Compound 18 could be oxidized to cage diketone 16 by using pyridinium dichromate in dimethylformamide solvent. The crude product was purified via elution chromatography (silica gel stationary phase, 20% ethyl acetate–hexane eluent), thereby affording a colorless microcrystalline solid: mp 310 °C, dec (lit.[9] mp 300 °C, dec). Authentic 16 was synthesized via intramolecular photocyclization of 15;[16] the material thereby prepared gave mp 310 °C, with decomposition. The mp of an intimate mixture of the two different samples of 16 (prepared from 18 and from 15 as described above) was undepressed.

Anal. Calcd for $C_{11}H_8Cl_6O_2$: C, 34.33; H, 2.09 Found: C, 34.29; H, 2.22.

Attempted Reduction of 12 and of 16 with $NaBH_4$–$CeCl_3$. Cage diketone 12[15] (378 mg, 1.0 mmol) was dissolved in a solution of cerium chloride heptahydrate (750 mg, 2.0 mmol) in methanol (20 mL). To this solution was added sodium borohydride (75 mg, 2.0 mmol) portionwise with stirring. The reaction mixture was then refluxed for 12 h. No reduction of 12 occurred under the conditions employed; only unreacted 12 could be recovered from these reduction attempts. Similarly, 16[9] (synthesized via intramolecular photocyclization of 15)[16] was found to be inert toward sodium borohydride–cerium chloride heptahydrate under comparable conditions.

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Registry No. 1, 2958-72-7; 3, 56143-86-3; 4, 74497-77-1; 5, 51175-59-8; 6, 101312-33-8; 7, 4378-84-1; 8, 87830-51-1; 9, 101199-19-3; 10, 101199-20-6; 11, 50874-38-9; 12, 50874-39-0; 13, 101199-21-7; 14, 101312-34-9; 15, 101312-35-0; 16, 53644-02-3; 17, 101199-22-8; 18, 101199-23-9; CeCl3, 7790-86-5; $NaBH_4$, 16940-66-2.

A Novel Synthesis of Prostaglandin D_2

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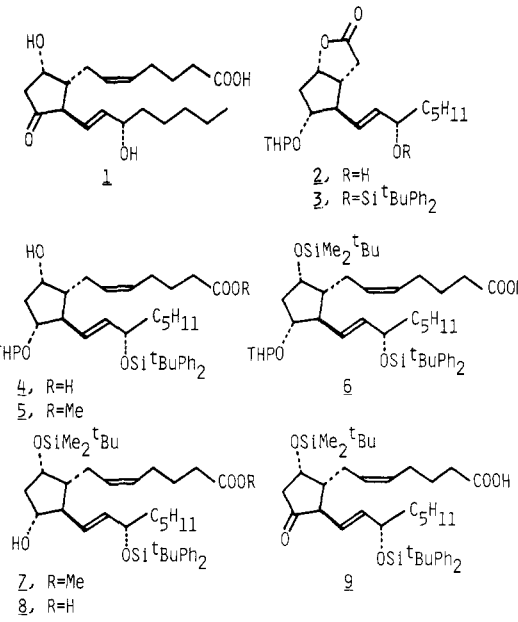
Among primary prostaglandins, recently much attention has been focused on prostaglandin D_2 (PGD_2) (1) (see Chart I) in view of its significant biological activities as a potent inhibitor of platelet aggregation and an antitumor substance.[2] A number of total syntheses of PGD_2 (1) have been reported over the past 10 years, including an elegant synthesis published recently by Noyori and his co-workers.[3] However, the regiocontrolled and short synthesis of 1 from the lactone 2, a key intermediate in a commerical prostaglandin synthesis, has never been achieved, probably owing to lack of the methodology for selective deprotection of tetrahydropyranyl ethers in the presence of silyl ethers.[4]

Chart I



In this paper we wish to report a novel synthesis of (+)-PGD_2 (1), in which the lactone 2 is regiospecifically transformed to 1 without a lengthy protection and deprotection sequence.

The lactone 2 was treated with *tert*-butyldiphenylsilyl chloride and imidazole in DMF to give 3, which, after reduction with diisobutylaluminium hydride in toluene, was subjected to the Wittig reaction using (4-carboxybutyl)triphenylphosphonium bromide and potassium *tert*-butoxide in THF.[5] The resulting acid 4 was treated with ethereal diazomethane, affording 5 in 87% overall yield from 2. The alcohol 5 was then converted to the disilyl ether 6 in a usual way[6] (100%).

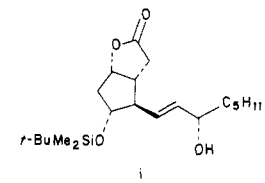
Selective deprotection of the THP ether in the presence of two silyl ethers is the central problem in the present total synthesis. After several attempts,[7] we have found that selective deprotection proceeds nicely under the thermal conditions. Namely, heating of 6 (950 mg) in CH_3CN (19 mL) at 135 °C for 14 days (sealed tube) resulted in the formation of the desired mono ol 7 in 76% yield.[8] Hydrolysis of 7 with NaOH in aqueous methanol

(1) Undergraduate trainee from Kitazato University (1984–1985).

(2) (a) Bundy, G. L.; Morton, D. R.; Peterson, D. C.; Nishizawa, E. E.; Miller, W. L. *J. Med. Chem.* **1983**, *26*, 790. (b) Fukushima, M.; Kato, T.; Ueda, R.; Oka, K.; Narumiya, S.; Hayaishi, O. *Biochem. Biophys. Res. Commun.* **1982**, *105*, 956. (c) For the activity as a celebral sleep-inducing substances in rats, see: Ueno, R.; Honda, K.; Inoue, S.; Hayaishi, O. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 1735.

(3) Suzuki, M.; Yanagisawa, A.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1383 and references cited therein.

(4) Since PGD_2 is extremely labile under basic conditions, it is absolutely necessary to carry out final cleavage of the protective groups under mild acidic conditions. Therefore, the synthesis of PGD_2 starting from the lactone 2 has involved a lengthy protection and deprotection sequence. Although it appears that the lactone i is an attractive intermediate for the synthesis of PGD_2, a facile 1,5-migration of the *tert*-butyldimethylsilyl group takes place during the Wittig reaction. See: Torisawa, Y.; Shibasaki, M.; Ikegami, S. *Chem. Pharm. Bull.* **1983**, *31*, 2607.



i

(5) Howard, C.; Newton, R. F.; Reynolds, D. P.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2049.

(6) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(7) Recently we have reported a method for selective cleavage of THP ethers in the presence of *tert*-butyldimethylsilyl ethers by the use of alkylaluminum halides. See: Ogawa, Y.; Shibasaki, M. *Tetrahedron Lett.* **1984**, *25*, 663. However, its application to the present case failed of success due to the faster reaction with the silyl ether at C-15 (PG numbering).

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led to the carboxylic acid **8** (86%), which was followed by oxidation with PCC–CH_3COONa to afford the ketone **9** in 87% yield. Final cleavage of the silyl ethers was carried out by treatment of **9** with HF in aqueous acetonitrile at −20 °C for 48 h, providing PGD_2 (**1**), $[\alpha]^{20}_D$ +9° (*c* 2.11, THF) (lit.[3] $[\alpha]^{20}_D$ +8.8° (*c* 0.169, THF)), mp 58–59 °C (recrystallized from AcOEt–*n*-hexane) (lit.[3] 58–58.5 °C), in 85% yield.[9]

Thus, the short and regiocontrolled total synthesis of (+)-PGD_2 (**1**) starting from the lactone **2** (ca. 42% overall yield) has been realized for the first time, in which the new conditions for selective removal of THP ethers in the presence of silyl ethers have been developed.

Experimental Section

Melting points are uncorrected. ^1H NMR spectra were recorded with tetramethylsilane as an internal standard.

In general, reactions were carried out under an argon atmosphere unless otherwise mentioned.

3α,5α-Dihydroxy-2β-[3α-((*tert*-butyldiphenylsilyl)oxy)-*trans*-1-octenyl]-1α-cyclopentaneacetic Acid γ-Lactone 3-(Tetrahydropyranyl ether) (3). To a stirred solution of the alcohol **2** (704 mg, 2 mmol) in DMF (2.1 mL) were added imidazole (477 mg, 7 mmol) and *t*-butyldiphenylsilyl chloride (1.649 g, 6 mmol) at room temperature, and the whole reaction mixture was stirred at the same temperature for 1.5 h. After dilution with brine, the aqueous layer was extracted with ether. The combined organic extracts were washed with water. Concentration of the dried solvent ($MgSO_4$) afforded an oily residue, which was purified by silica gel column chromatography (1/1 ether/*n*-hexane) to give the silyl ether **3** (1.181 g, 100%) as a nearly colorless oil: IR (neat) 1780, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, *J* = 6 Hz), 1.03 (9 H, s), 3.20–4.34 (4 H, m), 4.60 (1 H, m), 4.93 (1 H, m), 4.70–6.50 (2 H, m), 7.25–7.80 (10 H, m).

Methyl (5*Z*,13*E*)-9α-Hydroxy-11α-(tetrahydropyranyloxy)-15-[(*tert*-butyldiphenylsilyl)oxy]prosta-5,13-dienoate (5). To a stirred solution of the silyl ether **3** (726 mg, 1.23 mmol) in toluene (6 mL) was added diisobutylaluminum hydride (1.0 M hexane solution, 1.48 mL, 1.48 mmol) at −78 °C, and the whole reaction mixture was stirred at the same temperature for 1 h. The reaction was quenched by the addition of methanol (0.6 mL) followed by successive addition of brine (5.6 mL) and ether (14 mL). After stirring for 2 h at room temperature, the ether layer was separated. The aqueous layer was further extracted with ether, and the combined organic extracts were dried over $MgSO_4$. Concentration of the solvent in vacuo afforded the crude lactol (720 mg), which was directly used for the next reaction without further purification. To a stirrerd suspension of (4-carboxybutyl)triphenylphosphonium bromide (1.82 g, 4.1 mmol) in THF (5 mL) was added potassium *tert*-butoxide (0.84 g, 7.5 mmol) dissolved in THF (20 mL) at room temperature to generate the Wittig reagent, to which was added the crude lactol (720 mg) in THF (5 mL) at the same temperature. After being stirred for 1 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was then acidified with 10% HCl to pH 4–5 and extracted with ether. The combined organic extracts were washed with brine. Concentration of the dried solvent ($MgSO_4$) afforded the crude carboxylic acid **4**, which was immediately treated with ethereal CH_2N_2. The crude reaction mixture was purified by silica gel column chromatography (1/1 ether/*n*-hexane) to give the alcohol **5** (777 mg, 87%) as a nearly colorless oil: IR (neat) 3500, 1745, 1595, 975 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (9 H, s), 2.30 (2 H, t, *J* = 7 Hz), 3.63 (3 H, s), 3.27–4.30 (5 H, m), 4.58 (1 H, m), 5.12–5.60 (4 H, m), 7.20–7.80 (10 H, m).

Methyl (5*Z*,13*E*)-9α-[(*tert*-Butyldimethylsilyl)oxy]-11α-(tetrahydropyranyloxy)-15-[(*tert*-butyldiphenylsilyl)oxy]prosta-5,13-dienoate (6). To a stirred solution of the alcohol **5** (112 mg, 0.162 mmol) in DMF (0.33 mL) were added imidazole (72 mg, 1.06 mmol) and *tert*-butyldimethylsilyl chloride (122 mg, 0.807 mmol) at room temperature, and the whole reaction mixture was stirred at the same temperature for 1.5 h. After dilution with brine, the aqueous layer was extracted with ether. The combined organic extracts were washed with water. Concentration of the dried solvent ($MgSO_4$) afforded an oily residue, which was purified by silica gel column chromatography (1/5 ether/*n*-hexane) to give the disilyl ether **6** (130 mg, 100%) as a nearly colorless oil: IR (neat) 1740, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (6 H, s), 0.90 (9 H, s), 1.06 (9 H, s), 3.62 (3 H, s), 3.20–4.40 (5 H, m), 4.60 (1 H, m), 5.10–5.75 (4 H, m), 7.20–7.80 (10 H, m).

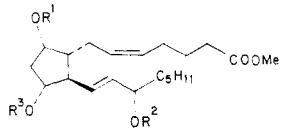
Methyl (5*Z*,13*E*)-9α-[(*tert*-Butyldimethylsilyl)oxy]-11α-hydroxy-15-[(*tert*-butyldiphenylsilyl)oxy]prosta-5,13-dienoate (7). The disilyl ether **6** (49 mg, 0.06 mmol) was dissolved in dry CH_3CN (1.2 mL). After deoxygenation by three freeze–pump–thaw cycles, the solution was heated at 135 °C for 14 days in a sealed tube (argon atmosphere). After evaporation of the solvent in vacuo, the residual oil was purified by silica gel column chromatography (1/6 ether/*n*-hexane) to give the alcohol **7** (33 mg, 76%) as a nearly colorless oil: IR (neat) 3550, 1740, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (3 H, s), 0.06 (3 H, s), 0.90 (9 H, s), 1.05 (9 H, s) 2.28 (2 H, t, *J* = 7 Hz), 3.63 (1 H, m), 3.67 (3 H, s), 3.90–4.20 (2 H, m), 4.83–5.60 (4 H, m), 7.20–7.79 (10 H, m).

(5*Z*,13*E*)-9α-[(*tert*-Butyldimethylsilyl)oxy]-11α-hydroxy-15-[(*tert*-butyldiphenylsilyl)oxy]prosta-5,13-dienoic Acid (8). A solution of the alcohol **7** (33 mg, 0.046 mmol), methanol (0.44 mL), and 30% aqueous NaOH (1.1 mL) was stirred at 0 °C for 17 h. After evaporation of methanol in vacuo, the aqueous layer was acidified with 10% HCl to pH 5–6 and extracted with ether. The combined ether extracts were washed with brine. Concentration of the dried solvent ($MgSO_4$) afforded an oily residue, which was purified by silica gel column chromatography (1/1 ether/*n*-hexane) to give the carboxylic acid **8** (28 mg, 86%) as a nearly colorless oil: IR (neat) 2400–3600, 1720, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (3 H, s), 0.06 (3 H, s), 0.90 (9 H, s), 1.05 (9 H, s), 2.32 (2 H, t, *J* = 7 Hz), 3.60 (1 H, m), 4.16 (2 H, m), 4.90–5.63 (4 H, m), 7.20–7.80 (10 H, m).

(5*Z*,13*E*)-9α-[(*tert*-Butyldimethylsilyl)oxy]-11-oxo-15-[(*tert*-butyldiphenylsilyl)oxy]prosta-5,13-dienoic Acid (9). To a stirred solution of the carboxylic acid **8** (18.8 mg, 0.26 mmol) in dry CH_2Cl_2 (0.3 mL) were added NaOAc (3.8 mg, 0.046 mmol) and PCC (7.8 mg, 0.036 mmol) at room temperature, and the brown black suspension was stirred at the same temperature for 1 h. The whole reaction mixture was then filtered through a short pad of silica gel. After washing thoroughly with ether, the filtrate was evaporated in vacuo to give an oily residue, which was purified by silica gel column chromatography (1/1 ether/*n*-hexane) to provide the carboxy ketone **9** (16 mg) (nearly colorless viscous oil, 87%): IR (neat) 2400–3600, 1752, 1720, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (3 H, s), 0.07 (3 H, s), 0.88 (9 H, s), 1.07 (9 H, s), 2.55–2.83 (1 H, dd, *J* = 7, 12 Hz), 4.00–4.26 (1 H, m), 4.41 (1 H, m), 5.09–5.63 (4 H, m), 7.20–7.80 (10 H, m).

PGD_2. A solution of the carboxy ketone **9** (107 mg, 0.152 mmol) in aqueous acetonitrile (8.8 mL) containing HF (3:7 40% HF–CH_3CN) was stirred at −20 °C for 48 h, and then the reaction mixture was extracted with cold AcOEt. Saturated aqueous $NaHCO_3$ was added to the AcOEt extract with stirring at 0 °C until the water layer became neutral. The water layer was again acidified to pH ~5 with saturated aqueous NH_4Cl, and then the

(8) Heating of ii in acetonitrile at 130 °C for 6 days provided the desired product iii in 21% yield. Likewise, heating of iv in toluene at 190 °C for 36 h gave v in 80% yield at 55% conversion. On the other hand,



ii, R^1 = $SiEt_3$, R^2 = Si-*t*-BuPh$_2$, R^3 = THP
iii, R^1 = $SiEt_3$, R^2 = Si-*t*-BuPh$_2$, R^3 = H
iv, R^1 = R^2 = $SiMe_2$-*t*-Bu, R^3 = THP
v, R^1 = R^2 = $SiMe_2$-*t*-Bu, R^3 = H
vi, R^1 = R^2 = Si-*t*-BuPh$_2$, R^3 = THP
vii, R^1 = R^2 = Si-*t*-BuPh$_2$, R^3 = H

the silyl ether vi has been reported to be deprotected selectively just by treatment with aqueous acetic acid to give vii. See: Sakata, S.; Torisawa, Y.; Ikegami, S. *Abstracts of Papers*, 104th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, April, 1984; p 281. However, conversion of vii to PGD_2 appears to be difficult.

(9) Newton, R. F.; Reynolds, D. P.; Webb, C. F.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2055.

organic layer was separated. After extraction with AcOEt thoroughly, the combined organic extracts were dried over $MgSO_4$. Concentration of the dried solvent afforded an oily residue, which was purified by silica gel column chromatography (40/1 → 40/2 ether/methanol) to give pure PGD_2 (1) (45.5 mg) as a colorless solid in 85% yield: IR (KBr) 3450, 1730, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (3 H, t, J = 6 Hz), 2.65–2.90 (1 H, dd, J = 7, 12 Hz), 4.00–4.30 (1 H, m), 4.45 (1 H, m), 5.30–5.70 (4 H, m); mass spectrum, m/e 334, 316, 246, 245, 191, 190, 161, 55; mass spectrum, m/e calcd for 1 ($C_{20}H_{30}O_4$, M^+–18) 334.2142, found 334.2159; $[\alpha]^{20}_D$ +9° (c 2.11, THF); mp 58–59 °C (recrystallized from AcOEt–n-hexane).

A New Preparation of α-Cycloheptatrienyl Ketones

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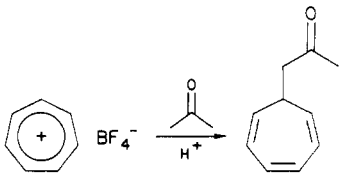
In the course of an investigation into the synthesis of tropyl alcohol, we have discovered a new, efficient synthesis of α-cycloheptatrienyl ketones. Tropyl acetate appeared to be a reasonable precursor to tropyl alcohol, but our initial attempts to prepare it by the method of Hoffmann[1] (tropylium fluoroborate, potassium acetate, and acetic anhydride in acetone) led instead to tropyl acetone 1.



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Reasoning that our tropylium fluoroborate might have been wet[2] and that the acetic anhydride had been hydrolyzed to acetic acid, we speculated that the reaction of acetone with tropylium salts might be acid catalyzed. Indeed, when tropylium fluoroborate is stirred in acetone with a few drops of acetic acid, a 97% yield of tropyl acetone is rapidly obtained. Previous preparations of tropyl acetone are quite laborious and provide product in significantly lower yields.[4]

The reaction presumably involves the enol of acetone reacting with tropylium salt, and thus the method should be quite general for enolizable ketones. Accordingly, a number of other substrates were examined to determine the scope and limitations of this reaction. Our most productive experiments were done in methanol or acetonitrile, using approximately a 1:1 ratio of tropylium salt and ketone; a slight excess of tropylium salt is preferable to an excess of ketone since the tropylium salt is easily removed. The results are presented in Table I.

Several comments are in order. First, the yields are good to excellent. Many of these compounds have been made before, but this is the first direct addition that produces product in high yields. The most general published method involves the treatment of tropylium salt with the enamines of ketones.[5] While excellent, the yields reported apply only to the alkylation step; when the preparation of the enamine is considered, yields reported here are uniformly better than or equal to those possible with the enamine procedure. Furthermore, several of the entries in Table I are not available from the enamine method, due to the unavailability of the appropriate enamines. On the other hand, much better control over regioselectivity is possible by using the earlier procedure. For example, 2-methylcyclohexanone affords a 3:2 mixture of the possible isomers with the present procedure, while a 20:1 ratio favoring the 6-substituted product is obtained with the enamine method. This latter ratio nearly corresponds to the ratio of the starting enamines isomers.

Second, no ditropyl adducts were observed with this procedure. To add a second tropyl group, the original adduct would have to enolize with loss of a proton. However, as Conrow has pointed out,[4a] it seems likely that enolization in these compounds always proceeds by loss of tropylium ion instead of proton, thus precluding multiple adducts. The results presented herein support this conclusion.

The third entry in Table I, the reaction of 2-butanone with tropylium salt, merits comment. As shown, when worked up after 5 h the product was almost entirely 3-tropyl-2-butanone (3). Shorter reaction times lead to a much higher percentage of 1-tropyl-2-butanone (2): after a reaction time of only 1 h, the ratio is closer to 2:1 favoring 3, as measured by gas chromatography, and a gradual increase in the ratio is observed, leveling off at about 4.5 h. It appears that production of 2 is kinetically controlled and that 3 is the thermodynamic product; thus the same equilibrium mixture should be obtained from a pure sample of the minor isomer 2 placed under the reaction conditions. However, a sample of nearly pure 2 in methanol containing acetic acid remained unchanged after 2 weeks.

Several possible explanations for this lack of equilibration have been considered. Adduct 2 does not actually revert directly to starting material, but rather to tropylium ion and the kinetic enol, the less substituted one. This enol may react again in the forward direction, unless there is something else present to scavenge the tropylium ion. Addition of excess 2-butanone (which would be present under the reaction conditions) had no effect, however. A second possible explanation is that the actual reaction conditions are more acidic than the ones we simulated, because the reaction generates fluoroboric acid. Addition of a few drops of 48% fluoroboric acid solution did cause the amount of "thermodynamic" isomer present to grow: the ratio of 2–3 changed from 40:1 to 10:1 in the course of a week. Although 3 may eventually have become the predominant isomer, the rate of isomerization was much too slow to account for the results observed during the reaction. At present, a suitable explanation for the observed results is not apparent.

Note should also be made of a few substrates that do not undergo this reaction. Acetaldehyde, propionaldehyde, ethyl acetate, and acetonitrile all failed to afford the desired adducts. The aldehydes decomposed under the reaction conditions to the same unidentified products which were obtained when they were stirred in methanol con-

(1) Hoffmann, R. W.; Loof, I. H.; Wentrup, C. *Liebigs Ann. Chem.* **1980**, 1198.

(2) Freshly prepared tropylium fluoroborate successfully provided tropyl acetate, identical with that reported in the literature.[1,3]

(3) Orlando, C. M., Jr.; Weiss, K. *J. Org. Chem.* **1962**, *27*, 4714. The NMR spectrum reported by these authors is displaced by about 0.5 ppm. The correct values are δ 2.0, 5.0, 5.5, 6.3, and 6.7. Our spectrum agrees with that obtained by Hoffmann: personal communication.

(4) (a) Conrow, K. *J. Am. Chem. Soc.* **1959**, *81*, 5461. (b) Vol'pin, M. E.; Akhrem, I. S.; Kursanov, D. N. *Zh. Obshch. Khim.* **1960**, *30*, 1187. (c) Conrow, K.; Naik, D. N. *J. Med. Chem.* **1963**, *6*, 69.

(5) Watanabe, T.; Soma, N. *Chem. Pharm. Bull.* **1970**, *18*, 1595.

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