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Hemisynthesis of two marine cheilanthane sesterterpenes from (–)-sclareol: First enantioselective synthesis of petrosaspongiolide R

Leticia Ferreiro-Mederos^a, Steve Lanners^b, Hichem Henchiri^c, Abdelwaheb Fekih^c and Gilles Hanquet^{a*}

^aLaboratoire de Stéréochimie Associé au CNRS, ECPM, Université Louis Pasteur, 25 rue Becquerel, 67087 Strasbourg, France; ^bDepartment of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK; ^cLaboratoire de Chimie, Département des Sciences Fondamentales et Mixtes, 5000 Monastir, Tunisia

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The synthesis of two marine sponge metabolites **5** and **8** from naturally occurring (–)-sclareol is described here. The sesterterpenolide (**5**) is synthesised for the first time, establishing the absolute configuration of this compound. The key intermediate, aldehyde (**10**), was obtained from (–)-sclareol in good overall yields. The use of Katsumura's Wittig reagent and subsequent photochemical oxidation delivered the sesterterpenolide (**8**), which was chemoselectively epoxidized on exocyclic terminal olefin using the oxaziridinium salt (**14**) and transformed in four steps to carboxylic acid (**5**).

Keywords: sclareol; cheilanthanes; petrosaspongiolide; oxaziridinium salt

1. Introduction

Marine sponges are recognised as a rich source of structurally unique and biologically active terpenoids (Gray, Davies-Coleman, & Rivett, 2003).

Petrosaspongiolides M–R **1–5** have been isolated from the New Caledonian marine sponge *Petrospongia nigra* Bergquist (Randazzo et al., 1998). They are potent and selective phospholipase A₂ inhibitors and present potent anti-inflammatory activity (Figure 1) (Basabe et al., 2005; Monti, Casapullo, Riccio, & Gomez-Paloma, 2004).

The structure of these sesterterpenolides was determined by NMR, while their absolute configurations have not been confirmed yet. Herein, we report the first synthesis of (–)-petrosaspongiolide R (**5**) and the determination of its absolute configuration. In this synthesis, we describe a new route to the known key aldehyde **6** from (–)-sclareol and a simple and efficient method for the preparation of the enantiomerically pure intermediate **8** (Scheme 1).

Cheilanthane (**8**) is a member of a recently extracted family of sesterterpenoids from the marine sponge *Irinia* sp., which possess protein kinase inhibitor properties (Buchanan, Edser, King, Whitmore, & Quinn, 2001; Monti, Casapullo, Riccio, & Paloma, 2004). Basabe et al. (2005) reported recently that the semisynthesis of compound **8** from methyl

*Corresponding author. Email: fekihus@yahoo.com

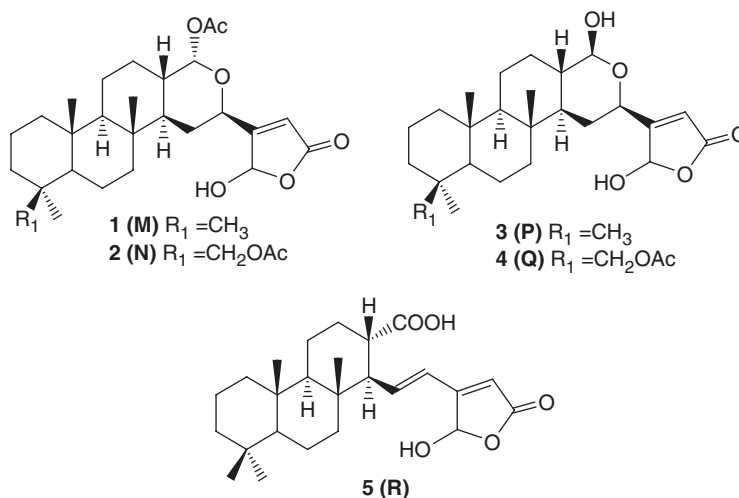
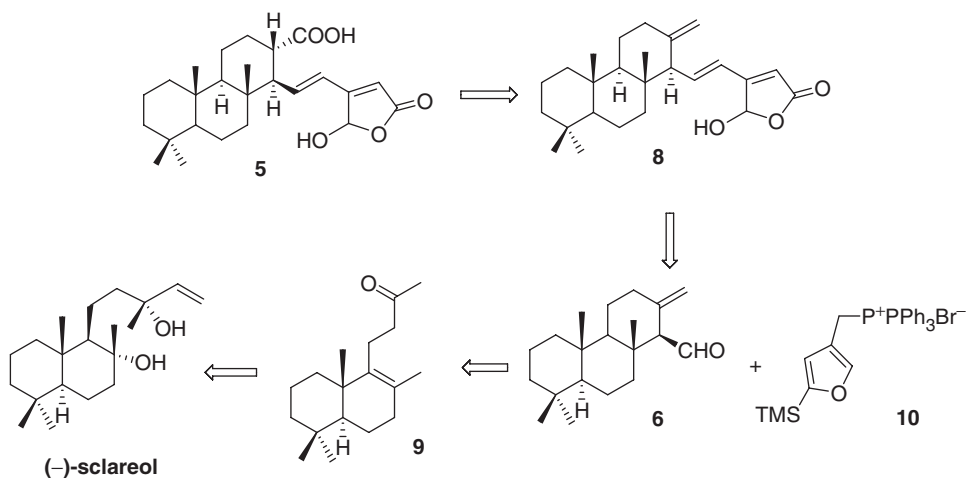


Figure 1. Petrosaspongionolides M–R.



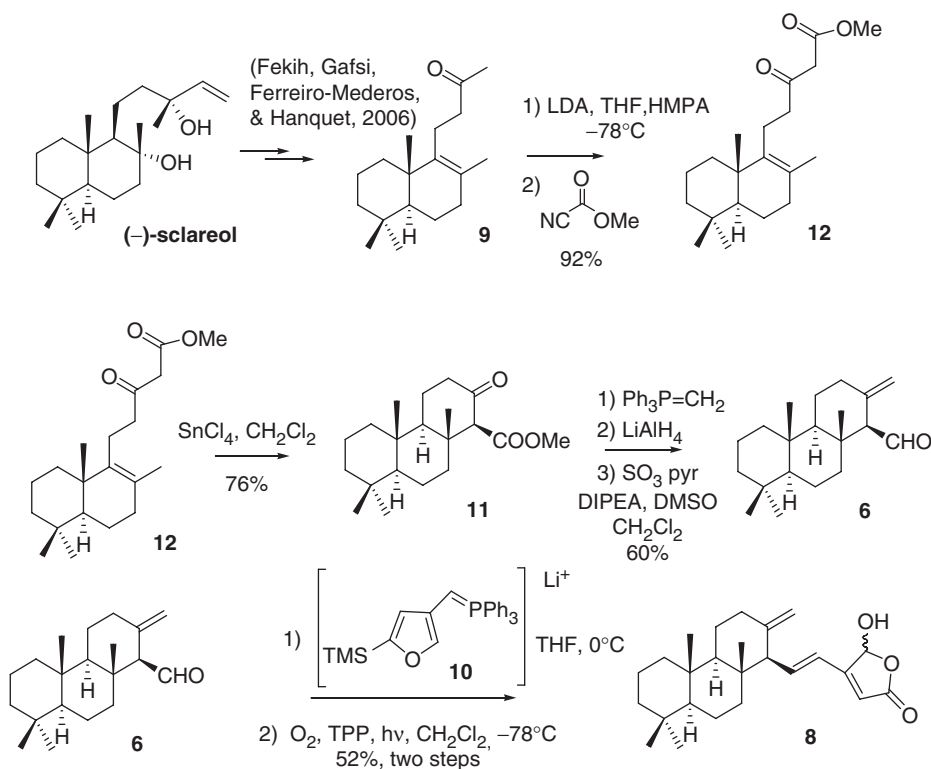
Scheme 1. Retrosynthetic analysis of compounds 5 and 8.

isoanticopalate (7) was easily obtained from (–)-sclareol. Their synthetic approach required 13 steps from (–)-sclareol, and cheilanthane (8) was finally obtained in 2% overall yield.

We expected that the use of Katsumura's Wittig reagent (10) (Furuichi, Hata, Soetjito, Kato, & Katsumura, 2001; Hata, Tanaka, & Katsumura, 1999) on the key aldehyde (6) prepared from (–)-sclareol via the ketone (9) (Scheme 1) would shorten the route to cheilanthane (8).

2. Results and discussion

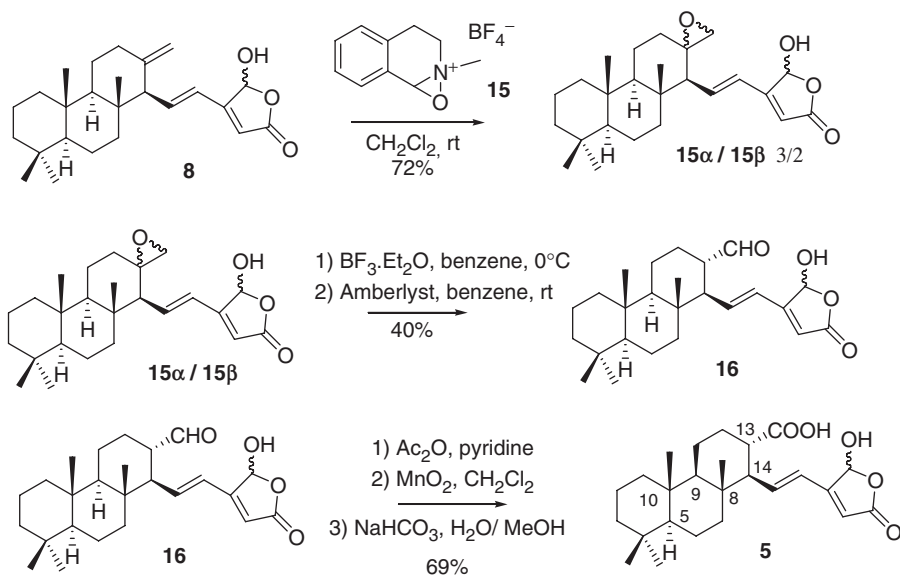
Some methods for synthesis of optically active tricyclic ketoester (11) have already been developed, including the derivation of the commercially available natural

Scheme 2. Preparation of butenolide (**8**).

terpenoid (–)-sclareolide (Zoretic, Fang, Ribeiro, & Dubay, 1998), biological resolution (Nair & Anilkumar, 1996, 1999; Tanimoto & Oritani, 1996) by an enzyme or microorganism, enantio- or diastereoselective polyene cyclisation (Ishihara, Ishibashi, & Yamamoto, 2001, and references cited therein) and olefin cyclisation followed by optical resolution (Furuichi, Hata, Soetjito, Kato, & Katsumura, 2001). We decided to prepare aldehyde (**6**) by a different route from (–)-sclareol *via* ketone (**9**) (Scheme 2). We previously prepared the Δ^8 -unsaturated ketone (**9**) as the key intermediate for the preparation of non-natural (+)-subersic acid analogues (Fekih, Gafsi, Ferreiro-Mederos, & Hanquet, 2006).

Regioselective acylation of the Δ^8 -unsaturated ketone (**9**) was achieved by condensation of the kinetic enolate with ethyl cyanofornate (Shimizu, Hiranuma, Hayashibe, & Yoshioka, 1991). A large excess of formylating reagent (3 equivalent) was required to obtain **12** in good yield (92%). The resulting β -ketoester (**12**) was treated with SnCl_4 in dichloromethane to afford the tricyclic ketoester (**11**) in 70% yield. In our experiments, anhydrous rather than wet dichloromethane gave the best yields (Ishihara et al., 2001).

Treatment of ketoester (**11**) with methylene-triphenylphosphonium ylide and subsequent LiAlH_4 reduction afforded exocyclic unsaturated primary alcohol (**13**) with partial epimerisation at C-14 position (90/10). The β -epimer was easily separated after

Scheme 3. Preparation of compound **5**.

flash chromatography. Finally, oxidation under Parikh–Doering conditions quantitatively afforded the desired aldehyde (**7**) (Parikh & Doering, 1967). The reaction of aldehyde (**7**) with furanmethylenide (**10**) cleanly produced the conjugated furan, which was converted by photochemical oxidation to butenolide (**8**) in 52% overall yield (Furuichi et al., 2001; Hata et al., 1999).

Chemoselective oxidation of butenolide (**8**) using carefully recrystallised oxaziridininium salt (**14**) (Hanquet & Lusinchi, 1997) delivered epoxides **15α/15β** in a 3/2 mixture (72%), which were rearranged to the corresponding aldehydes and equilibrated to the thermodynamically stable compound **16**, in 40% yield using the procedure described by Basabe et al. (2005) for the preparation of luffolide (Scheme 3) (Urones, Marcos, Basabe, Gomez, & Estrella, 1994). We also tried to use a dichloromethane solution of oxaziridininium salt (**14**) resulting from peracidic oxidation of the corresponding iminium salt without isolation, but epoxides **15α/15β** were obtained in lower yield (40%) (Hanquet & Lusinchi, 1997).

Finally, protection of the γ -hydroxybutenolide as acetate, followed by MnO_2 oxidation of the aldehyde and subsequent deprotection of the resulting γ -acetoxybutenolide using aqueous solution of NaHCO_3 in methanol yielded the petrosaspongianolide R (**5**) (Parikh & Doering, 1967), whose ^1H - and ^{13}C -NMR spectra and analytical data ($[\alpha]_{\text{D}} = -18$ ($c = 0.1$, MeOH); lit: $[\alpha]_{\text{D}} = -15.6$ ($c = 0.003$, MeOH)) are identical to those reported in the literature of Randazzo et al. (1998) and Monti et al. (2004).

In conclusion, we have accomplished a diastereoselective syntheses of sesterterpenolides (**5**) and (**9**) from (–)-sclareol. Butenolide (**8**) was readily prepared in 9 steps and 14% overall yield that competed favourably with Basabe's route. Thus, we achieved the first synthesis of (–)-petrosaspongianolide R (**5**) in 15 steps *via* a chemoselective epoxidation using the oxaziridininium salt (**14**) and also determined its absolute configuration as (5*S*, 8*R*, 9*R*, 10*S*, 13*S*, 14*S*) by the present synthesis.

3. Experimental

3.1. General

Unless otherwise stated, reagents and solvents were purchased as reagent grade and used without further purification. THF was distilled over sodium benzophenone ketyl. Dichloromethane was distilled over CaH_2 . Column chromatography: silica gel 60 (230–400 mesh, 0.040–0.063 mm) was purchased from E. Merck. Thin layer chromatography (TLC) was performed on glass sheets coated with silica gel 60 F₂₅₄ (unless otherwise stated) purchased from E. Merck, visualisation by UV light and/or appropriate staining reagents. IR (cm^{-1}) measurements were recorded using Universal ATR sampling accessories on a Perkin–Elmer Spectrum One spectrometer. NMR spectra (^1H and ^{13}C) were recorded on Bruker AC200 (200 MHz) or Bruker Avance (300 MHz or 400 MHz) spectrometers. Chemical shifts are reported in ppm relative to the residual solvent (CHCl_3) resonance at δ 7.26 ppm in ^1H spectra, and relative to the central CDCl_3 resonance at δ 77.0 ppm in ^{13}C spectra. Data are reported as, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br s=broad singlet; integration; coupling constant(s) in Hz. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a sodium lamp and are reported as follows: $[\alpha]_D^{25}$ (c g/100 mL, solvent).

3.1.1. Preparation of isoanticopal-13(16)-en-15-al (7) from (–)-sclareol

3.1.1.1. *Ketoester (12)*. To a solution of diisopropylamine (0.4 mL, 2.85 mmol) in anhydrous THF (5 mL), *n*-BuLi (1.48 mL, 2M in hexane, 2.96 mmol) at -78°C was added. After 30 min at this temperature, a solution of ketone (9) (Fekhi et al., 2006) (300 mg, 1.14 mmol) in dry THF (5 mL) was added drop-wise at -78°C and stirred for an additional 1 h at 0°C . The solution is cooled down at -78°C before adding HMPA (198 μL , 1.14 mmol) and methyl cyanofomate (271 μL , 3.42 mmol). The mixture is stirred for 1 h at -78°C and treated with cold water, warmed to room temperature and extracted with Et_2O (3×50 mL). The organic layer was washed with brine, and dried on MgSO_4 . The residue obtained after removal of the solvent was purified by chromatography (ethyl acetate/cyclohexane 1:30) to yield the ketoester (12) as a colourless oil (1.23 mmol, 92%).

$[\alpha]_D^{25} = +31$ ($c = 1.2$, EtOH), (lit. $[\alpha]_D^{25} = +29.1$ ($c = 1.02$, CHCl_3) (Shimizu et al., 1991), $R_f = 0.40$, (cyclohexane/AcOEt 10:1); ^1H -NMR (300 MHz, CDCl_3) δ in ppm: 3.74 (3H, s), 3.44 (2H, s), 0.95–2.75 (15H, m), 1.53 (3H, s), 0.94 (3H, s), 0.88 (3H, s), 0.83 (3H, s); ^{13}C -NMR (75 MHz) δ in ppm: 202.60, 167.66, 138.9, 127, 52.3, 51.9, 49, 43.9, 41.75, 39.1, 37, 33.65, 33.30, 21.65, 21.3, 19.9, 19.4, 18.9; IR (near) 1680 and 1712 cm^{-1} ($\nu\text{ C=O}$).

3.1.1.2. *Ketoester (11)*. To a solution of ketoester (12) (3 g, 12 mmol) in dry dichloromethane was added SnCl_4 (12 mL, 1M solution in dichloromethane) at 0°C and the mixture was stirred overnight after removing from the ice bath. Then, 100 mL of ether was added and the resulting solution was washed twice with 5% HCl aqueous solution and finally with water. The organic layer was washed with brine and dried over MgSO_4 . The residue obtained after removal of the solvent was purified by chromatography (dichloromethane/cyclohexane 2:1 to remove starting material then ethyl acetate) to afford pure ketoester (11) as white needles (2.4 g, 6.6 mmol, 76%).

$[\alpha]_{\text{D}} = +25$ ($c = 0.4$, acetone) (lit. $[\alpha]_{\text{D}} = +29.1$, $c = 1.02$, CHCl_3) (Shimizu et al., 1991), $R_{\text{f}} = 0.27$, (Cyclohexane/AcOEt. 10:1); m.p. = 168°C (lit. $170\text{--}172^\circ\text{C}$) (Shimizu et al., 1991); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ in ppm: 3.69 (3H, s), 3.24 (1H, s), 2.48 (1H, ddd, $J = 7.14, 3.57, 1.89$ Hz), 2.31 (1H, m), 1.99 (1H, m), 1.85–0.80 (13H, m), 1.18 (3H, s), 0.90 (3H, s), 0.88 (3H, s), 0.83 (3H, s); $^{13}\text{C-NMR}$ (75 MHz) δ in ppm: 205.5, 168.6, 40.1, 57.9, 56.6, 40.4, 40.8, 41.9, 38.0, 29.7, 33.4, 51.4, 19.4, 21.5, 21.9, 21.9, 18.4, 16.0; IR (near) 1692 and 1721 cm^{-1} ($\nu\text{ C=O}$).

3.1.1.3. *Alcohol (13)*. To a suspension of triphenylphosphonium bromide (1.5 g, 4.2 mmol, 4.5 equivalent) in dry THF was added to *tert*-BuOK (472 mg, 4.2 mmol, 4.5 equivalent) at room temperature. The mixture is stirred for 1 h, decanted for half an hour and finally transferred *via* canula to a solution of ketoester (**11**) (300 mg, 0.94 mmol, 1 equivalent) in dry THF (10 mL) and stirred for an additional 12 h. The reaction mixture was treated with water and extracted ($3 \times 25\text{ mL}$) with cyclohexane. The combined organic layer was washed with saturated NH_4Cl aqueous solution (50 mL), and dried over MgSO_4 . After removal of the solvent we obtained a crude oil which was used in the next step without further purification.

A suspension of LiAlH_4 (84 mg, 3.8 mmol, 2.1 equivalent) in dry ether (10 mL) was treated drop-wise with a solution of the previous crude product (764 mg) in ether (15 mL) and stirred for further 4 h at room temperature. The reaction mixture was quenched with ethyl acetate and water. After filtration on celite, the solvent was evaporated to give a residue which was purified by silica gel column chromatography (cyclohexane/ethyl acetate 20:3) to give pure primary alcohol (**13**) as a white solid (180 mg, 0.6 mmol, 63%).

$[\alpha]_{\text{D}} = -12.5$ ($c = 0.4$, CHCl_3) (lit. $[\alpha]_{\text{D}} = -11.7$ ($c = 1.05$, CHCl_3) (Shimizu et al., 1991), $R_{\text{f}} = 0.45$ (cyclohexane/AcOEt. 10:3); m.p. = 95°C (lit. $99\text{--}100^\circ\text{C}$) (Shimizu et al., 1991); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ in ppm: 4.93 (1H, d, $J = 1.6$ Hz), 4.64 (1H, d, $J = 1.6$ Hz), 3.79 (2H, m), 2.41 (1H, ddd, $J = 12.8, 4.4, 2.4$ Hz), 2.00 (2H, m), 1.66 (m, 5H), 1.36 (6H, m), 0.86 (2H, m), 0.86 (3H, m), 0.81 (3H, s), 0.80 (3H, s), 0.72 (3H, s); $^{13}\text{C-NMR}$: 147.8, 105.9, 59.8, 59.5, 58.7, 56.4, 42.0, 40.6, 40.0, 39.3, 37.8, 33.2, 29.7, 26.9, 23.0, 21.4, 18.9, 18.6, 18.2.

3.1.1.4. *Aldehyde (7)*. To a solution of alcohol (**13**) (360 mg, 1.2 mmol) in dry dichloromethane (5 mL) and dimethylsulfoxide (2 mL) at -15°C under nitrogen atmosphere was added diisopropylethylamine (464 mg, 3.6 mmol, 3 equivalent) and immediately a SO_3 -pyridine complex solution in dimethylsulfoxide (2 mL) *via* canula was added. The solution was cooled to -78°C and stirred for 1 h at this temperature and finally diluted with 50 mL of ether. The organic layer was washed with brine ($2 \times 50\text{ mL}$), water ($2 \times 50\text{ mL}$), a saturated solution of NaHCO_3 and a 10% solution of CuSO_4 . After drying on MgSO_4 and filtration, the solvent was evaporated to give nearly pure aldehyde (**7**), which was used in the next step without further purification (350 mg, 97%). Analytical data of aldehyde (**6**) were identical to those described by Basabe et al. (2005).

3.1.2. Preparation of cheilanthane (**8**) from isoanticopal-13(16)-en-15-al (**7**)

Cheilanthane (**8**) was prepared from aldehyde (**6**) following the procedure described by Katsumura for the synthesis of spongianolide A (Furuichi et al., 2001; Hata et al., 1999). The resulting compound **8** had data identical to those described by Basabe et al (2005).

3.1.3. *Chemoselective oxidation of cheilanthane (8) using the oxaziridinium salt (14)*

To a dichloromethane solution (10 mL) of cheilanthane (**8**) (220 mg, 0.57 mmol) recrystallized oxaziridinium salt (**14**) was added by portions at 0°C (oxaziridinium salt (**15**) was recrystallised from dry acetone by removing the entire acidity). The mixture was stirred until the disappearance of active oxygen (IK test <0) and evaporated until dryness. The resulting solid was triturated in dry ethyl acetate and after filtration the solvent was evaporated to give a crude solid which was filtered on bicarbonated silica gel to give a mixture of epoxide derivatives 15 α /15 β (164 mg, 0.41 mmol, 72%).

¹H-NMR (400 MHz, CDCl₃) δ in ppm (major epoxide): 6.21 (1H, br d), 6.57 (1H, dd, J = 16, 10 Hz), 6.22 (1H, d, J = 16 Hz), 5.97 (1H, s), 2.84 (1H, br s), 2.61 (1H, br m), 2.4 (1H, d, J = 10 Hz), 2–1.1 (16H, m), 0.86 (3H, s), 0.83 (6H, s), 0.79 (3H, s). ¹³C-NMR (100 MHz, CDCl₃) δ in ppm (major epoxide): 171.2, 162.8, 135.6, 122.7, 114.8, 98.1, 64.7, 56.7, 54.5, 53.3, 51.1, 41.9, 38.6, 38.1, 37.9, 36.7, 33.2, 31.1, 30.5, 27.6, 25.6, 20.4, 16.4, 16.1.

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