

is observed, the dose is the highest dose tested.

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## Prostaglandins and Congeners. 15.<sup>1</sup> Synthesis and Bronchodilator Activity of dl-11-Deoxy-15- or 16-alkylprostaglandins

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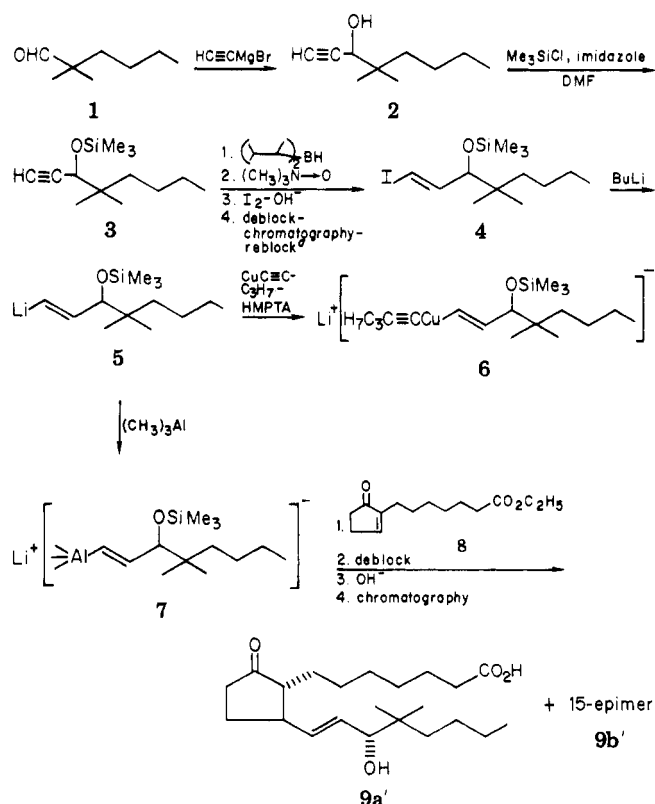
The synthesis of dl-11-deoxy-15- or 16-alkylprostaglandins by the conjugate addition of appropriately substituted lithium alanate or lithium cuprate reagents to several cyclopentenones is described as is the preparation of the requisite intermediate (*E*)-1-iodo-1-alkenyl compounds **4**, **22**, **23**, and **31**. The bronchodilator activity of these prostaglandin congeners is presented.

The introduction of alkyl groups at C<sub>15</sub> or C<sub>16</sub> in the prostaglandin molecule has provided compounds that are resistant to metabolic inactivation by 15-hydroxyprostaglandin dehydrogenase<sup>2</sup> with resulting enhancement of potency, oral activity at least as inhibitors of gastric acid secretion, and prolongation of effect.<sup>3</sup> Accordingly we were interested in the preparation and biological evaluation of related compounds in the 11-deoxy series, which afford advantages with respect to stability and perhaps also to selectivity of biological effect, a most important consideration. It also was of obvious interest to prepare such compounds in which the  $\alpha$  chain (C<sub>1</sub>-C<sub>7</sub>) would be expected to be resistant to fatty acid  $\beta$ -oxidation,<sup>4</sup> the second major course of prostaglandin metabolic inactivation.<sup>5</sup>

**Chemistry.** Our synthetic approach utilizes as its key step the facile conjugate addition of an appropriately blocked 3-oxy-3- or 4-substituted (C<sub>15</sub> or C<sub>16</sub> in the ultimate prostaglandin) (*E*)-1-alkenyllithium cuprate<sup>1,6</sup> or -lithium alanate<sup>4a</sup> to cyclopentenones. Critical to this approach is the synthesis of the requisite (*E*)-1-alkenyl 1-iodides for the preparation of the organometallic reagent.

For the 16,16-dimethyl series, the required vinyl iodide **4**<sup>7</sup> was prepared as illustrated in Scheme I. Condensation<sup>8</sup> of aldehyde **1**<sup>9</sup> with acetylenemagnesium bromide afforded alcohol **2**, which was converted to the trimethylsilyl ether **3**. The choice of blocking group is important since hindrance by the adjacent *gem*-dimethyl group increases the stability of the blocked ether. Thus, conditions required for effective deblocking of the more bulky trityl or dimethyl *tert*-butylsilyl ethers were now too vigorous and resulted in at least partial disruption of the allylic 15-hydroxy function and, in the 11-hydroxy series, of the  $\beta$ -ketol function. On the other hand, the usually highly labile trimethylsilyl ether was now sufficiently stable to

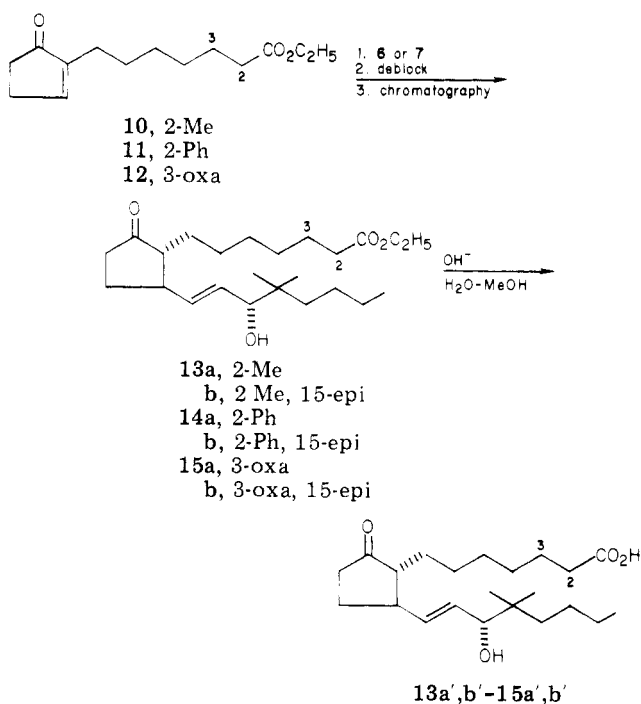
Scheme I



<sup>a</sup> See ref 11.

survive the conditions of conjugate addition. Hydroboration-oxidation-iodination of the acetylene function

## Scheme II



of 3 by the procedure of Kluge and co-workers<sup>10</sup> furnished vinyl iodide 4.<sup>11</sup>

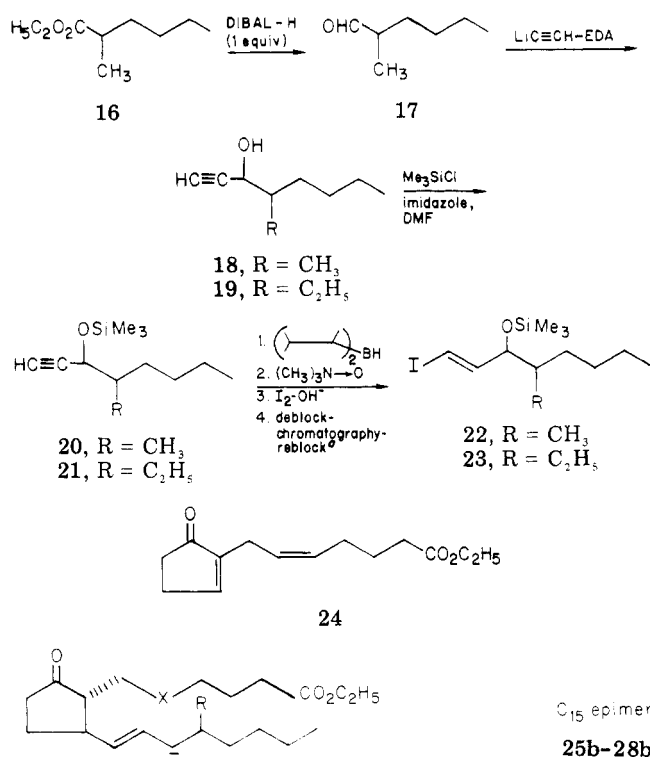
Metallation of 4 with butyllithium provided the corresponding alkenyllithium reagent 5, which was converted to either the lithium cuprate 6 or lithium alanate 7 by treatment with copper(I) pentyne ( $\text{CuC}\equiv\text{CC}_3\text{H}_7$ )<sup>12</sup>–hexamethylphosphorous triamide (HMPTA)<sup>12b</sup> or trimethylaluminum,<sup>4a</sup> respectively. Submission of 7 to cyclopentenone 8,<sup>13,14</sup> followed by deblocking, saponification, and dry column chromatography, gave *dl*-11-deoxy-16,16-dimethylprostaglandin  $\text{E}_1$  (9a') and its  $\text{C}_{15}$  epimer 9b'.<sup>15,16</sup> By analogous procedures, the ethyl esters of the 2-methyl (13a,b), 2-phenyl (14a,b), both of which are presumably mixtures of C-2 epimers, and 3-oxa (15a,b) derivatives of this series were obtained from cyclopentenones 10–12,<sup>14</sup> respectively, the 2-methyl analogues via 7, and the others by the cuprate procedure (Scheme II). Alkaline hydrolysis of these 11-deoxy esters afforded the corresponding acids.

For the 16 $\xi$ -methyl series (Scheme III), partial reduction of ethyl 2-methylhexanoate (16) with diisobutylaluminum hydride (DIBAL-H)<sup>17</sup> provided aldehyde 17<sup>18</sup> in 77% yield. Treatment of 17 with lithium acetylide–ethylenediamine complex ( $\text{LiC}\equiv\text{CH}\cdot\text{EDA}$ )<sup>19</sup> afforded the propargyl alcohol 18, which was trimethylsilylated and then converted to the 1-alkenyl 1-iodide 22 by the Kluge diisoamylborane procedure.<sup>10</sup> From vinyl iodide 22, by the lithium cuprate procedure, *dl*-11-deoxy-16 $\xi$ -methylprostaglandin  $\text{E}_1$  ethyl ester (25a) and *dl*-11-deoxy-16 $\xi$ -methylprostaglandin  $\text{E}_2$  ethyl ester (26a) and their respective  $\text{C}_{15}$  epimers<sup>15,16</sup> were prepared using cyclopentenones 8<sup>13,14</sup> and 24,<sup>20</sup> respectively. Saponification then provided the corresponding acids.<sup>21</sup>

The 16 $\xi$ -ethyl derivatives of *dl*-11-deoxyprostaglandin  $\text{E}_1$  (27a',b') and *dl*-11-deoxyprostaglandin  $\text{E}_2$  (28a',b') were similarly prepared (Scheme III). The requisite vinyl iodide 23 was obtained from commercially available 4-ethyl-3-hydroxy-1-octyne (19) by trimethylsilylation and hydroiodination.<sup>10</sup>

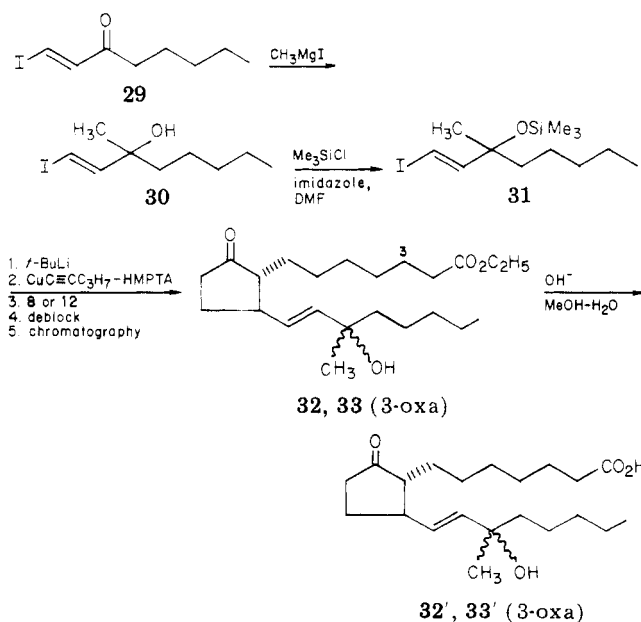
The synthesis of the *dl*-11-deoxy-15 $\xi$ -methylprostaglandins is illustrated in Scheme IV. Addition of methylmagnesium iodide to iodovinyl ketone 29<sup>10</sup> provided the tertiary alcohol 30 which was protected to give (*E*)-1-

## Scheme III



<sup>a</sup> See ref 11.

## Scheme IV



iodo-3-methyl-3-trimethylsilyloxy-1-octene (31). Conjugate addition of the cuprate derived from 31 to cyclopentenones 8<sup>13,14</sup> and 12<sup>14</sup> afforded *dl*-11-deoxy-15 $\xi$ -methylprostaglandin  $\text{E}_1$  ethyl ester (32) and *dl*-11-deoxy-15 $\xi$ -methyl-3-oxaprostaglandin  $\text{E}_1$  ethyl ester (33), respectively. For each of these preparations we were unable to effect separation of the 15-epimeric racemates,<sup>22</sup> the presence of which was demonstrated by <sup>13</sup>C NMR. Alkaline hydrolysis of 33 and 34 furnished acids 33'<sup>23</sup> and 34', respectively.

**Biology.** The various 15- and 16-alkyl derivatives were tested as potential bronchodilators by the guinea pig bronchodilator assays<sup>1,24</sup> (see Experimental Section) using the intravenous route against bronchoconstrictions induced by serotonin, histamine, and acetylcholine. The results are summarized in Table I. It is clear from these results that the introduction of one<sup>21</sup> or two methyl groups in the 16 position or of a methyl group to C<sub>15</sub><sup>23</sup> is consistent with high potency. However, a *gem*-dimethyl feature at C<sub>17</sub> leads to significantly diminished activity.<sup>25</sup> In the E<sub>2</sub> series, but apparently not in the E<sub>1</sub> series, a C<sub>16</sub>-ethyl group results in diminished activity relative to the corresponding 16 $\xi$ -methyl congener.

As to modifications of the  $\alpha$  chain (C<sub>1</sub>–C<sub>7</sub>), introduction of a methyl or phenyl group at C<sub>2</sub> was not consistent with activity in this assay. However, replacement of C<sub>3</sub> with oxygen did provide compounds of high potency.

The 15-epi derivatives of the active compounds of this series also appeared to be effective bronchodilators but of diminished potency. With a few exceptions the ethyl esters were significantly less potent than their corresponding acids, due perhaps to poor solubilization or poor resorption.

Despite the good potency displayed by many of these congeners, this series proved uninteresting since these compounds are generally characterized by initial, brief, spasmogenic effects. These latter effects are observed not only in the intravenous guinea pig assays but also with selected examples when administered by aerosol to pilocarpine-bronchoconstricted dogs.<sup>26,27</sup>

## Experimental Section

All organometallic reactions were performed under an inert atmosphere of argon or nitrogen. All organic extracts were dried with anhydrous MgSO<sub>4</sub> or Na<sub>2</sub>SO<sub>4</sub>. Solvents were removed under reduced pressure using a Büchi evaporator.

Infrared spectra were recorded with neat samples on a Perkin-Elmer Model 21 spectrophotometer. Proton magnetic resonance spectra were determined in CDCl<sub>3</sub> using Varian A-60 or HA-100D spectrophotometers. Chemical shifts are given in parts per million downfield from an internal (CH<sub>3</sub>)<sub>4</sub>Si standard. Those analytical results indicated by symbol only were within  $\pm 0.4\%$  of their calculated values. Mass spectra were recorded on an AEI MS-9 at 70 eV. Only characteristic spectral data are presented for each compound.

**General Alanate Conjugate Addition Procedure. Preparation of dl-11-Deoxy-16,16-dimethyl-2-methylprostaglandin E<sub>1</sub> Ethyl Ester (13a) and 15-Epimer 13b.** To a stirred solution of 27.3 g (60 mmol) of vinyl iodide 4 and 20 mL of anhydrous toluene cooled to  $-40^\circ\text{C}$  was added 26.1 mL (60 mmol) of *n*-BuLi (2.3 M in hexanes). The resulting solution was warmed to  $0^\circ\text{C}$  for 3 h and 40 min and then 79.8 mL (60 mmol) of trimethylaluminum (0.75 M in heptane) was added. The reaction mixture was warmed to  $20^\circ\text{C}$  for 30 min, diluted with 20 mL of anhydrous ether, and recooled to  $78^\circ\text{C}$ , and to it was added 15.35 g (60.1 mmol) of 2-(6-carbethoxyhexyl-6-methyl)cyclopent-2-en-1-one (10)<sup>14</sup> and 35 mL of anhydrous ether. The reaction mixture was warmed to ambient temperature, stirred for 24 h, and then poured into a solution of 20 mL of concentrated HCl and 500 g of iced water. After 30 min, the aqueous phase was separated and extracted with ether. The combined organic phases were washed with brine, dried, and concentrated in vacuo to give 30 g of an oil. The oil was applied to a silica gel dry column (3  $\times$  72 in.; 1:9 EtOAc–benzene). The product was isolated from the column to give 6.2 g of an oil. This oil was treated with a solution of 140 mL of acetic acid–THF–water (4:2:1) for 10 min, diluted with xylene, and concentrated in vacuo to give 5.3 g of oil. The oil was applied to a silica gel dry column (2  $\times$  72 in.; 1:4 EtOAc–benzene).

The more polar product 13a<sup>15,16</sup> was isolated as 1.937 g (8%) of an oil: IR 3700, 1739, and 975 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  5.63 (m, 2 H, C-13,14 H), 4.11 (q, 2 H,  $-\text{OCH}_2\text{CH}_3$ ,  $J = 7$  Hz), 3.81 (m, 1 H, C-15 H), 2.30 (m, 1 H, C-2 H), 1.62 (m, 1 H, OH), 1.11 (d, 3 H, C-2 CH<sub>3</sub>,  $J = 7$  Hz), 0.90 (t, 3 H, C-20 H), 0.87 and 0.83 (s and s, 6 H, *gem*-dimethyl H). Anal. (C<sub>25</sub>H<sub>44</sub>O<sub>4</sub>) C, H.

The less polar product 13b<sup>15,16</sup> was isolated as 1.512 g (6%) of an oil: IR 3640, 1739, and 975 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  5.65 (m, 2 H, C-13,14 H), 4.12 (q, 2 H,  $-\text{OCH}_2\text{CH}_3$ ,  $J = 7$  Hz), 3.82 (m, 1 H, C-15 H), 2.30 (m, 1 H, C-2 H), 1.62 (m, 1 H, OH), 1.11 (d, 1 H, C-2 CH<sub>3</sub>,  $J = 7$  Hz), 0.90 (t, 3 H, C-20 H), 0.83 and 0.81 (s and s, 6 H, *gem*-dimethyl H). Anal. (C<sub>25</sub>H<sub>44</sub>O<sub>4</sub>) C, H.

Also isolated was 0.217 g (1%) of a mixture of 13a and 13b.

**General Cuprate Conjugate Addition Procedure. Preparation of dl-11-Deoxy-16,16-dimethyl-2-phenylprostaglandin E<sub>1</sub> Ethyl Ester (14a) and 15-Epimer 14b.** To a stirred solution of 9.28 g (26.2 mmol) of vinyl iodide 4 and 5 mL of dry ether cooled to  $-78^\circ\text{C}$  was slowly added 66 mL (52.8 mmol) of *t*-BuLi (0.8 M in pentane). After 1 h, the solution was warmed to  $-10^\circ\text{C}$  for 1 h and recooled to  $-78^\circ\text{C}$ , and to it was added a solution of 3.50 g (26.8 mmol) of copper(I) pentyne,<sup>12</sup> 11 mL of hexamethylphosphorous triamide (HMPTA),<sup>12b</sup> and 60 mL of dry ether. After 1 h, a solution of 7.99 g (25.4 mmol) of 2-(6-carbethoxyhexyl-6-phenyl)cyclopent-2-en-1-one (11)<sup>14</sup> and 80 mL of dry ether was added. The solution was stirred for 30 min, warmed to  $-15^\circ\text{C}$  for 75 min, and poured into 600 mL of saturated NH<sub>4</sub>Cl. After vigorous stirring for 2 h the resulting blue solution was extracted with 500 mL of ether in four portions. The combined ether extracts were washed with 1% H<sub>2</sub>SO<sub>4</sub> and brine, dried, and concentrated in vacuo to give 13.26 g of brown liquid. A solution of the 13.26 g and 210 mL of acetic acid–THF–H<sub>2</sub>O (4:2:1) was stirred at ambient temperature for 20 min, diluted with toluene, and concentrated in vacuo to afford 10.82 g of brown oil. This oil was applied to a dry column of 1200 g of silica gel [3 in. flat  $\times$  47 in. packed; EtOAc–benzene (1:9); 300 mL of eluent was collected].

The more polar isomer 14a<sup>15,16</sup> was isolated from the column at  $R_f$  0.15–0.28 as 2.05 g (17%) of a yellow oil: IR 3600, 1740, 1600, 970, 735, and 700 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.33 (s, 5 H, C<sub>6</sub>H<sub>5</sub>), 5.63 (m, 2 H, C-13,14 H), 4.13 (q, 2 H,  $-\text{OCH}_2\text{CH}_3$ ,  $J = 7$  Hz), 3.83 (m, 1 H, C-15 H), 3.53 (t, 1 H, C-2 H,  $J = 7$  Hz), 0.90 (t, 3 H, C-20 H), 0.88 and 0.83 (s and s, 6 H, *gem*-dimethyl H). Anal. (C<sub>30</sub>H<sub>40</sub>O<sub>4</sub>) C, H.

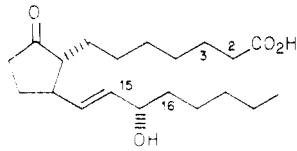
The less polar isomer 14b<sup>15,16</sup> was isolated from the column at  $R_f$  0.36–0.51 as 3.23 g (27%) of a yellow oil: IR 3600, 1740, 1600, 970, 735, and 700 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.35 (s, 5 H, C<sub>6</sub>H<sub>5</sub>), 5.67 (m, 2 H, C-13,14 H), 4.13 (q, 2 H,  $-\text{OCH}_2\text{CH}_3$ ,  $J = 7$  Hz), 3.82 (m, 1 H, C-15 H), 3.50 (t, 1 H, C-2 H,  $J = 7$  Hz), 0.90 (t, 3 H, C-20 H), 0.88 and 0.83 (s and s, 6 H, *gem*-dimethyl H). Anal. (C<sub>30</sub>H<sub>40</sub>O<sub>4</sub>) C, H.

**General Saponification Procedure. Preparation of dl-11-Deoxy-16,16-dimethyl-2-phenylprostaglandin E<sub>1</sub> (14a').** A solution of the ester and MeOH–H<sub>2</sub>O (1:1) containing NaOH or KOH ( $\sim 6$ –7 equiv) was stirred at ambient temperature for 24–72 h (for the 2-phenyl derivatives, 7–10 h of reflux were required). The resulting solution was extracted with ether, and the extracts were discarded. The remaining aqueous phase was acidified (5% HCl) and extracted with ether. The combined ether extracts were washed with brine, dried, and concentrated in vacuo to furnish the acid.

Thus, 845 mg (56%) of 14a' was obtained as an amber oil: IR 3600–3400, 2700–2500, 1740, 1690, 1600, 970, 725, and 695 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.00 (s, 5 H, C<sub>6</sub>H<sub>5</sub>), 6.43 (m, 2 H, OH), 5.63 (m, 2 H, C-13,14 H), 3.85 (m, 1 H, C-15 H), 3.53 (t, 1 H, C-2 H,  $J = 7$  Hz), 0.90 (t, 3 H, C-20 H), 0.87 and 0.83 (s and s, 6 H, *gem*-dimethyl H). Anal. (C<sub>28</sub>H<sub>42</sub>O<sub>4</sub>) C, H.

**4,4-Dimethyl-3-hydroxy-1-octyne (2).** (Acetylene was continuously bubbled into the reaction mixture during the entire procedure.) To 300 mL of anhydrous THF, saturated with acetylene, was added dropwise with stirring 156 mL (0.5 mol) of *n*-butylmagnesium chloride (3.2 M in THF) while maintaining the temperature between 20 and 25  $^\circ\text{C}$ . The reaction was stirred for 1 h after addition was complete, and then 29.5 g (0.23 mmol) of 2,2-dimethylhexanal (1)<sup>9</sup> in an equal volume of THF was added dropwise. After 1 h, the reaction mixture was poured into an ice-cold saturated NH<sub>4</sub>Cl solution. The aqueous phase was separated and extracted with ether. The combined organic phases were washed with brine, dried, and concentrated in vacuo to give a yellow liquid. Distillation afforded 27 g (76%) of 2 as a colorless liquid: bp 47–48  $^\circ\text{C}$  (0.8 mm); IR 3509 and 3390 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  4.10 [m, 1 H,  $-\text{CH}(\text{OH})-$ ], 2.45 (d, 1 H,  $\text{HC}\equiv\text{CCH}_2-$ ,  $J = 2$  Hz), 1.87 (m, 1 H, OH), 0.98 (t, 3 H, CH<sub>2</sub>CH<sub>3</sub>), and 0.96 (s, 6 H,

Table I. Bronchodilator Activity of *dl*-11-Deoxy-15- or 16-alkylprostaglandins

Compd <sup>a</sup>	α-Chain (C <sub>1</sub> -C <sub>5</sub> ) variant	β-Chain (C <sub>13</sub> -C <sub>20</sub> ) variant	Yield, %	Formula	Analyses <sup>b</sup>	Guinea pig bronchodilator assays, <sup>c</sup> ED <sub>50</sub> , g/kg			
						Sero- tonin	Hista- mine	Acetyl- choline	
									
<i>dl</i> -11-Deoxy-PGE <sub>1</sub>						397 × 10 <sup>-9</sup>	3.4 × 10 <sup>-6</sup>	> 32 × 10 <sup>-6</sup>	
9a <sup>i</sup>	None	16,16-Dimethyl	10 <sup>d</sup>	19 <sup>d,e</sup>	C <sub>22</sub> H <sub>38</sub> O <sub>4</sub>	C, H	25.9 × 10 <sup>-6</sup>	4.17 × 10 <sup>-6</sup>	42.9 × 10 <sup>-6</sup>
9b <sup>i</sup>	None	16,16-Dimethyl, 15-epi	7 <sup>d</sup>		C <sub>22</sub> H <sub>38</sub> O <sub>4</sub>	C, H	19.0 × 10 <sup>-6</sup>	107 × 10 <sup>-6</sup>	135 × 10 <sup>-6</sup>
13a	2ξ-Methyl, ethyl ester	16,16-Dimethyl	8	1 <sup>e</sup>	C <sub>25</sub> H <sub>44</sub> O <sub>4</sub>	C, H			
13b	2ξ-Methyl, ethyl ester	16,16-Dimethyl, 15-epi	6		C <sub>25</sub> H <sub>44</sub> O <sub>4</sub>	C, H			
13a <sup>i</sup>	2ξ-Methyl	16,16-Dimethyl	91 <sup>f</sup>		C <sub>23</sub> H <sub>40</sub> O <sub>4</sub>	C, H	<i>g</i>	<i>g</i>	<i>g</i>
13b <sup>i</sup>	2ξ-Methyl	16,16-Dimethyl, 15-epi	94 <sup>f</sup>		C <sub>23</sub> H <sub>40</sub> O <sub>4</sub>	C, H	<i>g</i>	<i>g</i>	<i>g</i>
14a	2ξ-Phenyl, ethyl ester	16,16-Dimethyl	17		C <sub>30</sub> H <sub>46</sub> O <sub>4</sub>	C, H	<i>g</i>	<i>g</i>	<i>g</i>
14b	2ξ-Phenyl, ethyl ester	16,16-Dimethyl, 15-epi	27		C <sub>30</sub> H <sub>46</sub> O <sub>4</sub>	C, H	<i>g</i>	<i>g</i>	<i>g</i>
14a <sup>i</sup>	2ξ-Phenyl	16,16-Dimethyl	56 <sup>f</sup>		C <sub>28</sub> H <sub>42</sub> O <sub>4</sub>	C, H	<i>g</i>	<i>g</i>	<i>g</i>
14b <sup>i</sup>	2ξ-Phenyl	16,16-Dimethyl, 15-epi	86 <sup>f</sup>		C <sub>28</sub> H <sub>42</sub> O <sub>4</sub>	C, H	<i>g</i>	<i>g</i>	<i>g</i>
15a	3-Oxa, ethyl ester	16,16-Dimethyl	7	4 <sup>e</sup>	C <sub>23</sub> H <sub>40</sub> O <sub>5</sub>	C, H	123 × 10 <sup>-6</sup>	69.6 × 10 <sup>-6</sup>	96.7 × 10 <sup>-6</sup>
15b	3-Oxa, ethyl ester	16,16-Dimethyl, 15-epi	11		C <sub>23</sub> H <sub>40</sub> O <sub>5</sub>	C, H	209 × 10 <sup>-6</sup>	194 × 10 <sup>-6</sup>	349 × 10 <sup>-6</sup>
15a <sup>i</sup>	3-Oxa	16,16-Dimethyl	78 <sup>f</sup>		C <sub>21</sub> H <sub>36</sub> O <sub>5</sub>	C, H	185 × 10 <sup>-6</sup>	(32 × 10 <sup>-6</sup> ) <sup>h</sup>	550 × 10 <sup>-6</sup>
15b <sup>i</sup>	3-Oxa	16,16-Dimethyl, 15-epi	77 <sup>f</sup>		C <sub>21</sub> H <sub>36</sub> O <sub>5</sub>	C, H	(32 × 10 <sup>-6</sup> ) <sup>h</sup>	373 × 10 <sup>-6</sup>	558 × 10 <sup>-6</sup>
25a	Ethyl ester	16ξ-Methyl	4	8 <sup>e</sup>	C <sub>23</sub> H <sub>40</sub> O <sub>4</sub>	H; C <sup>i</sup>	(320 × 10 <sup>-9</sup> ) <sup>h</sup>	(32 × 10 <sup>-9</sup> ) <sup>h</sup>	<i>g</i>
25b	Ethyl ester	16ξ-Methyl, 15-epi	3		C <sub>23</sub> H <sub>40</sub> O <sub>4</sub>	C, H	99.3 × 10 <sup>-6</sup>	(32 × 10 <sup>-6</sup> ) <sup>h</sup>	396 × 10 <sup>-6</sup>
25a <sup>j</sup>	None	16ξ-Methyl	57 <sup>f</sup>		C <sub>21</sub> H <sub>36</sub> O <sub>4</sub>	<i>k</i>	346 × 10 <sup>-6</sup>	(320 × 10 <sup>-6</sup> ) <sup>h</sup>	> 320 × 10 <sup>-6</sup>
25b <sup>i</sup>	None	16ξ-Methyl, 15-epi	96 <sup>f</sup>		C <sub>21</sub> H <sub>36</sub> O <sub>4</sub>	<i>k</i>	7.01 × 10 <sup>-6</sup>	73.2 × 10 <sup>-6</sup>	9.89 × 10 <sup>-6</sup>
26a	PGE <sub>2</sub> series, ethyl ester	16ξ-Methyl	15	2 <sup>e</sup>	C <sub>23</sub> H <sub>38</sub> O <sub>4</sub>	C, H	179 × 10 <sup>-9</sup>	65.7 × 10 <sup>-9</sup>	<i>g</i>
26b	PGE <sub>2</sub> series, ethyl ester	16ξ-Methyl, 15-epi	17		C <sub>23</sub> H <sub>38</sub> O <sub>4</sub>	C, H	9.65 × 10 <sup>-6</sup>	1.37 × 10 <sup>-6</sup>	> 320 × 10 <sup>-6</sup>
26a <sup>j</sup>	PGE <sub>2</sub> series	16ξ-Methyl	98 <sup>f</sup>		C <sub>21</sub> H <sub>34</sub> O <sub>4</sub>	H; C <sup>l</sup>	1.35 × 10 <sup>-6</sup>	108 × 10 <sup>-9</sup>	1.63 × 10 <sup>-6</sup>
26b <sup>i</sup>	PGE <sub>2</sub> series	16ξ-Methyl, 15-epi	99 <sup>f</sup>		C <sub>21</sub> H <sub>34</sub> O <sub>4</sub>	C, H	39.9 × 10 <sup>-6</sup>	2.99 × 10 <sup>-6</sup>	87.5 × 10 <sup>-6</sup>
27a	Ethyl ester	16ξ-Ethyl	8	18 <sup>e</sup>	C <sub>24</sub> H <sub>42</sub> O <sub>4</sub>	C, H	1.11 × 10 <sup>-3</sup>	(32 × 10 <sup>-6</sup> ) <sup>h</sup>	145 × 10 <sup>-6</sup>
27b	Ethyl ester	16ξ-Ethyl, 15-epi	26		C <sub>24</sub> H <sub>42</sub> O <sub>4</sub>	C, H	1.74 × 10 <sup>-3</sup>	2.70 × 10 <sup>-3</sup>	<i>g</i>
27a <sup>i</sup>	None	16ξ-Ethyl	87 <sup>f</sup>		C <sub>22</sub> H <sub>38</sub> O <sub>4</sub>	C, H	9.77 × 10 <sup>-6</sup>	(32 × 10 <sup>-6</sup> ) <sup>h</sup>	113 × 10 <sup>-6</sup>
27b <sup>i</sup>	None	16ξ-Ethyl, 15-epi	95 <sup>f</sup>		C <sub>22</sub> H <sub>38</sub> O <sub>4</sub>	H; C <sup>m</sup>	> 3.2 × 10 <sup>-6</sup>	(32 × 10 <sup>-6</sup> ) <sup>h</sup>	<i>g</i>
28a	PGE <sub>2</sub> series, ethyl ester	16ξ-Ethyl	17	9 <sup>e</sup>	C <sub>24</sub> H <sub>40</sub> O <sub>4</sub>	C, H			
28b	PGE <sub>2</sub> series, ethyl ester	16ξ-Ethyl, 15-epi	25		C <sub>24</sub> H <sub>40</sub> O <sub>4</sub>	H; C <sup>n</sup>			
28a <sup>i</sup>	PGE <sub>2</sub> series	16ξ-Ethyl	80 <sup>f</sup>		C <sub>22</sub> H <sub>36</sub> O <sub>4</sub>	C, H	79.1 × 10 <sup>-6</sup>	<i>g</i>	<i>g</i>
28b <sup>i</sup>	PGE <sub>2</sub> series	16ξ-Ethyl, 15-epi	80 <sup>f</sup>		C <sub>22</sub> H <sub>36</sub> O <sub>4</sub>	C; H <sup>o</sup>	2.21 × 10 <sup>-3</sup>	<i>g</i>	<i>g</i>
32	Ethyl ester	15ξ-Methyl	29 <sup>e</sup>		C <sub>23</sub> H <sub>40</sub> O <sub>4</sub>	C, H	6.99 × 10 <sup>-6</sup>	4.24 × 10 <sup>-6</sup>	(3.2 × 10 <sup>-6</sup> ) <sup>h</sup>
32 <sup>p</sup>	None	15ξ-Methyl	68 <sup>e,f</sup>		C <sub>21</sub> H <sub>36</sub> O <sub>4</sub>	C, H			
33	3-Oxa, ethyl ester	15ξ-Methyl	37 <sup>e</sup>		C <sub>22</sub> H <sub>38</sub> O <sub>5</sub>	C, H	78.8 × 10 <sup>-6</sup>	282 × 10 <sup>-6</sup>	618 × 10 <sup>-6</sup>
33 <sup>i</sup>	3-Oxa	15ξ-Methyl	92 <sup>e,f</sup>		C <sub>20</sub> H <sub>34</sub> O <sub>5</sub>	C, H	121 × 10 <sup>-6</sup>	25.6 × 10 <sup>-6</sup>	73.7 × 10 <sup>-6</sup>
34a <sup>q</sup>	None	17,17-Dimethyl					196 × 10 <sup>-6</sup>	316 × 10 <sup>-6</sup>	483 × 10 <sup>-6</sup>
<i>l</i> -PGE <sub>1</sub>							1.07 × 10 <sup>-6</sup>	7.0 × 10 <sup>-7</sup>	3.3 × 10 <sup>-6</sup>

## Footnotes to Table I

<sup>a</sup> Spectral data for all compounds are consistent with the assigned structures. See also ref 15 and 16. <sup>b</sup> Analyses indicated by letter only were within  $\pm 0.4\%$  of the calculated values. <sup>c</sup> The broncholytic activity of each compound was measured in at least four guinea pigs for each of the three spasmogenic substances at each dose level. The median standard error for  $ED_{50}$  values was 0.3 log unit. See also Experimental Section and ref 24. <sup>d</sup> Yields resulting from saponification of the conjugate adducts, followed by epimeric separation at the acid stage. <sup>e</sup> Yields of C-15 epimeric racemates. <sup>f</sup> Saponification yields. <sup>g</sup> At 3.2 mg/kg the inhibition of bronchoconstriction was less than 50%. <sup>h</sup> The lowest dose providing  $\geq 50\%$  inhibition of constriction; a flat dose-response effect was obtained. <sup>i</sup> C: calcd, 72.59; found, 71.72. <sup>j</sup> Reference 21. <sup>k</sup> Product identified by TLC, IR, and <sup>1</sup>H NMR. <sup>l</sup> C: calcd, 71.96; found, 71.22. <sup>m</sup> C: calcd, 72.09; found, 71.63. <sup>n</sup> C: calcd, 73.43; found, 72.76. <sup>o</sup> H: calcd, 9.96; found, 9.38. <sup>p</sup> Reference 23. <sup>q</sup> Prepared by an analogous procedure from 3,3-dimethylpentanal; unpublished observation from these laboratories.

*gem*-dimethyl H). Anal. ( $C_{10}H_{18}O$ ) H; C: calcd, 77.86; found, 77.36.

**4,4-Dimethyl-3-trimethylsilyloxy-1-octyne (3).** To a solution of 27 g (0.175 mol) of alcohol 2, 34 g (0.49 mol) of imidazole, and 300 mL of DMF, cooled in an ice bath, was added slowly 26.4 g (0.245 mol) of trimethylchlorosilane. The reaction mixture was stirred at room temperature overnight and then poured into a mixture of hexane-water. The hexane layer was separated, washed with water and brine, dried, and evaporated to dryness to yield a yellow liquid. Distillation afforded 30.5 g (77%) of 3: bp 38–40 °C (0.05 mm); IR 3225, 877, and 847  $cm^{-1}$ ; <sup>1</sup>H NMR  $\delta$  4.01 [d, 1 H,  $HC\equiv CCH(OSiMe_3)-$ ,  $J = 2$  Hz], 2.33 (d, 1 H,  $HC\equiv CCH-$ ,  $J = 2$  Hz), 0.92 (t, 3 H,  $CH_2CH_3$ ), 0.90 (s, 6 H, *gem*-dimethyl H), and 0.16 [s, 9 H,  $Si(CH_3)_3$ ].

**(E)-4,4-Dimethyl-1-iodo-3-trimethylsilyloxy-1-octene (4).** To a solution of 9.09 g (0.24 mol) of  $NaBH_4$ , 37.9 g (0.54 mol) of 2-methyl-2-butene, and 350 mL of glyme, cooled to 0 to –5 °C, was added 38.39 g (0.2 mol) of boron trifluoride etherate dropwise while maintaining the reaction mixture below 0 °C. The reaction mixture was stirred at this temperature for an additional 2 h. A solution of 30.5 g (0.135 mol) of 3 and 10 mL of glyme was then added slowly, maintaining the reaction mixture below 5 °C. The reaction mixture was then allowed to warm and stirred at room temperature for 2 h. After cooling to –5 °C, 72 g (0.95 mol) of anhydrous trimethylamine oxide was added portionwise over 10 min, maintaining the temperature at 15–20 °C. After stirring for 2 h at room temperature, the reaction mixture was added to 2390 mL of ice-cold 15% NaOH solution with simultaneous addition of a solution of 192 g of iodine and 500 mL of THF and stirred for 30 min. The organic phase was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed twice with a 5% sodium thiosulfate solution (500 mL each) and brine, dried, and then evaporated to dryness. The crude material<sup>11</sup> was treated with 700 mL of a solution of acetic acid-THF-water (4:2:1) for 10 min, diluted with toluene, and concentrated in vacuo to give 38 g of a yellow liquid, which was dry column chromatographed (silica gel; benzene) to give (E)-4,4-dimethyl-3-hydroxy-1-iodo-1-octene as a pale yellow liquid: IR 3400, 1605, and 950  $cm^{-1}$ ; <sup>1</sup>H NMR  $\delta$  6.66 (dd, 1 H,  $ICH=CH-$ ,  $J_{1,2} = 14$  Hz,  $J_{2,3} = 6$  Hz), 6.28 (d, 1 H,  $ICH=CH-$ ,  $J = 14$  Hz), 3.76 [d, 1 H,  $-CH(OH)-$ ,  $J = 6$  Hz], 2.55 (m, 1 H,  $-OH$ ), 0.90 (t, 3 H,  $-CH_2CH_3$ ), 0.83 and 0.80 (s and s, 6 H, *gem*-dimethyl H).

Silylation of this material by the procedure described above for 3 furnished 19.79 g (41% from 3) of 4 as a yellow oil: bp 72–74 °C (0.05 mm); IR 1600, 955, 885, and 845  $cm^{-1}$ ; <sup>1</sup>H NMR  $\delta$  6.56 (dd, 1 H,  $ICH=CH-$ ,  $J_{1,2} = 14$  Hz,  $J_{2,3} = 6$  Hz), 6.08 (d, 1 H,  $ICH=CH-$ ,  $J = 14$  Hz), 3.52 [d, 1 H,  $-CH(OSiMe_3)-$ ,  $J = 6$  Hz], 0.91 (t, 3 H,  $-CH_2CH_3$ ), 0.82 and 0.80 (s and s, 6 H, *gem*-dimethyl H), and 0.10 [s, 9 H,  $Si(CH_3)_3$ ]. Anal. ( $C_{13}H_{27}OISi$ ) C, H, I.

**Ethyl 2-Methylhexanoate (16).** A solution of 25 g (0.192 mol) of 2-methylhexanoic acid and 200 mL of absolute ethanol containing 400 mg of *p*-toluenesulfonic acid was refluxed under an argon atmosphere for 30 h. The solution was cooled and then evaporated to dryness in vacuo. The residual oil was dissolved in ether, washed with saturated  $NaHCO_3$  and brine, dried, and evaporated to dryness. Distillation of the crude material provided 21.9 g (73%) of 16 as a colorless liquid: bp 58 °C (11 mm); IR 1742  $cm^{-1}$ ; <sup>1</sup>H NMR  $\delta$  4.10 (q, 2 H,  $-OCH_2CH_3$ ,  $J = 7$  Hz), 2.33 (m, 1 H,  $-CHCO_2C_2H_5$ ), 1.13 (d, 3 H,  $-CH_3$ ,  $J = 7$  Hz), and 0.90 (t, 3 H,  $-CH_2CH_3$ ). Anal. ( $C_9H_{18}O_2$ ) C, H.

**2-Methylhexanal (17).** A solution of 9 g (56.9 mmol) of ethyl 2-methylhexanoate (16) in 100 mL of dry toluene was cooled to –75 °C and 75 mL (68.3 mmol) of 0.91 M diisobutylaluminum hydride was added. The solution was kept at –75 °C for 2 h before

150 mL of saturated bisulfite solution was added. The solution was allowed to warm to room temperature, solids were removed by filtration, and the layers were separated. The toluene layer was extracted twice with bisulfite which was combined with the aqueous layer, basified with 2 N NaOH to pH 8–9 (with cooling), and extracted with ether. The ether was washed with water, dried, and evaporated to give 5 g (77%) of 17 as a colorless oil: IR 2700 and 1724  $cm^{-1}$ ; <sup>1</sup>H NMR  $\delta$  9.63 (d, 1 H,  $CHO$ ,  $J = 2$  Hz), 2.30 (m, 1 H,  $-CHCHO$ ), 1.08 (d, 3 H,  $-CH_3$ ,  $J = 7$  Hz), and 0.93 (t, 3 H,  $-CH_2CH_3$ ).

**3-Hydroxy-4-methyl-1-octyne (18).** To a solution of 20 g (0.217 mol) of lithium acetylide-ethylenediamine complex in 160 mL of dry  $Me_2SO$  was added dropwise 15.49 g (0.1349 mmol) of 2-methylhexanal 17 in 10 mL of  $Me_2SO$ . The resulting mixture was stirred at ambient temperature for 18 h and then poured into iced HCl. The solution was extracted several times with ether. The combined extracts were washed with brine, dried, taken to dryness, and distilled to furnish 13.9 g (73%) of 18 as a pale yellow oil: bp 80–82 °C (11 mm); IR 3500, 3300, and 2105  $cm^{-1}$ .

**4-Methyl-3-trimethylsilyloxy-1-octyne (20).** Silylation of 18 by the procedure described above for 3 afforded 14.3 g (67%) of 20: bp 81–83 °C (11 mm);  $R_f$  0.8 (benzene); IR 3300, 873, and 840  $cm^{-1}$ ; <sup>1</sup>H NMR  $\delta$  4.25 (m, 1 H,  $HC\equiv CCHCH-$ ), 2.34 (d, 1 H,  $HC\equiv CCH-$ ,  $J = 2$  Hz), 0.96 (m, 6 H,  $-CH_2CH_3$  and  $CH_3$ ), and 0.23 [s, 9 H,  $(CH_3)_3Si$ ]. Anal. ( $C_{12}H_{24}OSi$ ) C, H.

**4-Ethyl-3-trimethylsilyloxy-1-octyne (21).** Silylation, by the procedure described above for 3, of 4-ethyl-3-hydroxy-1-octyne (19) provided 64 g (97%) of 4-ethyl-3-trimethylsilyloxy-1-octyne (21): bp 91–93 °C (15 mm); IR 3333, 880, and 845  $cm^{-1}$ . Anal. ( $C_{13}H_{26}OSi$ ) C, H.

**(E)-1-Iodo-4-methyl-3-trimethylsilyloxy-1-octene (22).** Hydroboration-oxidation-iodination of 20 by the procedure described above for 4 provided 12.8 g (56%) of 22: bp 70 °C (0.075 mm); IR 1613, 881, and 840  $cm^{-1}$ ; <sup>1</sup>H NMR  $\delta$  6.56 (dd, 1 H,  $ICH=CHCH-$ ,  $J_{1,2} = 14$  Hz,  $J_{2,3} = 6$  Hz), 6.13 (d, 1 H,  $ICH=CH-$ ,  $J = 14$  Hz), 3.93 [m, 1 H,  $CHCH(OSiMe_3)-$ ], 0.94 (m, 6 H,  $-CH_2CH_3$  and  $-CH_3$ ), and 0.10 [s, 9 H,  $(CH_3)_3Si$ ]. A satisfactory analysis could not be obtained, but the material was adequate for further transformations.

**(E)-4-Ethyl-1-iodo-3-trimethylsilyloxy-1-octene (23).** Conversion of 4-ethyl-3-trimethylsilyloxy-1-octene (21) to the vinyl iodide was effected by the method described above for 4, providing 46.4 g (48%) of 23: bp 78–80 °C (0.15 mm); IR 1600, 880, and 845  $cm^{-1}$ ; <sup>1</sup>H NMR  $\delta$  6.52 (dd, 1 H,  $ICH=CH-$ ,  $J_{1,2} = 14$  Hz,  $J_{2,3} = 6$  Hz), 6.16 (d, 1 H,  $ICH=CH-$ ,  $J = 14$  Hz), 4.08 [m, 1 H,  $CH=CHCH(OSiMe_3)-$ ], 0.90 (m, 6 H,  $-CH_2CH_3$ ), and 0.18 [s, 9 H,  $(CH_3)_3Si$ ]. Anal. ( $C_{13}H_{27}OISi$ ) C, H, I.

**(E)-3-Hydroxy-1-iodo-3-methyl-1-octene (30).** To a Grignard solution prepared from 1.05 g (0.41 mol) of Mg and 6.2 g (0.435 mol) of methyl iodide in 30 mL of dry ether under argon was added dropwise 10 g of (E)-1-iodo-1-octen-3-one (29)<sup>10</sup> in 45 mL of ether. The resulting solution was stirred at ambient temperature for 1 h. After the addition of 75 mL of saturated  $NH_4Cl$  solution, the ether layer was separated and the aqueous layer was extracted several times with ether. The combined ether extracts were washed successively with  $NH_4Cl$  solution and water, dried, and taken to dryness to give 9.24 g (73%) of 63 as an oil: IR 3460, 1602, and 952  $cm^{-1}$ .

**(E)-1-Iodo-3-methyl-3-trimethylsilyloxy-1-octene (31).** Silylation of 30 by the procedure described above for 3 afforded 14.7 g of oil. Distillation provided 13.4 g (90%) of 31 as a colorless oil: bp 65 °C (0.05 mm); IR 1610, 1250, 1111, 951, 840, and 758  $cm^{-1}$ ; <sup>1</sup>H NMR  $\delta$  6.55 (d, 1 H,  $CHI=CH-$ ,  $J = 14$  Hz), 6.15 (d, 1 H,  $CHI=CH-$ ,  $J = 14$  Hz), 0.90 (t, 3 H,  $-CH_2CH_3$ ), and 0.10

[s, 9 H, (CH<sub>3</sub>)<sub>3</sub>Si]. Anal. (C<sub>12</sub>H<sub>25</sub>IOSi) C, H, I.

**Guinea Pig Bronchodilator Assay.**<sup>1,24</sup> Hartley guinea pigs of either sex, weighing 250–500 g, were anesthetized by intraperitoneal injection of urethane (1.5 g/kg) and given an intravenous injection of gallamine. They were artificially ventilated through a tracheal cannula (60 strokes/min), the respiratory volume being adjusted according to the weight of the animal and the rate of the pump.<sup>28</sup> The two jugular veins were catheterized, the first one being used for curarization and administration of the drugs and the second for the injection of the spasmogenic agent. This injection was made at different selected speeds with a perfusion pump (Braun Unita 1). The intratracheal pressure was measured with a transducer (Sanborn 267 AC) connected to the tracheal cannula and recorded on a Sanborn polygraph.

Bronchial spasms were produced by intravenous injection of acetylcholine, histamine, or serotonin. The speed of injection of the spasmogenic solution and its concentration were chosen to produce an increase of the tracheal pressure of 20–50 cm of water. For acetylcholine that dose varied from 40 to 150 µg/kg, for histamine from 5.6 to 22.5 µg/kg, and for serotonin from 7.5 to 30 µg/kg.

Injections of 12-s duration were repeated every 5 min throughout the entire assay. When three successive control bronchoconstrictions of similar intensity were obtained, the animal was considered to be ready for the assay and received the first dose of the candidate compound 2 min later.

The water-soluble compounds (sodium salts) were injected through the jugular vein. The injection required 1 min and was repeated three or four times per animal at 15-min intervals so that three or four doses, in logarithmic progression, were assayed. Water-insoluble compounds (esters) were dispersed in 10% aqueous ethanol and administered in the same way.

The broncholytic activity of each compound was measured in at least four guinea pigs for each of the three spasmogenic substances. The amplitude of the spasms (i.e., the difference between the maximum total tracheal pressure during the spasms and the normal insufflation pressure without spasm) following the administration of the drug is expressed in centimeters of water. For each spasm the mean difference vs. the control [i.e., Σ(treated spasm-control spasm)/control spasm] was calculated. For an easier expression of the results, mean difference was transformed into a percentage of variation. When the percent of variation of the first spasm following any dose of the drug reached at least –50%, a regression line of the percent of variation vs. the dose was computed in a semilogarithmic system. The ED<sub>50</sub> (dose producing a –50% variation) was then calculated.

When a compound was not active enough to allow the calculation of an ED<sub>50</sub>, the ED<sub>50</sub> is considered to be greater than the maximal dose administered.

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- See footnote q to Table I.
- A long-acting bronchial spasm is induced by an injection of 400 µg/kg followed by perfusion of 4 µg/kg/min of pilocarpine. The increase of the airway's resistance must be at least 200–300% of the resting value. After a 15-min control period the compound is administered by means of an ultrasonic aerosol device (Monaghan 650). All the parameters are then followed for at least 1 h. The activity of the compound is expressed as a percentage of inhibition

