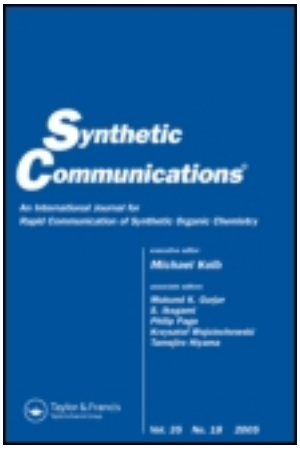

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Concise Synthesis of Dimethyl (2-Oxopropyl)phosphonate and Homologation of Aldehydes to Alkynes in a Tandem Process

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Abstract: The synthesis of dimethyl (diazomethyl)phosphonate, a useful reagent for the homologation of aldehydes to alkynes, is described as a one-pot process and comprises the generation of the azide transfer agent, diazotransfer to dimethyl (2-oxopropyl)phosphonate, and methanolysis, followed by a simple extraction protocol. Previously described syntheses for this bulk product are much more elaborate. The homologation of aldehydes to alkynes can also be extended to a single-step process by adding the aldehyde directly to the reaction mixture prior to isolation of the reagent. The homologation process using dimethyl (diazomethyl)phosphonate was shown to proceed also in nonprotic solvents with mild bases, emphasizing the importance of a facile access to the reagent. The oxidation of alcohols to the required aldehydes was performed by a TEMPO-mediated process using chloramine-T as electron acceptor.

Keywords: Alcohols, aldehydes, alkynes, homologation, oxidation

INTRODUCTION

The elaboration of aldehydes to terminal alkynes[1] with one additional carbon is a significant chemical transformation that has recently gained in importance with the increasing popularity of chemical reactions requiring this functional group.[2,3] Further to the traditional uses, many new

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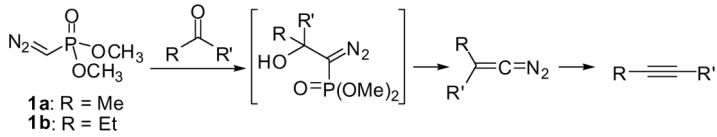
examples, such as three- and four-component reactions, a myriad of metathetic transformations, insertion reactions, click chemistry, cycloadditions, and numerous uses in natural product syntheses, underscore the pivotal role of terminally positioned acetylenes. We were primarily interested in the homologation of aldehydes to alkynes for the side-chain modification of vitamin D analogs because introduction of a C23-C24-alkyne moiety imparts metabolic resistance to the degradative sequence initiated by 24-hydroxylation.[4]

A number of protocols are available to achieve this homologation. The method of Corey and Fuchs[5] extends an aldehyde to a 1,1-dibromoalkene,[6] which is converted to the lithium acetylide by dehydrohalogenation and halogen exchange. Hydrolysis affords the terminal olefins, or, alternatively, reactions with electrophiles generate substituted alkynes. This reaction sequence was adapted to a solid-phase version within a "safety-catch" strategy,[7] while selective dehydrobrominations gave bromoacetylenes.[8] The analogous 1,1-dichloroalkene, prepared by the reaction of the aldehyde with the trichloromethyl anion followed by tosylation of the resulting alcohol and elimination, was similarly converted to the acetylene.[9] Alternatively, Wittig chloromethylenation of an aldehyde using chloromethyltriphenylphosphonium chloride and subsequent dehydrochlorination of the resulting 1-chloroalkene also leads to the terminal acetylene.[10] The conversion was also performed with dibromomethyltriphenylphosphonium bromide,[11] with diethyl dichloromethylphosphonate,[12] and by other methods. In a significant variation, Colvin and Hamill devised base-induced reactions with (diazomethyl)-trimethylsilane or (diazomethyl)phosphonic acid dimethyl ester **1a**[13] to produce acetylenes in one step. More recently, [diazo(trimethylsilyl)-methyl]phosphonous diamides served for this homologation without the addition of a base.[14] The required reagent is not readily available, however, and (1-hydroxyalkyl)phosphonic diamide, derived from the reactant aldehyde, is formed in an equimolar amount.

(Diazomethyl)trimethylsilane applications were emulated by others,[15] but the use of **1a** was fortunate because it stimulated general interest in aldehyde homologation to alkynes in view of the reaction simplicity. Procedures for the syntheses of **1a** and **1b** are available[13a,16,17] and were developed further.[18] Gilbert and Weerasooriya[19] studied the alkynylation reaction in detail and supported the originally proposed mechanism of Colvin and Hamill as shown in Scheme 1.

Homologations of aldehydes with **1a** were traditionally carried out with strong bases such as BuLi and t-BuOK, the available synthetic procedures for **1a** and **1b** are lengthy, and the products are afflicted with the stigma of instability.[20–22] Ohira[23] had shown that **2a**, the acetylated form of **1a**, was easier to prepare than **1a** itself by diazo transfer from



Scheme 1. Sequence of alkynylation reaction.

tosyl azide to dimethyl 2-(oxopropyl)phosphonate (**5a**) and that **2a** could serve directly for the homologation of aldehydes to acetylenes with potassium carbonate in methanol, hence avoiding previously employed strong bases. Accordingly, the use of **1a** was shunned in favor of **2a** and used either in accordance with the Ohira protocol, prepared in situ,[21,22] or incorporated into a solid-phase system in the form of the ROMPgel-supported reagent.[24] In actuality, however, **2a** is merely a precursor of **1a**,[23] and it is **1a** that homologates aldehydes to acetylenes under mild conditions; in other words, the notion that **1** requires strong bases for the homologation reaction is unfounded, and the need for a short synthesis of **1a** is apparent.

RESULTS AND DISCUSSION

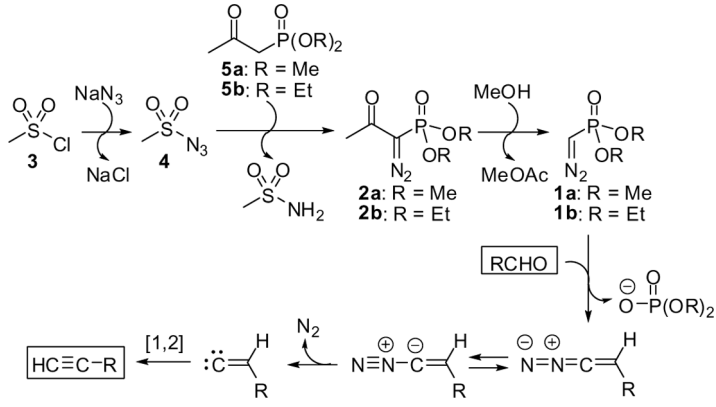
We have found that **1a**, contradicting previous beliefs, is stable for years when kept in the refrigerator; but more important, **1a** mediates, equally efficiently in crude or in pure form, the conversion of aldehydes to acetylenes with methanol and potassium carbonate or cesium carbonate. Because the required solvolytic de-acetylation process of **2** is already accomplished, the homologation step with **1a** also proceeds in nonprotic solvents. Using cesium carbonate as base, the reaction rates were fastest in methanol, but toluene, DMF, acetonitrile, THF, and 2-propanol also give acetylenes, although requiring extended reaction times without reaching the yields attained with methanol. Accordingly, these solvents are used more advantageously in combination with methanol. We have also tested a few solvent pairs for the conversion of **6** to **7** with cesium carbonate as base and found the fastest reaction rate in 1:1 methanol–dichloromethane and 4:1 methanol–THF, both comparable to neat methanol; the rate was only slightly slower in 1:1 methanol–toluene but lagged significantly behind the reaction in 1:1 methanol–acetonitrile or neat 2-propanol. When methanol was used as solvent for the conversion of **6** to **7**, we observed little difference between potassium carbonate and cesium carbonate, but the latter is preferred when solvent mixtures are employed. Triethylamine in THF was ineffective, but 1 equivalent

of DBU per equivalent of **1a**, when added as a 2 M solution in toluene to a solution of **1a** (1.5 eq) and **6** (1 eq) in THF at −10 °C, afforded crystalline **7**, in 50% yield, after allowing the reaction mixture to warm to 0 °C overnight and the workup described later for **7**. The unreacted starting material was quantitatively recovered, suggesting the possibility for further process optimization.

In view of these observations, **1a** became the focal point of an improved synthesis, which we describe herein as a one-pot process. It comprises the generation of the azide transfer agent, actual diazotransfer to dimethyl 2-(oxopropyl)phosphonate, and methanolysis of the resulting **2a**. A very simple filtration and evaporation protocol furnishes **1a**, which can be used directly in homologation experiments or may be further purified either by flash chromatography or distillation. Similar to distilled **1a** and **1b**, we found no detectable deterioration of the crude and chromatographed **1a** when stored in the freezer for more than 2 years, and there was no difference between the crude and further purified **1a** in terms of efficacy. To reduce exposure and handling of this potentially toxic and explosive substance, we recommend using the undistilled material as described here.

Further, we proffer a reaction sequence, illustrated in Scheme 2, which converts the aldehyde to the homologated acetylene in a tandem reaction comprising the generation of the azide transfer agent, diazotransfer, methanolysis, and homologation, all in one reaction vessel.

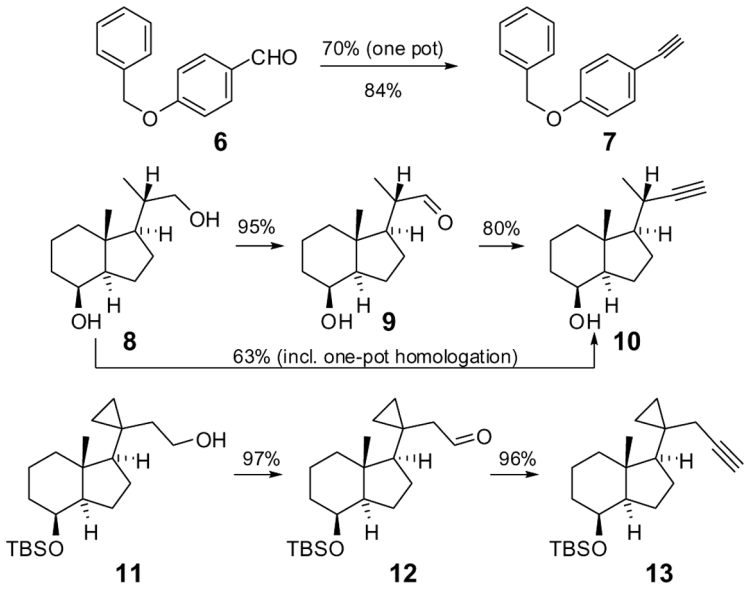
We selected mesyl azide in acetonitrile[25] and cesium carbonate[26] to effect the diazo transfer reaction and preferred TEMPO-based oxidations of the alcohols to obtain the required aldehydes for homologations. A number of electron acceptors have been employed for this transformation, but we found chloramine-T particularly propitious as it is



Scheme 2. One-pot homologation of aldehydes to alkynes in a tandem process.

inexpensive, stable, soluble in water, and has a built-in buffer capacity. TEMPO-based oxidations in a two-phase system of dichloromethane and aqueous buffers have been shown to be selective for primary alcohols[27] and with chloramine-T using a buffer such as 0.5 M dipotassium hydrogen phosphate as the aqueous component, this selectivity appears to be unaltered. The reaction time is longer in less basic solutions such as 0.5 M potassium hydrogen carbonate and thus requires larger quantities of chloramine-T. In the presence of a secondary hydroxyl group as in **8**, selectivity can be enhanced by lower reaction temperatures, limited quantities of the oxidant, and monitoring the consumption of the alcohol without enforcing the complete disappearance thereof. The generated benzenesulfonamide is removable either by filtration, extraction, or flash chromatography.

Representative examples are illustrated in Scheme 3. The homologation of **6** to **7** was compared using the one-pot method with a procedure employing preformed **1a**. First, generation of **1a** and subsequent homologation of **6** were conducted in acetonitrile and methanol using cesium carbonate (70% yield). In the second process, preformed and undistilled **1a** was employed with methanol and potassium carbonate (84% yield). The syntheses of alkyne **10** from the alcohol **8** were also compared by the two processes wherein the one-step method afforded **10** in 63%



Scheme 3. Examples of alkynylations.

overall yield from the alcohol, while the two-step alternate gave **10** in 80% yield. The equivalent conversion of **11** to **13** via **12** proceeded in 93% overall yield.

EXPERIMENTAL

(Diazomethyl)phosphonic Acid Dimethyl Ester (1a)

A mixture of powdered sodium azide (4.0 g, 61.5 mmol), acetonitrile (50 mL), and mesyl chloride (6.99 g, 61.0 mmol) was stirred overnight then cooled in an ice bath, and dimethyl 2-oxopropylphosphonate (9.14 g, 7.60 mL, 55 mmol)[28] was added. Cesium carbonate (19.55 g, 60 mmol) was added after 10 min, and the mixture was stirred for 1 h in the ice bath, for 2 h at ambient temperature, and again cooled in an ice bath. Then methanol (25 mL) was added within 5 min. The ice bath was removed after 4.5 h, and the mixture was diluted with toluene (75 mL), stirred for 5 min, and then filtered through a bed of Celite. The filter cake was washed with several portions of toluene, and the filtrate and washings were concentrated to a residue of ca. 38 g in the form of two liquid layers. The upper layer was decanted from the oily bottom layer, which was washed repeatedly with toluene. All toluene-containing liquids were evaporated and coevaporated from hexane to afford **1a** of sufficient purity for homologation experiments (for ^{1}H NMR, see additional data file 1). Alternatively, the toluene-containing liquids were charged to a silica-gel plug (65 × 30 mm), and the product was eluted with 1:1 ethyl acetate–hexane and ethyl acetate to yield **1a** as a straw-colored oil, 6.21 g, 75%; TLC (EtOAc) R_f 0.33, UV and I_2 detection; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (1H, $^2J_{HP} = 11$ Hz), 3.77 (6H, $^3J_{HP} = 11.7$ Hz); ^{13}C NMR ($CDCl_3$) δ 52.9 ($^2J_{C,P} = 5.3$ Hz), 28.4 ($^1J_{C,P} = 233$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.0. HR-MS calcd. for $C_3H_7N_2O_3P$ 150.0194; found 150.0194.[17]

1-Ethynyl-4-(phenylmethoxy)benzene (7)

One-Pot Reaction Commencing with **3**

A mixture of sodium azide (111 mg, 1.70 mmol), acetonitrile (1.5 mL), and mesyl chloride (0.189 g, 1.65 mmol, 128 μL) was stirred overnight, then cooled in an ice bath. Dimethyl 2-(oxopropyl)phosphonate (0.240 g, 1.45 mmol, 200 μL) was added, followed by cesium carbonate (0.521 g, 1.6 mmol). The cooling bath was removed after 30 min, and

stirring at ambient temperature continued for 2.5 h. The suspension was again cooled in an ice bath, stirred for 10 min, diluted with MeOH (0.75 mL), and stirred in the ice bath for 1 h. To this suspension, 4-benzyloxybenzaldehyde (154 mg, 0.725 mmol) was added, followed by cesium carbonate (0.43 g, 1.3 mmol). The ice bath was removed after 25 min; the mixture was stirred overnight and then evaporated. The residue was distributed between dichloromethane and water. The aqueous layer was extracted once with dichloromethane; the combined extracts were dried ($MgSO_4$) and evaporated. TLC (1:4 ethyl acetate–hexane, detection with phosphomolybdic acid) showed the complete disappearance of the starting material (R_f 0.42). The residue was flash chromatographed (1:19 ethyl acetate–hexane) to furnish **7** as a crystalline residue that was recrystallized from aqueous methanol, 0.1062 g, 70%; TLC (1:4 ethyl acetate–hexane) R_f 0.68; mp 66 °C. Anal. calcd. for $C_{15}H_{12}O$: C, 86.51; H, 5.81. Found: C, 86.66; H, 5.87.[29]

Reaction Using **1a**/MeOH/K_2CO_3

A mixture of undistilled **1a** (0.150 μL, 0.183 mg, 1.22 mmol), 4-benzyloxybenzaldehyde (149 mg, 0.70 mmol), and methanol (2.5 mL) was stirred in an ice bath for 10 min, and powdered potassium carbonate (0.202 g, 1.46 mmol) was added. The ice bath was removed after 2 h; the mixture was stirred overnight, then concentrated and distributed between ethyl acetate (20 mL) and water (10 mL). The organic phase was washed with water (3 mL) and brine (2 mL), dried, and evaporated to a crystalline residue of **7**, which was recrystallized from aqueous methanol (0.123 g, 84%).

(1R,3aR,4S,7aR)-7a-Methyl-1-((1S)-1-methyl-prop-2-ynyl)-octahydro-inden-4-ol (10)

A solution of the Inhoffen-Lythgoe diol **8**[30] (212 mg, 1 mmol) and TEMPO (32 mg, 0.2 mmol) in dichloromethane (8 mL) was vigorously stirred, and a solution of 0.5 M dipotassium phosphate (8 mL) containing tetrabutylammonium chloride hydrate (56 mg, 0.2 mmol) was added, followed by chloramine-T (0.423 g, 1.5 mmol). The mixture was stirred vigorously until only a trace of starting material remained (TLC, 1:1 ethyl acetate–hexane, R_f 0.45; ca. 4 h). The mixture was diluted with ethyl acetate (20 mL), and the organic layer washed with water (10 mL) and brine (5 mL), dried (sodium sulfate), and evaporated. The residue was triturated with 1:1 dichloromethane–hexane, and the resulting solution was purified by flash chromatography using 1:19 and 1:4 ethyl acetate–hexane

to furnish (S)-2-((1R,3aR,4S,7aR)-4-hydroxy-7a-methyl-octahydro-inden-1-yl)-propionaldehyde **(9)** as a colorless syrup, 0.20 g, 95%; TLC (1:1 ethyl acetate–hexane) R_f 0.72. This material was used directly in the next step. For analysis it was rechromatographed on silica gel using 1:19 methanol–dichloromethane to furnish pure **9**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 3H), 1.0 (d, 3H, $J = 6.8$ Hz), 1.06–1.18 (m, 1H), 1.22–1.48 (m, 5H), 1.5–1.6 (m, 1H), 1.66–1.8 (m, 4H), 1.8–1.87 (m, 1H), 1.88–2.0 (m, 1H), 2.27 (m, 1H), 4.00 (br, 1H), 9.47 (d, 1H, $J = 3.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 13.7, 17.4, 22.9, 26.2, 33.6, 40.2, 42.9, 49.2, 51.5, 51.9, 68.9, 205.0); IR ($CHCl_3$): 1720 cm^{-1} (CO); LR-MS-APCI (+) m/z 193 (100%, M + H-H_2O).[31]

One-Step Process from **9**

To a stirred suspension of sodium azide (130 mg, 2 mmol) and acetonitrile (2.1 mL), methanesulfonyl chloride (0.140 mL, 1.82 mmol) was added, and the mixture was stirred overnight. This suspension was added, via syringe, to a mixture of dimethyl 2-(oxopropyl)phosphonate (232 mg, 1.4 mmol), acetonitrile (1.5 mL), and cesium carbonate (0.50 g, 1.54 mmol) that had been previously stirred for 10 min. The resulting mixture was stirred for 4 h, and a solution of **9** (0.205 g, 0.965 mmol), as obtained previously and dissolved in methanol (2 mL), was added. After a few minutes of stirring, cesium carbonate (0.51 g) was added. The reaction was ca. 90% complete after 2 h but was stirred for an additional 14 h and then distributed between water (5 mL) and ethyl acetate (35 mL). The organic layer was dried and evaporated, and the residue was flash chromatographed using 1:19 ethyl acetate–hexane as mobile phase to yield **10** as a colorless syrup (0.13 g, 63%) from alcohol **8**; TLC (1:4 ethyl acetate–hexane) R_f 0.49; $[\alpha]^{30}_D + 50.1$ (c 0.52, methanol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.05–1.15 (m, 1), 1.18 (d, 3H, $J = 6.8$ Hz), 1.28–1.36 (m, 2H), 1.36–1.62 (m, 7H), 1.72–1.90 (m, 2H), 1.90–2.03 (m, 2H), 2.42 (m, 1H), 4.06 (br 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 17.4, 21.1, 22.5, 26.6, 27.3, 33.6, 39.8, 41.8, 52.4, 55.8, 68.4, 69.1, 89.2 ppm; LR-MS-EI(+) m/z 206 (M +).[32]

Two-Step Process from **8**

The oxidation of the diol **8** was repeated as described previously, the resulting aldehyde was dissolved in methanol (2.5 mL), **1a** (238 mg, 1.58 mmol, undistilled material) was added, and the solution was cooled in an ice bath. To the stirred solution, powdered potassium carbonate

(0.25 g, 1.8 mmol) was added. The ice was allowed to melt, and stirring continued overnight. The mixture was distributed between water (5 mL) and ethyl acetate (35 mL). The upper layer was washed with water (5 mL) and brine (3 mL), dried, and evaporated. The residue was flash chromatographed (1:19 ethyl acetate–hexane) to afford **10** as a colorless oil (173 mg, 80% from alcohol **8**).

tert-Butyl-dimethyl-[(1R,3aR,4S,7aR)-7a-methyl-1-(1-prop-2-ynyl-cyclopropyl)-octahydro-inden-4-yloxy]silane (13)

A mixture of 2-{1-[(1R,4S,7aR)-4-(tert-buty-dimethyl-silanyloxy)-7a-methyl-octahydro-inden-1-yl]-cyclopropyl}-ethanol (**11**) (860 mg, 2.44 mmol), dichloromethane (18 mL), and 0.5 M potassium hydrogen carbonate solution (18 mL) containing TBAC hydrate (112 mg, 0.4 mmol) was stirred vigorously, and TEMPO (63 mg, 0.4 mmol) was added, followed by chloramine-T (1.37 g, 4.86 mmol). TLC (1:4, ethyl acetate–hexane) monitored the conversion of **11** (R_f 0.40) to **12** (R_f 0.84). After 45 min, **11** was no longer detectable. The mixture was diluted with ethyl acetate (20 mL), and the organic layer was washed with water (10 mL), dried, and evaporated. The resulting crude {1-[(1R,4S,7aR)-4-(*tert*-butyl-dimethyl-silanyloxy)-7a-methyl-octahydro-inden-1-yl]-cyclopropyl}-acetaldehyde (**12**) was redissolved in hexane and flash chromatographed using 1:79 ethyl acetate–hexane as mobile phase to afford **12**, an oil that crystallized upon standing (0.83 g, mp 75–76 °C, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.02 (s, 3H), 0.0 (s, 3H), 0.3 (m, 2H), 0.5 (m, 1H), 0.8 (m, 1H), 0.88 (9H, s), 0.97 (s, 3H), 1.1 (m, 1H), 1.2–1.6 (m, 7H), 1.6–1.8 (m, 4H), 1.95 (m, 1H), 2.93 (ddd, 1H, $J_{gem} = 16.5$, $J = 3.8$, $J = 1.7$ Hz), 3.96 (br, 1H), 9.82 (m, 1H). Anal. calcd. for $C_{21}H_{38}O_2Si$: C, 71.94; H, 10.92. Found: C, 71.81; H, 11.02. The aldehyde **12**, obtained previously, was dissolved in 1:4 THF–methanol (10 mL), and undistilled **1a** (0.45 g, 3 mmol) was added. The solution was cooled in an ice bath, and powdered potassium carbonate (0.55 g, 4 mmol) was added to the stirred solution. The ice bath was removed after 15 min, then stirred at room temperature overnight. The disappearance of the starting material (R_f 0.64) and the generation of the product (R_f 0.94) was followed by TLC (1:9 ethyl acetate–hexane). The suspension was equilibrated with water (5 mL) and hexane (30 mL); the aqueous phase was re-extracted once with hexane (10 mL). The combined organic layers were washed with brine (5 mL), dried (sodium sulfate), and evaporated. The residue was flash chromatographed to elute **13** (hexane), which crystallized upon standing (0.79 g, 96%, mp 48 °C). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.86, −4.54, 8.05, 9.06, 15.61, 17.71, 17.92, 18.27, 22.78, 22.97, 26.09, 28.28,

34.64, 40.54, 43.98, 52.32, 53.28, 69.45, 69.70, 82.99. Anal. calcd. for C_{22} H_{38}OSi: C, 76.23; H, 11.05. Found: C, 76.08; H, 11.12.[33]

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