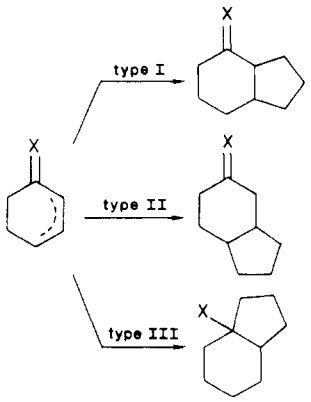
Scheme I[a]



[a] X = H_2, O, etc.

ring fusion is ≥98% cis as judged by inspection of their ^{1}H 2D NOESY NMR spectra and/or 1D ^{1}H-decoupled spectra as well as ^{13}C NMR spectra. For example, the ^{1}H 2D NOESY NMR spectrum of **9** clearly indicates that the proton that is β and cis to the COOMe group is also cis to the bridgehead proton and that the other β proton is trans to it.

The reaction of the lithium enolate of 3-cyclohexenone with **1b** and **2b** under mild and well-controlled conditions gave the corresponding deconjugated derivatives. Unfortunately, however, their treatment with $Pd(PPh_3)_4$–NEt_3 only induced double-bond isomerization to produce the conjugated enones which showed no sign of cyclization. The use of **10**, obtained by methylation of 3-cyclohexenone, however, cleanly produced **11** and **12** from **1b** and **2b**, respectively. As expected, their treatment with 3–5 mol % of $Pd(PPh_3)_4$ and NEt_3 (1.5–2.0 equiv) gave isomerically pure **13** and **14** in 82 and 71% yields, respectively. The stereochemical assignments are based on the same protocol as described above. Although the scope of these type I annulation procedures appears to be limited to the cases of β,γ-unsaturated carbonyl derivatives which cannot isomerize into the α,β-unsaturated derivatives, the results shown in eq 1–5 nonetheless represent efficient and selective [3 + 2] annulation procedures which appear to be of considerable synthetic utility.

To demonstrate the feasibility of type II annulation of 2-cyclohexenone derivatives, we prepared **16** and **17** by treating **15** with LDA, **1b**, and **2c**, respectively, followed by reduction with $LiAlH_4$ and deethylation with HCl. Under the Pd-catalyzed cyclization conditions, **16** was cleanly converted into **18** in 68% yield (91% by GLC), which is isomerically homogeneous. Likewise, **17** gave **19** in 50% yield. In addition to **19**, the double bond hydrogenated byproduct was also obtained in 30% yield. Similar radical cyclization procedures have recently been developed.[11] However, the C=C bond of the enone group is lost in the radical cyclization reactions.

Finally, the feasibility of achieving carbonylative [3 + 2 + 1] annulation was tested by treating **20**[12] with CO (600 psi) in the presence of 5 mol % of $Pd(PPh_3)_4$ and NEt_3 (1.5 equiv) at 100 °C. After 16 h, isomerically pure **21** was obtained in 67%. We are currently investigating the scope of this carbonylative annulation reaction.

The following procedure for the conversion of **10** into **13** is representative. 3-Cyclohexen-1-one[13] prepared by the Birch reduction of anisole was converted into **10** in 70% yield by sequential treatment with LDA (1 equiv, −78 °C, 1 h) in a 2:1 mixture by volume of THF and HMPA, CH_3I (3–5 equiv, −78 °C, 12 h), and 3 M HCl (−78 °C). Sequential treatment of **10** (5 mmol) in 10 mL of THF with LDA (5 mmol), HMPA (5 mL), and **1b** (2.10 g, 6 mmol, −78 °C, 6 h) gave a 62% yield of **11**. A mixture of **11** (0.664 g, 2 mmol), $Pd(PPh_3)_4$ (0.069 g, 0.06 mmol), NEt_3 (0.404 g, 4 mmol), and 10 mL of MeCN was refluxed for 6 h. The reaction mixture was quenched with 3 M HCl, extracted with ether, washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, concentrated, and flash chromatographed (silica gel, 1:10 ether–hexane) to give 0.334 g (82%) of **13**: IR (neat) 1670 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.89 (t, J = 7 Hz, 3 H), 1.24 (s, 3 H), 1.2–1.6 (m, 4 H), 1.8–2.0 (m, 2 H), 2.10 (d, J = 15 Hz, 1 H), 2.40 (dt, J = 19 and 4 Hz, 1 H), 2.58 (br d, J = 19 Hz, 1 H), 2.76 (br s, 1 H), 2.85 (d, J = 15 Hz, 1 H), 5.37 (s, 1 H), 5.99 (d, J = 10 Hz, 1 H), 6.77 (dt, J = 10 and 4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.80, 21.97, 22.40, 23.95, 28.92, 29.25, 41.12, 50.40, 53.21, 123.63, 129.68, 145.48, 145.65, 204.39; high-resolution MS calcd for $C_{14}H_{20}O$ 204.1514, found 204.1513.

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(11) Marinovic, N. N.; Ramanathan, H. *Tetrahedron Lett.* **1983**, *24*, 1871.

(12) The Pd-catalyzed cyclization reaction of **20** was recently reported as an isolated case of annulative carbocycle formation.[9d]

(13) Birch, A. J.; Bandara, B. M. R.; Chamberlain, K.; Chauncy, B.; Peter, D.; Day, A. I.; Jenkins, I. D.; Kelley, L. F.; Khor, T. *Tetrahedron, Suppl.* **1981**, 289.

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Prostaglandin Synthesis via Two-Component Coupling. Highly Efficient Synthesis of Chiral Prostaglandin Intermediates 4-Alkoxy-2-alkyl-2-cyclopenten-1-one and 4-Alkoxy-3-alkenyl-2-methylenecyclopentan-1-one

Summary: Starting with readily available (2*R*,3*S*)-1,2-epoxypent-4-en-3-ol (**5**), two chiral prostaglandin intermediates 4-alkoxy-2-alkyl-2-cyclopenten-1-one (**1**) and 4-alkoxy-3-alkenyl-2-methylenecyclopentan-1-one (**2**) are prepared in good overall yields through the common key intermediate 3,4-dialkoxy-2-methylenecyclopentan-1-one (**3**), thus making prostaglandin synthesis via two-component coupling an industrially viable process.

Sir: One of the most attractive methods for synthesis of prostaglandins (PGs) and their analogues is undoubtedly the two component coupling process via conjugate addition.[2] This process can be classified into two possible

(1) Fellow of the Japan Society for the Promotion of Science for Japanese Junior Scientists, 1988–1990.

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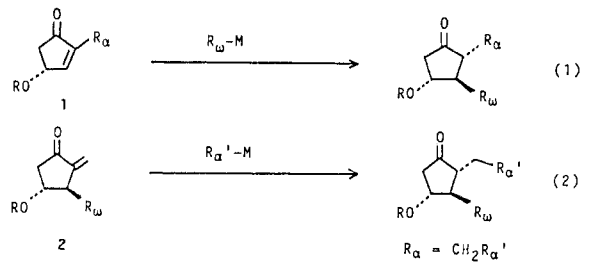
routes: introduction of the ω side chain onto a 4-alkoxy-2-alkyl-2-cyclopenten-1-one (**1**) (eq 1)[3] and introduction

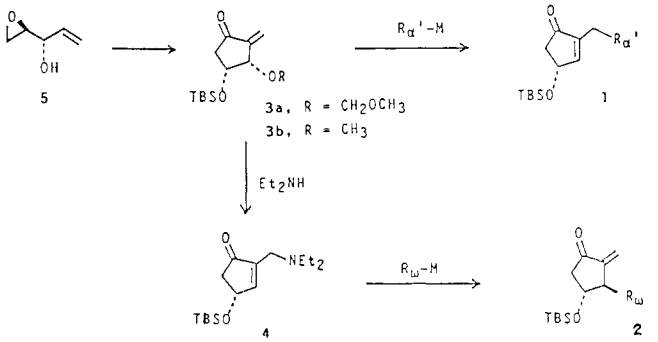


of the α side chain onto a 4-alkoxy-3-alkenyl-2-methylenecyclopentan-1-one (**2**) (eq 2).[4] In contrast to the PG synthesis via Corey lactone or via the three component coupling process developed by Noyori et al., these two routes, however, do not appear to be industrially viable because of the lack of an efficient way to obtain chiral **1** and **2**.[2]

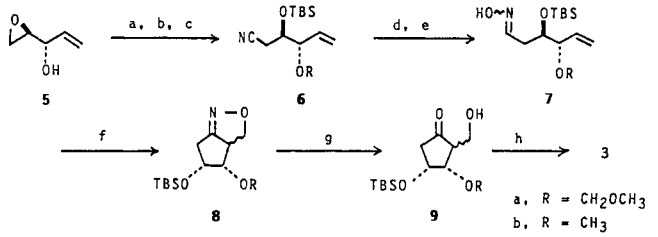
We now report a practical method for the synthesis of chiral **1** and **2**. The key features of our synthesis illustrated in Scheme I are as follows: The key intermediate enone **3** is prepared efficiently from readily available chiral epoxy alcohol (2*R*,3*S*)-1,2-epoxypent-4-en-3-ol (**5**). The enone **3** thus prepared reacts with an organometallic compound derived from the α side chain unit to give **1** via a 1,4-addition reaction which is accompanied by the direct elimination of the alkoxy group (OR).[5] Compound **3** is also converted into **2**, which involves the organocuprate conjugate addition of the ω side chain unit to **4**, obtained from **3** by the Michael addition of Et_2NH.

The synthesis of **3** (**a**, R = CH_2OCH_3; **b**, R = CH_3) was carried out by the procedure shown in Scheme II, starting with **5**, which is readily obtained in large quantity by the Sharpless asymmetric epoxidation of 1,4-pentadien-3-ol.[6] Protection of the hydroxyl group of **5** (>95% ee) followed by epoxide ring opening with cyanide ion and silylation with TBSCl afforded **6**. Reduction of **6** with Dibal followed by reaction of the resulting aldehyde with hydroxylamine gave oxime **7**. The conversion of **7** into the β-hydroxy ketone **9** was carried out according to the procedure reported by Kozikowski and Stein,[7] and Curran.[8] Thus, oxidation of **7** with aqueous NaOCl resulted in the nitrile oxide cycloaddition to afford **8** (a mixture of two diastereomeric isomers), which was partially purified by passage through a short silica gel column. Hydrogenolysis/hydrolysis of **8** with H_2 (1 atm) and 10% Pd/C in aqueous THF containing $B(OH)_3$ gave **9**. Mesylation of **9** was accompanied by direct elimination to give the enone **3**, which was purified by chromatography. In these reactions, the intermediates except **8** were used for the next reaction without purification. The overall yields of **3** from **5** were 52% for **3a** ($[\alpha]^{25}_D$ −60.9° (*c* 1.29, $CHCl_3$)) and 53% for **3b** ($[\alpha]^{25}_D$ −37.8° (*c* 2.32, $CHCl_3$)), respectively.[9]

Scheme I



Scheme II[a]



[a] (a) NaH (1.5 equiv), CH_3OCH_2Cl or CH_3I (1.2 equiv), THF, 0 °C, 2 h; (b) KCN (1.8 equiv), AcOH (1 equiv), MeOH, 40 °C, 3–6 h; (c) TBSCl (1.2 equiv), imidazole (2.2 equiv), DMF, room temperature, 10 h; (d) Dibal (1.2 equiv), hexane/Et_2O, −20 °C, 30 min; (e) $HONH_2$·HCl (1.5 equiv), pyridine (2 equiv), CH_2Cl_2, room temperature, 4 h; (f) 0.7 N NaOCl (1.5 equiv), CH_2Cl_2, room temperature, 4 h; (g) 10% Pd/C, H_2 (1 atom), $B(OH)_3$ (3 equiv), THF/H_2O (3:1), room temperature, 2–4 h; (h) CH_3SO_2Cl (1.5 equiv), Et_3N (3.5 equiv), CH_2Cl_2, 0 °C, 40 min.

With compound **3** in hand, we investigated the optimum conditions for the conversion of **3** into **1** using *n*-butyl organometallic compounds (Scheme I) and found that in the case of **3a** the best yield (95% yield) was realized when Bu_2CuLi was used (THF, −78 to 0 °C, 1 h), while in the case of **3b**, the use of a cyano mixed cuprate such as BuCu(CN)Li or BuCu(CN)$MgBr$[10] (THF, −78 to 0 °C, 1 h) resulted in essentially quantitative yield of **1**.[11] From the synthetic point of view, the reaction of **3b** with RCu(CN)Li or RCu(CN)MgX is more attractive, because in the reaction of R_2CuLi with **3a**, 1 equiv of the R group is inevitably wasted, and so this becomes a severe disadvantage when the R group is expensive or difficult to

(2) Bindra, J. S. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1981; Vol. 4. Roberts, S. M.; Scheinmann, F. *New Synthetic Routes to Prostaglandins and Thromboxanes*; Academic: New York, 1982. Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*; Academic: New York, 1977. Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847.

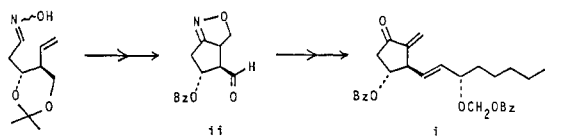
(3) Sih, C. J.; Price, P.; Sood, R.; Salomon, R. G.; Peruzzotti, G.; Casey, M. *J. Am. Chem. Soc.* **1972**, *94*, 3642. Kluge, A. F.; Untch, K. G.; Fried, J. H. *Ibid.* **1972**, *94*, 9256. Miller, J. G.; Kurz, W.; Untch, K. G.; Stork, G. *Ibid.* **1974**, *96*, 6774.

(4) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 4745.

(5) Takahashi, T.; Hori, K.; Tsuji, J. *Chem. Lett.* **1981**, 1189.

(6) Hatakeyama, S.; Sakurai, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1985**, 1759. Hatakeyama, S.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1986**, *27*, 4485. Babine, R. E. *Ibid.* **1986**, *27*, 5791. Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525.

(7) Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1982**, *104*, 4023. Kozikowski and Stein synthesized the racemic PG intermediate i via ii by using the intramolecular nitrile oxide cycloaddition as a key step as shown below (Kozikowski, A. P.; Stein, P. D. *J. Org. Chem.* **1984**, *49*, 2301):



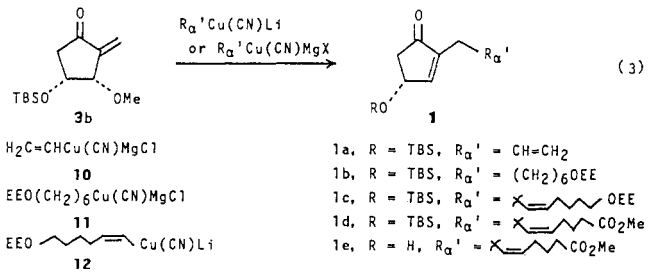
(8) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024.

(9) **3a**: ^1H NMR (CCl_4, PhH) δ 0.12 (s, 6 H), 0.91 (s, 9 H), 2.38 (dd, *J* = 1.7, 4.9 Hz, 2 H), 3.36 (s, 3 H), 4.27–4.60 (m, 2 H), 4.68 (dd, *J* = 7.2, 12 Hz, 2 H), 5.43 and 6.06 (2 br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 200.9, 144.2, 119.8, 94.5, 77.0, 69.0, 55.2, 45.3, 25.4, 17.8, −5.0. **3b**: ^1H NMR (CCl_4, PhH) δ 0.12 (s, 6 H), 0.89 (s, 9 H), 2.34 (d, *J* = 4.8 Hz, 2 H), 3.41 (s, 3 H), 4.00–4.20 (m, 1 H), 4.34–4.60 (m, 1 H), 5.41 and 6.05 (2 br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 201.3, 144.1, 119.8, 82.5, 68.5, 56.6, 45.5, 25.6, 17.9, −4.9.

(10) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980.

(11) In the case of **3b**, the use of Bu_2CuLi resulted in the formation of 4-((*tert*-butyldimethylsilyl)oxy)-3-butyl-2-pentylcyclopentanone via the further conjugate addition of *n*-butyl to the resulting **1**.

prepare. Thus, we carried out the synthesis of **1a–c**, the intermediates for synthesis of natural PGs or important PG analogues, from **3b** and the corresponding cyano mixed cuprates (eq 3). Compound **3b** reacted with the cyano

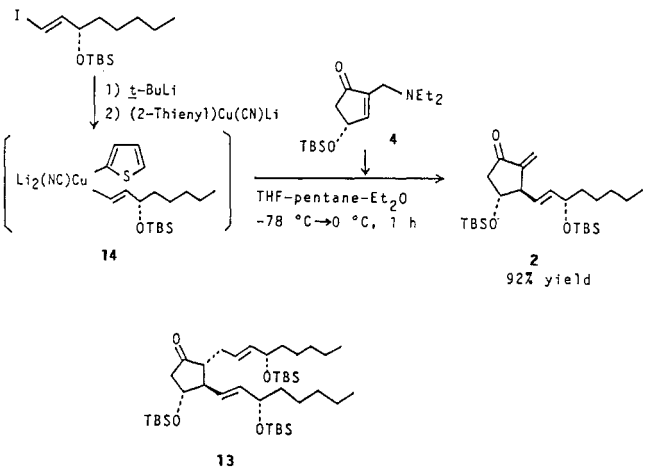


mixed cuprates **10** and **11** prepared from CuCN and the corresponding Grignard reagents to afford **1a**[12] and **1b**[2] in 85% and 86% yields, respectively. In the same manner, compound **3b** was converted into **1c**[2] in 88% yield by the reaction with cuprate **12** prepared from CuCN and (*Z*)-LiCH=CH(CH$_2$)$_4$OEE (EE = ethoxyethyl). The product (**1c**) thus obtained was converted into **1d** in 82% yield by the following sequence: (1) pyridinium *p*-toluenesulfonate (PPTS), MeOH, Et$_2$O; (2) CrO_3, H^+; (3) CH_2N_2. Desilylation of **1d** with Bu_4NF afforded the known compound **1e**, the spectral data and optical rotation of which are in good agreement with the reported values ([α]$^{23}_D$ +13.3° (*c* 1.01, CH_3OH); lit.[13] [α]$^{23}_D$ +12.4° (*c* 0.91, CH_3OH)).

Next we describe the synthesis of **2** from **3**. Treatment of **3a** with Et$_2$NH in THF at room temperature for 12 h afforded a 95% yield of **4** ([α]$^{25}_D$ +17.4° (*c* 1.04, $CHCl_3$)).[14,15] Thus, compound **4** was obtained in 50% overall yield from **5** through nine steps. The conjugate addition reaction of **4** with the organocuprate derived from the ω side chain unit afforded **2** in excellent yield without production of the double Michael adduct **13** (Scheme III). Thus, the higher ordered cyano mixed cuprate **14** prepared from the vinyllithium derived from (*S*,*E*)-3-((*tert*-butyldimethylsilyl)oxy)-1-iodo-1-octene (>99% ee)[16] and the Lipshutz reagent (2-thienyl)Cu(CN)Li[17] reacted with the enone **4** (THF/Et$_2$O/pentane, −78 to 0 °C, 1 h) to afford **2** in 92% yield after hydrolysis: [α]$^{25}_D$ −46.1° (*c* 0.781, $CHCl_3$).[18] Noteworthy is the fact that in the present reaction the double conjugate addition product **13** was not produced. However, we found that the reaction of **2** with **14** provided **13** in excellent yield. These results strongly indicate that **2** is formed at the time of the hydrolysis of the reaction mixture.

Finally we describe briefly the synthesis of natural PGEs using **1** or **2** via a two component coupling process. The reaction of **2** with cuprate **11** afforded the corresponding conjugate addition product in 98% yield, from which PGE$_1$ ([α]$^{20}_D$ −54.0° (*c* 1.0, THF), mp 114.5–116 °C; lit.[19] [α]$^{20}_D$ −54.3° (*c* 1.0, THF), mp 115–116 °C) was synthesized in

Scheme III



64% overall yield by the following sequences: (1) PPTS, MeOH, Et$_2$O; (2) CrO_3, H^+; (3) aqueous HF, CH_3CN. The disilyl ether of PGE$_2$ methyl ester ([α]$^{19}_D$ −49.3° (*c* 1.14, MeOH); lit.[20] [α]$^{19}_D$ −49.9° (*c* 1.02, MeOH)) was obtained from **1d** and cuprate **14** in 90% yield.[21]

As described above, we have succeeded in synthesizing the optically active enones **1** and **2** efficiently from the readily available **5**. We have previously developed efficient synthetic methods to prepare PG ω side chain units, γ-iodo or γ-tributylstannyl allylic alcohols, by using the Sharpless kinetic resolution as a key step.[16,22] Therefore, all chiral intermediates for the synthesis of PGs and their analogues via two-component coupling (eq 1 and 2) are now readily available. We hope that these findings make the two component coupling process an industrially applicable synthetic method.

Supplementary Material Available: Spectral and physical data for compounds **1a–d**, **6a–9a**, and **6b–9b** (3 pages). Ordering information is given on any current masthead page.

(12) Mase, T.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1984**, *25*, 5087. Bannai, K.; Tanaka, T.; Okamura, N.; Hazato, A.; Sugiura, S.; Manabe, K.; Tomimori, K.; Kurozumi, S. *Ibid.* **1986**, *27*, 6353. Bannai, K.; Toru, T.; Hazato, A.; Oba, T.; Tanaka, T.; Okamura, N.; Watanabe, K.; Kurozumi, S. *Chem. Pharm. Bull.* **1982**, *30*, 1102. Hazato, A.; Tanaka, T.; Watanabe, K.; Bannai, K.; Toru, T.; Okamura, N.; Manabe, K.; Ohtsu, A.; Kamimoto, F.; Kurozumi, S. *Chem. Pharm. Bull.* **1985**, *33*, 1815.

(13) Sih, C. J.; Heather, J. B.; Sood, R.; Price, P.; Peruzzotti, G.; Hsu Lee, L. F.; Lee, S. S. *J. Am. Chem. Soc.* **1975**, *97*, 865.

(14) Takahashi, T.; Hori, K.; Tsuji, J. *Tetrahedron Lett.* **1981**, *22*, 119.

(15) The reaction of **3b** with Et$_2$NH afforded **4** in 88% yield. **4**: IR (neat) 2940, 1710, 1080, 835, 780 cm^{-1}; ^{1}H NMR (CCl_4, PhH) δ 0.20 (s, 6 H), 0.96 (s, 9 H), 1.06 (t, *J* = 7.2 Hz, 6 H), 2.23 (dd, *J* = 2.5, 18 Hz, 1 H), 2.48 (q, *J* = 7.2 Hz, 4 H), 2.64 (dd, *J* = 6.3, 18 Hz, 1 H), 3.14 (br s, 2 H), 4.80–4.98 (m, 1 H), 7.12 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 205.0, 158.2, 144.7, 68.9, 47.3, 47.1, 45.6, 25.6, 17.9, 11.9, −4.8; bp 141–143 °C/0.45 mmHg.

(16) Okamoto, S.; Shimazaki, T.; Kobayashi, Y.; Sato, F. *Tetrahedron Lett.* **1987**, *28*, 2033. Kitano, Y.; Matsumoto, T.; Okamoto, S.; Shimazaki, T.; Kobayashi, Y.; Sato, F. *Chem. Lett.* **1987**, 1523. Kitano, Y.; Matsumoto, T.; Wakasa, T.; Okamoto, S.; Shimazaki, T.; Kobayashi, Y.; Sato, F.; Miyaji, K.; Arai, K. *Tetrahedron Lett.* **1987**, *28*, 6351.

(17) Lipshutz, B. H. *Synthesis* **1987**, 325. Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945.

(18) **2**: IR (neat) 2930, 1740, 1645, 1470, 1260, 1110, 840, 780 cm^{-1}; ^{1}H NMR (CCl_4, PhH) δ −0.04 and −0.02 (2 s, 6 H), 0.00 (s, 6 H), 0.98 (br s, 21 H), 1.20–1.80 (m, 8 H), 2.30 and 2.60 (2 dd, *J* = 7.8, 18.6 Hz and *J* = 18.6, 7.1 Hz, 2 H), 3.09–3.40 (m, 1 H), 3.92–4.30 (m, 2 H), 5.12 (br s, 1 H), 5.30–5.83 (m, 2 H), 5.99 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 202.8, 147.0, 137.8, 127.4, 118.9, 73.0, 72.6, 54.6, 47.0, 38.6, 31.9, 26.0, 25.8, 25.0, 22.7, 18.3, 18.1, 14.0, −4.2, −4.6; [α]$^{25}_D$ −46.1° (*c* 0.781, $CHCl_3$).

(19) Sih, C. J.; Salomon, R. G.; Price, P.; Sood, R.; Peruzzotti, G. *J. Am. Chem. Soc.* **1975**, *97*, 865.

(20) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348.

(21) The high efficiency of the conjugate addition reaction of **14** to **1** is noteworthy. See also: Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641.

(22) Another efficient preparation of an optically active PG ω side chain unit: Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717.

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