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A Practical Synthesis of the Cyclohexyl Part of the Immunosuppressant FK506

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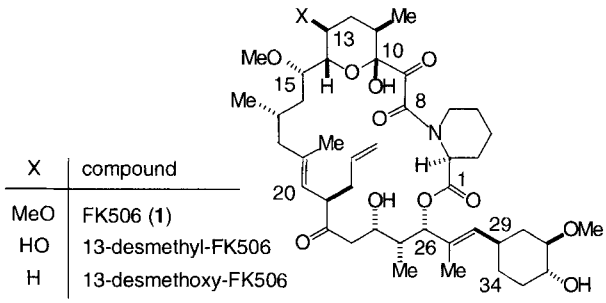
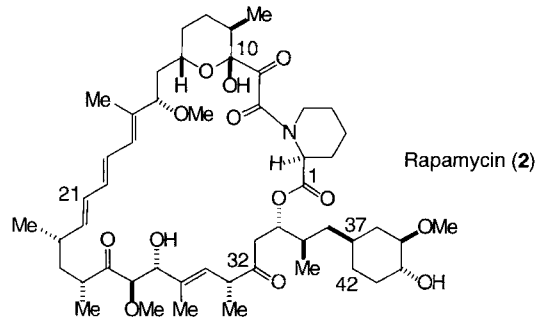
Abstract. Starting from the benzylidene lactone **3** of D-(–)-quinic acid the cyclohexyl fragment **15** (C-28-C-34 part) of the immunosuppressant FK506 was synthesized. Key steps include homolytic deoxygenation reactions on compounds **4** and **6** as well as a regioselective opening of the benzylidene acetal **5**. Opening of the lactone **7** to provide the methyl ester **8** was followed by methylation of the hydroxy group to give **9**. Further steps provided the aldehyde **12** which was elongated to the alkyne **15**. This sequence provides **15** in gram quantities.

The immunosuppressants FK506 (**1**) and rapamycin (**2**) not only have potential for clinical applications but have also proven very useful for studying cellular functions at the molecular level [1]. Common structural elements include the pyranose ring, the α-keto amide function, the cyclohexyl part, and the homoprolyl moiety. Even though they bind to the same cellular receptor, the so-called FKBP, they inhibit different signal transduction pathways in T-cells. This observation is explained by a dual domain model. That is, FK506 [2] and rapamycin [3] share a common binding domain for the FKBP, but other parts of these immunosuppressants interact with different targets [4]. Other issues that are pertinent to these macrolides are the role of substructures and the metabolism. For example, FK506 as well as rapamycin are degraded rapidly *in vivo* to a number of derivatives. The major metabolic reactions include demethylation of the various methyl ether functions [5]. In the case of FK506, 13-*O*-demethylation causes a dramatic decrease of the biological activity. In this compound the tetrahydropyrane ring is rearranged to a tetrahydrofuran ring [5a, 6]. Another major metabolite is 15-*O*-demethyl-FK506. Therefore, the design of analogs with better metabolic stability, for example 13-demethoxy-FK506, would be of high interest [7]. In this context, flexible synthetic routes to substructures which can easily be connected with each other are important. This paper describes a practical route to the cyclohexyl part of FK506.



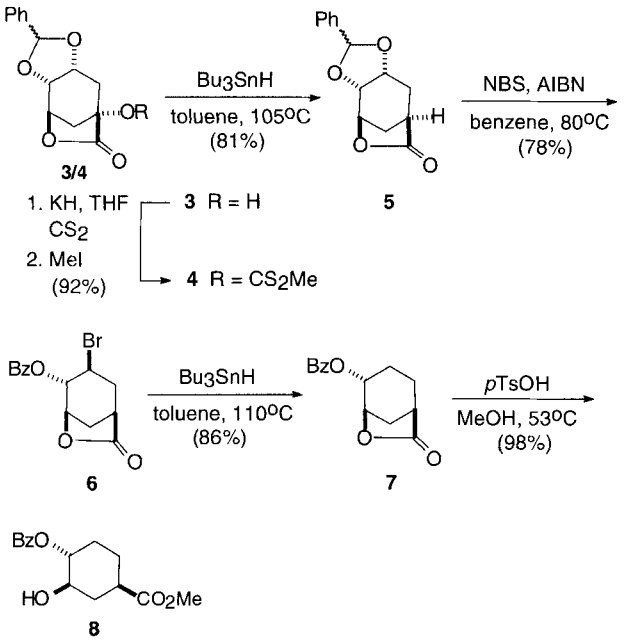


Scheme 1

The literature reveals several principal approaches to this substructure. Most of them build upon a Diels–Alder reaction between butadiene and an acrylate derivative [8]. In other syntheses, the six-membered ring is constructed through a cyclization reaction [9] or a

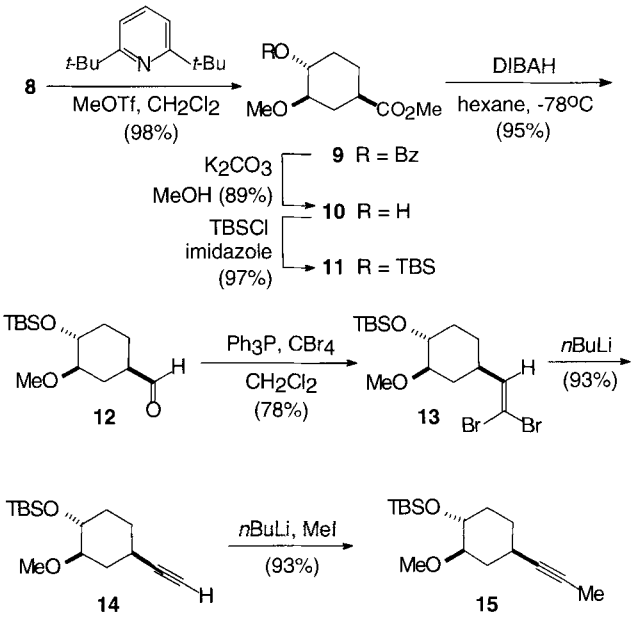
Claisen rearrangement [10]. In addition, the cyclohexyl part has been prepared from *D*-(–)-quinic acid [11]. The following route is also based on this chiron approach, but contains modified and optimized steps and can be performed on a large scale. It describes in more detail the experimental conditions of our earlier communication [9b].

According to the literature, *D*-(–)-quinic acid was first converted to its benzylidene derivative **3** [12]. The free hydroxy function of **3** was then transformed to the corresponding xanthate, providing compound **4**. Subsequent reaction of **4** with tributyltin hydride in the presence of a catalytic quantity of AIBN provided the deoxygenated lactone **5**. In order to remove the other superfluous hydroxy group, the lactone **5** was treated with *N*-bromosuccinimide which resulted in a regiospecific opening of the benzylidene acetal [13]. The bromine atom of **6** was removed by reduction with tributyltin hydride. Opening of the lactone **7** to the ester **8** was best achieved under acidic conditions using *p*-toluenesulfonic acid in methanol. In contrast, lactone opening under basic conditions [K_2CO_3 (cat.), MeOH] caused epimerisation at the carboxyl bearing carbon atom.



Scheme 2

Upon treatment of the hydroxy ester **8** with methyl triflate in the presence of 2,6-di-*tert*-butylpyridine, the methyl ether **9** was formed in high yield [2, 14]. Methanolysis of the benzoate **9** provided the hydroxy ester **10** which was protected as *tert*-butyldimethylsilyl ether [8a]. Reduction of the ester group of **11** with DIBAH in hexane furnished the aldehyde **12** [8a]. The latter was converted to the dibromo olefin **13** using CBr_4/PPh_3 in dichloromethane [15]. Subsequent treatment of the dibromo compound **13** with two equivalents of *n*-butyllithium [16] generated the alkyne **14**. Attempts to quench the intermediate acetylide directly with methyl iodide were unsatisfactory, producing a mixture of **14** and **15**. However, deprotonation of the alkyne **14** followed by addition of methyl iodide [10] gave the desired propargyl derivative **15** in almost quantitative yield. It seems that the presence of LiBr has a detrimental effect on the acetylide alkylation reaction. As we have shown in the earlier paper, the alkyne **15** was added under reductive conditions to a chiral aldehyde in a regio- and stereoselective manner [9b].



Scheme 3

In summary, we developed an efficient synthetic route to the cyclohexyl building block **15**.

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Experimental

^{1}H NMR: Bruker AC 250, Varian Gemini 200, Varian Unity 500; all spectra were recorded in $CDCl_3$ as solvent with tetramethylsilane as internal standard. – ^{13}C NMR: Bruker AC 250 (62.5 MHz), Varian Gemini 200 (50 MHz), Varian Unity 500 (125 MHz), broad-band decoupling. The signal multiplicities were determined by means of the DEPT 135 or the APT technique; + for CH or CH_3, – for CH_2, × for C. – IR: Mattson Polaris and

Perkin-Elmer Spectrum 1000. – Flash chromatography: J. T. Baker silica gel 30–60 μm. – Thin-layer chromatography: Macherey, Nagel & Co precoated TLC plates Polygram SIL G/UV_{254}. – All experiments were carried out under nitrogen or argon. Solvents were purified as described in ref. [17]; petroleum ether with a boiling range of 35–65 °C was used; THF was distilled from sodium benzophenone ketyl immediately before use; the pH-7 buffer solution used in the work-up procedures was prepared by dissolving potassium dihydrogen phosphate (85.0 g) and sodium hydroxide (14.5 g) in 1 l of water. All rotations were measured at 20 °C at the sodium D-line.

Although compounds **4**–**9** were reported in a communication by Rama Rao *et al.* [11a] the experimental details for their syntheses are also given, since no data were given or different procedures were used.

3,4-O-Benzylidene1,5-quinolactone 1-O-(S-methylxanthate (**4**)

To a suspension of potassium hydride (35%, 35.0 g, 305 mmol) in dry THF (800 ml) was added dropwise a solution of lactone **3**[12] (53.5 g, 204 mmol) in THF (230 ml) at 0 °C over a period of 1 h. After being stirred for 1 h at 0 °C, carbon disulfide (24.7 g, 19.5 ml, 324 mmol) was added rapidly, and the mixture was stirred for 30 min. This was followed by dropwise addition of methyl iodide (43.5 g, 19.1 ml, 306 mmol). After further 30 min stirring at 0 °C, a half-saturated NH_4 solution (600 ml) was added (carefully in the beginning), and the mixture extracted with diethyl ether (4 × 200 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*; yield 66.5 g (92%) of **4** as a colorless, viscous syrup (mixture of acetal diastereomers). – Major diastereomer: TLC (petroleum ether/methyl acetate, 2:1): R_f = 0.48. – [α] = 29.5 (c = 2.0 in $CHCl_3$). – ^{1}H NMR (200 MHz, $CDCl_3$): δ/ppm = 2.52 (s, 3H, SCH_3), 2.58–2.86 (m, 3H, cyclohexyl), 3.65–3.75 (m, 1H, cyclohexyl), 4.38 (d, br., *J*/Hz = 6.4, 1H, 5-H), 4.60 (ddd, *J*/Hz = 2.7, 7.1, 7.1, 1H, 3-H), 4.91 (dd, *J*/Hz = 2.1, 6.4, 1H, 4-H), 5.75 (s, 1H, benzylidene H), 7.38–7.51 (m, 5H, aromatic H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ/ppm = 19.4 (+, SCH_3), 29.9, 35.8 (2–, CH_2), 72.4, 73.1, 75.2 (3 +, CH), 82.1 (×, C-1), 103.8 (benzylidene C), 126.5, 128.5, 129.8 (3 +, aromatic C), 135.2 (×, aromatic C), 171.9 (C=O), 212.0 (C=S).

$C_{16}H_{16}O_5S_2$	Calcd.:	C 54.53	H 4.58 S 18.19
(352.4)	Found:	C 54.54	H 4.76 S 18.00.

3,4-O-Benzylidene-1,5-quinolactone (**5**)

A solution of the xanthate **4** (52.0 g, 148 mmol), tributyltin hydride (43.9 g, 40 ml, 151 mmol), and azobisisobutyronitrile (AIBN) (1.2 g, 7.3 mmol) in dry, degassed toluene (700 ml) was lowered into a hot oilbath (105 °C) and kept at that temperature for further 40 min. After the solvent was evaporated *in vacuo*, the residue was partitioned between acetonitrile and petroleum ether (300 ml of each), separated, and the upper petroleum ether phase was washed with acetonitrile (2 × 200 ml). The combined acetonitrile phases were washed with petroleum ether (100 ml) and then concentrated to leave a residue that was purified by flash chromatography (petroleum ether/methyl acetate, 4:1); yield 29.4 g (81%) of **5** as a colorless oil which solidifies on standing; *m.p.* 106–108 °C and [α] = –12.6 (*c* = 2.0 in $CHCl_3$). – TLC (petroleum ether/methyl acetate, 2:1): R_f = 0.53. – ^{1}H NMR (200 MHz, $CDCl_3$): δ/ppm = 2.21–2.71 (m, 5H, cyclohexyl), 4.38–4.41 (m, 1H, 3-H), 4.48–4.59 (m, 1H, 5-H), 4.78–4.81 (m, 1H, 4-H), 5.73 (s, 1H, benzylidene H), 7.33–7.51 (m, 5H, aromatic H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 27.8, 29.2 (2–, CH_2), 35.1 (+, C-1), 71.9, 73.3, 77.1 (3 +, CH), 103.5 (benzylidene C), 126.7, 128.6, 129.9 (3 +, aromatic C), 135.9 (×, aromatic C), 179.2 (×, C=O).

$C_{14}H_{14}O_4$	Calcd.:	C 68.28	H 5.73
(246.3)	Found:	C 67.57	H 5.86.

(1S,3S,4S,5R)-4-Benzoyloxy-3-bromo-6-oxabicyclo[3.2.1] octan-7-one (**6**)

A mixture of the benzylidene acetal **5** (59.9 g, 243 mmol), *N*-bromosuccinimide (45.0 g, 253 mmol) and AIBN (0.4 g, 2.43 mmol) in dry benzene (1 l) was refluxed for 1.5 h. After cooling to room temp. and then briefly in an ice-bath, the precipitate was removed by suction. It was washed with a small amount of cold diethyl ether and dissolved in ethyl acetate (500 ml). The solution was washed with a satd. aqueous $NaHSO_3$ solution (300 ml), satd. aqueous Na_2CO_3 solution (300 ml), water (200 ml), brine, and dried with $MgSO_4$. Filtration and evaporation of the solvent gave 47.3 g (60%) of **6** which was pure by NMR analysis. Treatment of the benzene filtrate as before followed by flash chromatography (petroleum ether/methyl acetate, 3:1) gave additional **6** (14.1 g, 18%) as a colorless solid; *m.p.* 124–126 °C (from ethyl acetate) and [α] = 92.6 (*c* = 2.0 in $CHCl_3$). – TLC (petroleum ether/methyl acetate, 2:1): R_f = 0.32. – ^{1}H NMR (200 MHz, $CDCl_3$): δ/ppm = 2.27–2.32 (m, 1H, cyclohexyl), 2.40–2.49 (m, 1H, cyclohexyl), 2.55–2.61 (m, 2H, cyclohexyl), 2.71–2.75 (m, 1H, cyclohexyl), 4.38–4.42 (m, 1H, C<u>H</u>Br), 4.93–4.97 (m, 1H, 1-H), 5.62–5.65 (m, 1H, C<u>H</u>OBz), 7.42–7.50 (m, 2H, aromatic H), 7.57–7.66 (m, 1H, aromatic H), 7.96–8.03 (m, 2H, aromatic H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ/ppm = 30.8, 33.5 (2–, CH_2), 35.2 (+, C-1), 41.2 (+, C-3), 72.2 (+, C-5), 76.1 (+, C-4), 128.6, 129.7, 133.8 (3 +, aromatic C), 164.5, 176.8 (2 ×, C=O).

$C_{14}H_{13}BrO_4$	Calcd.:	C 51.71	H 4.03
(325.15)	Found:	C 51.79	H 3.99.

(1R,4R,5R)-4-Benzoyloxy-6-oxabicyclo[3.2.1]octan-7-one (**7**)

A solution of the bromide **6** (47.0 g, 144 mmol), tributyltin hydride (50.5 g, 46 ml, 174 mmol), and azobisisobutyronitrile (AIBN) (250 mg, 1.52 mmol) in dry, degassed toluene (1 l) was refluxed for 1 h. After cooling to room temp. the solvent was removed *in vacuo*. The residue was partitioned between acetonitrile and petroleum ether (250 ml of each), separated and the upper petroleum ether phase was washed with acetonitrile (2 × 200 ml). The combined acetonitrile phases were washed with petroleum ether (100 ml) and then concentrated to leave a residue that was purified by flash chromatography (petroleum ether/methyl acetate, 3:1) to yield 30.5 g (86%) of **7** as a colorless solid. An analytical sample was recrystallized from a small amount of ethyl acetate; *m.p.* 141–142 °C and [α] = –16.3 (*c* = 1.0 in MeOH). – TLC (petroleum ether/methyl acetate, 2:1): R_f = 0.42. – ^{1}H NMR (200 MHz, $CDCl_3$): δ/ppm = 1.87–2.18 (m, 4H, cyclohexyl), 2.33–2.35 (m, 2H, cyclohexyl), 2.68–2.71 (m, 1H, 1-H), 4.88–4.92 (m, 1H, 5-H), 5.32–5.47 (m,

1H, CHOBz), 7.42–7.51 (m, 2H, aromatic H), 7.54–7.62 (m, 1H, aromatic H), 8.01–8.07 (m, 2H, aromatic H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ/ppm = 22.9, 24.3, 32.1 (3–, CH_2), 37.9 (+, C-1), 67.7 (+, C-4), 76.1 (+, C-5), 128.5, 129.5 (2+, aromatic C), 129.6 (×, aromatic C), 133.3 (+, aromatic C), 165.2, 177.6 (2×, C=O).

$C_{14}H_{14}O_4$	Calcd.:	C 68.28 H 5.73
(246.3)	Found:	C 68.34 H 5.97.

Methyl (1R,3R,4R)-4-benzoyloxy-3-hydroxy-cyclohexane-1-carboxylate (**8**)

A solution of the lactone **7** (31.9 g, 129 mmol) and *p*-toluenesulfonic acid monohydrate (2.47 g, 13 mmol) in dry methanol (800 ml) was stirred at 53 °C for about 2.5 h (TLC control). The mixture was then treated with pH 7 buffer (100 ml) and most of the methanol removed *in vacuo*. After addition of water (300 ml), the ester was extracted with diethyl ether (3 × 300 ml). The combined organic layers were washed with brine and dried with $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified by flash chromatography (petroleum ether/methyl acetate, 3:1) to give **8** as a colorless oil; yield 35.9 g (98%). – TLC (petroleum ether/methyl acetate, 2:1): R_f = 0.33. – $[\alpha]$ = –47.8 (c = 2.0 in $CHCl_3$). – ^{1}H NMR (200 MHz, $CDCl_3$): δ/ppm = 1.38–1.68 (m, 3H, cyclohexyl), 1.95–2.04 (m, 1H, cyclohexyl), 2.12–2.48 (m, 3H, cyclohexyl), 2.83 (s, br., 1H, OH), 3.65 (s, 3H, OCH_3), 3.68–3.78 (m, 1H, 2-H), 4.78–4.88 (m, 1H, CHOBz), 7.35–7.40 (m, 2H, aromatic H), 7.48–7.55 (m, 1H, aromatic H), 7.97–8.03 (m, 2H, aromatic H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ/ppm = 26.4, 28.5, 35.0 (3–, CH_2), 40.9 (+, C-4), 51.8 (+, CH_3), 71.6 (+, C-2), 77.6 (+, C-1), 128.3, 129.6 (2+, aromatic C), 130.0 (×, aromatic C), 133.0 (+, aromatic C), 166.6, 174.5 (2×, C=O).

$C_{15}H_{18}O_5$	Calcd.:	C 64.74 H 6.52
(278.3)	Found:	C 64.86 H 6.74.

Methyl (1R,3R,4R)-4-benzoyloxy-3-methoxy-cyclohexane-1-carboxylate (**9**)

To a solution of the hydroxy ester **8** (8.50 g, 30.5 mmol), 2,6-di(*tert*-butyl)pyridine (21.0 g, 110 mmol) in dry dichloromethane (50 ml) was added by syringe methyl triflate (11.16 g, 7.7 ml, 68.0 mmol) at 0 °C. The resulting mixture was stirred for 1-2 d at room temp. (TLC control). Subsequently, pH 7 buffer solution (500 ml) was added and the mixture extracted with dichloromethane (3 × 100 ml). The combined organic layers were washed with brine, and dried with $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified by flash chromatography (petroleum ether/methyl acetate, 5:1, column 7 × 14 cm). The base elutes before the product and can be recycled [TLC (petroleum ether/methyl acetate, 2:1): R_f = 0.87)]. The ester **9** was isolated as a colorless oil; yield 8.8 g (98%). – TLC (petroleum ether/ethyl acetate, 2:1): R_f = 0.40. – $[\alpha]$ = –66.5 (c = 1.2 in ethanol). – ^{1}H NMR (200 MHz, $CDCl_3$): δ/ppm = 1.38–1.72 (m, 3H, cyclohexyl), 1.95–2.03 (m, 1H, 5-H), 2.17–2.26 (m, 1H, 6-H), 2.36–2.48 (m, 2H, cyclohexyl), 3.28–3.39 (m, 1H, 2-H), 3.37, 3.67 (2 s, 3H each, OCH_3), 4.91–5.02 (m, 1H, CHOBz), 7.38–7.44 (m, 2H, aromatic H), 7.51–7.58 (m, 1H, aromatic H), 8.01–8.06 (m, 2H, aromatic H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ/ppm = 26.1, 28.7, 31.9 (3–, CH_2), 40.7 (+, C-4), 51.7 (+, CH_3), 57.5 (+, CH_3), 75.3 (+, C-2), 80.1 (+, C-1), 128.2, 129.5 (2+, aromatic C), 130.5 (×, aromatic C), 132.8 (+, aromatic C), 165.8, 174.4 (2×, C=O).

$C_{16}H_{20}O_5$	Calcd.:	C 65.74 H 6.90
(292.3)	Found:	C 65.90 H 7.00.

Methyl (1R,3R,4R)-4-hydroxy-3-methoxycyclohexane-1-carboxylate (**10**)

To a solution of the benzoate **9** (42.0 g, 144 mmol) in dry methanol (800 ml) was added dry potassium carbonate (10.1 g, 73.0 mmol). The mixture was stirred for 2.5 h at 50 °C (TLC control). Subsequently, the mixture was poured into satd. NH_4Cl solution (1 l) and pH 7 buffer solution (300 ml). Most of the solvent was removed *in vacuo* to leave about 200 ml of liquid. The pH was checked and then readjusted to pH 7 with satd. NH_4Cl solution (400 ml) and pH 7 buffer solution (200 ml). The aqueous mixture was extracted with dichloromethane (6 × 250 ml), the combined organic layers were washed with brine and dried with $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified by flash chromatography (petroleum ether/methyl acetate, 2:1) to yield 23.9 g (89%) of **10** as a colorless oil. – TLC (petroleum ether/ethyl acetate, 2:1): R_f = 0.18. – $[\alpha]$ = –79.7 (c = 1.0 in $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ/ppm = 1.19–1.49 (m, 3H, cyclohexyl), 1.91–2.07 (m, 2H, cyclohexyl), 2.26–2.41 (m, 2H, cyclohexyl), 2.73 (s, br., 1H, OH), 2.96 (ddd, J/Hz = 4.1, 8.8, 11.1, 3-H), 3.36–3.45 (m, 1H, 4-H) 3.38, 3.66 (2 s, 3H each, OCH_3). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ/ppm = 24.4, 30.6, 30.7 (3–, CH_2), 41.0 (+, C-1), 51.4 (+, CH_3), 56.2 (+, CH_3), 72.6 (+, C-4), 83.5 (+, C-3), 174.5 (×, C=O). – IR (film): /cm^{-1} = 3613, 1745.

$C_9H_{16}O_4$:	Calcd.:	C 57.43 H 8.57
(188.2)	Found:	C 57.14 H 8.53.

Methyl (1R,3R,4R)-4-[(tert-butyldimethylsilyl)oxy]-3-methoxycyclohexane-1-carboxylate (**11**)[8a]

To a solution of the hydroxy ester **10** (11.0 g, 58.4 mmol) in dry DMF (300 ml) was added imidazole (4.80 g, 70.5 mmol) and *tert*-butyldimethylsilyl chloride (10.6 g, 70.3 mmol). The mixture was stirred at room temp. for 7 h before it was poured into half-saturated $NaHCO_3$ solution (1 l). The resulting aqueous solution was extracted with diethyl ether, the combined organic layers were washed with brine and dried with $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified by flash chromatography (petroleum ether/methyl acetate, 5:1) to give **11** as a colorless oil; yield 17.13 g (97%). – TLC (petroleum ether/methyl acetate, 2:1): R_f = 0.65. – $[\alpha]$ = –50.4 (c = 1.2 in $CHCl_3$) {ref. [8a] $[\alpha]$ = –44.6 (c = 5 in $CHCl_3$)}. – ^{1}H NMR (250 MHz, $CDCl_3$): δ/ppm = 0.04, 0.05 [2 s, 3H each, $Si(CH_3)_2$], 0.86 (s, 9H, $SiC(CH_3)_3$], 1.23–1.50 (m, 3H, cyclohexyl), 1.83–1.93 (m, 2H, cyclohexyl), 2.21–2.34 (m, 2H, cyclohexyl), 2.92 (ddd, J/Hz = 4.3, 8.2, 10.9, 1H, 3-H), 3.36 (s, 3H, OCH_3), 3.36–3.47 (m, 1H, 4-H) 3.64 (s, 3H, OCH_3).

$C_{15}H_{30}O_4Si$	Calcd.:	C 59.56 H 10.00
(302.5)	Found:	C 59.42 H 9.72.

(1R,3R,4R)-4-[(tert-butyldimethylsilyl)oxy]-3-methoxy-cyclohexane-1-carbaldehyde (**12**)

To a solution of the ester **11** (17.0 g, 56.2 mmol) in dry hexane (300 ml) at –78 °C was added dropwise DIBAH (67.4 ml, 1M in hexanes, 67.4 mmol). The reaction mixture was stirred for 1.5 h and allowed to warm to –20 °C. Subsequently, aqueous 10%

potassium sodium tartrate solution (1 l) was added and the mixture stirred for 3 h at room temp. Diethyl ether (300 ml) was added, and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 200 ml), the combined organic layers were washed with brine and dried with $MgSO_4$. After filtration and evaporation of the solvent, the aldehyde **12** was obtained as a colorless oil; yield 14.6 g (95%). It was used as such for the next step. TLC (petroleum ether/methyl acetate, 2:1): $R_f = 0.62$. – ^{1}H NMR (250 MHz, $CDCl_3$): δ/ppm = 0.04, 0.05 [2 s, 3H each, $Si(CH_3)_2$], 0.87 (s, 9H, $SiC(CH_3)_3$], 1.30–1.50 (m, 3H, cyclohexyl), 1.83–1.93 (m, 2H, cyclohexyl), 2.15–2.28 (m, 2H, 1-H, 2-H), 3.01 (ddd, *J*/Hz = 3.5, 7.1, 8.7, 1H, 3-H), 3.35 (s, 3H, OCH_3), 3.48–3.55 (m, 1H, 4-H), 9.61 (s, 1H, CHO). The aldehyde was used immediately for the next step.

(1R,2R,4R)-1-[(tert-Butyldimethylsilyl)oxy]-4-(2,2-dibromovinyl)-2-methoxycyclohexane (**13**)

A solution of the aldehyde **12** (15.6 g, 57.3 mmol) and triphenylphosphane (60.25 g, 229.7 mmol) in dry dichloromethane (330 ml) was treated dropwise at 0 °C with a solution of tetrabromomethane (38.1 g, 114.8 mmol) in dry dichloromethane (170 ml). After stirring for 40 min at 0 °C, the brown slurry was treated with petroleum ether, and stirring was continued for 10 min. The resulting precipitate was removed by suction and the filter cake washed with petroleum ether (3 × 50 ml). The filtrate was washed with a satd. aqueous $NaHCO_3$ solution (1 l) and brine. After drying of the organic phase with $MgSO_4$, filtration, and evaporation of the solvent, the semisolid residue was subjected to flash chromatography (petroleum ether/methyl acetate, 20:1) to give **13** as a colorless oil, which solidifies upon standing; yield 19.1 g (78%); *m.p.* 62–64 °C and $[\alpha]$ = –15.4 (*c* = 1.0 in CCl_4). – TLC (petroleum ether/methyl acetate, 4:1): $R_f = 0.81$. – ^{1}H NMR (250 MHz, $CDCl_3$): δ/ppm = 0.40, 0.52 [2 s, 3H each, $Si(CH_3)_2$], 0.86 (s, 9H, $SiC(CH_3)_3$], 0.97–1.12 (m, 1H, 3-H_{ax}), 1.02–1.19 (m, 1H, 5-H_{ax}), 1.28–1.44 (m, 1H, 6-H), 1.64–1.75 (m, 1H, 6-H), 2.01–2.11 (m, 1H, 3-H_{eq}), 2.22–2.38 (m, 1H, 4-H), 2.94 (ddd, *J*/Hz = 4.4, 8.3, 10.8, 1H, 2-H), 3.33–3.43 (m, 1H, 1-H), 3.38 (s, 3H, OCH_3), 6.20 (d, *J*/Hz = 9.0, 1H, C<u>H</u>=CBr_2). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ/ppm = –5.6, –5.4 [$Si(\underline{C}H_3)_2$], 17.3 [×, $Si\underline{C}(CH_3)_3$], 25.0 [+, $SiC(\underline{C}H_3)_3$], 28.0, 32.2, 33.3 (3–, CH_2), 39.7 (+, C-4), 57.0 (+, CH_3), 73.5 (+, C-1), 82.6 (+, C-2), 87.4 (CH=$\underline{C}Br_2$), 141.1 (<u>C</u>H=CBr_2).

$C_{15}H_{28}Br_2O_2Si$	Calcd.:	C 42.07	H 6.59
(428.28)	Found:	C 42.16	H 6.53.

(1R,2R,4R)-1-[(tert-Butyldimethylsilyl)oxy]-4-ethynyl-2-methoxycyclohexane (**14**)

To a solution of the dibromide **13** (11.56 g, 27.00 mmol) in dry THF (140 ml) was added dropwise *n*-BuLi (34 ml, 1.6M in hexane, 54 mmol) at –78 °C. Stirring was continued for 15 min at 78 °C, then the cooling bath was removed followed by stirring of the solution for ca. 2 h. The mixture was treated with aqueous half-saturated NH_4Cl solution (300 ml) and extracted with diethyl ether (5 × 150 ml). The combined organic layers were washed with brine and dried with $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified by flash chromatography (petroleum ether/methyl acetate, 20:1) to give **14** as a colorless oil, which is rather volatile under high vacuum; yield 6.74 g (93%). – TLC (petroleum ether/methyl acetate, 20:1): $R_f = 0.60$. – $[\alpha] = -47.8$ (*c* = 1.0 in CCl_4). – ^{1}H NMR (250 MHz, $CDCl_3$): δ/ppm = 0.37, 0.48 [2 s, 3H each, $Si(CH_3)_2$], 0.85 (s, 9H, $SiC(CH_3)_3$], 1.19–1.44 (m, 3H, cyclohexyl), 1.79–1.91 (m, 2H, 5-H, 6-H), 2.01 (d, *J* = 2.3 Hz, 1H, alkyne H), 2.20–2.31 (m, 2H, 4-H, 5-H), 2.85 (ddd, *J*/Hz = 4.2, 8.4, 11.0, 1 H, 2-H), 3.34–3.44 (m, 1H, 1-H), 3.37 (s, 3H, OCH_3). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ/ppm = –4.8, –4.5 [$Si(\underline{C}H_3)_2$], 18.1 [×, $Si\underline{C}(CH_3)_3$], 25.9 [+, $SiC(\underline{C}H_3)_3$], 27.6 (–, CH_2), 30.7 (+, C-4), 33.4 (–, CH_2), 35.8 (–, CH_2), 57.8 (+, CH_3), 67.9 (+, alkyne <u>C</u>H), 74.3 (+, C-1), 83.4 (+, C-2), 87.1 (×, alkyne C). – IR (film): /cm^{-1} = 3318, 2952, 2861, 2284, 1545, 1468.

$C_{15}H_{28}O_2Si$	Calcd.:	C 67.11	H 10.51
(268.5)	Found:	C 67.26	H 10.51.

(1R,2R,4R)-1-[(tert-Butyldimethylsilyl)oxy]-2-methoxy-4-(1-propynyl)cyclohexane (**15**)

To a solution of the alkyne **14** (6.3 g, 23.5 mmol) in dry THF (230 ml) was added dropwise *n*-BuLi (17.6 ml, 1.6M in hexane, 28.2 mmol) at –78 °C. Stirring was continued for 30 min at 78 °C, then the reaction mixture was allowed to reach –35 °C during 2 h. The solution of the anion was then recooled to –78 °C, followed by the addition of methyl iodide (66.7 g, 29.0 ml, 470 mmol). The resulting mixture was stirred for 12 h and allowed to reach room temp. The mixture was treated with an aqueous half-saturated $NaHCO_3$ solution (300 ml) and extracted with diethyl ether (5 × 150 ml). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (petroleum ether/methyl acetate, 60:1) gave **15** as a colorless oil; yield 6.2 g (93%). – TLC (petroleum ether/methyl acetate, 20:1): $R_f = 0.60$. – $[\alpha] = -62.3$ (*c* = 1.0 in CCl_4). – ^{1}H NMR (250 MHz, $CDCl_3$): δ/ppm = 0.03, 0.04 [2 s, 3H each, $Si(CH_3)_2$], 0.85 [s, 9H, $SiC(CH_3)_3$], 1.00–1.36 (m, 3H, cyclohexyl), 1.74 (d, *J*/Hz = 2.2, 3H, alkyne C<u>H</u>$_3$), 1.77–1.85 (m, 2H, 5-H, 6-H), 2.12–2.25 (m, 2H, 3-H, 4-H), 2.83 (ddd, *J*/Hz = 4.1, 8.4, 11.0, 1H, 2-H), 3.31–3.41 (m, 1H, 1-H), 3.35 (s, 3H, OCH_3). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ/ppm = –4.8, –4.5 [$Si(\underline{C}H_3)_2$], 3.4 (+, alkyne <u>C</u>H$_3$), 18.2 [×, $Si\underline{C}(CH_3)_3$], 25.8 [+, $SiC(\underline{C}H_3)_3$], 28.0 (–, CH_2), 31.4 (+, C-4), 33.6 (–, CH_2), 36.5 (–, CH_2), 57.7 (+, CH_3), 74.6 (+, C-1), 75.3 (×, alkyne <u>C</u>CH$_3$), 82.0 (×, alkyne *C*), 83.7 (+, C-2). – IR (film): /cm^{-1} = 2938, 2854, 2291, 1580, 1244.

$C_{16}H_{30}O_2Si$	Calcd.:	C 68.03	H 10.70
(282.5)	Found:	C 68.03	H 10.72.

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