(1 L) and ether (2 L). The ether layer was washed with saturated NaCl (300 mL) and dried (K_2CO_3). Methanol (1 L) was added and the ether evaporated. Additional methanol (1.5 L) was added to the solution followed by Pearlman's catalyst (38 g of 10% Pd/C) and a solution of ammonium formate (149.8 g, 2.38 mol) in water (480 mL). The mixture was refluxed for 1.5 h, cooled, and filtered through Celite. The filtrate was evaporated to an oil, and the oil was partitioned between 1 M NaOH (1 L) and CH_2Cl_2 (1 L). The CH_2Cl_2 layer was washed with saturated NaCl (500 mL), dried (K_2CO_3), and evaporated to an oil; yield 94.7 g (97.9% purity by HPLC). The oil was dissolved in boiling ethyl acetate (1.8 L), and a solution of HCl(g) in 2-propanol (52.3 mL, 0.383 mol of HCl) was added. The solution was cooled, and the white crystalline solid was filtered off; yield 93.2 g (63%). A portion (10.1 g) of this material was freeze-dried from water (40 mL) to give a white amorphous solid: yield 9.8 g (98.9% pure by HPLC); mp 133-137 °C; IR (KBr) 3400, 2950, 1592, 1448, 1001, 702 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 1.48 (m, 2 H, propyl C_2), 2.42 (m, 2 H, propyl C_1), 2.74 (t, 2 H, propyl C_3), 6.1 (s, 1 H, OH), 7.14-7.89 (m, 8 H, phenyl and pyridyl C_3, C_4, C_5), 8.00 (s, 3 H, NH_3), 8.5 (d, 1 H, pyridyl C_6); MS m/z 242 (M^+). Anal. Calcd for $C_{15}H_{18}N_2O \cdot 1.21HCl \cdot 0.11H_2O$: C, 62.47; H, 6.79; N, 9.71; Cl, 14.87. Found: C, 62.47; H, 6.96; N, 9.75; Cl, 14.89.

Alkylation of Dibenzylamine. A suspension of K_2CO_3 (20 mmol) in a solution of the alkyl halide or epoxide (10.0 mmol) and dibenzylamine (12.0 mmol) in diglyme (10 mL) was heated at 140 °C under nitrogen. After 24 h, the mixture was cooled, and the insolubles were filtered off and washed with ether. The filtrate and washings were evaporated in vacuo (bath temperature 40 °C) to an oil, and the oil was chromatographed on silica gel (100 g) using CH_2Cl_2 as eluent. Fractions containing product were combined and evaporated to give the free base as an oil. The free bases were not characterized.

Hydrochloride Salt Formation. A solution of HCl gas (1 equiv) in dry 2-propanol was added to a solution of the free base in dry 2-propanol or dry ether. The mixture was stored in a freezer (-5 °C) overnight. The resulting crystals were filtered off, washed, and dried. The salts could be recrystallized from 2-propanol. The following HCl salts were prepared in this manner.

***N,N*-Bis(phenylmethyl)octanamine hydrochloride (11a)**: mp 109.5-110.5 °C; IR (KBr) 2926, 1460, 754, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.86 (t, 3 H, CH_3), 1.21 (s, 10 H, C_3 to C_7), 1.92 (m, 2 H, C_2), 2.83 (m, 2 H, C_1), 4.04-4.33 (2 dd, 4 H, benzylic), 7.46 (m, 6 H, phenyl C_3', C_4', C_5'), 7.69 (m, 4 H, phenyl C_2', C_6'), 12.7 (s, 1 H, NH); MS m/z 309 (M^+). Anal. Calcd for $C_{22}H_{31}N \cdot HCl$: C, 76.38; H, 9.32; N, 4.05; Cl, 10.25. Found: C, 76.12; H, 9.34; N, 3.85; Cl, 10.27.

2-Ethyl-*N,N*-bis(phenylmethyl)hexanamine hydrochloride (11b): mp 110-111 °C; IR (KBr) 2929, 1461, 742, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.62 (t, 3 H, C_6), 0.82 (t, 3 H, ethyl C_2), 0.8-1.5 (m, 8 H, C_3, C_4, C_5, ethyl C_1), 1.81 (m, 1 H, C_2), 2.66 (m, 2 H, C_1), 4.06 and 4.60 (m, 2 H + 2 H, benzylic), 7.47 (m, 6 H, phenyl, C_3', C_4', C_5'), 7.70 (m, 4 H, phenyl, C_2', C_6'), 11.6 (s, 1 H, NH); MS m/z 309 (M^+). Anal. Calcd for $C_{22}H_{31}N \cdot HCl$: C, 76.38; H, 9.32; N, 4.05; Cl, 10.25. Found: C, 76.43; H, 9.76; N, 3.94; Cl, 10.30.

***N,N*-Bis(phenylmethyl)benzenepropanamine hydrochloride (11c)**: mp 184.0-186.5 °C; IR (KBr) 2930, 1604, 1455, 1219, 931, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.26 (m, 2 H, C_β), 2.56 (t, 2 H), 2.85 (m, 2 H), 4.04 and 4.28 (m, 4 H, benzylic), 7.06 (m, 2 H, phenyl, C_2, C_6), 7.24 (m, 3 H, phenyl, C_3, C_4, C_5), 7.40 (m, 6 H, phenyl, C_3', C_4', C_5'), 7.58 (m, 4 H, phenyl, C_2', C_6') 12.60 (s, 1 H, NH); MS m/z 315 (M^+). Anal. Calcd for $C_{23}H_{25}N \cdot HCl$: C, 78.50; H, 7.45; N, 3.98; Cl, 10.07. Found: C, 78.50; H, 7.49; N, 3.94; Cl, 9.80.

***N,N*-Bis(phenylmethyl)benzeneethanamine hydrochloride (11d)**: mp 205.0-205.5 °C; IR (KBr) 2953, 1458, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.03-3.15 (m, 2 H, C_β), 3.20-3.39 (m, 2 H, C_α), 4.14-4.50 (m, 4 H, benzylic), 7.02-7.07 (m, 2 H, phenyl C_2, C_6), 7.13-7.40 (m, 3 H, phenyl, C_3, C_4, C_5), 7.40-7.60 (m, 6 H, phenyl, C_3', C_4', C_5'), 7.60-7.90 (m, 4 H, phenyl, C_2', C_6'), 13.0 (1 H, NH); MS m/z 302 (M + 1). Anal. Calcd for $C_{22}H_{23}N \cdot HCl$: C, 78.20; H, 7.16; N, 4.15; Cl, 10.49. Found: C, 78.60; H, 7.25; N, 4.26; Cl, 10.71.

1-[Bis(phenylmethyl)amino]-3-(3-methylphenoxy)-2-propanol hydrochloride (11e): mp 144.0-145.2 °C; IR (KBr) 2934, 1604, 1458, 1264, 1053, 753, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.33 (s, 3 H, CH_3), 3-4.5 (baseline, 1 H, OH), 3.07-3.36 (m, 2 H, C_1), 3.72 (t, 1 H, C_2), 3.98-4.12 (m, 2 H, C_3), 4.30-4.62 (m, 4 H, benzylic), 6.62 (d, 1 H, phenyl, C_6'), 6.65 (s, 1 H, phenyl, C_2'), 6.80 (d, 1 H, phenyl, C_4'), 7.17 (t, 1 H, phenyl, C_5'), 7.45-7.59 (m, 6 H, phenyl, C_3'', C_4'', C_5''), 7.59-7.68 (m, 4 H, phenyl, C_2'', C_6''), 12.1 (s, 1 H, NH); MS m/z 362 (M + 1). Anal. Calcd for $C_{24}H_{27}NO_2 \cdot HCl$: C, 72.44; H, 7.09; N, 3.52; Cl, 8.91. Found: C, 72.38; H, 7.23; N, 3.42; Cl, 8.92.

CAT Hydrogenolysis Procedure. A suspension of Pearlman's catalyst (10% Pd/C, 100 mg) in a solution of 11 (2.0 mmol) and HCO_2NH_4 (8.0 mmol) in methanol (10 mL) was refluxed for 2 h. The mixture was allowed to cool, and the suspension was filtered through Celite. The filtrate was evaporated to a white solid which was free of organic impurities by 200-MHz ^1H NMR and MS analyses. The solids did contain approximately 5-10 mol % of HCO_2NH_4. Therefore samples for melting point and elemental analysis were first crystallized from CH_3CN. The following amines were prepared in this manner:

1-Octanamine hydrochloride (12a): mp 197-198 °C; IR (KBr) 2931, 1595, 1517, 1469, 1152, 724 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 0.87 (t, 3 H, CH_3), 1.26 (s, 10 H, C_3 to C_7), 1.54 (m, 2 H, C_2), 2.74 (t, 2 H, C_1), 7.8 (s, 3 H, NH_3); MS m/z 130 (M + 1). Anal. Calcd for $C_8H_{19}N \cdot HCl \cdot 0.04H_2O$: C, 57.75; H, 12.14; N, 8.42; Cl, 21.31. Found: C, 57.75; H, 12.12; N, 8.20; Cl, 20.99.

2-Ethyl-1-hexanamine hydrochloride (12b): mp (glass); IR (KBr) 3455, 2960, 1617, 1507, 1466, 1558, 668, 468 cm^{-1}; ^1H NMR (DMSO-d_6, 250 MHz) δ 0.83 (t, 3 H, C_6), 0.88 (t, 2 H, ethyl C_2), 1.25-1.45 (m, 9 H, C_3, C_4, C_5, ethyl C_1), 1.58 (m, 1 H, C_2), 2.66 (m, 2 H, C_1), 8.13 (s, 3 H, NH_3); MS m/z 129 (M^+). Anal. Calcd for $C_8H_{19}N \cdot HCl \cdot 0.18H_2O$: C, 56.87; H, 12.15; N, 8.29; Cl, 20.98. Found: C, 56.86; H, 12.17; N, 7.95; Cl, 20.47.

Benzenepropanamine hydrochloride (12c): mp 211-213 °C; IR (KBr) 3448, 2998, 1603, 1487, 1473, 749, 698 cm^{-1}; ^1H NMR (DMSO-d_6, 250 MHz) δ 1.86 (m, 2 H, C_β), 2.65 (t, 2 H), 2.76 (t, 2 H), 7.25 (m, 5 H, phenyl), 8.05 (s, 3 H, NH_3); MS m/z 135 (M^+). Anal. Calcd for $C_9H_{13}N \cdot HCl$: C, 62.97; H, 8.22; N, 8.16; Cl, 20.65. Found: C, 62.85; H, 8.22; N, 7.92; Cl, 20.17.

Benzeneethanamine hydrochloride (12d): mp 218-221 °C; IR (KBr) 3027, 2990, 1466, 1144, 940, 752, 744, 695 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 2.91 (m, 2 H, C_β), 3.02 (m, 2 H, C_α), 7.31 (m, 5 H, phenyl), 8.03 (s, 3 H, NH_3); MS m/z 122 (M + 1). Anal. Calcd for $C_8H_{11}N \cdot HCl \cdot 0.13H_2O$: C, 60.06; H, 7.72; N, 8.75; Cl, 22.16. Found: C, 60.31; H, 7.65; N, 8.74; Cl, 21.81.

1-Amino-3-(3-methylphenoxy)-2-propanol hydrochloride (12e): mp 136-138 °C; IR (KBr) 3403, 3010, 1595, 1494, 1267, 1058, 775 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 2.28 (s, 3 H, CH_3), 2.81 and 3.01 (2 dd, 2 H, C_3), 3.4 (s, 1 H, OH), 3.94 (d, 2 H, C_1), 4.05 (m, 1 H, C_2), 6.76 (m, 3 H, C_2', C_4', C_6'), 7.18 (t, 1 H, C_5'), 7.9 (s, 3 H, NH_3); MS m/z 182 (M + 1). Anal. Calcd for $C_{10}H_{15}NO_2 \cdot HCl$: C, 55.17; H, 7.41; N, 6.43; Cl, 16.29. Found: C, 55.19; H, 7.48; N, 6.20; Cl, 16.12.

Hypervalent Iodine in Synthesis. 4. Oxidative Coupling of Isopropylidene 5-Alkylmalonates Using (Diacetoxyiodo)benzene

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Oxidative coupling of electron-rich intermediates has emerged in recent years as an efficient method for the formation of carbon-carbon bonds. Various methods which have been used for a variety of enolate and carbanion dimerizations include electrochemical procedures and the oxidants silver oxide,[1] cupric chloride,[2] cupric

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0022-3263/91/1956-0459$02.50/0

Table I. 5,5′-Bis(isopropylidene alkylmalonates) 2

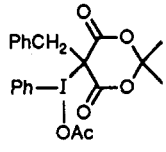
product	reaction time, h	yield,[a] %	mp,[b] °C	anal. calcd/found C	anal. calcd/found H	IR[c] (KBr), cm^{-1}	^{1}H NMR (CDCl$_3$/TMS)[d]
2a	10	47	237–238	66.95/67.01	5.58/5.76	1770, 1735, 1600, 1490, 1390, 1380, 730, 710	0.58 (s, 6 H), 1.57 (s, 6 H), 4.01 (s, 4 H), 7.27 (s, 10 H)
2b	11	42	238–239	67.98/67.68	6.07/6.13	1765, 1735, 1610, 1510, 1395, 1380, 820	0.61 (s, 6 H), 1.57 (s, 6 H), 2.29 (s, 6 H), 3.96 (s, 4 H), 7.10 (s, 8 H)
2c	10	48	231–232	63.88/63.76	5.70/5.95	1765, 1735, 1610, 1510, 1395, 1380, 840	0.68 (s, 6 H), 1.58 (s, 6 H), 3.75 (s, 6 H), 3.94 (s, 4 H), 6.82–7.13 (dd, J = 8, 19 Hz, 8 H)
2b	8	52	235–236	58.32/58.18	4.49/4.60	1760, 1730, 1600, 1490, 1400, 1380, 840	0.71 (s, 6 H), 3.58 (s, 6 H), 3.95 (s, 4 H), 7.13–7.32 (dd, J = 9, 13 Hz, 8 H)
2e	11	39	189–190	55.10/55.19	5.10/5.16	2250, 1765, 1730, 1400, 1385	0.68 (s, 6 H), 1.59 (s, 6 H), 2.25–2.60 (m, 8 H)
2f	7	45	197–198	53.50/53.08	5.77/5.81	1760, 1735, 1390, 1385	1.76 (s, 12 H), 2.03 (s, 6 H)

[a] Yield of isolated analytically pure product, based on I. [b] All melting points are uncorrected. [c] Recorded on a Perkin-Elmer 683 spectrophotometer. [d] Recorded on a JEOL FX90Q spectrometer.

triflate,[3] ferric chloride,[4] and molecular iodine.[5]

During the past 10 years there has been much interest in hypervalent iodine species as oxidants in organic chemistry.[6-8] (Diacetoxyiodo)benzene is by far the most frequently used reagent. In a continuing study of the applications of hypervalent organoiodine(III) compounds to organic synthesis,[9] we report the use of (diacetoxyiodo)benzene as oxidative coupling agent[10] for the formation of 5,5′-bis(isopropylidene alkylmalonates) **2** which have not been reported in literature.

Preliminary attempts to couple isopropylidene 5-benzylmalonate (**1a**) using (diacetoxyiodo)benzene in acetonitrile under neutral condition resulted in a rather low yield (~30%) of the expected 5,5′-bis(isopropylidene benzylmalonate) (**2a**). Although no direct experimental evidence exists yet, it is reasonable to assume that the first step of this reaction occurs via the initial nucleophilic substitution on the *tricoodinate* iodine of (diacetoxyiodo)benzene by isopropylidene 5-benzylmalonate to give **3** as the first intermediate.



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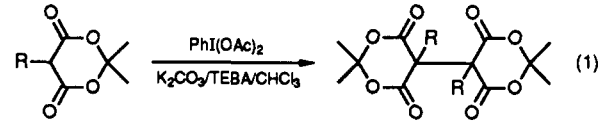
In order to increase the nucleophilic power of the isopropylidene 5-alkylmalonates and improve the yield of this reaction, we have further devised a procedure which is based upon the use of basic conditions. Thus, stirring the isopropylidene 5-alkylmalonates **1** with (diacetoxyiodo)benzene and potassium carbonate in the presence of benzyltriethylammonium chloride in chloroform at room temperature gave, after workup, the desired 5,5′-bis(isopropylidene alkylmalonates) **2** (eq 1) in moderate yields (Table I).



(1)

1a–f **2a–f**

a: R = $C_6H_5CH_2$
b: R = p-$CH_3C_6H_4CH_2$
c: R = p-$CH_3OC_6H_4CH_2$
d: R = p-$ClC_6H_4CH_2$
e: R = $NCCH_2CH_2$
f: R = CH_3

The products **2** were characterized by spectral and analytical means as summarized in the Table I. This reaction represents a general, simple, mild procedure for the direct synthesis of 5,5′-bis(isopropylidene alkylmalonates). Furthermore, since the substituted isopropylidene malonates are easily hydrolyzed to carboxylic acids[11] or converted into carboxylic esters,[12] the method described here may also be considered as a useful complement of the oxidative coupling of carboxylic acid dianions or ester enolates.

In conclusion, an efficient preparation of 5,5′-bis(isopropylidene alkylmalonates) by oxidative coupling of isopropylidene 5-alkylmalonates using (diacetoxyiodo)benzene has been demonstrated. The range of useful applications of this reagent as an oxidative coupling agent in organic chemistry has been extended.

Experimental Section

Oxidative Coupling of 1: General Procedure. To a stirred solution of the isopropylidene 5-alkylmalonate **1** (2.5 mmol) in chloroform (10 mL) was added finely powdered potassium carbonate (0.35 g, 2.5 mmol) and benzyltriethylammonium chloride (0.11 g, 0.5 mmol). The resultant mixture was stirred for 20 min. Then (diacetoxyiodo)benzene (0.48 g, 1.5 mmol) was added, and stirring was continued at room temperature for the time given in the Table I until the reaction was complete. Then water (10 mL) was added, the organic layer was separated, and the aqueous layer was extracted with chloroform (2 × 10 mL). The combined organic solution was washed with water (10 mL) and dried with magnesium sulfate. The solvent was removed, and the residue was triturated with 10 mL of petroleum ether, and the mixture was allowed to stand in a refrigerator overnight. The resulting crystals were collected by suction filtration and purified by recrystallization from acetone/ethanol.

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Registry No. **1a**, 3709-27-1; **1b**, 130296-61-6; **1c**, 61958-46-1; **1d**, 88466-67-5; **1e**, 90734-81-9; **1f**, 3709-18-0; **2a**, 130296-62-7; **2b**, 130296-63-8; **2c**, 130296-64-9; **2d**, 130296-65-0; **2e**, 130296-66-1; **2f**, 130296-67-2; (diacetoxyiodo)benzene, 3240-34-4.

A Novel Convergent Synthesis of (+)-1α,25-Dihydroxyvitamin D_3 Using a Chromium(II)-Mediated Coupling Reaction

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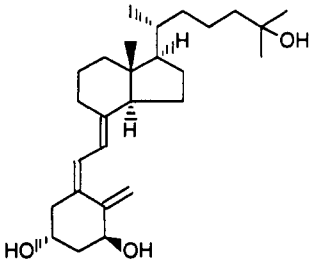
Of the known vitamin D_3 metabolites, 1α,25-dihydroxyvitamin D_3 (1) is known to play a central role in the maintenance of calcium homeostasis. More recently, this hormone has also been found to induce cellular differentiation of human meyloid leukemia cells.[1] These findings, therefore, have spurred much research on the syntheses[2] of 1 and its analogues due to the potential utility of 1 in the treatment of certain cancers.

We have recently reported[3] that chromium(II)-mediated addition[4] of the allyl iodide **2**, prepared from (*R*)-(−)-carvone in 10 steps (46% yield), to [(*p*-methoxybenzyl)oxy]acetaldehyde proceeded with complete threo selectivity in almost quantitative yield. This observation prompted us to investigate a new convergent synthesis of **1** which relies on chromium(II)-mediated coupling of the A-ring fragment **2** and the C/D-ring fragment **3**.



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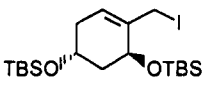

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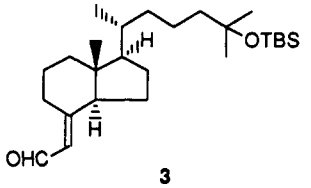

3

TBS = ^{t}BuMe$_2$Si–

The known keto alcohol **4**, easily obtained from the Inhoffen–Lythgoe diol[5] according to Castedo's procedure,[6] was converted to alcohol **7** by sequential Grignard reaction, monoacetylation, silylation, and DIBAL reduction (79% overall yield). After oxidation of **7**, the resulting ketone (**8**) was directly transformed into the α,β-unsaturated aldehyde **3** by reaction with lithiated *N*-*tert*-butyl-2-(trimethylsilyl)acetaldimine followed by acid hydrolysis[7] (88% overall yield).

Reaction of iodide **2** with aldehyde **3** in the presence of chromium(II) species, prepared in situ by LAH reduction of chromium(III) chloride,[4] led to a highly diastereoselective coupling to give alcohol **9** as the sole product.[8] It is worthy of note that, in this particular case, at least 1.5 equiv of aldehyde **3** should be used because concomitant reduction of **3** to alcohol **10** always takes place. In order to make purification easy, the crude reaction mixture was reduced with DIBAL to give alcohol **9** (83% yield) along with **10** (67% yield based on the excess of **3** used), oxidation of which allowed us to recover starting aldehyde **3** in quantitative yield. The observed excellent diastereoselectivity of this chromium(II)-mediated coupling reaction can be explained by assuming the transition state resembling **11**.[3,4]

It was anticipated at this point that the construction of the conjugated triene of **1** might be achieved by stereo- and regioselective dehydration through an E_2 elimination process. However, this transformation turned out to be very difficult. For example, the usual dehydrating agents (e.g. methanesulfonyl chloride/DMAP, thionyl chloride, or phosphorus oxychloride in pyridine) gave a >10:1 mixture of the unconjugated triene **13** and the conjugated triene **12**. In our hands the best method of converting **9** to 1α,25-dihydroxyvitamin D_3 (**1**) involved dehydration catalyzed by copper(II) sulfate on silica gel[9] followed by deprotection. Thus, heating **9** with the catalyst at 50 °C in benzene gave an inseparable mixture of **12** and **13** which, upon desilylation using hydrofluoric acid, furnished **1** and **14** in a ratio of 3:5 in 90% yield. The synthetic 1α,25-dihydroxyvitamin D_3 (**1**), mp 117–118 °C (lit.[10] mp 118–119 °C), $[\alpha]^{29}_D$ +47.8° (*c* 1.00, EtOH) [lit.[10] $[\alpha]_D$ +47.9° (*c* 0.5, EtOH)], exhibited spectral properties (^{1}H NMR, IR, MS) in accord with those reported.[10]

Although improvement of the dehydration step will be necessary in order for the present synthetic route to be translated into a more practical process, this synthetic study provides a new method of potential value in the synthesis of **1** and related vitamin D_3 metabolites.

Experimental Section

General. Melting points were measured on a micro-hot stage apparatus and are uncorrected. Optical rotations were measured with a JASCO-DIP-370 polarimeter. ^{1}H NMR spectra were re-

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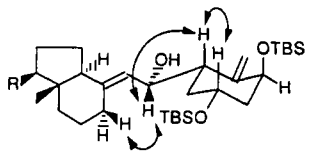

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