



Enantioselective formal synthesis of (–)-ovalicin using quinic acid as a chiral template[†]

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Abstract

The key intermediate **18** for the synthesis of (–)-ovalicin was synthesized using (–)-quinic acid as the chiral source, through a series of stereocontrolled and efficient chemical reactions, thus establishing a new, formal synthesis of the natural target. The featuring spirocyclic epoxide function has been installed by internal Williamson ether synthesis using the functionalities originally present at C-1 of (–)-quinic acid after the appropriate adjustments required to introduce the necessary functionality at C-2. © 1998 Elsevier Science Ltd. All rights reserved.

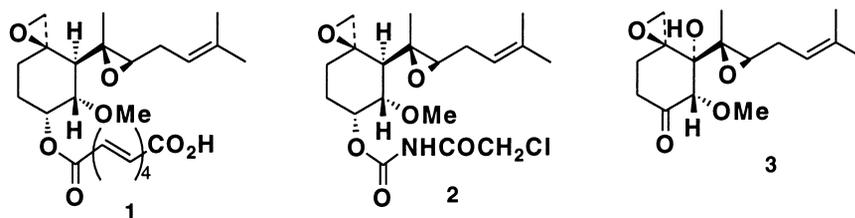
1. Introduction

Angiogenesis, the formation and growth of new blood capillaries from pre-existing vessels, takes place normally during wound healing. But abnormal angiogenesis is an important contributor to certain diseases and accumulating evidence indicates that progressive tumor growth is dependent on angiogenesis. Anti-angiogenesis treatments are designed to prevent the growth of tumor blood vessels and researchers have been looking for inhibitors of angiogenesis because they can inhibit the growth of cancers. Even though no definitive conclusions can be drawn, antiangiogenic therapy combined with conventional anticancer therapies may represent a useful tool in the future care of patients with cancer.¹

Recently, it has been reported that fumagillin **1**, an antitumor, antibacteriophage and antiameba metabolite isolated from *Aspergillus fumigatus*, exhibits a potent antiangiogenic activity. Although the effectiveness of fumagillin as an inhibitor of tumor growth is limited because of its high toxicity, its semi-synthetic analog AGM-1470 **2** has just entered clinical trials for the treatment of human cancer.²

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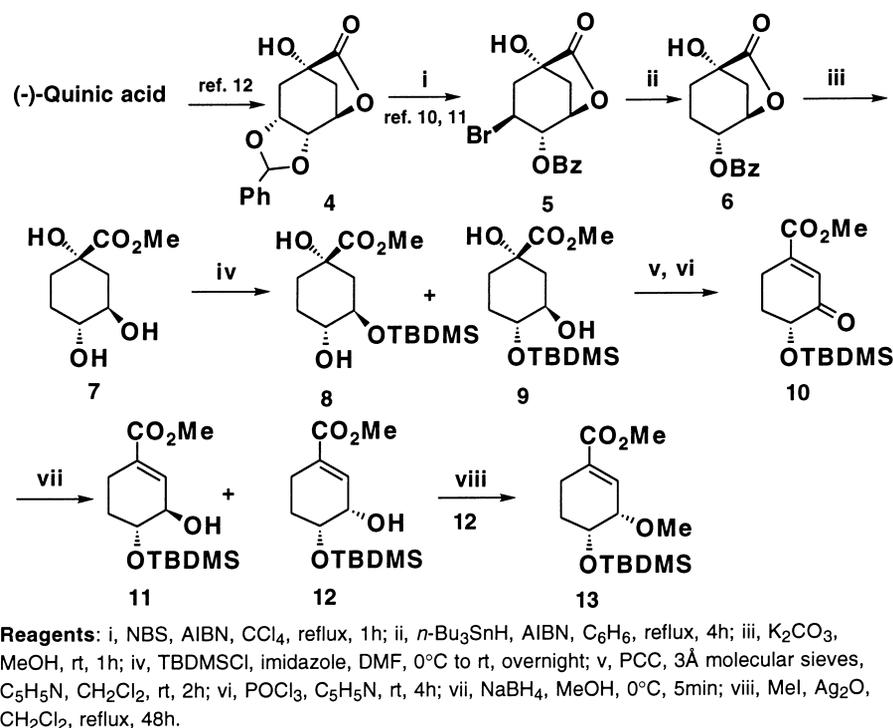
On the other hand, the related sesquiterpene (–)-ovalicin **3**, first isolated by cultures of *Pseudorotium ovalis* Stolk,³ was found to be non-toxic, non-inflammatory and, above all, more potent than the structural analog of fumagillin. As a result of these positive observations, Corey et al.⁴ modified the original total synthesis of racemic ovalicin reported by himself and Dittami⁵ to obtain the natural enantiomer by a catalytic asymmetric process, while Barton et al.⁶ described the total synthesis of (–)-ovalicin using the naturally occurring cyclitol *L*-quebrachitol as the chiral synthon.

Our continuous interest in applications of (–)-quinic acid as the chiral template for asymmetric synthesis,^{7,8} led us to recognize an opportunity to extend these studies in devising a new synthetic entry to (–)-ovalicin. We envisaged the structure and the absolute stereochemistry⁹ of (–)-quinic acid amenable for an efficient elaboration to the advanced chiral intermediate **18** from which (–)-ovalicin has been obtained by application of the sequence reported by Barton et al.,⁶ thus establishing a new, formal synthesis of the natural target. We were particularly intrigued by the possibility of installing the spirocyclic epoxide function by internal Williamson ether synthesis using the functionalities originally present at C-1 of (–)-quinic acid after the appropriate adjustments required to introduce the oxygenated functionality at C-2.

2. Results and discussion

The starting point of the synthetic approach was the readily available bromobenzoate **5**,^{10,11} easily obtained in a high-yield two-step sequence involving the regioselective *N*-bromosuccinimide promoted opening of the lactone ring of the benzylidene quinide **4**¹² derived from (–)-quinic acid following the protocol developed by Hanessian.¹³ The bromine atom was subsequently successfully removed by a free-radical mediated hydride reduction using *n*-tributyltin hydride in the presence of AIBN to produce the intermediate **6**. Opening of the lactone ring and concomitant saponification of the benzoate ester occurred cleanly by treatment of **6** with methanolic potassium carbonate affording the triol ester **7**. At this point, having as the goal the interception of the advanced intermediate **18** already transformed by Barton et al.⁶ into (–)-ovalicin, we tried the selective protection of the vicinal diol moiety of **7** using triethylsilyl chloride (TESCl) in order to minimize unnecessary manipulations. Unfortunately, this operation proceeded with poor selectivity producing a mixture of mono- and bis-protected derivatives, the latter being prevalent, forcing us to choose a more hindered silylating agent. Thus, we selected *tert*-butyldimethylsilyl chloride (TBDMSCl) for the selective protection of the C-3 hydroxy group of **7**. This was accomplished performing the reaction in *N,N*-dimethylformamide at 0°C for 30 min then at room temperature overnight giving rise to the formation of an unseparable mixture of mono-protected derivatives **8** and **9** (combined yield 72%). Gratifyingly, the oxidation of the mixture of **8** and **9** with pyridinium chlorochromate in the presence of 3 Å molecular sieves followed by phosphorus oxychloride/pyridine dehydration produced the α,β -unsaturated ketone **10** as the only isolated product (overall yield of 60%) after flash chromatography of the crude mixture. It is likely that the regioisomer **8** could undergo a more complicated transformation during these operations with formation of aromatized products. The reduction of the carbonyl group of **10** with sodium borohydride proceeded smoothly

at 0°C to produce a 1:4 mixture of the diastereomers **11** and **12**, which were separated by silica gel chromatography as reported by Giese and Almstead¹⁴ for the racemic compound. The alkylation of the predominant α -alcohol **12** with methyl iodide in the presence of silver oxide led to the formation of the corresponding methyl ether **13**. The overall sequence from (–)-quinic acid to **13** is summarized in Scheme 1.



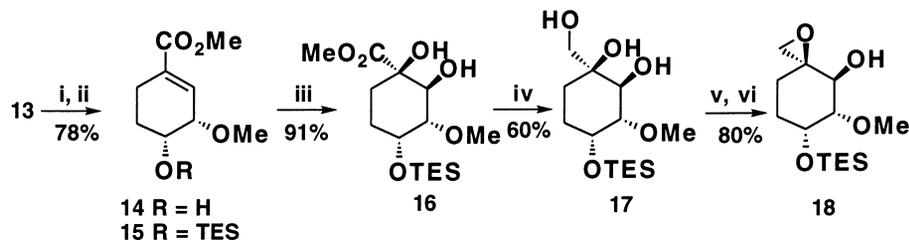
Scheme 1.

Having in hand **13**, the stage was set to perform the *cis*-dihydroxylation of the double bond, requiring, as anticipated, a modification of the TBDMS protecting group into TES in order to intercept the advanced intermediate **18** already transformed by Barton et al.⁶ into (–)-ovalicin.

The deprotection–reprotection manipulation was accomplished by standard procedure in excellent overall yield to furnish the cycloalkene **15**, which was submitted to osmylation to give diastereoselectively **16** as the sole product, the osmium reagent undergoing a more favored addition from the less hindered convex face. The stereochemistry of the newly introduced hydroxyl groups was inferred by ¹H NMR spectroscopic analysis (*J*_{2,3}=9.6 Hz).

To introduce the spirocyclic epoxide function, the crude diol **16** was sequentially transformed by treatment with lithium aluminum hydride into the triol **17**, then mono-tosylated at the primary hydroxyl function and submitted to basic treatment in order to perform the crucial intramolecular Williamson ether synthesis to give **18** in good overall yield. The complete sequence is summarized in Scheme 2.

In summary, using one of the two original chiral centers of (–)-quinic acid,⁹ the other one being removed in the initial debromination step, the required configuration at the different chiral centers of the natural target (–)-ovalicin has been correctly established. The synthesis of (–)-ovalicin from **18** has been reported,⁶ so the present synthesis of this compound represents an alternative formal synthesis of (–)-ovalicin, stressing once more the versatility¹⁵ of (–)-quinic acid as a chiral template for the synthesis of natural compounds.



Reagents: i, TBAF, THF, rt, 3h; ii, TSCl, C₅H₅N, rt, 30min; iii, OsO₄, NMO, C₅H₅N, H₂O, ^tBuOH, reflux, 30min; iv, LiAlH₄, THF, 0°C, 2h; v, TsCl, Et₃N, DMAP, CH₂Cl₂, rt, 36h; vi, K₂CO₃, MeOH, rt, 5h.

Scheme 2.

3. Experimental section

3.1. General remarks

Melting points were determined on a Büchi–Tottoli apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. Infrared (IR) spectra were taken on a Perkin–Elmer FT-IR Paragon 500 spectrometer. Nuclear magnetic resonance (¹H NMR) spectra were recorded on a Bruker AC-200 spectrometer for solutions in CDCl₃ unless otherwise noted and chemical shifts are given in parts per million downfield from tetramethylsilane as the internal standard. Coupling constants (J) are given in hertz. Organic solutions were dried over anhydrous magnesium sulfate and evaporated with a rotary evaporator. Light petroleum refers to the fractions boiling in the range 40–60°C and ether to diethyl ether. Flash chromatography was carried out with Merck silica gel (230–400 mesh). All reactions were carried out under an Ar atmosphere. Elemental analyses were effected by the microanalytical laboratory of the Dipartimento di Chimica, University of Ferrara.

3.2. (1*S*,3*R*,4*R*)-4-Benzoyloxy-1-hydroxycyclohexane-1,3-carbolactone **6**

A solution of **5** (16 g, 46.92 mmol) in anhydrous benzene (150 ml) containing *n*-Bu₃SnH (18.65 ml, 70.38 mmol) and a catalytic amount of AIBN was heated at reflux for 4 h. After cooling, most of the solvent was removed under reduced pressure and the solid residue was taken up in light petroleum (250 ml). The resulting suspension was stirred overnight, then filtered to give **6** (12 g, 97%) as a white solid, which could be used in the next step without further purification. An analytical sample was obtained by crystallization (EtOAc) or flash chromatography (eluent: EtOAc:light petroleum, 1:3), m.p.: 143–145°C, [α]_D²⁵ –29 (c 0.77, MeOH). IR (KBr): 3448, 1786, 1720 cm⁻¹; ¹H NMR (DMSO-d₆): δ 1.8–2.3 (m, 6H), 2.83 (s, 1H), 4.97 (m, 1H), 5.34 (m, 1H), 7.4–7.7 (m, 3H), 8.04 (d, 2H, J=7). Anal. calcd for C₁₄H₁₄O₅: C, 64.10; H, 5.38. Found: C, 64.03; H, 5.45.

3.3. (1*S*,3*R*,4*R*)-1-Methoxycarbonyl-cyclohexane-1,3,4-triol **7**

A solution of **6** (3.37 g, 12.86 mmol) in MeOH (45 ml) was treated with K₂CO₃ (0.23 g) and stirred at room temperature for 1 h. The cooled (0°C) reaction mixture was neutralized with AcOH and the solvent evaporated. The residue was purified by flash chromatography (eluent: EtOAc:MeOH, 9.5:0.5) to afford **7** (2.17 g, 89%) as a white solid, m.p.: 101–103°C, [α]_D²⁵ –17.6 (c 0.74, MeOH). IR (KBr): 3351, 1730 cm⁻¹; ¹H NMR (DMSO-d₆): δ 1.4–1.7 (m, 5H), 1.85 (m, 1H), 3.13 (m, 1H), 3.38 (m, 1H),

3.61 (s, 3H), 4.56 (d, 1H, $J=4.2$, D₂O exchangeable), 4.58 (d, 1H, $J=3.74$, D₂O exchangeable), 5.25 (s, 1H, D₂O exchangeable). Anal. calcd for C₈H₁₄O₅: C, 50.50; H, 7.42. Found: C, 50.48; H, 7.44.

3.4. (1*S*,3*R*,4*R*)-1-Methoxycarbonyl-3-(1,1-dimethylethyl)dimethylsilyloxy-cyclohexane-1,4-diol **8** and (1*S*,3*R*,4*R*)-1-methoxycarbonyl-4-(1,1-dimethylethyl)dimethylsilyloxy-cyclohexane-1,3-diol **9**

To an ice-cooled solution of **7** (2.83 g, 14.9 mmol) and imidazole (2.23 g, 32.78 mmol) in dry DMF (13 ml) was added TBDMSCl (2.69 g, 17.88 mmol). After being stirred for 30 min at 0°C, the reaction mixture was allowed to stand at room temperature overnight. The solvent was evaporated and the crude product was subjected to flash chromatography (eluent: EtOAc:light petroleum, 1:3) affording the solid mixture of **8** and **9** (3.28 g, 72%). IR (film): 3466, 1740 cm⁻¹; ¹H NMR: δ 0.10 and 0.11 (2s, 6H), 0.89 and 0.90 (2s, 9H), 1.6–2.1 (m, 6H), 2.42 (d, 1H, $J=1.7$, D₂O exchangeable), 2.46 (d, 1H, $J=1.85$, D₂O exchangeable), 3.02 (s, 1H), 3.45 (m, 1H), 3.7–3.9 (overlapping s, 3H and m, 1H).

3.5. (6*R*)-3-Methoxycarbonyl-6-(1,1-dimethylethyl)dimethylsilyloxy-cyclohex-2-en-1-one **10**

To a solution of **8** and **9** (0.74 g, 2.43 mmol) in dry CH₂Cl₂ (5 ml), 3 Å powder molecular sieves (1.4 g), pyridine (0.78 ml, 9.72 mmol) and PCC (2.09 g, 9.72 mmol) were added and the mixture was stirred for 2 h at room temperature. Ether and Celite (0.5 g) were added and the resulting suspension was filtered through a pad of Celite. The solids were washed with ether (5×20 ml) and the filtrate evaporated to an oil which was dissolved in pyridine (3.6 ml) and treated with POCl₃ (0.59 ml, 6.45 mmol) at 0°C. The mixture was kept at room temperature for 4 h, treated with ice-cold saturated aqueous NH₄Cl (20 ml), extracted with CH₂Cl₂ (5×10 ml), dried and evaporated. The crude product was purified by flash chromatography (eluent: EtOAc:light petroleum, 1:9) to furnish **10** (0.37 g, 60%) as a yellowish oil which crystallized on standing in the freezer, m.p.: 26–28°C, [α]_D²⁵ +70.3 (c 0.35, CHCl₃). IR (KBr): 1723, 1703 cm⁻¹; ¹H NMR: δ 0.08 (s, 3H), 0.15 (s, 3H), 0.9 (s, 9H), 2.0–2.3 (m, 2H), 2.5–2.7 (m, 1H), 2.7–2.9 (dt, 1H, $J=4.7$), 3.83 (s, 3H), 4.18 (dd, 1H, $J=10.7, 5$), 6.73 (d, 1H, $J=2$). Anal. calcd for C₁₄H₂₄SiO₄: C, 59.12; H, 8.51. Found: C, 59.08; H, 8.53.

3.6. (1*R*,6*R*)-3-Methoxycarbonyl-6-(1,1-dimethylethyl)dimethylsilyloxy-cyclohex-2-en-1-ol **11** and (1*S*,6*R*)-3-methoxycarbonyl-6-(1,1-dimethylethyl)dimethylsilyloxy-cyclohex-2-en-1-ol **12**

To a stirred solution of **10** (1.14 g, 4.01 mmol) in MeOH (20 ml) at 0°C was added sodium borohydride (0.15 g, 4.01 mmol) in one portion. After 5 min, the mixture was neutralized with AcOH, the solvent removed under reduced pressure and the residue extracted with ether (3×10 ml). The combined extracts were dried and evaporated. Purification of the residue by flash chromatography (eluent: ether:light petroleum, 1:4) furnished **11** (0.18 g) and **12** (0.8 g) as colorless oils (86% overall yield). **11**: [α]_D²⁵ –19.6 (c 5.56, CHCl₃). IR (neat): 3550, 1720 cm⁻¹; ¹H NMR: δ 0.11 (s, 6H), 0.90 (s, 9H), 1.5–2.0 (m, 2H), 2.17 (d, 1H, $J=3.79$), 2.2–2.6 (m, 2H), 3.6–3.7 (m, 1H), 3.74 (s, 3H), 4.14 (m, 1H), 6.76 (bs, 1H). **12**: [α]_D²⁵ +42.54 (c 0.55, CHCl₃). IR (neat): 3546, 1720 cm⁻¹; ¹H NMR: δ 0.12 (s, 6H), 0.90 (s, 9H), 1.5–1.8 (m, 1H), 1.8–2.1 (m, 1H), 2.1–2.5 (m, 2H), 2.56 (d, 1H, $J=7.5$), 3.75 (s, 3H), 4.00 (m, 1H), 4.15 (m, 1H), 6.78 (d, 1H, $J=3$). Anal. calcd for C₁₄H₂₆SiO₄: C, 58.71; H, 9.16. Found: C, 58.74; H, 9.13.

3.7. (3S,4R)-1-Methoxycarbonyl-3-methoxy-4-(1,1-dimethylethyl)dimethylsilyloxy-cyclohex-1-ene **13**

A solution of **12** (0.97 g, 3.39 mmol) in CH₂Cl₂ (12 ml) was treated with CH₃I (2.11 ml, 33.9 mmol) and Ag₂O (1.3 g, 5.59 mmol) and heated at reflux in the dark for 24 h. Additional CH₃I (4.22 ml) and Ag₂O (1.3 g) were added and reflux was continued for 24 h. The cooled reaction mixture was filtered through Celite and the solvent evaporated. Purification of the residue by flash chromatography (eluent: ether:light petroleum, 1:9) afforded **13** (0.9 g, 88%) as a yellow oil, [α]_D²⁵ +77.8 (c 0.27, CHCl₃). IR (neat): 1721, 1650 cm⁻¹; ¹H NMR: δ 0.09 (s, 6H), 0.89 (s, 9H), 1.5–1.7 (m, 1H), 1.8–2.05 (m, 1H), 2.1–2.3 (m, 1H), 2.4–2.6 (m, 1H), 3.49 (s, 3H), 3.73 (overlapping s, 3H and m, 1H), 4.04 (m, 1H), 6.82 (bs, 1H). Anal. calcd for C₁₅H₂₈SiO₄: C, 59.96; H, 9.40. Found: C, 60.01; H, 9.35.

3.8. (3S,4R)-4-Hydroxy-1-methoxycarbonyl-3-methoxy-cyclohex-1-ene **14**

To a solution of **13** (0.52 g, 1.73 mmol) in THF (10 ml) was added *n*-Bu₄NF·3H₂O (1.64 g, 5.19 mmol) and the mixture stirred at room temperature for 3 h. The solvent was evaporated and the residue extracted with CH₂Cl₂ (3×10 ml). Evaporation of the dried organic extracts gave a brown oil, which was subjected to flash chromatography (eluent: ether:light petroleum, 4:1) to yield **14** (0.3 g, 94%) as a colorless oil, [α]_D²⁵ +120 (c 1.07, CHCl₃). IR (neat): 3478, 1715, 1652 cm⁻¹; ¹H NMR: δ 1.64 (m, 1H), 1.95 (m, 1H), 2.1–2.3 (m, 1H), 2.3–2.6 (m, 2H), 3.44 (s, 3H), 3.68 (s, 3H), 3.77 (m, 1H), 4.0 (m, 1H), 6.76 (bs, 1H). Anal. calcd for C₉H₁₄O₄: C, 58.04; H, 7.58. Found: C, 58.00; H, 7.63.

3.9. (3S,4R)-1-Methoxycarbonyl-3-methoxy-4-triethylsilyloxy-cyclohex-1-ene **15**

To a solution of **14** (0.3 g, 1.61 mmol) in pyridine (28 ml) was added TESCl (0.54 ml, 3.22 mmol). The reaction mixture was stirred for 30 min at room temperature. Evaporation of the solvent followed by flash chromatography of the residue (eluent: EtOAc:light petroleum, 1:9) afforded **15** (0.4 g, 83%) as a yellow oil, [α]_D²⁵ +102.5 (c 0.89, CHCl₃). IR (neat): 1720, 1654 cm⁻¹; ¹H NMR: δ 0.62 (q, 6H, J=8), 0.97 (t, 9H, J=8), 1.55–1.75 (m, 1H), 1.8–2.05 (m, 1H), 2.1–2.35 (m, 1H), 2.4–2.6 (m, 1H), 3.51 (s, 3H), 3.73 (overlapping s, 3H and m, 1H), 3.99 (m, 1H), 6.86 (m, 1H). Anal. calcd for C₁₅H₂₈SiO₄: C, 59.96; H, 9.40. Found: C, 60.01; H, 9.35.

3.10. (1R,2S,3S,4R)-1-Methoxycarbonyl-3-methoxy-4-triethylsilyloxy-cyclohexane-1,2-diol **16**

A solution of **15** (0.52 g, 1.73 mmol), NMO (0.28 g, 2.07 mmol), pyridine (0.84 ml, 10.38 mmol), water (0.17 ml, 9.51 mmol) and OsO₄ (0.027 g, 0.106 mmol) was refluxed in the dark for 30 min. After cooling, the reaction mixture was filtered through a pad of Celite and florisil and washed with EtOAc (20 ml). The eluant was concentrated *in vacuo* and the crude product purified by flash chromatography (eluent: ether:light petroleum, 1:1) to afford **16** (0.53g, 91%) as a yellowish oil, [α]_D²⁵ –65.91 (c 0.22, CHCl₃). IR (neat): 3480, 1739 cm⁻¹; ¹H NMR: δ 0.61 (q, 6H, J=8), 0.98 (t, 9H, J=8), 1.5–1.9 (m, 3H), 2.24 (td, 1H, J=4.8), 2.55 (bs, 1H), 3.18 (dd, 1H, J=2.5, 9.6), 3.42 (overlapping s, 3H and m, 1H), 3.81 (s, 3H), 4.19 (d, 1H, J=9.6), 4.27 (m, 1H). Anal. calcd for C₁₅H₃₀SiO₆: C, 53.86; H, 9.05. Found: C, 53.88; H, 9.03.

3.11. (1S,2S,3S,4R)-1-Hydroxymethyl-3-methoxy-4-triethylsilyloxy-cyclohexane-1,2-diol **17**

A solution of **16** (0.5 g, 1.49 mmol) in THF (5 ml) was added slowly to a slurry of lithium aluminum hydride (0.11 g, 2.98 mmol) in THF at 0°C and the reaction mixture stirred at the same temperature for 2 h. Excess hydride was quenched by careful addition of water, then Celite (0.5 g) was added and the slurry vigorously stirred for 30 min. The solids were filtered through Celite and washed with EtOAc (40 ml). The filtrate was stripped of solvent *in vacuo* and the residue purified by flash chromatography (eluent: EtOAc:light petroleum, 3:1) yielding **17** (0.27 g, 60%) as a clear viscous oil, $[\alpha]_{\text{D}}^{25} -63.3$ (c 0.94, CHCl₃). IR (neat): 3401 cm⁻¹; ¹H NMR: δ 0.59 (q, 6H, J=8), 0.96 (t, 9H, J=8), 1.4–2.0 (m, 4H), 2.6–3.1 (br, 3H), 3.23 (dd, 1H, J=2.5, 9.6), 3.43 (overlapping s, 3H and m, 1H), 3.77 (d, 1H, J=11), 3.91 (d, 1H, J=9.5), 4.25 (m, 1H). Anal. calcd for C₁₄H₃₀SiO₅: C, 54.87; H, 9.87. Found: C, 54.89; H, 9.85.

3.12. (3S,4S,5S,6R)-5-Methoxy-6-triethylsilyloxy-1-oxaspiro[2.5]octan-4-ol **18**

A cooled (0°C) solution of **17** (0.1 g, 0.32 mmol) in CH₂Cl₂ (1 ml) was treated with Et₃N (0.11 ml, 0.76 mmol), *p*-toluenesulfonyl chloride (0.16 g, 0.84 mmol) and a catalytic amount of DMAP. After being stirred at 0°C for 30 min, the reaction mixture was kept at room temperature for 24 h. Additional triethylamine (0.05 ml, 0.35 mmol) was added and stirring was continued for 12 h. The mixture was treated with water (5 ml), extracted with CH₂Cl₂ (5×5 ml), dried and evaporated. The crude orange oil residue was dissolved in MeOH (1 ml) and stirred at room temperature for 5 h in the presence of K₂CO₃ (0.05 g, 0.36 mmol). Most of the solvent was evaporated and the residue was extracted with EtOAc (3×5 ml). The extracts were dried and concentrated to furnish a crude oil, which was purified by flash chromatography (eluent: EtOAc:light petroleum, 1:6) yielding **18** (0.076 g, 81%) as a colorless oil, $[\alpha]_{\text{D}}^{25} -63$ (c 2.39, CHCl₃) {lit.⁶: $[\alpha]_{\text{D}}^{25} -60$ (c 1.28, CHCl₃)}. IR (neat): 3430 cm⁻¹; ¹H NMR: δ 0.60 (q, 6H, J=8), 0.96 (t, 9H, J=8), 1.26 (m, 1H), 1.71 (m, 2H), 2.26 (m, 2H), 2.61 (d, 1H, J=5), 3.09 (dd, 1H, J=2.5, 9), 3.10 (d, 1H, J=5), 3.43 (s, 3H), 4.08 (dd, 1H, J=5.4, 9), 4.32 (m, 1H). ¹³C NMR: 4.90, 6.84, 26.24, 28.94, 50.15, 57.76, 60.07, 66.71, 67.47, 85.24. Anal. calcd for C₁₄H₂₈SiO₄: C, 59.12; H, 8.51. Found: C, 59.10; H, 8.53.

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References

1. Powell, D.; Skotnicki, J.; Upešlacis, J., *Annu. Rep. Med. Chem.*, **1997**, 32, 161–170.
2. Folkman, J.; Ingber, D. E., *Semin. in Cancer Biol.*, **1992**, 3, 555–557.
3. Sigg, H. P.; Weber, H. P., *Helv. Chim. Acta*, **1968**, 51, 1395–1408.
4. Corey, E. J.; Guzman-Perez, A.; Noe, M. C., *J. Am. Chem. Soc.*, **1994**, 116, 12109–12110.
5. Corey, E. J.; Dittami, J. P., *J. Am. Chem. Soc.*, **1985**, 107, 256–257.
6. Barton, D. H. R.; Bath, S.; Billington, D. C.; Gero, S. D.; Quiclet-Sire, B.; Samadi, M., *J. Chem. Soc., Perkin Trans. 1*, **1995**, 1551–1558.
7. Albertini, E.; Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Zanirato, V., *Tetrahedron Lett.*, **1997**, 38, 681–684.
8. Albertini, E.; Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Zanirato, V., *Tetrahedron*, **1997**, 53, 17177–17194.
9. Eliel, E. L.; Ramirez, M. B., *Tetrahedron: Asymmetry*, **1997**, 8, 3551–3554.

10. Bartlett, P. A.; Maitra, U.; Chouinard, P. M., *J. Am. Chem. Soc.*, **1986**, *108*, 8068–8071.
11. White, J. D.; Cammack, J. H.; Sakuma, K.; Rewcastle, G. W.; Widener, R. K., *J. Org. Chem.*, **1995**, *60*, 3600–3611.
12. Lesuisse, D.; Berchtold, G. A., *J. Org. Chem.*, **1985**, *50*, 888–890.
13. Hanessian, S.; Plessas, N. R., *J. Org. Chem.*, **1969**, *34*, 1035–1044.
14. Giese, B.; Almstead, N. G., *Tetrahedron Lett.*, **1994**, *35*, 1677–1680 and references cited therein.
15. Barco, A.; Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V., *Tetrahedron: Asymmetry*, **1997**, *8*, 3515–3545.