. (4) to Eq. (1).

So far the phase effect due to the mixed grating has not been considered for the analysis of FRS decay profiles. This is likely due to one of the following reasons; (1) the both shifted and unshifted state of the photoprobes do not show a significant absorption at the wavelength of reading beam so that most of the experiments have been carried out at near pure phase grating limit, *e.g.*, use of He/Ne laser reading beam for most of azobenzene derivatives which absorb negligibly at 632.8 nm wavelength; (2) the decay time constants of complementary gratings (*i.e.*, diffusivities of the shifted and the unshifted states) are the same; (3) the shape of decay profiles is such that it is hard to recognize the existent phase effect. If the effect (3) is operational, analysis of the signal by Eq. (2) could lead to an erroneous result.

As can be seen from the simulation results in Figure 1,