Synthesis of (±)-15-thia-15-deoxy-PGE_1 methyl ester[1]

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This paper is dedicated to Professor David B. MacLean

HERBERT L. HOLLAND, ELAREF S. RATEMI, and (in part) LUIS CONTRERAS. Can. J. Chem. **72**, 1 (1994).

The 15-thia-15-deoxy analogue of prostaglandin E_1 methyl ester has been prepared by the zirconocene chloride mediated conjugate addition of an *n*-pentyl ethynyl sulfide derived anion to an appropriately substituted cyclopentenone. Similar methodology has also been used to prepare other 3-(3′-thia-1′-octenyl)-cyclopentanones.

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On a préparé l'analogue 15-thia-15-désoxy de l'ester méthylique de la prostaglandine E_1 en procédant à une addition conjuguée, catalysée par le chlorure de zirconocène, d'un anion dérivé du sulfure d'éthynyle et de *n*-pentyle à une cyclopenténone substituée d'une façon appropriée. On a utilisé une méthodologie semblable pour préparer d'autres 3-(3′-thia-1′-octényl)cyclopentanones.

[Traduit par la rédaction]

The synthesis of natural prostaglandins and structurally modified prostanoids has a long and extensive history (see, for example, refs. 1–3). One of the long-term goals in the production of modified prostaglandins has been the suppression or reduction of the normally rapid metabolic deactivation of these compounds (for an overview of PG activity and metabolism, see ref. 4); in this regard, the significance of C-15 in prostanoid metabolism is apparent from the rapid oxidation of the 15-hydroxyl group of natural PG's by the enzyme 15-hydroxyprostaglandin dehydrogenase, and modification of the molecule at or close to C-15 has indeed been productive in the development of longer term physiologically active prostanoids (5–7).

As a part of this endeavour, prostanoids modified by the presence of heteroatoms in place of ring or side-chain carbons have also been investigated, resulting in the synthesis of compounds incorporating, for example, sulfur atoms in both side chains (8, 9). However, there have been no reports to date of the preparation of prostanoids, such as **11**, containing sulfur at the metabolically important C-15 position. In view of this fact, we have undertaken the synthesis of a structurally modified prostanoid incorporating sulfur in place of C-15.

The 15-deoxy-15-thia analogue of PGE_1 methyl ester (**11**) was chosen as the synthetic target in view of the central position occupied by the PGE series in prostaglandin biochemistry (1), and also the comparative difficulty in simple construction of the PG_1 (as opposed to the PG_2) skeleton (10, 11). Thus, any synthetic method for **11** based on a conjugate addition approach should be in principle applicable to its PGE_2 analogue, via Noyori's "three-component coupling" method (11), whereas the reverse is not necessarily true. It is our intention in further studies to investigate both chemical and enzymatic methods for the oxidation of **11** at the 15 position, hence the choice of a 15-deoxy analogue as the initial synthetic target.

The essential feature of our synthetic approach is the conjugate addition of a 3-thia-alkenyl anion equivalent, corresponding to the lower side chain of the final product, to a suitably substituted cyclopentenone, such as **6** (Scheme 1). To establish the viability of this approach, it was necessary first to demonstrate that this addition would proceed with stereospecific formation of a product having *E* geometry about the double bond, and to this end the addition of a terminal anion equivalent of *E*-3-thia-1-octene (**14**) (12) to cyclopentenone (**1**), giving the 3-substituted cyclopentanone **7** (Scheme 2, line 1), was first investigated.

Of the methods available for the in situ generation of a terminal anion equivalent of *E*-3-thia-1-octene, the most successful was found to be that based on 3-thia-1-octyne (**13**), via generation of the higher order cuprate complex **14** (Scheme 3) using Schwartz's reagent (zirconocene hydride chloride) (12–14). Prepared using this methodology, the cyclopentanone **7**, obtained in 70% yield, clearly possessed *E* geometry about the olefinic bond based on an observed coupling constant of 16 Hz between the two olefinic hydrogens (12).

Addition of the complex **14** to a protected 4-hydroxycyclopentenone **3** (Scheme 2, line 3) proceeded in 55% yield to give product **9**. The 2-substituted cyclopentenones **4** and **6**, prepared as outlined in Scheme 1, were also used for the conjugate addition reaction of Scheme 2 (lines 4 and 6, respectively), and gave the corresponding *trans*-2,3-dialkyl cyclopentanones **10** and **12**. The synthesis of **4** by the route of Scheme 1 in an overall yield of 38% from 2-carboethoxycyclopentanone represents an improvement in both yield and utility on a similar route originally developed by Bagli et al. (10% overall yield) (15, 16). The preparation of the alcohol **5** in 62% yield from **4** by the allylic hydroxylation procedure of Baraldi et al. (17) is also superior to the previously reported method for this conversion stated to proceed in 40% yield (18).

When addition of **14** to the 2,4-disubstituted cyclopentenone **6** was carried out, giving the protected 15-thiaprostanoid **12** in 60% yield, careful control of the reaction conditions was found to be essential; when the reaction was carried out at –78°C, product formation was very slow (less than 10% conversion in 6 h, whereas stereoisomeric product mixtures were obtained at temperatures above –40°C. The all-*trans* relative stereochemistry of the ring substituents of the final product **11**, obtained following deprotection of **12**, was confirmed by analysis of both ^{1}HMR and ^{13}CMR spectra; a close correspondence of the resonance positions of the relevant carbons (C-8, -11, and -12; 54.6, 55.5, and 72.2 ppm) with the corresponding carbons of PGE_1

[1]This paper commemorates the professional career of our mentor, David B. MacLean, on the occasion of his retirement and elevation to the position of Professor Emeritus at McMaster University, Hamilton, Ontario.

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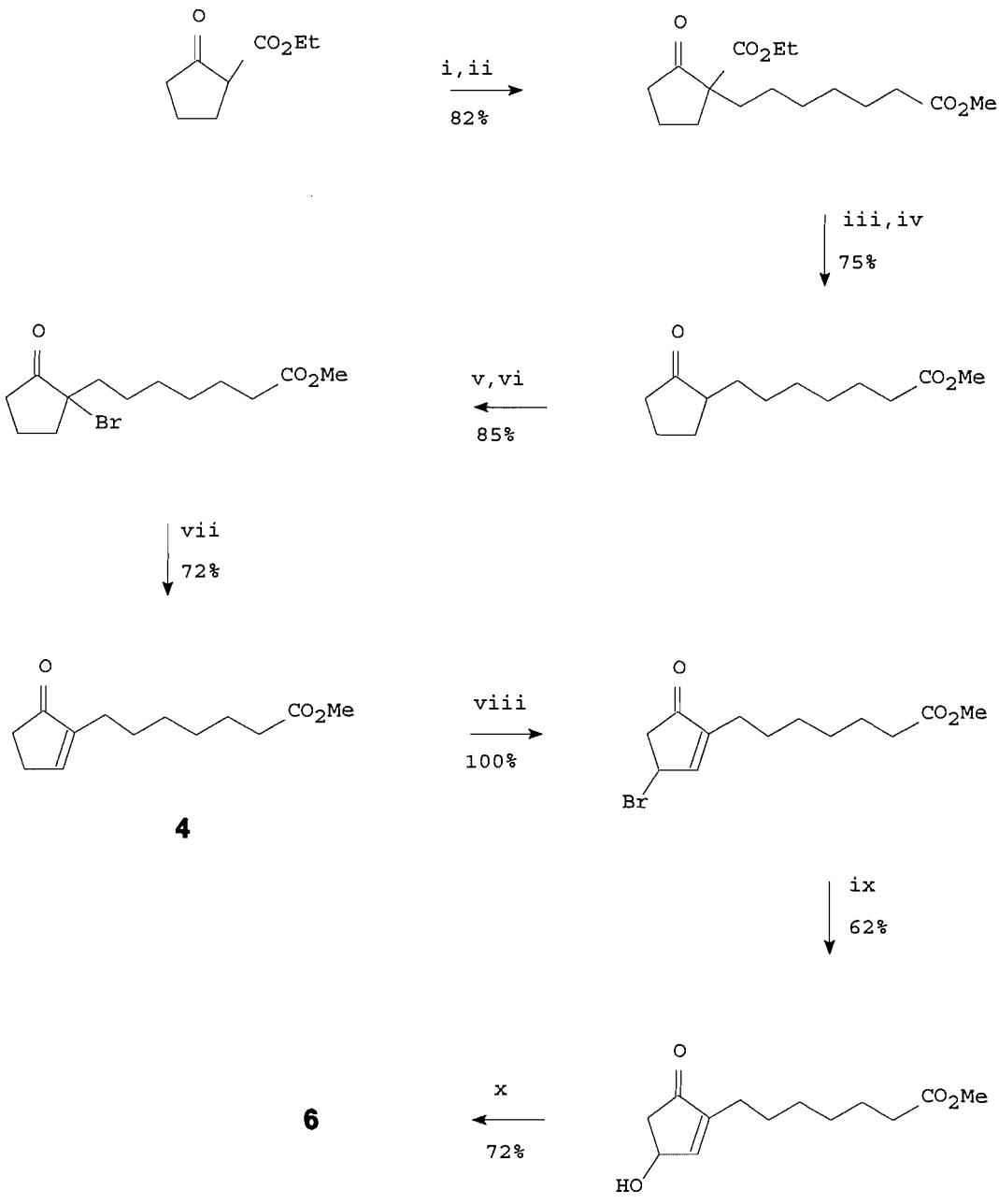

SCHEME 1: i, NaH/DME; ii, methyl 7-bromoheptanoate; iii, H^+; iv, *p*-toluenesulfonic acid/MeOH; v, Ac_2O/H^+; vi, Br_2; vii, $LiBr/Li_2CO_3$; viii, NBS; ix, H_2O/dioxane; x, DHP/H^+

(54.2, 54.6, and 71.6 ppm) and other closely related compounds of known *trans* stereochemistry was observed, together with a similar correspondence of the appropriate hydrogen resonance positions and coupling constants of **11** deduced from 2D ^{1}HMR analysis (19–21). This finding is consistent with the observation that the *trans* product is formed in similar conjugate additions of hydrocarbon-derived anion equivalents to substituted cyclopentenones (13, 14).

The production of **11** by the synthetic route outlined in the accompanying scheme provides an efficient method for the construction of 15-thiaprostanoids. The availability of intermediates, such as **5**, in chiral form (22) opens the possibility of synthesis of chiral 15-thia-PGE derivatives. Preliminary studies of the biological activity of **11** are currently being undertaken.

Experimental

Apparatus, materials, and methods

Melting points were determined on a Kofler heating stage and are uncorrected. Infrared spectra were recorded with an Analect 6260FX spectrometer. Proton NMR spectra were recorded at 200 MHz and carbon NMR spectra at 50.3 MHz (JMOD mode) with a Bruker AC200 spectrometer using deuteriochloroform as solvent and chloroform as internal standard. Mass spectra were obtained with a Kratos concept IS mass spectrometer in EI or CI mode (isobutane) as indicated. Thin-layer chromatography was performed on Merck silica gel 60F-254 and preparative column chromatography using 230–400 mesh silica gel (Merck 9385 or equivalent). HPLC analysis was carried out using a Perkin Elmer Series 3 chromatograph.

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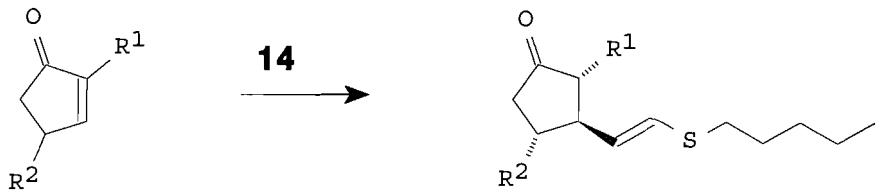
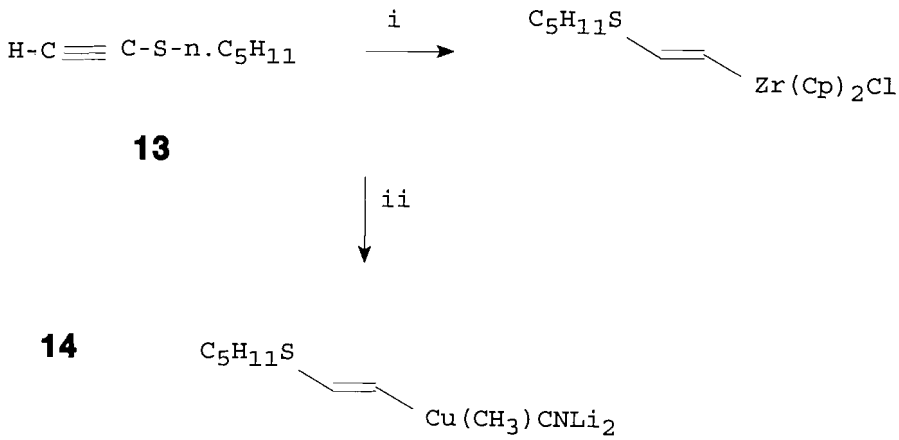


1	**7**	$R^1 = R^2 = H$
2	**8**	$R^1 = H$, $R^2 = OH$
3	**9**	$R^1 = H$, $R^2 = OSiEt_3$
4	**10**	$R^1 = (CH_2)_6CO_2CH_3$, $R^2 = H$
5	**11**	$R^1 = (CH_2)_6CO_2CH_3$, $R^2 = OH$
6	**12**	$R^1 = (CH_2)_6CO_2CH_3$, $R^2 = OTHP$

SCHEME 2



SCHEME 3: i, Cp_2ZrHCl; ii, MeLi/CuCN

4-Hydroxycyclopent-2-enone (2)

This was prepared as described (23) by acid-catalyzed rearrangement of furfuryl alcohol to give, following chromatography (elution with hexane:ethyl acetate, 3:2), the title compound in 45% yield; R_f 0.34 (ethyl acetate); IR ν_{max}: 1720, 3425 cm^{-1}; ^{1}HMR δ: 2.21 (1H, dd, J = 2, 16 Hz, H-5), 2.72 (1H, dd, J = 6, 12 Hz, H-5), 5.02 (1H, m, H-4), 6.19 (1H, d, H-2), and 7.64 (1H, dd, H-3) ppm; ^{13}CMR δ: 43.4 (C-5), 69.2 (C-4), 133.7 (C-2), 164.2 (C-3), 207.2 (C-1) ppm; MS (EI) *m/z* (%): 98(88), 97(34), 80(3), 70(67), 55(77), 43(100).

4-Triethylsilyloxycyclopent-2-enone (3)

Triethylsilyl chloride (3 g) was added to a solution of the hydroxyketone **2** (1.47 g) in dry pyridine (20 mL). The mixture was stirred at ambient temperature for 30 min, then heated at 55°C for 45 min, cooled, diluted with water (40 mL), and extracted with dichloromethane. The extract was dried and evaporated to give an oil, which was chromatographed (ethyl acetate:hexane, 2:3) to give the title compound (2.92 g) as a pale yellow oil; R_f 0.66 (ethyl acetate: hexane 3:7); IR ν_{max}: 1590, 1720 cm^{-1}; ^{1}HMR δ: 0.65 (6H, q, CH_3CH_2-Si), 0.97 (9H, t, CH_3CH_2-Si), 2.22 (1H, m, H-5), 2.68 (1H, dd, J = 6, 16 Hz, H-5), 4.99 (1H, m, H-4), 6.15 (1H, dd, J = 1.1, 5.7 Hz, H-2), and 7.46 (dd, J = 2.2, 5.6 Hz, H-3) ppm; ^{13}CMR δ: 4.3 (3C), 6.2 (3C), 44.6 (C-5), 70.2 (C-4), 134.0 (C-2), 163.3 (C-3), and 205.6 (C-1) ppm; MS (EI) *m/z* (%): 212(3), 183(100), 155(35), 127(43), 125(73).

2-Carboethoxy-2-(6′-methoxycarbonylhexyl)-cyclopentanone

2-Carboethoxycyclopentanone (49.5 g) was added over 35 min to a stirred suspension of sodium hydride (8.1 g) in dry DME (320 mL), with the reaction temperature being maintained at 25°C. When gas evolution was complete, methyl 7-bromoheptanoate (70.7 g) was added, and the resulting mixture then refluxed under argon for 26 h. The mixture was cooled and filtered, the solids washed with ether, and the combined filtrate and washings evaporated. The resulting residue was added to water (200 mL) and the mixture acidified (10% HCl). Extraction with ether followed by drying and evaporation of the extract gave an orange oil (80 g) that, following chromatography (hexane:-ethyl acetate, 1:1), gave the title compound (75 g) as a colourless oil; R_f 0.45 (ethyl acetate:hexane 3:1); IR ν_{max}: 1730, 1748 cm^{-1}; ^{1}HMR included signals at δ: 1.24 (3H, t, OCH_2CH_3), 2.25 (2H, t, CH_2CO_2), 3.67 (3H, s, OCH_3), 4.17 (2h, q, OCH_2CH_3) ppm; ^{13}CMR δ: 13.9 (CH_3), 19.4, 24.4, 24.6, 28.6, 29.3, 32.6, 33.5, 33.8, 37.7, 51.2 (OCH_3), 61.1 (OCH_2), 64.0 (C-2), 170.9, 173.9, and 214.6 (C-1) ppm.

2-(6′-Methoxycarbonylhexyl)-cyclopentanone

A mixture of the above diester (65.5 g), acetic acid (195 mL), water (273 mL), and H_2SO_4 (77 mL) was heated under reflux for 20 h. The cooled mixture was then treated with 10% sodium bicarbonate (250 mL), and extracted with ether. The extract was washed (2 × 400 mL water followed by 400 mL 10% $NaHCO_3$), dried, and evaporated. Distillation of the residue (159–163°C, 0.09 Torr; 1 Torr = 133.3 Pa)

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afforded a clear oil (R_f 0.3 (ethyl acetate:hexane 1:1); IR ν_{max}: 1710, 1748, 3102 cm^{-1}), which was esterified using dry methanol (250 mL), benzene (800 mL), and *p*-toluenesulfonic acid (1 g), refluxing in a Dean–Stark apparatus for 7 h. Conventional work-up gave the title ester (37 g), bp 120–125°C, 0.7 Torr (lit. (24) bp 135–140°C, 0.4 Torr); R_f 0.55 (ethyl acetate:hexane 4:1); IR ν_{max}: 1739, 1745 cm^{-1}; ^{1}HMR δ: 1.22–1.32 (8H, m), 1.55–1.98 (6H, m), 3.67 (3H, s, OCH_3); ^{13}CMR δ: 20.5, 24.7, 27.1, 28.7, 29.0, 29.4 (2C), 33.8, 37.9, 48.8 (C-2), 51.1 (OCH_3), 173.9, 221.0 ppm; MS (EI) *m/z* (%): 226(5), 195(9), 143(5), 97(9), 84(100).

1-Acetoxy-2-(6′-methoxycarbonylhexyl)-cyclopentene

A stirred solution of the above ester (28.2 g) and *p*-toluenesulfonic acid (270 mg) in acetic anhydride (57 mL) was heated while the acetic acid that formed was fractionally distilled. The original volume was maintained by periodic addition of acetic anhydride. When no more acetic acid distilled, the mixture was briefly heated to 140°C, then cooled and poured onto a stirred ice-cold mixture of saturated $NaHCO_3$ (400 mL) and hexane (300 mL). The organic phase was removed, dried, and evaporated, and the residue distilled to give a colourless oil (28.6 g, bp 81–85°C, 0.07 Torr); R_f 0.6 (ethyl acetate:hexane 4:1); IR ν_{max}: 1698, 1742 cm^{-1}; ^{1}HMR δ: 1.25–1.40 (6H, m), 1.61 (2H, m), 1.93 (4H, m), 2.14 (3H, s, $COCH_3$), 2.28 (4H, m), 2.45 (2H, m), 3.67 (3H, s, OCH_3) ppm; ^{13}CMR δ: 19.7, 20.6 (CH_3CO), 24.8, 26.2, 26.8, 28.8, 28.9, 30.9, 31.0, 33.9, 51.3 (OCH_3), 126.5 (C-2), 143.9 (C-1), 168.7, 174.1 ppm; MS (EI) *m/z* (%): 268(5), 194(100), 166(30), 123(33), 97(76), 84(37).

2-Bromo-2-(6′-methoxycarbonylhexyl)-cyclopentanone

A 500-mL 3-neck flask was fitted with a mechanical stirrer and two dropping funnels, cooled in ice, and charged with calcium carbonate (9 g) and chloroform (100 mL). To this cooled and stirred mixture were added simultaneously over 15 min a solution of the above enol acetate (22.5 g) in chloroform (10 mL) and a solution of bromine (13.4 g) in carbon tetrachloride (10 mL). The mixture was stirred at 5°C for a further 30 min, and the organic layer was then separated, washed (5% sodium thiosulphate, water, then saturated NaCl), dried, and evaporated at <40°C to yield the desired bromoketone, which was used directly in the next step without further manipulation.

*2-(6′-Methoxycarbonylhexyl)-cyclopent-2-enone (**4**)*

The crude bromoketone prepared as above (25.5 g) was added to an anhydrous, refluxing, and well-stirred mixture of LiBr (16.5 g) and Li_2CO_3 (16.5 g) in DMF (200 mL) under argon. The mixture was refluxed for a further 30 min, then cooled, poured into water (1 L), acidified (10% HCl), and extracted with ether. The ether extract was washed (water, saturated NaCl), dried, and concentrated to give an oil, which after distillation gave 13.5 g of the title compound, bp 95°C, 0.05 Torr (lit. (24) bp 145–150°C, 0.2 Torr); R_f 0.4 (ethyl acetate:hexane 1:1); IR ν_{max}: 1633, 1703, 1736 cm^{-1}; ^{1}HMR δ: 1.30–1.66 (8H, m), 2.16 (2H, m), 2.56 (2H, m), 3.66 (3H, s, OCH_3), 7.33 (1H, m, H-3) ppm; ^{13}CMR δ: 24.6, 24.8, 26.3, 27.5, 28.8, 28.9, 34.0, 34.5, 51.4 (OCH_3), 146.3 (C-2), 157.3 (C-3), 174.1, 209.9 ppm; MS (EI) *m/z* (%): 224(13), 193(43), 150(53), 123(42), 109(75), 96(100).

2-(6′-Methoxycarbonylhexyl)-4-bromocyclopent-2-enone

A stirred mixture of the above ketone (6 g), *N*-bromosuccinimide (freshly crystallized from water, 5.52 g), and 2,2-azadiisobutyronitrile (19 mg) in carbon tetrachloride (25 mL) was heated under reflux, and the reaction monitored by ^{1}HMR (appearance of peaks at δ 5.01, (H-4), 7.59 (H-3) ppm). After 5 h, the mixture was cooled to 5°C and filtered. The solids were washed with cold CCl_4 (3 × 20 mL), and the combined organic phase was washed (water, 5% sodium thiosulphate), dried, and evaporated to give 8.47 g of an orange oil, which was used directly in the next step.

*2-(6′-Methoxycarbonylhexyl)-4-hydroxycyclopent-2-enone (**5**)*

The crude bromoketone (above) was refluxed in aqueous dioxane (80 mL, 1:1) for 2.5 h. The reaction mixture was then cooled, the solvent evaporated, and the residue extracted with chloroform (4 × 40 mL). The extract was dried, evaporated, and purified by chromatography (10% stepwise elution from benzene to ethyl acetate) to give the title compound, 4.0 g, mp 46–48°C (lit. (25) mp 48–49°C); R_f 0.2 (ethyl acetate:hexane 3:7); IR ν_{max}: 1630, 1695, 1735 cm^{-1}; ^{1}HMR δ: 1.26–1.64 (8H, m), 2.13–2.36 (5H, m), 2.80 (1H, dd, J = 6, 14 Hz), 3.67 (3H, s, OCH_3), 3.45–3.95 (1H, br s, OH), 4.93 (1H, m, H-4) ppm; ^{13}CMR δ: 24.3, 24.7, 27.1, 28.7, 28.8, 34.0, 44.8, 51.4 (OCH_3), 68.4 (C-4), 147.0 (C-3), 155.9 (C-2), 174.0, 206.3 ppm; MS (EI) *m/z* (%): 240(2), 222(33), 190(89), 163(33), 111(48), 95(100).

*2-(6′-Methoxycarbonylhexyl)-4-(tetrahydropyranyloxy)cyclopent-2-enone (**6**)*

One drop of concentrated hydrochloric acid was added to a stirred mixture of the hydroxyester **5** (3.2 g) and dihydropyran (3.28 g), and the resulting mixture stirred at room temperature for 4 h. The solution was then diluted with ether, washed (saturated $NaHCO_3$ followed by saturated NaCl), dried, and evaporated to give an oil, 4.52 g, which was purified by chromatography (10% stepwise gradient elution from hexane to ethyl acetate) to give **6** (3.1 g), R_f 0.75 (ethyl acetate:hexane 3:1), IR ν_{max}: 1720, 1740 cm^{-1}; ^{1}HMR included signals at δ: 3.66 (3H, s, OCH_3), 3.85 (2H, m, $COCH_2$), 4.83–4.91 (2H, m, HC-O-CH), and 7.26 (1H, m, H-3) ppm; ^{13}CMR δ: 19.8, 24.4, 24.7, 25.3, 27.1, 28.7, 28.9, 30.8, 33.9, 42.2/43.2, 51.3, 62.7, 72.9/73.0, 98.4/98.6, 148.0/148.2, 153.5/155.3, 174.1, and 205.8/206.1 ppm; MS (EI) *m/z* (%): 324(0.2), 293(1), 223(12), 191(25), 163(22), 85(100).

*Preparation of the alkenyl cuprate complex **14***

All manipulations were performed in flame-dried apparatus under an argon atmosphere. A 50-mL 2-neck flask equipped with a low-temperature thermometer, magnetic stirrer bar, and a septum was charged with a solution of ethynyl *n*-pentyl sulfide (**13**, 61 mg) (12) in dry THF (3 mL). To this was added solid zirconocene hydride chloride (130 mg), and the mixture stirred until a yellow solution formed (ca. 30 min). This solution was cooled to –70°C, and then treated with methyllithium (0.75 mL, 1.4 M in ether). The resulting mixture was allowed to reach –50°C for 5 min, then recooled to –70°C.

Concurrently, copper(I) cyanide (43 mg) was placed in a 25-mL 2-neck flask fitted with a septum, low-temperature thermometer, and a magnetic stirrer bar. Tetrahydrofuran (2 mL) was added and the resulting slurry cooled to –70°C, then treated with methyllithium (0.38 mL, 1.4 M in ether). The mixture was allowed to reach –50°C, stirred until clear, recooled to –70°C, then cannulated into the alkenyl zirconocene solution, keeping both solutions at –70°C. The flask containing the cyanocuprate was washed with 1 mL of THF, and the washing cannulated as above. The resulting mixture was maintained at –50°C for 30 min, then cooled to –70°C in readiness for the conjugate addition reaction.

*3-(E-3′-Thia-1′-octenyl)cyclopentanone (**7**)*

A solution of cyclopent-2-enone (**1**) (0.25 mmol) in dry THF (2 mL) was added at –70°C to the reagent **14**, prepared as described above. The stirred mixture was allowed to reach –50°C and maintained at that temperature for 5 h. It was then cooled to –70°C and quenched with the addition of saturated ammonium chloride:ammonium hydroxide (9:1, 20 mL). Vigorous stirring of the mixture for 30 min produced a deep blue aqueous layer and a pale yellow organic layer, which was separated. The aqueous layer was extracted with ether (3 × 25 mL), and the combined organic extracts washed (saturated ammonium chloride:ammonium hydroxide, 9:1), dried, filtered through Celite, and evaporated. The residue was purified by chromatography (5% stepwise elution from hexane to ethyl acetate) to give the title compound in 70% yield; R_f 0.5 (ethyl acetate:hexane 1:4); IR ν_{max}: 1740 cm^{-1}; ^{1}HMR included signals at δ: 0.92 (3H, t, H-8′), 1.25–1.39 (8H, m, CH_2′s), 6.24 (1H, d, J = 16 Hz, H-2′), and 6.46 (dd, J = 6, 16 Hz, H-1′) ppm; ^{13}CMR δ: 13.8, 21.7, 22.3, 29.1, 30.9, 37.8, 39.2, 43.8, 54.0, 132.6, 141.0, and 216.4 ppm; MS (EI) *m/z* (%): 212(66), 141(64), 109(57), 91(32), 85(100); HRMS M^+: 212.1257; calcd. for $C_{12}H_{20}OS$: 212:1235.

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trans-*2-(6′-Methoxycarbonylhexyl)-3-(*E*-3″-thia-1″-octenyl)-cyclopentanone (**10**)*

Conjugate addition of the complex **14** to 2-(6′-methoxycarbonylhexyl)-cyclopent-2-enone (**4**) as described above gave, following chromatography, the title compound in 62% isolated yield; R_f 0.55 (ethyl acetate:hexane 3:2); IR ν_{max}: 1740 cm^{-1}; ^{1}HMR included signals at δ: 0.90 (3H, t, H-8″), 1.1–1.8 (12H, m), 6.16 (1H, d, J = 16 Hz, H-2″) and 6.46 (dd, J = 6.5, 16 Hz, H-1″) ppm; ^{13}CMR δ: 13.8, 22.1, 24.7, 26.4, 27.7, 28.8, 29.0, 30.5, 30.6, 33.9, 35.7, 41.0, 43.6, 51.2, 54.0, 127.4, 131.9, 174.0, and 219.4 ppm; MS (EI) *m/z* (%): 354(0.4), 290(41), 259(28), 258(31), 230(17), 147(64), 92(100); HRMS M^+: 354.2245; calcd. for $C_{20}H_{34}O_3S$: 354:2228.

trans-*3-(*E*-3′-Thia-1′-octenyl)-4-triethylsilyloxycyclopentanone (**9**)*

Conjugate addition of the complex **14** to 4-triethylsilyloxycyclopent-2-enone (**3**), as described above gave, following chromatography (elution with hexane:ethyl acetate 7:3), the title compound in 55% isolated yield; R_f 0.54 (ethyl acetate:hexane 3:7); IR ν_{max}: 1742 cm^{-1}; ^{1}HMR included signals at δ: 0.56 (6H, q, CH_3CH_2Si), 0.92 (12H, t, CH_3CH_2Si and H-8′), 4.02 (1H, q, H-4), 5.51 (1H, dd, J = 7.5, 15 Hz, H-1′), and 6.11 (d, J = 15 Hz, H-2′) ppm; ^{13}CMR δ: 4.7(3C), 6.7(3C), 13.9, 22.6, 28.7, 28.9, 29.8, 41.7, 42.6, 53.5, 74.0, 127.3, 131.4, and 214.5 ppm; MS (EI) *m/z* (%): 342(8), 313(26), 271(14), 258(14), 249(24), relative to 183(100). HRMS M^+: 342.2035; calcd. for $C_{18}H_{34}O_2SSi$: 342.205.

trans-*2-(6′-Methoxycarbonylhexyl)-3-(*E*-3″-thia-1″-octenyl)-4-tetrahydropyranyloxycyclopentanone (**12**)*

Addition of the cuprate complex **14** to 2-(6′-methoxycarbonylhexyl)-4-(tetrahydropyranyloxy)-cyclopent-2-enone (**6**) (80 mg) as described above, followed by chromatography of the product (5% stepwise elution from hexane to ethyl acetate), gave **12** (80 mg, 60%) as a pale yellow oil, R_f 0.5 (ethyl acetate:hexane 1:4), which was used directly in the next step.

trans-*2-(6′-Methoxycarbonylhexyl)-3-(*E*-3″-thia-1″-octenyl)-4-hydroxycyclopentanone, (±)-15-thia-15-deoxy-PGE$_1$ methyl ester (**11**)*

A solution of the tetrahydropyranyl ether **12** (75 mg) in acetic acid:water:THF (4:2:1, 7 mL), was stirred at room temperature for 24 h. The yellow mixture was then neutralized by the addition of solid sodium bicarbonate and worked up with ether. The ethereal extract was washed with saturated $NaHCO_2$, dried, and evaporated to yield 39 mg of material, which after purification by chromatography (10% stepwise elution from benzene to ethyl acetate) gave (±)-15-thia-15-deoxy-PGE$_1$ methyl ester (**11**) (22 mg); R_f 0.3 (chloroform:methanol 97.3); IR ν_{max}: 1746, 3392 cm^{-1}; ^{1}HMR (PG numbering) δ: 0.92 (3H, t, H-20), 1.30–1.40 (8H, m, CH_2′s), 1.57–1.66 (7H, m, CH_2′s), 1.88 (1H, br s, OH), 2.0 (1H, m, H-8), 2.16–2.49 (2H, m, including H-12 as dd at 2.40), 2.30 (2H, t), 2.71 (2H, t), 2.78 (2H, dd), 3.67 (3H, s, OCH_3), 4.05 (1H, q, H-11), 5.45 (1H, dd, J = 8, 16 Hz, H-13), and 6.18 (1H, d, J = 14 Hz, H-14) ppm; ^{13}CMR (PG numbering) δ: 13.9 (C-20), 22.2 (C-19), 24.8 (C-3), 26.6 (C-7), 27.6 (C-6), 28.9, 29.0, 29.3 (C-4, -5, -17), 30.9 (C-18), 32.6 (C-16), 34.0 (C-2), 46.0 (C-10), 51.4 (OCH_3), 54.6 (C-8), 55.5 (C-12), 72.2 (C-11), 127.2 (C-13), 128.1 (C-14), 174.1 (C-1), and 214.3 (C-9) ppm; MS (CI) *m/z* (%): 371(1.5), 352(0.4), 306(1), 279(15), 241(11), 167(27), 149(85), 129(100); HPLC (15 × 0.46 cm ODS2-C_{18} column, chloroform eluent, 1.5 mL/min, UV_{254} detection): single peak at retention time 7.5 min.

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