Organocuprate Conjugate-addition–Enolate-alkylation Reactions: A New Synthesis of 11-Deoxyprostaglandins

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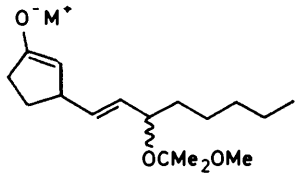
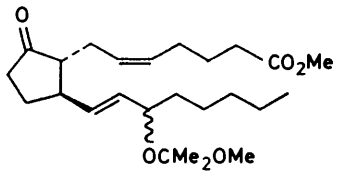
A short synthesis of a key 11-deoxyprostaglandin precursor, 6β-[(*E*)-3-oxo-oct-1-enyl]-*cis*-α-2-oxabicyclo-[3.3.0]octan-3-one (11), is reported. Important reactions in the synthesis include preparation of 2α-allyl-3β-{(*E*)-3-[dimethyl-(t-butyl)silyloxy]oct-1-enyl}cyclopentanone (4) by an organocuprate conjugate-addition–enolate-alkylation reaction, regiospecific epoxidation–cyclisation of the alcohol (7) to give 6β-{(*E*)-3-[dimethyl-(t-butyl)silyloxy]oct-1-enyl}-3-hydroxymethyl-*cis*-α-2-oxabicyclo[3.3.0]octane (9), and oxidative degradation of (9) with manganese dioxide to give 6β-{(*E*)-3-[dimethyl-(t-butyl)silyloxy]oct-1-enyl}-*cis*-α-2-oxabicyclo-[3.3.0]octan-3-one (10).

One of the most convergent synthetic approaches to 2,3-disubstituted cyclopentanones involves organocuprate conjugate addition to cyclopent-2-enone followed by regiospecific trapping of the resulting enolate with alkyl



(1)



(2)

halides,[1] aldehydes,[2] or other electrophiles.‡ Patterson and Fried [4] attempted to use the direct alkylation of the cuprate-generated enolate (1) for the preparation of the 11-deoxyprostaglandin precursor (2) but without success.§

Attempts to use the alkylation of cuprate-generated enolates for the synthesis of 11-hydroxylated prostaglandins have also failed,[2] although regiospecific enolate trapping has been achieved with more reactive electrophiles.[2,‖]

We were interested in devising a short versatile route to 11-deoxyprostaglandin [6] and prostacyclin analogues. Retrosynthetic analysis indicated that the disubstituted cyclopentanone (4) was a suitable precursor and we decided to investigate the possibility of preparing (4) by the 'one-pot' conjugate-addition–enolate-alkylation procedure shown in Scheme 1 (all compounds are racemic).

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‡ For Michael acceptors see ref. 2*b*; for acyl halides and chloroformate esters see ref. 3.

§ However, the enolate (1) could be trapped as its trimethylsilyl enol ether, then regenerated in liquid ammonia and alkylated to give (2) in *ca.* 47% yield (ref. 4).

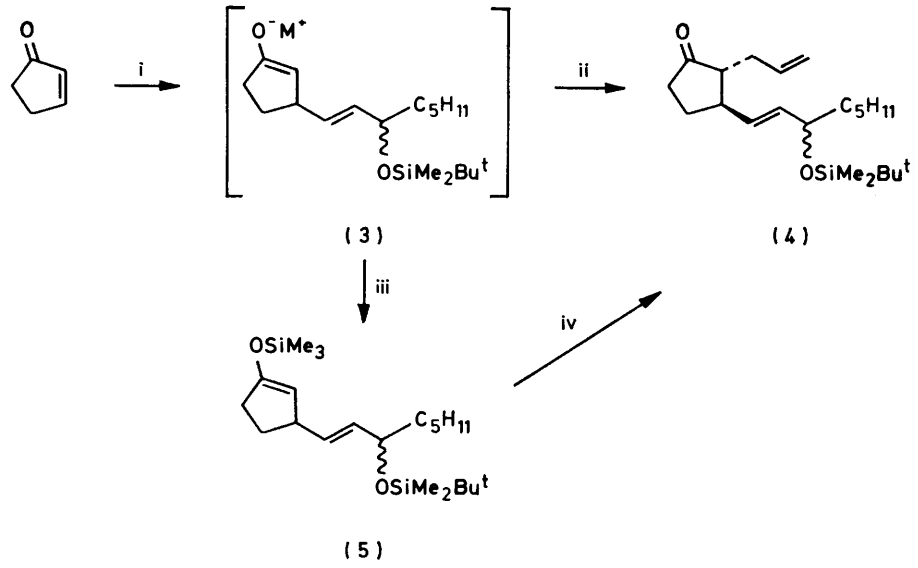
The conjugate-addition reaction between cyclopent-2-enone and the mixed organocuprate (6a) was carried out in diethyl ether at −78 °C but alkylation of the enolate (3) with allyl bromide in ether at various temperatures (−78 to 0 °C) gave little or none of the desired product (4). Similar experiments using tetrahydrofuran as solvent, allyl iodide as alkylating agent, or (6b) as cuprate reagent also failed. It has been reported that the alkylation of cuprate-generated enolates occurs more readily in the presence of hexamethylphosphoramide [1a,5c] but this procedure also proved unsuccessful. It was eventually discovered that the enolate (3), generated in ether using the cuprate (6a), could be alkylated with allyl bromide if dry liquid ammonia was used as co-solvent. Using this method the 'one-pot' conjugate-addition alkylation gave (4) in *ca.* 24% yield after chromatography.

An alternative preparation of (4) involved the two-step silyl-trapping process [4,7] also shown in Scheme 1. The enolate (3), generated as described above, was first trapped as the silyl enol ether (5) (which could be purified by distillation). Regeneration of the enolate (3) in tetrahydrofuran–liquid ammonia and addition of allyl bromide gave (4) in *ca.* 25% after chromatography.

The *trans*-relationship between the vicinal substituents in (4) was assumed on the basis of related studies [1,4] and this assumption was borne out by subsequent transformations. With (4) in hand we turned our attention to completing the synthesis of 11-deoxyprostaglandin analogues. The results are shown in Scheme 2.

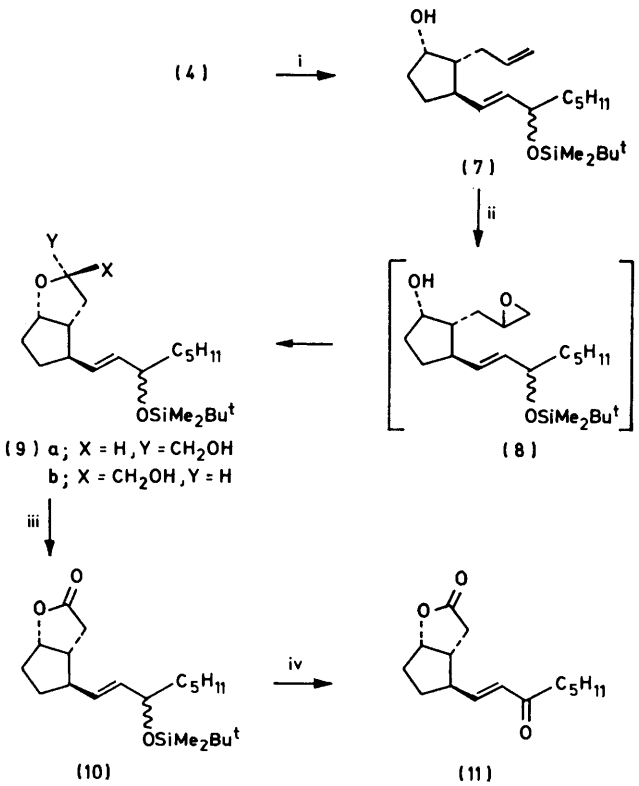
Stereoselective reduction of the ketone (4) to the α-alcohol (7) was achieved in 92% yield using potassium tri-s-butylborohydride. Selective epoxidation of the α-side-chain double bond was carried out using a modification of the method of Sharpless and Michaelson.[8] Treatment of (7) with t-butyl hydroperoxide and vanadyl acetylacetonate gave diastereoisomeric bicyclic alcohols (9a) and (9b), presumably by way of the hydroxy-

‖ Although cuprate-generated enolates derived from cyclopent-2-enone and its protected 4-hydroxy-derivatives are relatively difficult to alkylate, the reaction is much more successful with related αβ-unsaturated ketones such as 2-methylcyclopent-2-enone (*e.g.* ref. 5*a*) and cyclohex-2-enone (*e.g.* refs. 5*b* and *c*). See also refs. 1*b* and *c*.

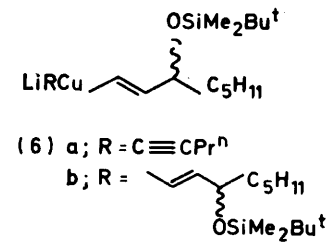


SCHEME 1 *Reagents:* i, (6a)–diethyl ether; −78 °C; ii, allyl bromide–liquid NH_3; iii, Me_3SiCl; iv, (*a*) $LiNH_2$–liquid NH_3, (*b*) allyl bromide

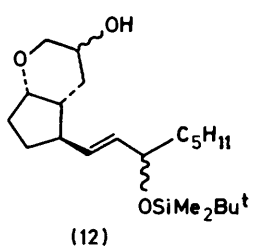
epoxide (8). The exclusive cyclisation of (8) into the tetrahydrofuranyl rather than to the tetrahydropyranyl alcohols (12) is in accord with the guidelines presented by Baldwin [9] who states that the preferred mode of ring-opening of epoxides is *exo*. This structural assignment was confirmed by n.m.r. analysis. Comparison of the ^1H and ^{13}C n.m.r. spectra of (9a) and (9b) with the model compounds (13a) and (13b) showed marked similarities (Table 1). The hydroxymethyl carbon atoms C-9 in (9a) and (9b) have very similar ^{13}C chemical shifts to those in (13a) and (13b) and these values are typical of hydroxymethyl carbon atoms in related carbohydrates (*e.g.* β-D-ribofuranose, δ 62.9 p.p.m.[10]). The signal for the methylene carbon next to oxygen in the tetrahydropyranols (12) would be expected to be at significantly



SCHEME 2 *Reagents:* i, $KHBBu^s_3$; ii, Bu^tOOH, $VO(acac)_2$; iii, MnO_2; iv, (*a*) H^+, (*b*) MnO_2



lower field: the α-carbon in tetrahydropyran is at δ 69.5 p.p.m.[11] and a β-hydroxy-group normally causes a downfield shift of 5—12 p.p.m.[12] This evidence indicates that cyclisation of (7) gave (9a) and (9b) rather than (12).



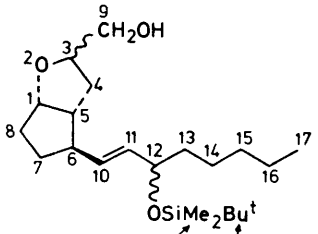
The assignment of α- and β-stereochemistry to the diastereoisomeric alcohols (9) was also possible from the n.m.r. data in Table 1. In related 2-oxabicyclo-octanes C-1 and C-3 absorb at higher field for the 3β-substituted isomer while H-1 and H-3 absorb at higher field for the

3α-substituted compound.[13] This relationship holds for (9a) and (9b) [and (13a) and (13b)] and leads to the structural assignments shown.

Oxidation of the alcohols (9), either together or separately, to the corresponding aldehyde could not be achieved with a wide variety of reagents. Similar problems were reported during the oxidation of tetrahydrofurfuryl alcohol itself.[14] Oxidation was eventually achieved using activated manganese dioxide but the product of this reaction was a lactone (10) resulting from

TABLE 1

Critical ^1H and ^{13}C chemical shifts (p.p.m. from Me_4Si) for (9a and b) and (13a and b)



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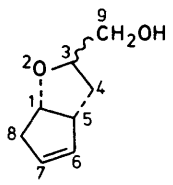

(13)

a ; α - CH_2OH

b ; β - CH_2OH

Cmpd.	C-1	C-3	C-9	H-1	H-3
(9a)	85.4	81.4	64.3	4.45	3.95
(9b)	84.6	78.9	64.2	4.57	4.15
(13a)	82.3	80.3	64.3	4.58	
(13b)	81.3	78.7	63.6	4.75	

oxidative degradation. The yield of this novel reaction varied according to the experimental conditions (Table 2).

To our knowledge manganese dioxide has not previously been used for the conversion of 2-hydroxy-ethers into lactones [16] although it can be used to cleave vicinal

TABLE 2

Preparation of the lactone (10) by oxidative degradation

Substrate	Reagent (mol equiv.)[a]	Solvent (time/h) [b]	Yield (%)
(9a)	MnO_2 (50)	LP (15)	34
(9b)	MnO_2 (50)	LP (8)	34
(9a) + (9b)	MnO_2 (40)	LP (20)	38
(9a) + (9b)	MnO_2 (50)	acetone (20)	30
(9a)	MnO_2 (50)	toluene (2)	44
(9b)	MnO_2 (50)	toluene (8)	46
(9a) + (9b)	Ag_2CO_3 on Celite (15)	benzene (72)	31
(9a) + (9b)	Ag_2CO_3 on Celite (50)	toluene (6)	37

[a] Either commercial (Alfa) or Attenburrow active manganese dioxide [15] could be employed; silver carbonate on Celite was prepared according to M. Fetizon and M. Golfier, *C. R. Acad. Sci., Ser. C*, 1968, **267**, 900. [b] Under reflux; no appreciable reaction was observed at ambient temperature; the use of refluxing xylene led to considerable decomposition. LP = light petroleum (b.p. 60—80 °C).

diols [16] and the two processes are presumably related mechanistically. Silver carbonate on Celite, however, has been reported to convert tetrahydrofuryl alcohol into γ-butyrolactone [17] and, as can be seen from Table 2, this reagent can also be used for the conversion of (9) nto (10).

The structure of the lactone (10) was proved beyond all doubt by converting it into the known [18] αβ-unsaturated ketone (11) (Scheme 2). Compound (11) has been converted into 11-deoxy-$PGF_{2\alpha}$ and 11-deoxy-PGE_2 and so the work described in this paper formally constitutes a novel synthesis of these compounds. We are now extending this work to the synthesis of other prostaglandin and prostacyclin analogues.

EXPERIMENTAL

N.m.r. spectra were recorded on Perkin-Elmer R12B, Bruker WP60, Varian EM390, or JEOL FX100 spectrometers. I.r. spectra were obtained on a Pye-Unicam SP1050 spectrophotometer and u.v. spectra on a Perkin-Elmer–Coleman 575 instrument. Mass spectra were obtained on a Kratos–AEI MS30/74 or MS50 instrument. A normal ethereal work-up consisted of three extractions with diethyl ether, washing the combined extracts with saturated brine, drying with anhydrous magnesium sulphate, and removal of the solvent under reduced pressure.

Column chromatography (medium pressure) was carried out using silica gel H (Merck 7736). T.l.c. was carried out with Camlab ' Polygram ' pre-coated silica plates and Merck 2-mm-thickness preparative plates were used for preparative t.l.c.

2α-Allyl-3β-{(E)-3-[dimethyl-(t-butyl)silyloxy]oct-1-enyl}-cyclopentanone (4).—(a) *' One-pot ' procedure.* n-Butyllithium (55 mmol) was added to a stirred solution of 3-[dimethyl-(t-butyl)silyloxy]oct-1-enyl iodide (18.4 g, 50 mmol) in dry diethyl ether (40 ml) under nitrogen at −78 °C. After 1 h a freshly prepared solution of pent-1-ynylcopper (7.2 g, 55 mmol) in dry diethyl ether (50 ml) and hexamethylphosphoric triamide (21 ml, 110 mmol) was added slowly and the mixture was stirred for a further 1 h at −78 °C to complete formation of the cuprate (6a). Cyclopent-2-enone (6.15 g, 75 mmol) in dry diethyl ether (100 ml) was then added to the solution of (6a) very slowly over 30 min and the mixture stirred for a further 1 h at −78 °C. Dry distilled liquid ammonia (150 ml) was then added followed by allyl bromide (28 g, 0.23 mol). The cooling bath was then removed and the ammonia allowed to evaporate. The mixture was then poured into distilled water, worked up, and purified by column chromatography giving the *ketone* (4) as an oil [24%, based on (6a)], $\nu_{max.}$ (liquid film) 1 750, 1 255, and 835 cm^{-1}; δ 5.86—5.85 (1 H, m, C*H*=CH_2), 5.60—5.46 (2 H, m, CH=CH), 5.12—4.94 (2 H, m, CH=C*H*$_2$), 4.12—4.00 (1 H, m, CHOSi), 0.90 [12 H, m and s, CH_2CH_3 and $SiC(CH_3)_3$], and 0.06 and 0.02 [6 H, 2 s, $Si(CH_3)_2$] (Found: C, 72.5; H, 10.8. $C_{22}H_{40}O_2Si$ requires C, 72.5; H, 11.1%).

(b) *Silyl-trapping procedure.* The above procedure was followed as far as the slow addition of the cyclopent-2-enone solution followed by stirring for 1 h at −78 °C. Tetrahydrofuran (100 ml) was then added followed by a mixture of trimethylsilyl chloride (30 ml) and triethylamine (40 ml). The reaction was allowed to warm to ambient temperature, ice was added, and the mixture was extracted with hexane (3 × 200 ml). The combined extracts were washed with ice-cold 2% sulphuric acid (4 × 150 ml) followed by 8% sodium hydrogencarbonate solution (200 ml). Drying ($MgSO_4$) and evaporation *in vacuo* gave the silyl enol ether (5) as an oil which was then dissolved in tetrahydrofuran (100 ml) and added to a mixture of lithium amide (50 mmol) in liquid ammonia (150 ml) at −78 °C.

The reaction was warmed to −40 °C and allyl bromide (28 g, 0.23 mol) in tetrahydrofuran (50 ml) was added rapidly, the cooling bath was removed, and the ammonia was allowed to evaporate. The mixture was then poured into distilled water, worked up, and purified by column chromatography giving the *ketone* (4) as an oil [25% based on the organocuprate (6a)].

2α-Allyl-3β-{(E)-3-[dimethyl-(t-butyl)silyloxy]oct-1-enyl}-cyclopentan-1α-ol (7).—A solution of potassium tri-s-butylborohydride in tetrahydrofuran (Aldrich K-selectride, 2.67 mmol) was slowly added to a stirred solution of ketone (4) (650 mg, 1.78 mmol) in tetrahydrofuran (30 ml) under nitrogen at −40 °C. The temperature was allowed to rise to 0 °C over 1 h and the excess of reagent was hydrolysed by the careful addition of water. 3M-Aqueous sodium hydroxide (0.98 ml, 2.94 mmol) was then added followed by 30% hydrogen peroxide (1.1 ml, 9.6 mmol) and the mixture was stirred at 0 °C for 1 h. Normal ethereal work-up followed by column chromatography gave the *alcohol* (7) as an oil (92%), $\nu_{max.}$ (liquid film) 3 380, 1 250, and 830 cm^{-1}; δ 6.00—5.73 (1 H, m, C*H*=CH_2), 5.50—5.34 (2 H, m, CH=CH), 5.16—4.95 (2 H, m, CH=CH_2), 4.32—4.17 (1 H, m, C*H*OH), 4.10—3.96 (1 H, m, CHOSi), 0.91 [12 H, m and s, CH_2CH_3) and $SiC(CH_3)_3$], and 0.08 and 0.04 [6 H, 2 s, $Si(CH_3)_2$] (Found: C, 72.2; H, 11.6. $C_{22}H_{42}O_2Si$ requires C, 72.1; H, 11.6).

6β-{(E)-3-[Dimethyl-(t-butyl)silyloxy]oct-1-enyl}-3-hydroxymethyl-cis-α-2-oxabicyclo[3.3.0]octane (9).—The alcohol (7) (2.92 g, 7.96 mmol) was dissolved in toluene (250 ml) containing vanadyl acetylacetonate (80 mg, 0.29 mmol) and toluene-4-sulphonic acid (one crystal). The mixture was stirred and t-butyl hydroperoxide (2.16 g, 24 mmol) was added over 30 min. The reaction was then stirred at ambient temperature for 7 days and then poured into 10% sodium metabisulphite solution. Normal ethereal work-up afforded a mixture of (9a) and (9b) (*ca.* 1 : 1) which were partially separated by column chromatography. Elution with diethyl ether–light petroleum (b.p. 60—80 °C) (1 : 3 v/v) gave first the *α-hydroxymethyl diastereoisomer* (9a) as an oil (300 mg, 10%), $\nu_{max.}$ (liquid film) 3 430, 1 250, and 835 cm^{-1}; δ ($CDCl_3$) 5.45—5.3 (2 H, m, H-10 and -11), 4.45 (1 H, m, H-1), 4.02 (1 H, m, H-12), 3.95 (1 H, m, H-3), 3.78 and 3.58 (2 H, AB of ABX, J_{AB} 11.7, J_{AX} 3.0, J_{BX} 5.7 Hz, H-9), 2.45—2.3 (2 H, m, H-6 and OH), 0.88 [12 H, m and s, $SiC(CH_3)_3$ and CH_2CH_3], 0.04 and 0.00 [6 H, 2 s, $Si(CH_3)_2$], and 2.2—1.2 (17 H, m, remainder); *m/e* 369 ($M^+ - 15$), 351 ($M^+ - 31$), 325 ($M^+ - 57$), and 311 ($M^+ - 71$) (Found: *m/e*, 351.2723. $C_{21}H_{39}O_2Si$ requires $M^+ - 31$, 351.2719). Next eluted was a mixture of (9a) and (9b) (1.26 g, 41%) and finally the *β-diastereoisomer* (9b) as an oil (327 mg, 11%), $\nu_{max.}$ (liquid film) 3 440, 1 250, and 835 cm^{-1}; δ ($CDCl_3$) 5.55—5.3 (2 H, m, H-10 and -11), 4.57 (1 H, m, H-1), 4.15 (1 H, m, H-3), 4.02 (1 H, m, H-12), 3.69 and 3.52 (2 H, AB of ABX, J_{AB} 1.7, J_{AX} 3.0, J_{BX} 5.7 Hz, H-9), 0.88 [12 H, m and s, $SiC(CH_3)_3$ and CH_2CH_3], 0.04 and 0.00 [6 H, 2 s, $Si(CH_3)_2$], and 2.4—1.2 (17 H, m, remainder); *m/e* 369 ($M^+ - 15$), 351 ($M^+ - 31$), 325 ($M^+ - 57$), and 311 ($M^+ - 71$).

6β-{(E)-3-[Dimethyl-(t-butyl)silyloxy]oct-1-enyl}-cis-α-2-oxabicyclo[3.3.0]octan-3-one (10).—The bicyclic alcohol (9a) (40 mg, 0.104 mmol) was dissolved in toluene (10 ml), active manganese dioxide [15] (440 mg, 5 mmol) was added, and the mixture was boiled under reflux. After 8 h the mixture was cooled and filtered through Celite. The Celite was washed well with diethyl ether, the filtrates were combined and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Preparative t.l.c. gave recovered (9a) (4 mg) and the *lactone* (10) as an oil (46% based on recovered starting material), $\nu_{max.}$ (liquid film) 1 765, 1 265, and 845 cm^{-1}; δ 5.52—5.44 (2 H, m, CH=CH), 5.02—4.92 (1 H, m, OCH), 4.15—4.03 (1 H, m, CHOSi), 0.96 [12 H, m and s, CH_2CH_3 and $SiC(CH_3)_3$], and 0.09 and 0.07 [6 H, 2 s, $Si(CH_3)_2$] (Found: C, 69.0; H, 10.3. $C_{21}H_{38}O_2Si$ requires C, 68.8; H, 10.4%).

6β-[(E)-3-Oxo-oct-1-enyl]-cis-α-2-oxabicyclo[3.3.0]octan-3-one (11).—The lactone (10) (164 mg, 0.447 mmol) was stirred in tetrahydrofuran containing 10% hydrochloric acid for 4 days at ambient temperature. Normal ethereal work-up followed by preparative t.l.c. gave the desilylated alcohols, which were dissolved in dichloromethane (10 ml). Active manganese dioxide [15] (440 mg, 5 mmol) was added and the mixture was stirred at ambient temperature for 5 days. Filtration through Celite, removal of the solvent *in vacuo*, and preparative t.l.c. gave the enone (11) as an oil (67%), $\nu_{max.}$ (liquid film) 1 780, 1 675, 1 630, and 970 cm^{-1}; $\lambda_{max.}$ (MeOH) 224 nm (log ε 4.15); δ ($CDCl_3$) 6.68 and 6.13 (2 H, dd, *J* 6 and 16 Hz), and 0.89 (3 H, s), identical with an authentic sample.[18]

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