*Tetrahedron* Vol 47, No 10/11, pp 1861-1876, 1991
Printed in Great Britain

0040-4020/91 $3 00+ 00


# SHORT SYNTHESIS OF ISOCARBACYCLIN BY REGIOSELECTIVE $S_N2'$ ALKYLATION OF BICYCLIC ALLYLIC ESTERS WITH ZINC-COPPER REAGENTS[1]

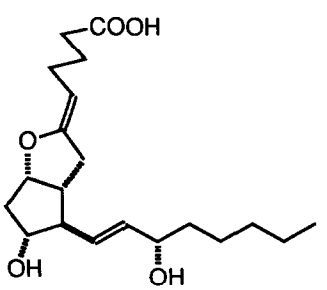
Toshio Tanaka,* Kiyoshi Bannai, Atsuo Hazato, Masahiro Koga,[2]
Seizi Kurozumi, and Yoshinori Kato

Institute for Bio-Medical Research, Teijin Ltd , 4-3-2 Asahigaoka, Hino, Tokyo 191, JAPAN

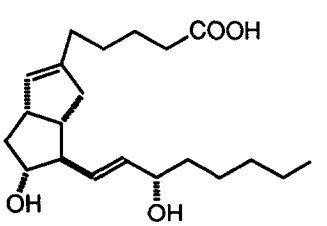
(*Received in Japan* 18 *September* 1990)

**Abstract:** Isocarbacyclin [(+)-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin $I_1$] (**2**) was synthesized from bicyclic synthons such as 2-phosphorylated, 2-(thio)phosphorylated, 2-tosylated, 2-methoxycarbonylated, and 2-chloro-3-methylenebicyclo[3 3 0]octanes *via* highly regioselective $S_N2'$ alkylation with zinc-copper reagents **9** in excellent yields

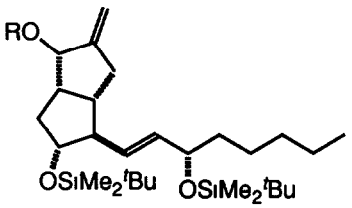
Chemically stable analogs of prostacyclin[3] (prostaglandin $I_2$, **1**) have been developed as hopeful therapeutic agents for treatment of various vascular diseases[4] Isocarbacyclin[5] [(+)-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin $I_1$] (**2**) is one of the most promising candidates because of both its potent prostaglandin like activity and chemical stability, hence intensive efforts have been made focusing on the efficient synthesis of isocarbacyclin[6] and its congeners[6c,7] Previously, we reported several synthetic routes to them, which involve regioselective deoxygenative allylic alkylation[6h,6n] of the bicyclic alcohol **3** with the lithiated ortho-ester moiety **7** in the presence of copper iodide or regiospecific decarboxylative alkylation[8] of the methoxycarbonylated intermediates **4** with the bis(sulfone)-ester **8** in the presence of Pd(0) catalyst as a key step These synthetic routes required additional deprotecting reactions to obtain the final product after the alkylation reactions In order to introduce directly a butanoate chain, zinc-copper reagents[9] were selected as the most suitable organometallics to construct the isocarbacyclin framework Here, we report the short synthesis of isocarbacyclin by the use of several bicyclic synthons, *i e* , the phosphates **5** and the tosylates **6**, *via* regioselective $S_N2'$ alkylation with the ester-containing zinc-copper (Zn-Cu) reagents **9** prepared from methyl 4-iodobutanoate



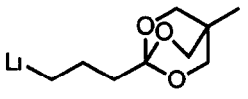

Prostacyclin (Prostaglandin $I_2$) **1**




Isocarbacyclin **2**



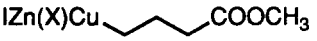
**3:** R = H
**4:** R = MeOCO
**5a:** R = $(EtO)_2P(=O)$
**5b:** R = $(PhO)_2P(=O)$
**6:** R = $p$-$MeC_6H_4SO_2$



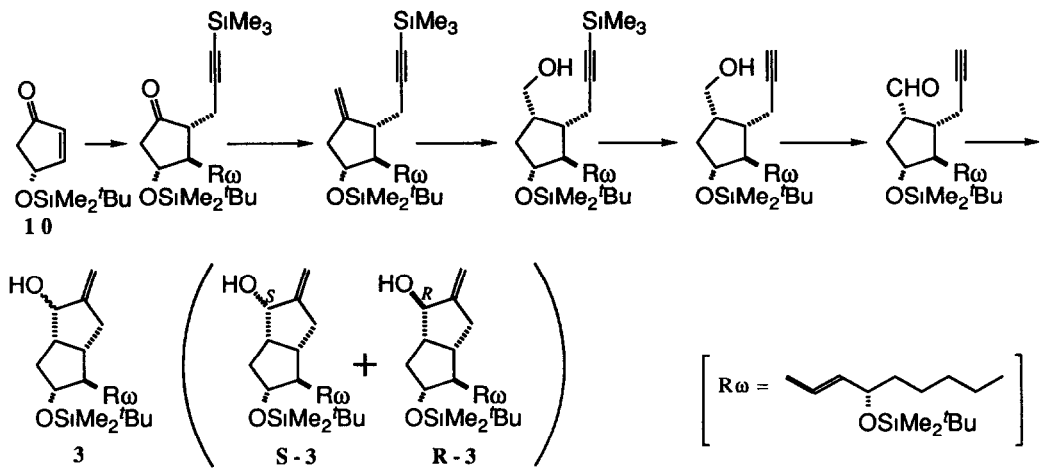
**7**

$(PhSO_2)_2CHCH_2CH_2COOCH_3$

**8**

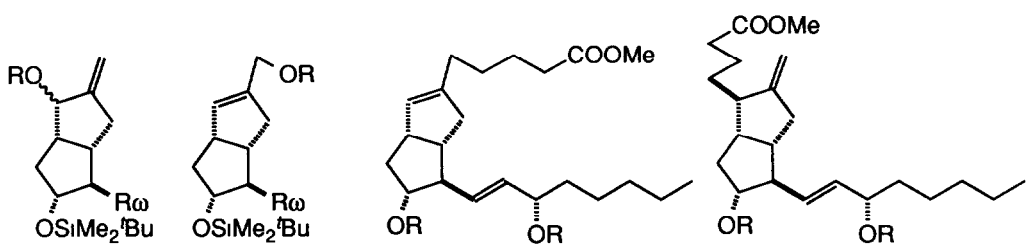


**9a:** X = CN
**9b:** X = I
**9c:** X = Br
**9d:** X = Cl



**10**

**Scheme 1** Synthetic rout to the key intermediate **3**



**11:** X=MeCO **13:** X=H
**12:** X=$Me_3CCO$ **14:** X=$(EtO)_2P(=O)$

**21:** R=$OSiMe_2{}^tBu$
**23:** R=H

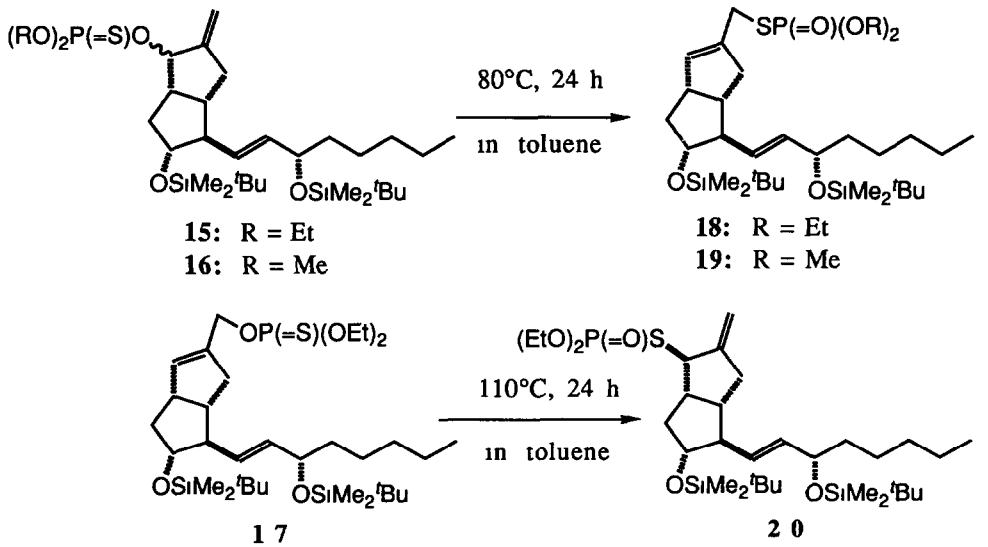
**22:** R=$OSiMe_2{}^tBu$
**24:** R=H

Previously, we reported[6h,6m] the preparation of the bicyclic allylic alcohol **3** as a key intermediate starting from the protected chiral (*R*)-4-hydroxy-2-cyclopentenone **10** in six steps as follows (1) conjugate addition of an organocuprate to the cyclopentenone **10** followed by a silyl protected iodoalkyne trapping of the resulting enolate,[10] (2) methylenation of the resulting cyclopentanone, (3) stereoselective hydroboration of the exocyclic methylene group, (4) desilylation of the protected acetylene, (5) oxidation of the alcohol to the aldehyde, (6) reductive cyclization of the γ-ethynyl aldehyde (Scheme 1) The final reductive cyclization reaction resulted in the formation of the bicyclic allylic alcohol **3** as a mixture of two diastereomers, **S-3** and **R-3**, in a *ca* 1 3 ratio The product mixture of **3** is separable into each diastereomer, **S-3** and **R-3**, by chromatography The phosphorylated bicyclic allylic alcohols **5** (**S-5** and **R-5**) were the first substrates for the zinc-copper alkylation reaction Phosphorylation of the bicyclic alcohols **3** (**S-3** and **R-3**) was achieved by treatment of the alcohols with *n*-butyllithium ($^n$BuLi) followed by reaction of the resulting lithium alkoxide with diethyl chlorophosphate in tetrahydrofuran (THF) to yield the corresponding allylic phosphates **5a** (85%), **S-5a** (76%), and **R-5a** (86%), respectively The product **5a** was found to be constituted of **S-5a** and **R-5a** with the corresponding ratio to the initial ratio of the starting alcohol isomers Similarly, phosphorylation of **3** with diphenyl chlorophosphate afforded the corresponding phosphate **5b** (80%) Acylation of **3** with acetic anhydride, pivaloyl chloride, or methyl chloroformate was accomplished to give acetate **11** (90%), pivalate **12** (77%), or methoxycarbonate **4** (88%) as a diastereomeric mixture Thus, the obtained substrates **4**, **5**, **11**, and **12** were submitted to the subsequent reaction with the zinc-copper reagents **9**

The bicyclic phosphates were reacted with the functionalized zinc-copper reagents **9** Methyl 4-iodobutanoate was treated with zinc powder activated with 1,2-dibromoethane and then chlorotrimethylsilane according to Knochel procedure[9b] to generate an organozinc reactant The supernatant obtained as a solution of the organozinc reagent was subsequently treated with a variety of cuprous salts and lithium chloride (LiCl) to result in the *in situ* formation of the Zn-Cu reagents **9** Firstly, diastereomeric **5a** (**S-5a** **R-5a** = *ca* 1 3) was alkylated with the Zn-Cu reagent **9a** obtained by using cuprous cyanide (CuCN) to afford a mixture of the γ-adduct **21** as a major product and the α-adduct **22** as a minor one in 95% yield (entry 1) The mixture of **21** and **22** was treated with tetrabutylammonium fluoride to obtain a desilylated mixture containing the corresponding products **23** and **24** The product ratio of **23** and **24** was determined to be 98 7 1 3 by HPLC measurement This indicated that the reaction proceeded with high $S_N2'$ regioselectivity This result was compatible with that calculated by their olefinic protons of **21** and **22** in the NMR spectrum Alkylation of other substrates obtained above were also studied using the Zn-Cu reagents prepared by several cuprous salts The results are summarized in Table 1 Alkylation of **5a** by using cuprous halides (CuI, CuBr, CuCl) instead of CuCN in the presence of LiCl were examined to result in higher regioselective formation (more than 99%) of **21** as a γ-adduct in high yields (entries 2, 3, and 4) These alkylations of the phosphorylated derivative **5a** with the ester-containing Zn-Cu reagents **9** proceeded with the highest regioselectivity among other reported $S_N2'$ alkylations[9a,9b, 11, 12] Moreover, effects of cuprous salts on the γ-regioselectivity in the present zinc-copper alkylation reaction were different from those in the copper(I)-

catalyzed cross-coupling reactions of allylic carboxylates with $sp^3$-Grignard reagents, where CuCN showed γ-regioselectivity and CuCl did α-one[12] Cuprous salts such as CuI-tributylphosphine, CuBr-$Me_2S$, 1-pentynylcopper(I) in the presence of hexamethylphosphorous triamide were ineffective in the allylic alkylation reaction of the phosphate **5a** The reaction of diastereomeric **S-5a** prepared from **S-3a** showed complete regioselectivity by using CuCl in comparison with **R-5a** (entries 5 and 6) This alkylation reaction was also performed in one-pot sequence starting from the allylic alcohol **3** through *in situ* formation of the phosphonate intermediate **5a**, to furnish alkylated **23** with similar high regioselectivity (entry 7) Reaction of the phenyl derivative **5b** in the presence of CuCl brought about similar selectivity (entry 8) Instead of phosphorylated synthons, the methoxycarbonyl synthon **4** gave the poor alkylated products with similar regioselectivity, whereas acetyl and pivaloyl synthons **11** and **12** gave no alkylated products recovering the starting materials (entries 9, 10, and 11)

To investigate the $S_N2'$ regioselectivity of this zinc-copper alkylation, the allylic isomer **14** was prepared from the corresponding alcohol **13** and was allowed to react with the Zn-Cu reagents, **9a** and **9d**, obtained from both CuCN and CuCl In both cases, the γ-adduct **22** was obtained as a major product showing $S_N2'$ regioselectivity (entries 12 and 13) This $S_N2'$ selectivity for the isomeric **14** was lower than 90%, probably due to both more difficult attack of the zinc-copper reagent to the γ-position of the synthon **14** and difficult elimination of the primary phosphoryloxy group from **14** than in the case of **5a** In this reaction, the γ-adduct **22** and desilylated product **24** were homogeneous by HPLC and NMR analyses indicating the preferential formation of a single isomer presumably with *R*-configuration



Further examination of the regioselective allylic alkylation with Zn-Cu reagents was carried out on the sulfur-containing phosphates A similar phosphorylation of diastereomeric **3** with diethyl chlorothiophosphate in THF after treatment of **3** with $^{n}$BuLi provided desired thiophosphate **15** (86%) accompanied by a small amount of rearranged isomer **18** (4%) Heating of resulting thiophosphate **15** in toluene at 80°C for 24 h gave **18** (88%) as a [3,3]-sigmatropic rearrangement product This type of thermally [3,3]-sigmatropic rearrangement was reported by Pudovik and Aladzheva in the cases of crotyl or methallyl thiophosphate system [13] In a similar manner, the thiophosphate **16** was obtained in 77% yield from diastereomeric **3** and the thiophosphate **17** from **13** in 98% yield The product **16** was converted into thermally rearranged

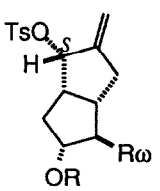
**Table 1. Alkylation of Phosphates and Esters with Zinc-Copper Reagents**

| entry | substrate | CuX | condition | yield(%) | 21(23*) | 22(24*) |
|---|---|---|---|---|---|---|
| 1 | **5a** | CuCN | 0°C, 2 h, then r t, 18 h | 95% | 98 7 | 1 3 |
| 2 | **5a** | CuI | 0°C, 2 h, then r t, 18 h | 94% | 99 3 | 0 7 |
| 3 | **5a** | CuBr | 0°C, 1 h, then r t, 4 h | 97% | 99 8 | 0 2 |
| 4 | **5a** | CuCl | 0°C, 2 h, then r t, 3 h | 97% | 99 7 | 0 3 |
| 5 | **S-5a** | CuCl | 0°C, 2 h, then r t, 3 h | 97% | 100 | N D |
| 6 | **R-5a** | CuCl | 0°C, 2 h, then r t, 18 h | 96% | 98 3 | 1 7 |
| 7 | **(5a)** | CuCl | 0°C, 2 h, then r t, 18 h | 84%** | 99 5 | 0 5 |
| 8 | **5b** | CuCl | r t, 3 h | 94% | 98 3 | 1 7 |
| 9 | **4** | CuCl | r t, 18 h | 68% | 96 8 | 3 2 |
| 10 | **11** | CuCl | 0°C, 1 5 h, then r t, 20 h | trace | trace | N D |
| 11 | **12** | CuCl | 0°C, 1 5 h, then r t, 20 h | trace | trace | N D |
| 12 | **14** | CuCN | 0°C, 1 h, then r t, 3 days | 42% | 16 8 | 83 2 |
| 13 | **14** | CuCl | 0°C, 1 h, then r t., 8 h | 86% | 12 7 | 87 3 |
| 14 | **15** | CuCl | r t, 3 h | 90% | 97 9 | 2 1 |
| 15 | **16** | CuCl | 0°C, 2 h, then r t, 18 h | 91% | 96 4 | 3 6 |
| 16 | **20** | CuCl | 0°C, 2 h, then r t, 8 h | 95% | 98 4 | 1 6 |
| 17 | **17** | CuCl | 0°C, 2 h, then r t, 8 h | 84% | 11 9 | 88 1 |
| 18 | **18** | CuCl | 0°C, 2 h, then r t, 18 h | 95% | 15 8 | 84 2 |
| 19 | **19** | CuCl | 0°C, 2 h, then r t, 18 h | 96% | 14 0 | 86 0 |

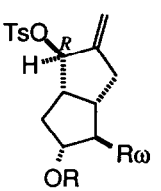
* Product ratio determined by HPLC measurement of **23** and **24** after desilylation
** Yield based on the starting alcohol by one-pot sequence

product **19** (97%) by heating in toluene The isomer **17** was also heated in toluene under reflux for 24 h to obtain thermally rearranged product **20** (63%) as a homogeneous product The Zn-Cu reagent **9d** prepared by use of CuCl was allowed to react with thiophosphoates **15** and **16** as well as rearranged phosphorylthio derivative **20** to give expected product **21** in high yields with high $S_N2'$ regioselectivities (entries 14, 15, and 16) On the other hand, either thiophosphoate **17** or rearranged products **18, 19** gave the γ-adduct **22** in good yields with good $S_N2'$ regioselectivity (entries 17, 18, and 19)

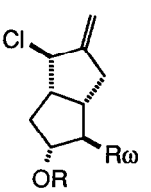
Sulfonates were other substrates for the zinc-copper alkylation Treatment of the diastereomeric allylic alcohol **3** (**S-3** **R-3** = *ca* 1 3) with tosyl chloride after lithium alkoxidation with $^n$BuLi resulted in the *in situ* formation of the tosylate **6** accompanied by a small amount of the chlorides **25** and **26** (*vide infra*) detected by TLC [9a] Attempts to isolate the resultant tosylate **6** were unsuccessful because of its labile property Therefore, the alkylation of the crude tosylate **6** with the Zn-Cu reagent **9a** was performed to obtain an alkylated mixture of **21** and **22** (90 10) in 75% yield (entry 20) Similar results were obtained for each diastereomer **S-6** or **R-6** *in situ* generated from **S-3** or **R-3**, respectively (entries 21 and 22) The $S_N2'$ regioselectivities for the tosylates (**6**, **S-6**, and **R-6**) were lower than 90% Since the allylic chlorides were also considered to be the substrates for the Zn-Cu alkylation, chlorination of each allylic alcohol **S-3** or **R-3** and the reactions of the resulting chlorides with the Zn-Cu reagents were subsequently studied The allylic alcohol **R-3** was chlorinated with tosyl chloride in the presence of 4-(dimethylamino)pyridine to give the labile chloride **25** accompanied by a small amount of the chloride **26** as an 85 15 mixture On the other hand, the epimeric alcohol **S-3** was chlorinated in a similar manner to result in the major formation of **26** (**25** **26** = 10 90) Chlorination of **13** in a similar manner afforded the chloride **26** as a major product (**25** **26** = 4 96) Thus, the isolated chloride **25** was alkylated with the Zn-Cu reagent **9a** prepared by using CuCN to give the alkylated product in a 94% yield, which included the product **21** as a major product (**21** **22** = 97 3) The other primary chloride **26** was similarly alkylated to obtain the γ-adduct **22** in 95% yield as a major product (**21** **22** = 18 82) It was considered that the poor regioselectivity for the *in situ* generated diastereomeric tosylate **6** might be due to the undesired formation of **22** from the concomitantly formed chloride **26** *via* the tosylation of **3**



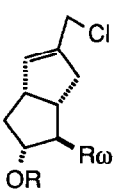

**S-6**



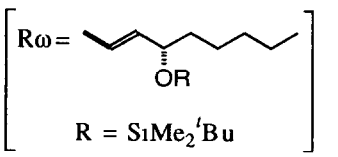

**R-6**




**25**




**26**



According to Yoshida's report[9a] and other,[12] the secondary chloride **25** was expected to be alkylated with the zinc reagent in the presence of catalytic CuCN to give the $S_N2'$ alkylated product **21**. However, this type of the catalytic alkylation resulted in the poor $S_N2'$ regioselectivity affording a mixture of the alkylated product **21** and **22** in a 40:60 ratio in 71% yield. Previously, Shibasaki *et al.* reported that allylic alkylations of a bromo derivative corresponding to **26** with several 3-butenylated organometallics were found to result in poor regioselectivities ($\alpha:\gamma$ = 1:10 to 3:1), and that alkylation of the acetate of **13** with the Gilman reagent generated from 3-butenyllithium and CuI afforded the desired α-adduct (*ca.* 90%) together with a small amount of the undesired γ-adduct (*ca.* 3%) in a highly selective manner.[6f] Yamamoto *et al.* also reported that reactions of allylzinc bromides with allylphosphates in the presence of CuCN/2LiCl proceeded in a similar $S_N2'$ fashion with high regioselectivities.[14]

In conclusion, it was found that 2-phosphorylated bicyclic synthons as well as sulfur-containing phosphates were good substrates for the regioselective alkylation of the zinc-copper reagent to construct the protected isocarbacyclin skeleton in excellent yields. The *in situ* generated 2-tosyl and the 2-chloro synthons were also substrates for the alkylations under similar conditions. These highly regioselective alkylation reactions of the phosphate derivatives with the Zn-Cu reagents provides an effective way for new carbon-carbon bond formation at the γ-position of allylic alcohols.

**Table 2. Alkylation of Tosylates and Chlorides with Zinc-Copper Reagents**

| entry | substrate | CuX | condition | yield(%) | 21(23*) | 22(24*) |
|---|---|---|---|---|---|---|
| 20 | (**6**) | CuCN | 0°C, 2 h | 75%** | 90 | 10 |
| 21 | (**S-6**) | CuCN | 0°C, 3 h | 80%** | 87 | 13 |
| 22 | (**R-6**) | CuCN | 0°C, 2.5 h | 71%** | 86 | 14 |
| 23 | **25** | CuCN | 0°C, 2 h | 94% | 97 | 3 |
| 24 | **26** | CuCN | 0°C, 2 h | 95% | 18 | 82 |
| 25 | **25** | cat CuCN*** | 60°C, 3 h | 71% | 40 | 60 |

* Product ratio determined by HPLC measurement of **23** and **24** after desilylation.

** Yield based on the starting alcohol by one-pot sequence.

*** Procedure according to the cited method.[9a]

## Experimental

IR spectra were recorded on a JASCO A102 spectrometer $^1$H- and $^{13}$C-NMR spectra were obtained on a JEOL JNM-GX400 (400 MHz) or HITACHI R-90H (90 MHz) spectrometer Chemical shifts and coupling constants (J) are given in δ (ppm) relative to internal tetramethylsilane and Hz, respectively The following abbreviations are used s (singlet), d (doublet), t (triplet), m (multiplet), b (broad) Mass spectra (MS) were taken at 70 eV on a HITACHI M-80B mass spectrometer Optical rotations were measured on a Union Giken PM-101 automatic polarimeter For high-performance liquid chromatography (HPLC) analysis, a Shimadzu Model LC-6A equipped with a Shimadzu SPD-6A UV detector (210 nm) and a Shimadzu C-R3A chromatopac was employed Silica gel column chromatography was performed using Daiso gel IR-60 silica gel Thin-layer chromatography (TLC) was performed using Merck silica gel (Kiesel gel 60 $F_{254}$) analytical plate The plates were sprayed with a solution of 2% *p*-anisaldehyde in 5% ethanolic sulfuric acid and then heated until the spots became clearly visible All reactions were carried out under nitrogen Solvents for reactions were purified if necessary before use by distillation from suitable drying agents Solvents for extraction and chromatography were GR grades

**Preparation of (1*S*,2*R*,3*R*,5*S*)-3-*t*-butyldimethylsilyloxy-2-[(*S*,*E*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-6-methoxycarbonyloxy-7-methylenebicyclo[3.3.0]octane (4).**

Methyl chloroformate (567 mg, 6 0 mmol) was added at 0°C to a mixture of diastereomeric **3** (1 16 g, 2 0 mmol) and pyridine (10 ml) in $CH_2Cl_2$ and the resulting mixture was stirred at 0°C for 1 h Saturated aqueous $NH_4Cl$ solution was added and then extracted with EtOAc (3 × 100 ml) The combined extracts were washed with saturated aqueous $KHSO_4$ solution, saturated aqueous $NaHCO_3$ solution, and then brine Drying ($MgSO_4$), filtration, and evaporation of the solvents gave a crude oily product, which was chromatographed on silica gel (50 g) eluting with hexane-EtOAc (20 1) to provide **4** (996 mg, 1 76 mmol, 88%) as a diastereomeric mixture, $R_f$ 0 49 (9 1 hexane/EtOAc), IR (neat) 3080, 1750, 1665, 1265, 1120, 955, 925, 850, 835, 770 cm$^{-1}$, $^1$H-NMR ($CDCl_3$) δ 0 02 (s, 12H), 0 86 (s, 9H), 0 89 (s, 9H), 0 8-3 0 (m, 18H), 3 77 (s, 3H), 3 5-3 9 (m, 1H), 3 9-4 2 (m, 1H), 4 9-5 4 (m, 3H), 5 4-5 6 (m, 2H), MS (m/z) 551 ($M^+$-15), 509 ($M^+$-57), 433, 359, 319, 227, 171, 133, 131, 73, High-resolution MS for $C_{27}H_{49}O_5Si_2$ ($M^+$-$^t$Bu) Calcd m/z 509 3116 , Found 509 3120

**Preparation of (1*S*,2*R*,3*R*,5*S*)-3-*t*-butyldimethylsilyloxy-2-[(*S*,*E*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-6-diethoxyphosphoryloxy-7-methylenebicyclo[3.3.0]octane (5a)**

A 1 50 M hexane solution of $^n$BuLi (3 40 ml, 5 10 mmol) was added at -78°C to a stirred solution of a diastereomeric mixture (6*S* 6*R* = *ca* 1 3) of (1*S*,2*R*,3*R*,5*S*)-3-*t*-butyldimethylsilyloxy-2-[(*S*,*E*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-6-hydroxy-7-methylenebicyclo[3 3 0]octane (**3**) (2 37 g, 4 66 mmol) in THF (40 ml), and the resulting mixture was stirred at -78°C for 10 min Diethyl chlorophosphate (1 21 g, 7 0 mmol) was then added at -78°C to the resulting lithium alkoxide solution, and the mixture was stirred at 0°C for 2 h The reaction mixture was poured into saturated aqueous $NH_4Cl$ solution (100 ml) and the organic layer was taken up in EtOAc (100 ml) The organic layer was separated and aqueous layer was extracted twice with EtOAc (2 × 50 ml) The combined organic extracts were washed with brine (100 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to leave a crude product, which was separated by silica gel column chromatography (200 g) with a 4 1 and then 3 1 mixture of hexane and EtOAc as eluants, to give phosphoate **5a** (2 55 g, 3 96 mmol, 85%) as a diastereomeric mixture (6*S* 6*R* = *ca* 1 3), $R_f$ 0 33 (2 1 hexane/EtOAc), IR (neat) 3080, 1260, 1105, 1035, 1000, 975, 900, 855, 835, 775 cm$^{-1}$, $^1$H-NMR ($CDCl_3$) δ 0 02 (s, 12H), 0 84 (s, 9H), 0 90 (s, 9H), 0 8-3 0 (m, 18H), 1 38 (t × 2, 6H, J = 7 Hz), 3 5-4 4 (m, 6H), 4 6-4 8 (bd, 1H, J = 7 Hz), 4 9-5 35 (m, 2H), 5 4-5 53 (m, 2H), MS (m/z) 629 ($M^+$-15), 587 ($M^+$-57), 451, 433, 429, 359, 229, 227, 215, 211, 75, 73, High-resolution MS for $C_{29}H_{56}O_6PSi_2$ ($M^+$-$^t$Bu) Calcd m/z 587 3350, Found 587 3350

**Preparation of (1*S*,2*R*,3*R*,5*S*,6*S*)-3-*t*-butyldimethylsilyloxy-2-[(*S*,*E*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-6-diethoxyphosphoryloxy-7-methylenebicyclo[3.3.0]octane (S-5a).**

The titled compound (**S-5a**) was also prepared in 76% yield with a similar procedure using the less polar 6*S*-isomer (**S-3**, 115 mg, 0 226 mmol, $R_f$ 0 48, 4 1 hexane/EtOAc), $^n$BuLi (1 50 M hexane solution, 0 18 ml, 0 27 mmol), and diethyl chlorophosphate (59 mg, 0 34 mmol) in THF (5 ml), $[\alpha]_D^{25}$ +37 0° (*c* 1 99, MeOH), $^1$H-NMR ($CDCl_3$) δ 0 02 (s, 12H), 0 86 (s, 9H), 0 89 (s, 9H), 0 8-3 0 (m, 18H), 1 34 (t × 2, 6H, J = 7 Hz), 3 5-4 4 (m, 6H), 4 85-5 3 (m, 3H), 5 4-5 6 (m, 2H), $^{13}$C-NMR ($CDCl_3$) δ -4 8, -4 7, -4 5, -4 3, 14 0, 16 1, 16 2, 18 1, 18 2, 22 6, 25 1, 25 9, 31 9, 33 7, 34 5, 38 6, 40 3, 41 5, 57 6, 63 8, 63 9, 73 2, 77 6, 79 8, 79 9, 108 6, 130 4, 135 0, 148 2, 148 4

**Preparation of (1*S*,2*R*,3*R*,5*S*,6*R*)-3-*t*-butyldimethylsilyloxy-2-[(*S*,*E*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-6-diethoxyphosphoryloxy-7-methylenebicyclo[3.3 0]octane (R-5a).**

The 6*R*-epimer (**R-5a**) was analogously prepared in 86% yield using the more polar 6*R* alcohol (**R-3**, 318 mg, 0 625 mmol, $R_f$ 0 43), $^n$BuLi (0 5 ml, 0 75 mmol), and diethyl chlorophosphate (162 mg, 0 938 mmol) in THF (5 ml), $[\alpha]_D^{25}$ -11 1° (*c* 1 68, MeOH), $^1$H-NMR ($CDCl_3$) δ 0 02 (s, 12H), 0 86 (s, 9H), 0 89(s, 9H), 0 8-3 0 (m, 18H), 1 32 (t × 2, 6H), 3 6-4 5 (m, 6H), 4 6-4 85 (d, 1H, J = 7 Hz), 5 12 (bs, 1H), 5 27 (bs, 1H), 5 4-5 6 (m, 2H), $^{13}$C-NMR ($CDCl_3$) δ -4 8, -4 7, -4 6, -4 3, 14 0, 16 0, 16 2, 18 1, 18 3, 22 6, 25 2, 25 9, 26 0, 31 9, 35 4, 38 6, 38 7, 43 1, 45 7, 45 8, 56 7, 63 6, 63 7, 73 2, 77 8, 86 8, 86 9, 112 7, 130 5, 135 1, 149 0, 149 1,

**Preparation of (1*S*,2*R*,3*R*,5*S*)-3-*t*-butyldimethylsilyloxy-2-[(*S*,*E*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-6-diphenoxyphosphoryloxy-7-methylenebicyclo[3 3.0]octane (5b).**

The phosphorylation reaction was conducted with a similar procedure (r t , 20 h) to that described in the syntheses of a series of **5a** by using diastereomeric **3** (452 mg, 0 89 mmol) in THF (10 ml), $^n$BuLi (1 50 M hexane solution, 0 8 ml, 1 2 mmol), and diphenyl chlorophosphate (403 mg, 1 5 mmol) The crude reaction product obtained after extractive work-up and solvent removal was subjected to silica gel column chromatography (50 g) with 10 1 mixture of hexane and EtOAc as eluant to give **5b** (525 mg, 0 71 mmol, 80%) as a diastereomeric mixture, $R_f$ 0 48 (4 1 hexane/EtOAc), IR (neat) 3080, 1590, 1490, 1460, 1285, 1250, 1190, 1110, 1045, 1005, 945, 835, 770, 685 cm$^{-1}$, $^1$H-NMR ($CDCl_3$) δ 0 04 (s, 12H), 0 85 (s, 9H), 0 88 (s, 9H), 0 8-3 0 (m, 18H), 3 5-3 9 (m, 1H), 4 0-4 3 (m, 1H), 4 8-5 3 (m, 3H), 5 4-5 5 (m, 2H), 7 0-7 5 (m, 10H), MS (m/z) 725 ($M^+$-15), 683 ($M^+$-57), 551, 439, 433, 419, 359, 325, 307, 227, 94, 73, High-resolution MS for $C_{36}H_{68}O_6PSi_2$ ($M^+$-$^t$Bu) Calcd m/z 683 4288, Found 683 4168

**Preparation of (1*S*,5*S*,6*R*,7*R*)-2-acetoxy-7-*t*-butyldimethylsilyloxy-6-[(*S*,*E*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-3-methylenebicyclo[3.3.0]octane (11).**

To a stirred solution of diastereomeric **3** (278 mg, 0 547 mmol) in pyridine (2 ml), acetic anhydride (1 ml) was added at 0°C After being stirred at r t for 20 h, MeOH (2 ml) was added to the mixture, and the resulting mixture was stirred at the same temperature for 30 min Ethyl acetate (100 ml) was added and the organic layer was washed with saturated aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and then brine The filtered organic layer was dried ($MgSO_4$), and concentrated *in vacuo* to leave an oily residue, which was separated by silica gel column chromatography (30 g) with a 10 1 mixture of hexane and EtOAc to give acetate **11** (270 mg, 0 49 mmol, 90%) as a diastereomeric mixture, $R_f$ 0 62 (9 1 hexane/EtOAc), IR (neat) 3100, 1745, 1670, 1250, 1240, 1120, 1060, 1020, 970, 855, 835, 775 cm$^{-1}$, $^1$H-NMR ($CDCl_3$) δ 0 02 (s, 12H), 0 84 (s, 9H), 0 86 (s, 9H), 0 8-3 0 (m, 18H), 2 01 (s, 3H), 3 5-3 9 (m, 1H), 4 0-4 3 (m, 1H), 4 9-5 3 (m, 3H), 5 35-5 65 (m, 2H), $^{13}$C-NMR ($CDCl_3$) δ -4 9, -4 8, -4 6, -4 3, 14 0, 18 2, 21 3, 22 6, 25 1, 25 8, 25 9, 31 8, 35 9, 38 6, 39 0, 43 3, 44 9, 56 4, 73 2, 77 8, 83 4, 112 6, 130 5, 135 0, 148 9, 170 9, MS (m/z) 535 ($M^+$-15), 493 ($M^+$-57), 433, 355, 319, 227, 117, 73, High-resolution MS for $C_{27}H_{49}O_4Si_2$ ($M^+$-$^t$Bu) Calcd m/z 493 3167, Found 493 3191

**Preparation of (1*S*,2*R*,3*R*,5*S*)-3-*t*-butyldimethylsilyloxy-2-[(*S*,*E*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-6-methylene-7-pivaloyloxybicyclo[3.3.0]octane (12).**

To a stirred solution of diastereomeric **3** (508 mg, 1 0 mmol) in pyridine (3 ml), pivaloyl chloride (603 mg, 5 0 mmol) was added at 0°C and the resulting mixture was stirred at r t for 20 h The reaction mixture was poured into saturated aqueous $KHSO_4$ and the organic layer was taken up in EtOAc (100 ml) The separated organic layer was washed with saturated aqueous $NaHCO_3$ and then brine, dried ($MgSO_4$), and evaporated under reduced pressure to afford a crude product The residual oil was subjected to silica gel column chromatography (30 g) with hexane-EtOAc (30 1) to yield pivalate **12** (458 mg, 0 774 mmol, 77%) as a diastereomeric mixture, $R_f$ 0 75 (9 1 hexane/EtOAc), IR (neat) 3100, 1735, 1670, 1280, 1260, 1160, 1120, 970, 855, 835, 775 $cm^{-1}$, $^1$H-NMR ($CDCl_3$) δ 0 02 (s, 12H), 0 86 (s, 9H), 0 89 (s, 9H), 1 18 (s, 9H), 0 8-2 9 (m, 18H), 3 5-3 9 (m, 1H), 4 0-4 3 (m, 1H), 4 9-5 4 (m, 3H), 5 4-5 6 (m, 2H), $^{13}$C-NMR ($CDCl_3$) δ -4 8, -4 7, -4 6, -4 3, 14 0, 18 1, 18 2, 22 6, 25 1, 25 9, 26 0, 26 5, 27 1, 27 2, 31 9, 36 0, 38 6, 39 0, 43 2, 44 9, 56 4, 73 2, 77 9, 83 1, 112 3, 130 6, 135 0, 149 0, 178 4, MS (m/z) 577 ($M^+$-15), 535 ($M^+$-57), 433, 359, 317, 287, 227, 201, 159, 73, High-resolution MS for $C_{30}H_{55}O_4Si_2$ ($M^+$-$^t$Bu) Calcd m/z 535 3636, Found 535 3631

**Preparation of (1*S*,5*S*,6*R*,7*R*)-7-*t*-butyldimethylsilyloxy-6-[(*S*,*E*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-3-(diethoxyphosphoryloxymethyl)bicyclo[3.3.0]-2-octene (14)**

Diethyl chlorophosphate (120 mg, 0 7 mmol) was added at r t to a stirred solution of (1*S*,5*S*,6*R*,7*R*)-7-*t*-butyldimethylsilyloxy-6-[(*S*,*E*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-3-(hydroxymethyl)bicyclo[3 3 0]-2-octene (**13**, 171 mg, 0 337 mmol) and pyridine (0 5 ml) in $CH_2Cl_2$, and the resulting mixture was stirred at the same temperature for 18 h Ethyl acetate (100 ml) was added to the reaction mixture and the resulting organic layer was washed with saturated aqueous $KHSO_4$ solution, and then saturated aqueous $NaHCO_3$ solution The separated organic layer was dried over $MgSO_4$, filtered, and evaporated to afford a crude product, which was chromatographed on silica gel (30 g) using a 4 1 and then 3 1 mixture of hexane and EtOAc as eluants, providing titled compound **14** (184 mg, 0 286 mmol, 85%) as a colorless oil, $R_f$ 0 22 (2 1 hexane/EtOAc), $[\alpha]_D^{25}$ -18 4° (*c* 1 03, MeOH), IR (neat) 1255, 1110, 1035, 970, 855, 835, 770 $cm^{-1}$, $^1$H-NMR ($CDCl_3$) δ 0 02 (s, 12H), 0 84 (s, 9H), 0 86 (s, 9H), 0 8-3 2 (m, 18H), 1 2 (t × 2, 6H, J = 7 Hz), 3 5-4 3 (m, 6H), 4 4-4 6 (d, 2H, J = 7 Hz), 5 4-5 55 (m, 2H), 5 62 (bs, 1H), $^{13}$C-NMR ($CDCl_3$) δ -4 7, -4 6, -4 5, -4 2, 14 1, 16 1, 16 3, 18 1, 18 3, 22 7, 25 2, 26 0, 32 0, 37 6, 38 8, 40 2, 43 7, 45 6, 57 2, 63 8, 63 9, 66 2, 66 3, 73 4, 78 1, 130 8, 133 5, 135 1, 137 0, 137 2, MS (m/z) 587 ($M^+$-57), 359, 309, 287, 227, 211, 183, 155, 127, 99, 75, 57, High-resolution MS for $C_{29}H_{56}O_6PSi_2$ ($M^+$-$^t$Bu) Calcd m/z 587 3350, Found 587 3278

**Preparation of (1*S*,2*R*,3*R*,5*S*)-3-*t*-butyldimethylsilyloxy-2-[(*S*,*E*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-6-diethoxythiophosphoryloxy-7-methylenebicyclo[3 3 0]octane (15).**

The phosphorylation reaction was conducted with a similar procedure (r t, 20 h) to that described in the preparation of **5a** by using diastereomeric **3** (397 mg, 0 782 mmol) in THF (10 ml), $^n$BuLi (1 50 M hexane solution, 0 63 ml, 0 938 mmol), and diethyl chlorothiophosphate (192 mg, 1 02 mmol) instead of diethyl chlorothiophosphate The residual oil obtained after extractive work-up and evaporation was separated by silica gel column chromatography (50 g) eluting with a 10 1 and then 3 1 mixture of hexane-EtOAc to yield less polar **15** (446 mg, 0 676 mmol, 86%) as a diastereomeric mixture accompanied by more polar (1*S*,5*S*,6*R*,7*R*)-7-*t*-butyldimethylsilyloxy-6-[(*S*,*E*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-3-(diethoxyphosphorylthiomethyl)bicyclo[3 3 0]-2-octene (**18**) (19 mg, 0 029 mmol, 4%) Less polar **15** was found to be converted into more polar **18** with silica gel on TLC plate **15**, $R_f$ 0 67 (4 1 hexane/EtOAc), IR (neat) 3080, 1665, 1255, 1100, 1025, 970, 900, 835, 775 $cm^{-1}$, $^1$H-NMR ($CDCl_3$) δ 0 02 (s, 12H), 0 86 (s, 9H), 0 89 (s, 9H), 0 8-3 0 (m, 18H), 1 33 (t × 2, 6H, J = 7 Hz), 3 5-4 7 (m, 6H), 4 7-5 35 (m, 3H), 5 4-5 6 (m, 2H), MS (m/z) 645 ($M^+$-15), 603 ($M^+$-57), 458, 434, 360, 302, 287, 245, 227, 73, High-resolution MS for $C_{29}H_{56}O_5PSSi_2$ ($M^+$-$^t$Bu) Calcd m/z 603 3121, Found 603 3098 **18**, $R_f$ 0 22 (4 1 hexane/EtOAc), $[\alpha]_D^{25}$ +1 3° (*c* 1 54, MeOH), IR (neat) 1255, 1105, 1045, 1020, 965, 905, 835, 775 $cm^{-1}$, $^1$H-NMR ($CDCl_3$) δ 0 02 (s, 12H), 0 86 (s, 9H), 0 89 (s, 9H), 0 8-3 2 (m, 18H), 1 35 (t × 2, 6H, J = 7 Hz), 3 4-3 55 (d, 2H, J = 13 Hz), 3 6-4 5 (m, 6H), 5 4-5 55 (m, 2H), 5 6 (bs, 1H), $^{13}$C-NMR ($CDCl_3$) δ -5 0, -4 8, -4 7, -4 4, 13 9, 15 9, 16 0, 17 9, 18 1, 22 5, 25 1,

25 7, 25 8, 31 3, 31 7, 38 6, 38 7, 39 9, 43 6, 45 5, 56 9, 63 4, 63 5, 73 2, 77 7, 130 5, 133 5, 134 9, 136 7, MS (m/z) 645 ($M^+$-15), 603 ($M^+$-57), 491, 471, 457, 433, 287, 245, 227, 171, 129, 73, High-resolution MS for $C_{29}H_{56}O_5PSSi_2$ ($M^+$-$^t$Bu) Calcd m/z 603 3122, Found 603 3100

**Preparation of (1*S*,2*R*,3*R*,5*S*)-3-*t*-butyldimethylsilyloxy-2-[(*S*,*E*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-6-dimethoxythiophosphoryloxy-7-methylenebicyclo[3.3.0]-octane (16).**

Similar phosphorylation process (r t, 3 h) using diastereomeric **3** (508 mg, 1 0 mmol), $^n$BuLi (0 8 ml, 1 2 mmol), and dimethyl chlorothiophosphate (241 mg, 1 5 mmol) in THF (10 ml) furnished desired product **16** (487 mg, 0 77 mmol, 77%) as a diastereomeric mixture after usual work-up and silica gel column chromatography (60 g, hexane EtOAc = 10 1), $R_f$ 0 56 (4 1 hexane/EtOAc), IR (neat) 3100, 1665, 1255, 1110, 1040, 990, 900, 835, 775 cm$^{-1}$, $^1$H-NMR ($CDCl_3$) δ 0 02 (s, 12H), 0 86 (s, 9H), 0 88 (s, 9H), 0 8-2 9 (m, 18H), 3 6-3 9 (d × 2, 6H, J = 14 Hz), 3 6-4 3 (m, 2H), 4 8-5 4 (m, 3H), 5 4-5 6 (m, 2H), MS (m/z) 617 ($M^+$-15), 575 ($M^+$-57), 443, 433, 429, 301, 287, 227, 199, 75, 73, High-resolution MS for $C_{27}H_{52}O_5PSSi_2$ ($M^+$-$^t$Bu) Calcd m/z 575 2809, Found 575 2584

**Preparation of (1*S*,5*S*,6*R*,7*R*)-7-*t*-butyldimethylsilyloxy-6-[(*S*,*E*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-3-(diethoxythiophosphoryloxymethyl)bicyclo[3.3.0]-2-octene (17).**

Analogous phosphorylation process (r t, 3 h) using **13** (311 mg, 0 612 mmol), $^n$BuLi (0 49 ml, 0 734 mmol), and diethyl chlorothiophosphate (173 mg, 0 918 mmol) in THF (5 ml) provided **17** (396 mg, 0 60 mmol, 98%) after usual work-up followed by purification by silica gel column chromatography (30 g, hexane EtOAc = 19 1), $R_f$ 0 67 (4 1 hexane/EtOAc), $[\alpha]_D^{25}$ -8 7° (*c* 2 42, MeOH), IR (neat) 1255, 1160, 1000, 1020, 970, 835, 775 cm$^{-1}$, $^1$H-NMR ($CDCl_3$) δ 0 02 (s, 12H), 0 86 (s, 9H), 0 89 (s, 9H), 0 8-3 2 (m, 18H), 1 40 (t × 2, 6H, J = 7 Hz), 3 6-3 9 (m, 1H), 3 9-4 7 (m, 7H), 5 4-5 6 (m, 2H), 5 65 (bs, 1H), $^{13}$C-NMR ($CDCl_3$) δ -4 7, -4 6, -4 5, -4 2, 14 1, 15 9, 16 1, 18 1, 18 3, 22 7, 25 3, 26 0, 31 9, 37 7, 38 8, 40 1, 43 6, 45 6, 57 1, 64 4, 66 8, 66 9, 73 4, 78 0, 130 8, 133 6, 135 1, 136 8, 136 8, MS (m/z) 645 ($M^+$-15), 603 ($M^+$-57), 528, 433, 419, 287, 245, 227, 75, 73, High-resolution MS for $C_{29}H_{56}O_5PSSi_2$ ($M^+$-$^t$Bu) Calcd m/z 603 3122, Found 603 3150

**Preparation of 18 by thermal rearrangement of 15**

A stirred solution of **15** (220 mg, 0 333 mmol) in toluene (5 ml) was heated at 80°C for 24 h The reaction mixture was concentrated under vacuum to leave an oily residue, which was chromatographed on silica gel (30 g) with hexane-EtOAc (3 1) to give **18** (193 mg, 0 292 mmol, 88%) The product **18** was identical with the by-product of **18** obtained by the above-mentioned phosphorylation reaction of **3** with diethyl chlorothiophosphate

**Preparation of (1*S*,5*S*,6*R*,7*R*)-7-*t*-butyldimethylsilyloxy-6-[(*S*,*E*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-3-(dimethoxyphosphorylthiomethyl)bicyclo[3.3 0]-2-octene (19) by thermal rearrangement of 16**

A stirred solution of **16** (274 mg, 0 433 mmol) in toluene (10 ml) was heated at 80°C for 24 h Similar work-up and purification to that described above provided rearranged product **19** (265 mg, 0 420 mmol, 97%), $R_f$ 0 23 (4 1 hexane/EtOAc), $[\alpha]_D^{25}$ -0 7° (*c* 2 33, MeOH), IR (neat) 1255, 1110, 1040, 1020, 970, 905, 835, 775 cm$^{-1}$, $^1$H-NMR ($CDCl_3$) δ 0 02 (s, 12H), 0 86 (s, 9H), 0 89 (s, 9H), 0 8-3 3 (m, 18H), 3 4-3 7 (d, 2H, J = 13 Hz), 3 6-4 3 (m, 2H), 3 7-3 9 (d, 6H, J = 13 Hz), 5 4-5 55 (m, 2H), 5 6 (bs, 1H), $^{13}$C-NMR ($CDCl_3$) δ -4 7, -4 6, -4 5, -4 2, 14 1, 18 1, 18 3, 22 7, 25 3, 26 0, 31 5, 31 9, 36 2, 38 8, 40 1, 43 8, 45 8, 53 8, 53 9, 57 1, 73 4, 78 0, 130 7, 134 0, 135 1, 136 9, MS (m/z) 610 ($M^+$-15), 575 ($M^+$-57), 443, 433, 429, 301, 287, 227, 199, 75, 73, High-resolution MS for $C_{27}H_{52}O_5PSSi_2$ ($M^+$-$^t$Bu) Calcd m/z 575 2809, Found 575 2841

**Preparation of (1*S*,2*R*,3*R*,5*S*)-3-*t*-butyldimethylsilyloxy-2-[(*S*,*E*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-6-diethoxyphosphorylthio-7-methylenebicyclo[3 3.0]octane (20) by thermal rearrangement of 17.**

A stirred solution of **17** (264 mg, 0 40 mmol) in toluene (10 ml) was refluxed for 24 h Similar work-up and separation afforded rearranged product **20** (166 mg, 0 251 mmol, 63%) as a diastereomerically almost pure product accompanied by unreacted substrate **17** (74 mg, 0 112 mmol, 28%), $R_f$ 0 33 (4 1 hexane/EtOAc), $R_t$ 20 6 min (Zorbax, hexane THF = 20 1), $[\alpha]_D^{25}$ -6 2° (*c* 2 16, MeOH), IR (neat) 3090, 1660, 1255, 1110, 1045, 1020, 970, 910, 835, 775 $cm^{-1}$, $^1$H-NMR ($CDCl_3$) δ 0 02 (s, 12H), 0 86 (s, 9H), 0 89 (s, 9H), 0 8-3 0 (m, 18H), 1 35 (t × 2, 6H, J = 7 Hz), 3 5-4 4 (m, 7H), 5 05 (bs, 1H), 5 24 (bs, 1H), 5 4-5 55 (m, 2H), $^{13}$C-NMR ($CDCl_3$) δ -4 7, -4 6, -4 5, -4 2, 14 1, 16 0, 16 2, 18 2, 18 3, 22 7, 25 2, 26 0, 31 9, 36 2, 38 7, 41 2, 43 5, 47 8, 48 0, 55 6, 56 5, 63 6, 63 7, 73 3, 77 6, 111 5, 130 4, 135 3, 150 8, MS (m/z) 645 ($M^+$-15), 603 ($M^+$-57), 491, 471, 433, 419, 245, 227, 171, 75, 73, High-resolution MS for $C_{29}H_{56}O_5PSSi_2$ ($M^+$-$^t$Bu) Calcd m/z 603 3122, Found 603 3142

**General procedure for the alkylation of phosphonates with zinc-copper reagents.**

In a 10 ml flask were placed zinc powder (196 mg, 3 0 mmol) and THF (2 5 ml) According to the cited procedure,[9b] to this was added 1,2-dibromoethane (15 μl) and the mixture was heated at 65°C for 1 min The mixture was cooled to r t , and stirred at the same temperature for 30 min Then, chlorotrimethylsilane (20 μl) was added and the mixture was stirred at r t for 30 min To the reaction mixture was added methyl 4-iodobutanoate (570 mg, 2 5 mmol) in THF (2 5 ml), prepared from methyl 4-chlorobutanoate by treatment with NaI in methyl ethyl ketone under refluxing for 10 h, and the resulting mixture was heated at 40°C for 18 h In another 25 ml flask were placed 2 5 mmol of cuprous salt (CuCl, 248 mg, CuBr, 359 mg, CuI, 476 mg, CuCN, 112 mg), anhydrous LiCl (213 mg, 5 0 mmol), and THF (5 ml) To this cooled suspension at 0°C was added a supernatant of the organozinc solution by using a syringe, and the mixture was stirred at 0°C for 30 min To the zinc-copper solution was added at 0°C a solution of a bicyclic substrate (0 20 mmol) in THF (5 ml), and then the reaction mixture was stirred at 0°C for several hours and successively at r t for additional several hours The resulting reaction mixture was poured into saturated aqueous $NH_4Cl$ solution and EtOAc (100 ml) was added for extraction The separated aqueous layer was extracted with EtOAc (2 × 50 ml) The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure The residual oil was subjected to silica gel column chromatography (30 g) eluting with a 19 1 mixture of hexane and EtOAc to give a product fraction ($R_f$ 050, 4 1 hexane/EtOAc) as an isomeric mixture of the α-adduct and the γ-adduct The yield was evaluated on the basis of the isomeric mixture The isomeric ratio of the product was roughly estimated by $^1$H-NMR measurement of this product 11,15-*O*-Bis(*t*-butyldimethylsilyl)-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin $I_1$ methyl ester (**21**), $[\alpha]_D^{25}$ -14 3° (*c* 0 99, MeOH), IR (neat) 1740, 1255, 1110, 1005, 970, 835, 775 $cm^{-1}$, $^1$H-NMR ($CDCl_3$) δ 0 02 (s, 12H), 0 86 (s, 9H), 0 89 (s, 9H), 0 8-3 2 (m, 26H), 3 5-3 8 (m, 1H), 3 63 (s, 3H), 4 0-4 3 (m, 1H), 5 23 (bs, 1H), 5 35-5 6 (m, 2H), $^{13}$C-NMR ($CDCl_3$) δ -4 9, -4 7, -4 6, -4 3, 14 0, 18 1, 18 2, 22 6, 24 7, 25 2, 25 9, 26 2, 27 2, 30 6, 31 8, 34 0, 39 9, 40 7, 43 3, 45 4, 51 5, 57 1, 73 4, 77 9, 128 5, 131 1, 134 6, 141 6, 174 6, MS (m/z) 592 ($M^+$), 577 ($M^+$-15), 561 ($M^+$-31), 535 ($M^+$-57), 521, 329, 303, 171, 147, 75, 73, High-resolution MS for $C_{30}H_{55}O_4Si_2$ ($M^+$-$^t$Bu) Calcd m/z 535 3636, Found 535 3658 (1*S*,2*R*,3*R*,5*S*, 6*R*)-3-*t*-butyldimethylsilyloxy-2-[(*S*,*E*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-6-(3-methoxycarbonylpropyl)-7-methylenebicyclo[3 3 0]octane (**22**), $[\alpha]_D^{25}$ -7 1° (*c* 0 77, MeOH), IR (neat) 3080, 1740, 1660, 1255, 1110, 1005, 970, 835, 775 $cm^{-1}$, $^1$H-NMR ($CDCl_3$) δ 0 02 (s, 12H), 0 86 (s, 9H), 0 89 (s, 9H), 0 8-2 5 (m, 25H), 3 6-3 95 (m, 1H), 3 68 (s, 3H), 4 0-4 2 (m, 1H), 4 7-5 0 (m, 2H), 5 35-5 6 (m, 2H), $^{13}$C-NMR ($CDCl_3$) δ -4 7, -4 5, -4 2, 14 1, 18 2, 18 3, 22 7, 23 2, 25 3, 26 0, 32 0, 34 3, 37 3, 38 8, 42 2, 44 0, 44 9, 51 7, 52 6, 56 7, 73 5, 78 6, 106 7, 131 1, 134 8, 155 4, 174 7, MS (m/z) 577 ($M^+$-15), 535 ($M^+$-57), 403, 328, 309, 279, 149, 132, 105, 75, 57, High-resolution MS for $C_{30}H_{55}O_4Si_2$ ($M^+$-$^t$Bu) Calcd m/z 535 3636, Found 535 3628

To determine these product ratios exactly, each of the products (a mixture of **21** and **22**) was treated at r t for several hours with a 1 0 M solution of tetrabutylammonium fluoride in THF The reaction mixture was diluted with EtOAc (100 ml) and washed with saturated aqueous $KHSO_4$ solution, saturated aqueous $NaHCO_3$, and then brine The aqueous phase was extracted twice with EtOAc (2 × 50 ml) The combined organics were dried ($MgSO_4$), filtered, and evaporated to afford a crude desilylated product ($R_f$ 0 45, 1 4 hexane/EtOAc) including the corresponding desilylated products, 9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin $I_1$ methyl ester (**23**, $R_t$ 21 6 min) and (1*S*,2*R*,3*R*,5*S*,

6*R*)-7-hydroxy-6-[(*S*,*E*)-3-hydroxy-1-octenyl]-2-(3-methoxycarbonylpropyl)-3-methylenebicyclo[3 3 0]octane (**24**, $R_f$ 25 1 min), respectively The crude samples were subjected without further purification to HPLC analysis (Nucleosil, 25 cm × 4 6 mm I D.) using 3% ethanol-hexane as a mobil phase at 0 8 ml/min as a flow rate Each product of **23** and **24** for analysis was further purified by preparative HPLC (YMC-PACK SH-043 S-15 SIL column, 25 cm × 20 mm I D ) eluting with 3% ethanolic hexane (9 9 ml/min) One of the desilylated product, **24**, was found to be a single isomer judged by both HPLC analysis of their crude samples and $^{13}$C-NMR spectrum of an isolated **24**. **23**, $[\alpha]_D^{25}$ +9 5° (*c* 1 02, MeOH), IR (neat) 3360, 3040, 1740, 1435, 1200, 1170, 1090, 1020, 995, 965, 830 cm$^{-1}$, $^1$H-NMR ($CDCl_3$)· δ 0 89 (t, 3H, J = 7 Hz), 1 2-2 5 (m, 24H), 2 9-3 1 (m, 1H), ² 67 (s, 3H), 3 7-3 85 (m, 1H), 4 15-4 25 (m, 1H), 5 27 (bs, 1H), 5 5-5 65 (m, 2H), $^{13}$C-NMR ($CDCl_3$) δ 14 0, 22 6, 24 7, 25 2, 27 2, 30 6, 31 8, 34 0, 37 2, 39 6, 39 7, 44 4, 45 7, 51 5, 58 2, 73 2, 77 2, 128 4, 133 5, 135 6, 141 3, 174 2, MS (m/z) 346 ($M^+$- 18), 328 ($M^+$- 36), 315 ($M^+$-49), 302 ($M^+$- 62), High-resolution MS for $C_{22}H_{34}O_3$ ($M^+$-$H_2O$) Calcd m/z 346.2508, Found 346 2516 **24**, IR (neat) 3360, 3080, 1740, 1660, 1435, 1200, 1170, 1090, 1020, 970, 885 cm$^{-1}$, $^1$H-NMR ($CDCl_3$) δ 0 89 (t, 3H, J = 7 Hz), 1 2-2 9 (m, 24H), 3 67 (s, 3H), 3 6-3 75 (m, 1H), 3 95-4 05 (m, 1H), 4 80 (bs, 1H), 4 85 (bs, 1H), 5 4-5 55 (m, 2H), $^{13}$C-NMR ($CDCl_3$) δ 14 0, 22 6, 23 1, 25 2, 31 8, 34 2, 34 3, 36 8, 37 2, 41 0, 44 6, 44 7, 51 5, 52 6, 57 6, 73 2, 77 2, 107 0, 133 2, 135 5, 154 4, 174 1, MS (m/z) 346 ($M^+$-18), 328 ($M^+$-36), 315 ($M^+$-49), 302 ($M^+$- 62), High-resolution MS for $C_{22}H_{34}O_3$ ($M^+$-$H_2O$) Calcd m/z 346 2508, Found 346 2560

Reagents, conditions, yields, and product ratios for each substrate are summarized in Table 1

**One-pot alkylation of 3 *via* the *in situ* generated phosphate intermediate (5a).**

According to the above-mentioned procedure, phosphorylation reaction was performed by using **3** (1 02 g, 2 0 mmol), $^n$BuLi (1 50 M hexane solution, 1 67 ml, 2 5 mmol), and diethyl chlorophosphate (432 mg, 2 5 mmol) After being stirred at r t for 30 min, to the reaction mixture of the *in situ* generated phosphate **5a** was added at 0°C the Zn-Cu reagent solution which was prepared by a similar manner to general procedure by using zinc powder (392 mg, 6 0 mmol), methyl 4-iodo-butanoate (1 14 g, 5 0 mmol), CuCl (495 mg, 5 0 mmol), and LiCl (425 mg, 10 mmol) in THF (20 ml) The resulting mixture was stirred at 0°C for 2 h and at r t for additional 18 h A similar work-up and chromatographic separation (silica gel 100 g, hexane EtOAc = 19 1) gave a product (995 mg, 1 68 mmol, 84%) involving two adducts The product (136 mg, 0 23 mmol) was treated with a solution of tetrabutylammonium fluoride (2 ml, 2 0 mmol) at r t for 20 h Usual work-up supplied a crude desilylated product The ratio of **23** and **24** was determined to be 99 5 0 5 by HPLC analysis of the crude product mixture

**One-pot alkylation of 3 *via* the *in situ* generated tosylate intermediate (6).**

A 1 50 M hexane solution of $^n$BuLi (0 36 ml, 0 54 mmol) was added at -78°C to a stirred solution of a diastereomeric mixture (6*S* 6*R* = *ca* 1 3) of **3** (200 mg, 0 394 mmol) in THF (2 ml), and the mixture was stirred at -78°C for 10 min To the reaction mixture was added tosyl chloride (90 mg, 0 48 mmol) at 0°C and the resulting mixture was stirred at r t for 3 h TLC analysis of the reaction mixture showed to form tosylates (**6**, $R_f$ 0 33 and 0 38, 9 1 hexane/EtOAc) accompanied by a small amount of the chlorides **25** and **26** ($R_f$ 0 70) The Zn-Cu reagent **9a** (16 ml, 9 6 mmol) prepared in a similar method by use of CuCN was added at 0°C to the reaction mixture, and the resulting mixture was stirred at 0°C for 2 h Similar work-up (quenching, extraction, drying, filtration, and evaporation) gave a crude oily product (344 mg), which was chromatographed on silica gel (50 g) with hexane-EtOAc (1 99) as an eluant to provide γ-alkylated compound **21** (175 mg, 0 296 mmol, 75%) as a major product The product distribution for major **21** and minor **22** was determined as 90 10 by the same HPLC analysis

**One-pot alkylation of S-3 *via* the *in situ* generated tosylate intermediate (S-6).**

The *in situ* genarated tosylate **27** by treatment of the diastereomerically pure **S-3** (83 mg, 0 163 mmol) with $^n$BuLi (0 136 ml, 0 204 mmol), tosyl chloride (44 mg, 0 228 mmol) in THF (1 2 ml) at 0°C for 3 hr was also allowed to react with the above-mentioned solution of **9a** (0 83 M in THF solution, 4 7 ml, 3 9 mmol) Similar work-up and chromatographic separation provided a mixture (77 mg, 0 130 mmol, 80%) of **21** and **22**, which was constituted of 87 13 of a product ratio judged by a similar HPLC examination

**One-pot alkylation of R-3 *via* the *in situ* generated tosylate intermediate (R-6).**

Another diastereomerically pure **R-3** (114 mg, 0 224 mmol) was similarly treated with $^{n}$BuLi (0 187 ml, 0 280 mmol), tosyl chloride (60 mg, 0 314 mmol) in THF (1 2 ml) at r t for 1 5 h, followed by a solution of **9a** (0 83 M, 6 5 ml, 5 4 mmol) at 0°C for 2 5 h Similar work-up and chromatographic separation gave a mixture (95 mg, 0 160 mmol, 71%) of **21** and **22**, which was constituted of 86 14 of a product ratio judged by a similar HPLC assay

**Chlorination of 3 with tosyl chloride and 4-(dimethylamino)pyridine.**

To a stirred solution of diastereomeric **3** (6*S* 6*R* = *ca* 1 3, 200 mg, 0 39 mmol) in $CH_2Cl_2$ (1 ml) was added 4-(dimethylamino)pyridine (195 mg, 1 6 mmol) and the mixture was cooled at 0°C To the mixture was added tosyl chloride (229 mg, 1 2 mmol) and the resulting mixture was stirred at 0°C for 1 5 h After being stirred at r t for additional 3 h, the reaction mixture was quenched by addition of saturated aqueous $NH_4Cl$ solution (30 ml) The mixture was extracted twice with diethyl ether (2 × 50 ml) The combined extracts were washed with saturated aqueous $KHSO_4$ solution, and then saturated aqueous $NaHCO_3$ solution The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to leave a crude product (232 mg) The residual product was chromatographed on silica gel (30 g) with a 19 1 mixture of hexane and EtOAc as an eluant, giving a product fraction ($R_f$ 0 75 9 1 hexane/EtOAc, 142 mg, 0 27 mmol, 69%), which included two types of chlorides, (1*S*,2*R*,3*R*,5*S*,6*R*)-3-*t*-butyldimethylsilyloxy-2-[(*S*,*E*)-3-*t*-butyldimethyl-silyloxy-1-octenyl]-6-chloro-7-methylenebicyclo[3 3 0]octane (**25**) and (1*S*,5*S*,6*R*,7*R*)-7-*t*-butyldimethyl-silyloxy-6-[(*S*,*E*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-3-(chloromethyl)bicyclo[3 3 0]-2-octene (**26**) The product ratio of the chlorides **25** ($R_t$ 12 2 min) and **26** ($R_t$ 13 1 min) was assessed as 62 38 by HPLC analysis of the product mixture (Zorbax Sil, 25 cm × 4 6 mm I D , 210 nm) using 0 01% 2-propanol-hexane as a mobil phase at 2 0 ml/min as a flow rate Each product was isolated by preparative HPLC (YMC-PACK SH-043 S-15 SIL column, 25 cm × 20 mm I D ) eluting with hexane (9 9 ml/min) to give **25** and **26** as an almost pure form The chloride **25** was however found to be unstable under either silica gel column chromatographic condition or preparative HPLC separation **25**, $^{1}$H-NMR ($CDCl_3$) δ 0 03 (s, 12H), 0 86 (s, 9H), 0 89 (s, 9H), 0 8-3 1 (m, 18H), 3 5-3 9 (m, 1H), 3 9-4 2 (m, 1H), 4 36 (bs, 1H), 5 08 (bs, 1H), 5 23 (bs, 1H), 5 4-5 6 (m, 2H), $^{13}$C-NMR ($CDCl_3$) δ -4 7, -4 6, 14 0, 18 1, 22 6, 25 1, 25 9, 26 0, 31 9, 35 3, 38 6, 40 0, 43 2, 49 4, 56 7, 68 0, 73 1, 111 3, 130 0, 134 9, 150 5, MS (m/z) 471 ($M^+$- 57), 469 ($M^+$- 57), 455, 337, 323 **26**, $^{1}$H-NMR ($CDCl_3$) δ 0 03 (s, 12H), 0 86 (s, 9H), 0 89 (s, 9H), 0 8-3 2 (m, 18H), 3 6-3 9 (m, 1H), 3 9-4 3 (m, 1H), 4 10 (s, 2H), 5 4-5 55 (m, 2H), 5 65 (bs, 1H), $^{13}$C-NMR ($CDCl_3$) δ -4 7, -4 6, -4 4, -4 1, 14 0, 18 1, 18 3, 22 6, 25 2, 25 9, 26 0, 31 9, 37 9, 38 7, 39 9, 43 4, 43 7, 45 7, 57 0, 73 2, 77 9, 130 4, 134 2, 134 8, 137 5, MS (m/z) 471 ($M^+$- 57), 469 ($M^+$- 57), 455, 359, 323

**Chlorination of R-3 with tosyl chloride and 4-(dimethylamino)pyridine.**

Epimeric **R-3** (100 mg, 0 20 mmol) was analogously chlorinated in 60% yield by treatment with 4-(dimethylamino)pyridine (116 mg, 0 95 mmol) and tosyl chloride (115 mg, 0 60 mmol) in $CH_2Cl_2$ (5 ml) at r t for 24 h The chlorides **25** and **26** were found to be 85 15 by HPLC analysis

**Chlorination of S-3 with tosyl chloride and 4-(dimethylamino)pyridine.**

The diastereomerically pure allylic alcohol **S-3** (110 mg, 0 22 mmol) was also chlorinated in 50% yield with a similar procedure (r t , 20 h) using 4-(dimethylamino)pyridine (130 mg, 1 06 mmol), tosyl chloride (127 mg, 0 67 mmol), and $CH_2Cl_2$ (5 ml) The product ratio of **25** and **26** was determined as 10 90 by a similar HPLC analysis of the sample obtained by chromatographic separation

**Chlorination of 13 with tosyl chloride and 4-(dimethylamino)pyridine.**

To a stirred solution of **13** (201 mg, 0 40 mmol) in $CH_2Cl_2$ (1 5 ml) was added 4-(dimethylamino)pyridine (195 mg, 1 60 mmol) at 0°C Then, tosyl chloride (229 mg, 1 20 mmol) was added at 0°C and the mixture was stirred at 0°C for 3 5 h The reaction mixture was quenched by addition of water (5 ml) and extracted twice with EtOAc (2 × 50 ml) Similar work-up (washing, filtration, and concentration) afforded a crude product (210 mg), which was separated by silica

gel column chromatography (30 g) with hexane-benzene (7 3) to give almost pure **26** (112 mg, 0 212 mmol, 53%) The product ratio of **25** and **26** was determined to be 4 96 by HPLC analysis

**Alkylation of chlorides 25 and 26 with zinc-copper reagent 9a.**

In the same manner as used for the foregoing alkylation of phosphates, a solution of the Zn-Cu reagent **9a** was prepared by treatment of a supernatant solution of zinc powder (850 mg, 13 mmol) and methyl 4-iodobutanoate (2 85 g, 12 5 mmol) in THF (7 ml) with a solution of CuCN (990 mg, 11 mmol) and LiCl (950 mg, 22 mmol) in THF (10 ml) at 0°C for 10 min The Zn-Cu solution (6 ml, 4 mmol) was added at -25°C to a solution of the above chloride **25** (42 mg, 0 079 mmol, 97% purity by HPLC estimation) in THF (1 ml) and the resulting mixture was stirred at 0°C for 2 h Similar work-up (quenching, extraction, drying, filtration, and evaporation) gave a crude oily product (84 mg), which was chromatographed on silica gel (30 g) with hexane-EtOAc (1 99) as an eluant to provide γ-alkylated product **21** (44 mg, 0 074 mmol, 94%) as an approximately pure product The product distribution for major **21** ($R_f$ 13 6 min) and minor **22** ($R_f$ 15 4 min) was estimated to be 97 3 by HPLC analysis (Zorbax Sil, 25 cm × 4 6 mm I D , 210 nm) using 0 07% ethanol-hexane at 1 2 ml/min

Similarly, a solution (6 ml, 4 mmol) of the Zn-Cu reagent **9a** obtained above was allowed to react with a solution of **26** (76 mg, 0 14 mmol, 96% purity by HPLC estimation) in THF (1 ml) at 0°C for 4 h The crude reaction product (137 mg) obtained after extractive work-up and solvent removal was subjected to silica gel column chromatography (30 g) with the same solvent system to yield γ-alkylated compound **22** (79 mg, 0 133 mmol, 95%) as a minor product The product ratio of minor **21** and major **22** was determined to be 18 82 by the same HPLC system

**Catalytic alkylation of chloride 25 with zinc reagent**

According to the cited procedure,[9b] a suspension of a zinc-copper couple (13 mg, 0 2 mmol) and methyl 4-iodobutanoate (46 mg, 0 2 mmol) in THF (1 ml) was stirred at r t for 1 h and then at 60°C for 1 h The resulting organozinc mixture was filtered through Celite to obtain a organozinc filtrate, which was added at r t to a solution of the chloride **25** (49 mg, 0 093 mmol) in THF (1 ml) To the reaction mixture, CuCN (4 5 mg, 0 05 mmol) was added and the resulting mixture was stirred at 60°C for 3 h The reaction was quenched by addition of water and the organic layer was taken up in ether (50 ml) The separated organic layer was washed with brine, dried over $MgSO_4$, filtered Removal of solvents left a crude residue, which was chromatographed on silica gel (20 g) using a 50 1 and then 30 1 mixture of hexane and EtOAc to obtain a mixture of **21** and **22** (39 mg, 0 066 mmol, 71%) The product ratio of **21** and **22** was estimated by NMR measurement to be about 40 60

**Acknowledgements**

The authers are grateful to Professor R Noyori at Nagoya university for his helpful discussion

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