New Chiral Propargylic Silanes and the First Examples of Asymmetric Intramolecular Sakurai Reactions

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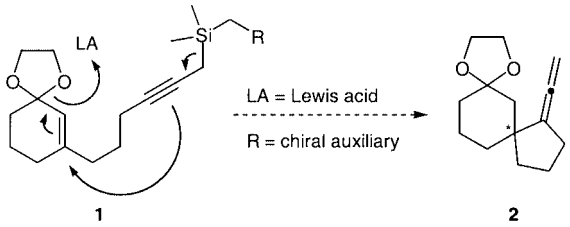
Abstract: The syntheses of four new chiral propargylic silanes are reported. The syntheses of these cyclization precursors offer the possibility of studying the asymmetry of the first examples of the intramolecular version of the Sakurai reaction.

Key words: chiral auxiliaries, cyclizations, Lewis acids, Sakurai reaction, spiro compounds

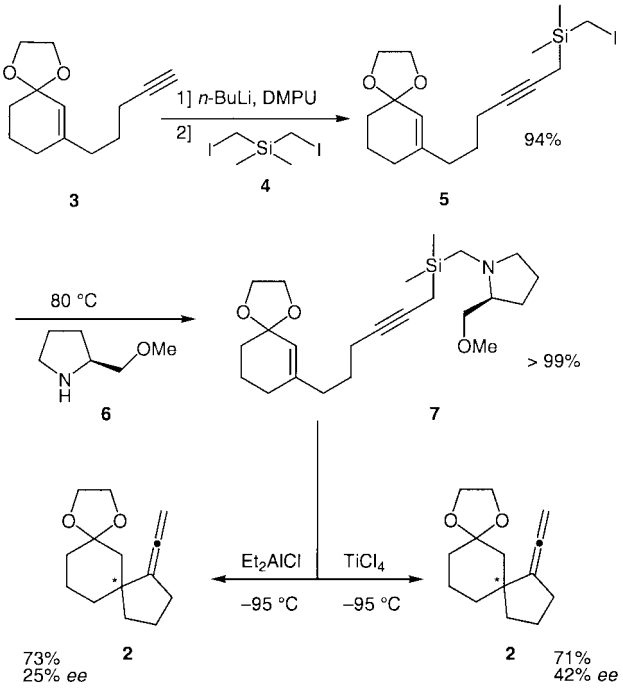
The last three decades witnessed an enormous development of methods in the use of organosilicon compounds for organic synthesis.[1,2] Nowadays, in nearly every major synthesis, an organosilicon reagent is used for C–C bond formation, functional group transformation, or protection. With the current challenge in synthesis being focussed on enantio- and diastereoselectivity, it is not surprising that increasing attention has been directed towards the use of organosilicon compounds for asymmetric synthesis.[3]

Optically active Si-centered chiral organosilicon compounds became available in the early 1960s by the pioneering work of Sommer and his co-workers.[4] Most of these compounds were derivatives of the methyl-α-naphthylphenylsilyl system. One of the limitations in using Si-centered chiral organosilicon compounds is the need to prepare these compounds by optical resolution. Furthermore, since organosilicon compounds can easily undergo racemization, recovery and recycling of the valuable optically active silicon compounds with its optical purity intact cannot be guaranteed. Therefore, considerable interest has been focused on the preparation of C-centered chiral organosilicon compounds where the chiral moiety, while attached to a silicon, is located at a carbon center.[5] For potential application in organic synthesis such compounds have to be prepared in synthetically useful quantities from readily available optically active natural products, the so-called "chiral pool". Seeking an extension of such enantioselective chemistry, we became interested in the synthesis of optically active propargylic silanes and studied their ability to induce asymmetry in the intramolecular version of the Sakurai reaction (Scheme 1).[6]

Starting from the hitherto unknown acetylene **3**, which is readily available from the corresponding enone described by Gleiter et al.,[7] the coupling with the bis(iodomethyl)dimethylsilane (**4**)[8] afforded the iodide **5** in 94% yield. The chiral precursor **7** for asymmetric Sakurai cyclization was then prepared by the action of iodide **5** with the known SAMP precursor (2*S*)-(+)-2-(methoxymethyl)pyrrolidine (**6**) developed by Seebach and Enders.[9] Finally, treatment of **7** with diethylaluminum chloride in dichloromethane at –95 °C resulted in the formation of the spiroannulated ketal **2** in 73% yield and 25% ee. The use of titanium tetrachloride as Lewis acid afforded the compound **2** in 71% yield and 42% ee (Scheme 2).[10]



Scheme 1 Asymmetric intramolecular Sakurai reactions



Scheme 2 The proline model

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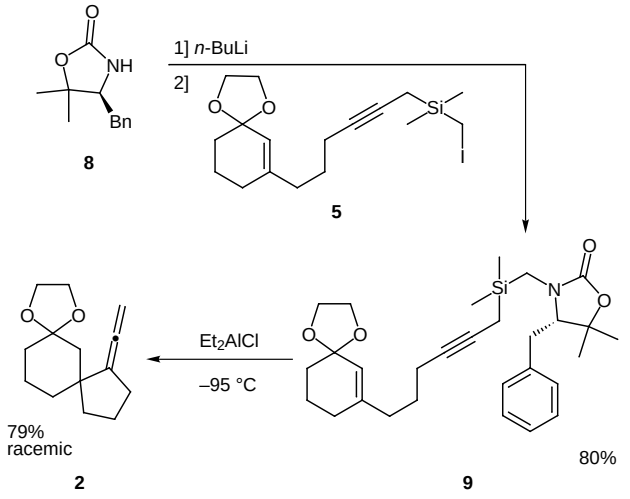
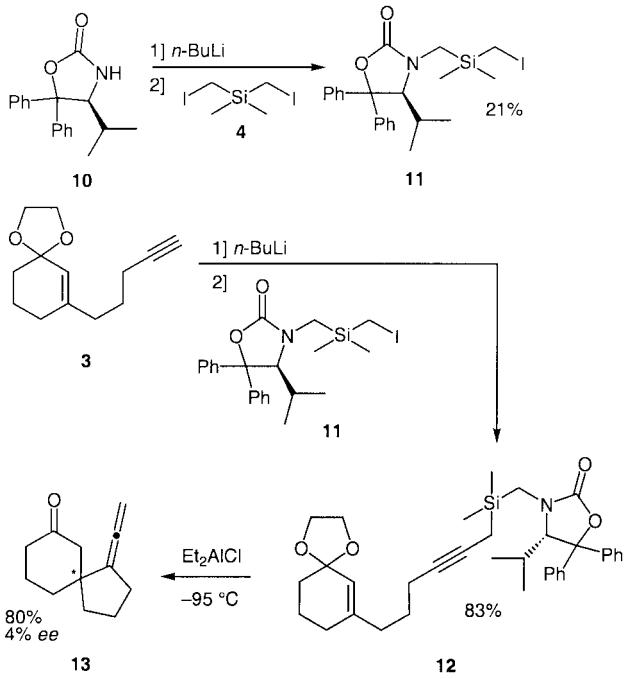
The versatile oxazolidin-2-one based methodology developed by Evans has been widely used in asymmetric synthesis for the preparation of highly functionalized homochiral molecules.[11] Encouraged by these results, we focused on the synthesis of propargylic silanes bearing the chiral information derived from an oxazolidin-2-one. According to Davies the oxazolidin-2-one auxiliary **8** was easily prepared in 4 steps from L-phenylalanine in 40% overall yield.[12] Ensuing alkylation with the iodide **5** in THF in the presence of BuLi generated the chiral organosilane **9** in excellent yield. Subsequent cyclization with diethylaluminum chloride in dichloromethane at –95 °C led to the spiroketal **2** in 79% yield. In this case no enantioselectivity was observed. Compound **2** was obtained as a racemate (Scheme 3).[10] Attempts to use titanium tetrachloride as Lewis acid also led to the racemic compound **2**.



Scheme 3 The SuperQuat model

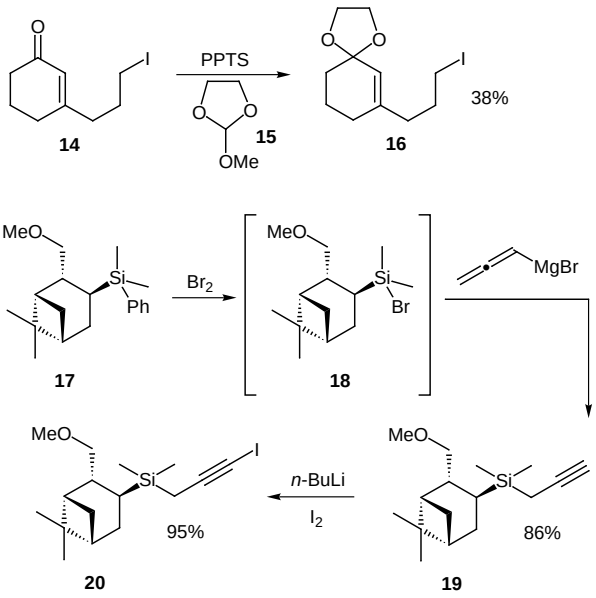
In order to increase the stability of the transition state of the latter cyclization, the more steric hindered oxazolidin-2-one **10** was used to generate a chiral precursor for asymmetric intramolecular Sakurai reactions. Thus, treatment of the chiral Seebach auxiliary **10**,[13] available in 4 steps from L-valine in 45% overall yield, with bis(iodomethyl)dimethylsilane (**4**)[8] gave the iodide **11** in 21% yield. Subsequent coupling of the iodide **11** with the acetylene **3** according to Scheme 4 gave the chiral cyclization precursor **12** in 83% yield. Terminal ring closure with diethylaluminum chloride in dichloromethane afforded the spiroketone **13** in 80% yield. The stereoselectivity however was very poor (4% ee).[10] The use of titanium tetrachloride as Lewis acid resulted in the decomposition of the starting material.

In compliance with Scheme 5, 3-(3-iodopropyl)cyclohex-2-en-1-one (**14**)[14] was first converted to its ketal **16** in 38% yield without isomerization of the double bond, using 2-methoxy-1,3-dioxolane (**15**) in the presence of pyridinium *p*-toluenesulfonate as catalyst. In addition, the starting material was recovered in 60% yield. The chiral phenylsilane **17**, available by a procedure of Taddei in 3



Scheme 4 The Seebach "HyperQuat" auxiliary

steps from (1*R*)-(–)-myrtenal,[15] was converted to the propargylic silane **19** in 2 steps in 86% overall yield. Final iodination gave the compound **20** in excellent yield (Scheme 5).



Scheme 5 Synthesis of the iodide **16** and the new chiral propargylic silane **20**

We would like to point out that the absolute configuration of **17** is the same as that of myrtenal and the relative configuration of the two new stereocenters is "*trans*" and not "*cis*" as previously mentioned in the literature.[15,16] This fact was proven by the first X-ray crystal analysis of **17** (Figure).[17]

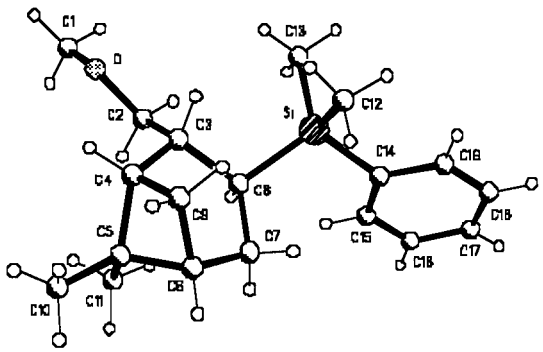
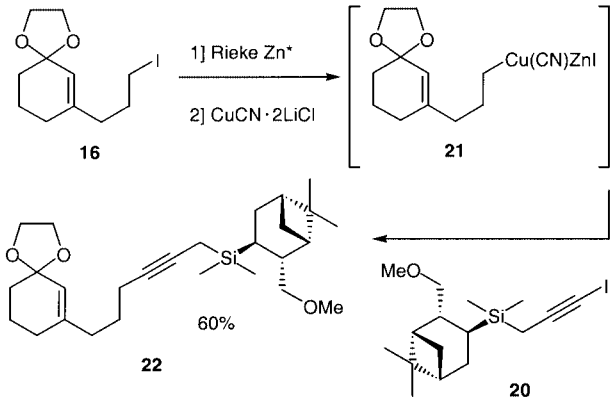


Figure Molecular structure of the chiral phenylsilane **17** in the crystal

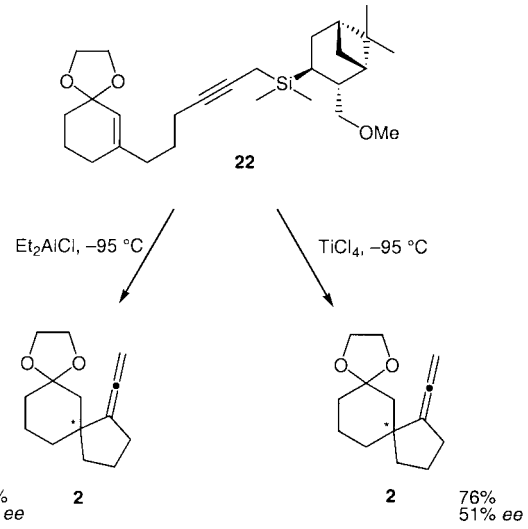
The coupling of the chiral propargylic silane **20** with iodide **16**, using the Knochel protocol gave a new chiral cyclization precursor **22** in fair yield (Scheme 6).[18,19]



Scheme 6 Synthesis of cyclization precursor **22**

Cyclization of **22** with diethylaluminum chloride in dichloromethane at –95 °C yielded the optically active spiroketal **2** in good yield, but with a low enantioselectivity of 8% ee. However, the use of titanium tetrachloride as Lewis acid afforded compound **2** in 76% yield and a remarkable 51% ee (Scheme 7).[10]

Our results demonstrate the possibility of building C-centered optically active organosilanes for asymmetric synthesis. Considering the fact that the generation of chiral quaternary centers is nontrivial, we presented four cyclization precursors which led to optically active products in the range of a low 4% ee up to a remarkable 51% ee. Even though the enantioselectivity is too weak for application in natural product synthesis, this approach nonetheless demonstrated the synthetic potential of such asymmetric cyclizations, and it underscores the importance of improving the enantioselectivity of these kinds of reactions. Further investigations along these lines are currently underway in our laboratory.



Scheme 7 The myrtenal model

Solvents were dried by standard procedures and redistilled under N_2 prior to use. All organometallic reactions were run under N_2 or argon, and pure products were obtained after flash chromatography using Merck silica gel 60 (40–63 mm). Mass spectra were recorded on Finnigan MAT 95, 8430 and SSQ 7000 spectrometers and high resolution mass spectra were obtained on the first two spectrometers (reference PFK, peak matching method, accuracy ±2 ppm). IR spectra were recorded on Perkin-Elmer 2000, 580, FT 1710 and Nicolet 320 FT-IR spectrometers. NMR spectra were recorded on Bruker AC 200, AM 400, and DPX 400 spectrometers. Optical rotations were recorded with a Perkin Elmer 241 polarimeter. GC analyses were accomplished with a Hewlett Packard 5890A gas chromatograph using a 12 m × 0.25 mm (i.d.) fused silica capillary column, containing immobilized octakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin, 120 °C, 1 bar hydrogen.

3-[5-(Trimethylsilyl)pent-4-ynyl]cyclohex-2-en-1-one,[7] bis(iodomethyl)dimethylsilane (**4**),[8] (2*S*)-(+)-2-(methoxymethyl)pyrrolidine (**6**),[9] (4*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one (**8**),[12] (4*S*)-4-isopropyl-5,5-diphenyloxazolidin-2-one (**10**),[13] 3-(3-iodopropyl)cyclohex-2-en-1-one (**14**)[14] and (1*S*,2*R*,3*S*,5*R*)-(2-methoxymethyl-6,6-dimethylbicyclo[3.1.1]hept-3-yl)dimethylphenylsilane (**17**)[15] were prepared according to the literature.

7-Pent-4-ynyl-1,4-dioxaspiro[4.5]dec-6-ene (3)

Ethane-1,2-diol (11 g, 177.2 mmol) and pyridinium *p*-toluenesulfonate (251 mg, 1.0 mmol) were added to a solution of 3-[5-(trimethylsilyl)pent-4-ynyl]cyclohex-2-en-1-one[7] (5.94 g, 25.3 mmol) in anhyd benzene (50 mL). The mixture was refluxed for 22 h with water separation by a Dean–Stark trap. After removal of the solvents in vacuo, Et_2O (50 mL) was added to the residue. The solution was washed with sat. aq $NaHCO_3$ solution (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated in vacuo. To the crude product was added THF (10 mL) and a solution of 1.0 M TBAF (tetrabutylammonium fluoride) in THF (38 mL, 38 mmol). The mixture was stirred at r.t. for 1 h. Finally aq $NaHCO_3$ solution (50 mL) was added and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (pentane–Et_2O, 10:1) to afford the pure ketal **3** (4.5 g, 86%) as a colorless oil which solidified during storage at low temperature (–40 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62–1.70 (m, 2 H), 1.71–1.81 (m, 4 H), 1.95 (t, *J* = 2.7 Hz, 1 H), 1.96 (t, *J* = 1.5 Hz, 2 H), 2.11 (br t, *J* = 7.6 Hz, 2 H), 2.18 (dt, *J* = 2.7 Hz, *J* = 7.1 Hz, 2 H), 3.91–4.01 (m, 4 H), 5.36 (br t, *J* = 1.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.99 (t), 20.88 (t), 26.00 (t), 28.38 (t), 33.26 (t), 36.06 (t), 64.30 (t), 68.46 (s), 84.04 (s), 106.45 (s), 122.15 (d), 144.13 (s).

MS (EI): *m*/*z* (%) = 206 ([M$^+$], 10), 178 (20), 167 (95), 126 (100), 106 (45), 99 (27), 91 (35), 79 (16), 77 (18), 53 (10).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{18}O_2$: 206.1307, found: 206.1306.

IR (neat): 3291 (s), 2944 (s), 2875 (s), 2361 (s), 2341 (s), 1667 (m), 1439 (m), 1355 (m), 1099 (s), 1078 (s), 933 (s), 642 (m) cm^{-1}.

[6-(1,4-Dioxaspiro[4.5]dec-6-en-7-yl)hex-2-ynyl]iodomethyldimethylsilane (5)

To a stirred solution of **3** (69 mg, 0.33 mmol) in anhyd THF (3 mL) at –78 °C was added a solution of 2.5 M BuLi in hexane (150 μL, 0.37 mmol). Stirring was continued for 1 h at this temperature and the mixture was treated with DMPU [1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one, 80 μL, 0.67 mmol]. After 10 min at –78 °C, a solution of **4**[8] (125 mg, 0.37 mmol) in THF (1 mL) was added and the mixture was allowed to warm up to r.t. over a period of 15 h. The mixture was quenched with sat. aq $NaHCO_3$ solution (5 mL) and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (pentane–Et_2O, 15:1) to afford the iodide **5** (130 mg, 94%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.24 (s, 6 H), 1.56–1.65 (m, 4 H), 1.73–1.80 (m, 4 H), 1.94–1.97 (m, 2 H), 2.05–2.15 (m, 6 H), 3.92–4.02 (m, 4 H), 5.35 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –14.90 (t), –3.56 (q), 5.49 (t), 18.69 (t), 21.02 (t), 26.99 (t), 28.53 (t), 33.38 (t), 36.46 (t), 64.42 (t), 76.36 (s), 79.18 (s), 106.63 (s), 121.99 (d), 144.71 (s).

MS (EI): *m*/*z* (%) = 418 ([M$^+$], 5), 199 (100), 170 (46), 167 (23), 128 (51), 99 (32), 73 (17), 55 (5).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{27}IO_2Si$: 418.0825, found: 418.0829.

IR (neat): 3292 (w), 2941 (s), 2877 (s), 1669 (m), 1250 (s), 1099 (s), 933 (s), 842(s) cm^{-1}.

(2*S*)-1-({[6-(1,4-Dioxaspiro[4.5]dec-6-en-7-yl)hex-2-ynyl]dimethylsilyl}methyl)-2-methoxymethylpyrrolidine (7)

A neat mixture of **6**[9] (522 mg, 4.53 mmol) and the iodide **5** (84 mg, 0.20 mmol) was heated at 80 °C with magnetic stirring for about 24 h. The crude mixture was purified by flash chromatography on silica gel (Et_2O, 1% Et_3N) to furnish the pure ketal **7** (81 mg, >99%) as a colorless oil; $[\alpha]_D^{20}$ –49.6 (*c* = 1.88, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.16 (s, 6 H), 1.21 (t, *J* = 6.9 Hz, 1 H), 1.50 (t, *J* = 2.6 Hz, 2 H), 1.56–1.66 (m, 2 H), 1.68–1.83 (m, 5 H), 1.86–1.98 (m, 4 H), 2.09 (t, *J* = 7.4 Hz, 2 H), 2.12–2.16 (m, 2 H), 2.18–2.24 (m, 1 H), 2.44–2.53 (m, 1 H), 2.57 (d, *J* = 14.5 Hz, 1 H), 3.09–3.19 (m, 1 H), 3.27 (dd, *J* = 6.3 Hz, *J* = 9.4 Hz, 2 H), 3.35 (s, 3 H), 3.45–3.50 (m, 1 H), 3.92–4.00 (m, 4 H), 5.35 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –3.38 (q), –3.26 (q), 5.53 (t), 18.72 (t), 20.99 (t), 23.14 (t), 27.08 (t), 28.20 (t), 28.52 (t), 33.35 (t), 36.46 (t), 44.54 (t), 57.53 (t), 59.09 (q), 64.37 (t), 65.81 (d), 67.90 (t), 75.67 (s), 78.75 (s), 106.61 (s), 121.93 (d), 144.73 (s).

MS (EI): *m*/*z* (%) = 405 ([M$^+$], 2), 363 (4), 362 (20), 361 (74), 360 (100), 316 (4), 206 (5), 186 (6), 128 (18), 91 (4), 59 (4).

HRMS (EI): *m*/*z* calcd for $C_{23}H_{39}NO_3Si$: 405.2699, found: 405.2699.

IR (neat): 3501 (w), 2944 (s), 2875 (s), 2830 (s), 2810 (s), 2219 (w), 1668 (m), 1456 (m), 1248 (s), 1186 (s), 1100 (s), 934 (s), 844 (s) cm^{-1}.

(4*S*)-4-Benzyl-3-({[6-(1,4-dioxaspiro[4.5]dec-6-en-7-yl)hex-2-ynyl]dimethylsilyl}methyl)-5,5-dimethyloxazolidin-2-one (9)

To a solution of **8**[12] (90 mg, 0.44 mmol) in anhyd THF (2 mL) at –78 °C was added a solution of 2.5 M BuLi in hexane (176 μL, 0.44 mmol). The resulting red-orange solution was warmed to r.t. within 1 h. Finally, a solution of **5** (183 mg, 0.44 mmol) in THF (1 mL) was added and the mixture was stirred for 15 h at 60 °C. Subsequent flash chromatography on silica gel (pentane–Et_2O, 1:2) of the crude reaction mixture yielded pure **9** (173 mg, 80%) as a colorless oil; $[\alpha]_D^{20}$ –5.6 (*c* = 1.98, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.21 (s, 3 H), 0.22 (s, 3 H), 1.19 (s, 3 H), 1.31 (s, 3 H), 1.54 (t, *J* = 2.7 Hz, 2 H), 1.57 (qui, *J* = 7.5 Hz, 2 H), 1.73–1.78 (m, 4 H), 1.91–1.96 (m, 2 H), 2.05 (t, *J* = 7.5 Hz, 2 H), 2.11 (tt, *J* = 2.7 Hz, *J* = 7.1 Hz, 2 H), 2.51 (d, *J* = 15.4 Hz, 1 H), 2.72 (dd, *J* = 9.5 Hz, *J* = 14.4 Hz, 1 H), 2.83 (d, *J* = 15.4 Hz, 1 H), 3.13 (dd, *J* = 5.1 Hz, *J* = 14.4 Hz, 1 H), 3.74 (dd, *J* = 5.1 Hz, *J* = 9.5 Hz, 1 H), 3.91–4.00 (m, 4 H), 5.33 (br s, 1 H), 7.21–7.35 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –3.37 (q), –3.13 (q), 5.99 (t), 18.75 (t), 20.97 (t), 22.21 (q), 27.02 (t), 28.06 (q), 28.47 (t), 32.04 (t), 33.33 (t), 34.73 (t), 36.47 (t), 64.38 (t), 67.79 (d), 77.06 (s), 79.11 (s), 80.85 (s), 106.59 (s), 121.98 (d), 126.86 (d), 128.79 (d), 128.88 (d), 136.89 (s), 144.64 (s), 157.56 (s).

MS (EI): *m*/*z* (%) = 495 ([M$^+$], 2), 278 (8), 277 (25), 276 (100), 232 (21), 145 (8), 99 (6), 91 (14), 86 (4), 75 (4).

HRMS (EI): *m*/*z* calcd for $C_{29}H_{41}NO_4Si$: 495.2805, found: 495.2809.

IR (neat): 3474 (w), 2942 (s), 1748 (s), 1456 (s), 1398 (s), 1098 (s), 1077 (s), 933 (s), 843 (s), 701 (m), 531 (w) cm^{-1}.

(4*S*)-3-[(Iodomethyldimethylsilyl)methyl]-4-isopropyl-5,5-diphenyloxazolidin-2-one (11)

To a slurry of **10**[13] (3 g, 10.66 mmol) in anhyd THF (20 mL) at –10 °C was added a solution of 2.5 M BuLi in hexane (5 mL, 12.5 mmol). The resulting violet solution was warmed to r.t. within 1 h. Finally a solution of **4**[8] (5.7 g, 16.76 mmol) in anhyd THF (10 mL) was added and the mixture was stirred for 6 h at 50 °C. The mixture was quenched with sat. aq $NaHCO_3$ solution (50 mL) and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (pentane–Et_2O, 1:1) to give the pure iodide **11** (1.1 g, 21%) as a white solid; $[\alpha]_D^{20}$ –160.1 (*c* = 1.10, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.04 (s, 3 H), 0.76 (d, *J* = 7.0 Hz, 3 H), 1.17 (d, *J* = 7.0 Hz, 3 H), 1.73 (d, *J* = 12.5 Hz, 1 H), 1.91 (d, *J* = 12.5 Hz, 1 H), 1.97–2.05 (m, 1 H), 2.71 (d, *J* = 15.4 Hz, 1 H), 3.22 (d, *J* = 15.4 Hz, 1 H), 4.31 (d, *J* = 1.4 Hz, 1 H), 7.24–7.68 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –14.10 (t), –3.27 (q), –3.20 (q), 15.48 (q), 22.81 (q), 30.03 (d), 35.04 (t), 71.42 (d), 87.49 (s), 124.99 (d), 125.94 (d), 127.51 (d), 128.18 (d), 128.59 (d), 138.79 (s), 144.81 (s), 157.03 (s).

MS (EI): *m*/*z* (%) = 493 ([M$^+$], 1), 478 (14), 450 (14), 406 (22), 353 (29), 352 (98), 222 (66), 207 (100), 199 (32), 165 (22), 129 (16), 91 (16), 73 (14), 61 (16).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{28}INO_2Si$: 493.0934, found: 493.0930.

IR (KBr): 3448 (m), 2961 (m), 2928 (m), 2362 (w), 1740 (s), 1450 (s), 1255 (s), 1034 (s), 843 (s), 706 (s) cm^{-1}.

(4*S*)-3-({[6-(1,4-Dioxaspiro[4.5]dec-6-en-7-yl)hex-2-ynyl]dimethylsilyl}methyl)-4-isopropyl-5,5-diphenyloxazolidin-2-one (12)
To a solution of **3** (122 mg, 0.59 mmol) and anhyd THF (10 mL) at –30 °C was added a solution of 2.5 M BuLi in hexane (300 μL, 0.75 mmol). The mixture was allowed to reach 0 °C within 1 h. Finally a solution of **11** (255 mg, 0.52 mmol) in anhyd THF (5 mL) was added and the mixture was heated at 45 °C for 16 h. The mixture was quenched with sat. aq $NaHCO_3$ solution (20 mL) and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (pentane–Et_2O, 1:1) to afford pure **12** (246 mg, 83%) as a colorless oil; $[\alpha]_D^{20}$ –150.0 (*c* = 1.04, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.12 (s, 3 H), 0.00 (s, 3 H), 0.77 (d, *J* = 7.0 Hz, 3 H), 1.17 (d, *J* = 7.0 Hz, 3 H), 1.27 (t, *J* = 2.6 Hz, 1 H), 1.35 (t, *J* = 2.6 Hz, 1 H), 1.64 (qui, *J* = 7.4 Hz, 2 H), 1.78–1.82 (m, 4 H), 1.99–2.03 (m, 3 H), 2.11 (t, *J* = 7.8 Hz, 2 H), 2.16 (tt, *J* = 2.6 Hz, *J* = 7.1 Hz, 2 H), 2.70 (d, *J* = 15.4 Hz, 1 H), 3.21 (d, *J* = 15.4 Hz, 1 H), 3.94–4.03 (m, 4 H), 4.32 (d, *J* = 1.6 Hz, 1 H), 5.39 (br s, 1 H), 7.23–7.69 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.18 (q), –4.16 (q), 5.29 (t), 15.35 (q), 18.60 (t), 20.86 (t), 22.64 (q), 26.94 (t), 28.40 (t), 29.90 (d), 33.22 (t), 34.33 (t), 36.33 (t), 64.24 (t), 71.13 (d), 76.91 (s), 78.80 (s), 87.22 (s), 106.44 (s), 121.98 (d), 124.91 (d), 125.31 (d), 125.88 (d), 127.33 (d), 127.96 (d), 128.02 (d), 128.41 (d), 138.87 (s), 144.41 (s), 144.79 (s), 156.86 (s).

MS (EI): *m*/*z* (%) = 571 ([M$^+$], 1), 354 (8), 353 (24), 352 (100), 308 (18), 252 (8), 233 (8), 208 (12), 167 (12), 91 (8).

HRMS (EI): *m*/*z* calcd for $C_{35}H_{45}NO_4Si$: 571.3118, found: 571.3125.

IR (neat): = 3474 (w), 2940 (s), 1736 (s), 1451 (s), 1252 (s), 1099 (s), 843 (s), 756 (s), 708 (s) cm^{-1}.

7-(3-Iodopropyl)-1,4-dioxaspiro[4.5]dec-6-ene (16)
To a mixture of **14**[14] (4.07 g, 15.4 mmol) and **15** (6 mL, 61.6 mmol) in anhyd benzene (15 mL) was added pyridinium *p*-toluenesulfonate (193 mg, 5 mol%). The resulting solution was stirred at r.t. for 24 h. The mixture was quenched with sat. aq $NaHCO_3$ solution (20 mL) and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (pentane–Et_2O, 8:1) to afford the pure ketal **16** (1.79 g, 38%) as a colorless oil. In addition, unreacted starting material **14** (2.44 g, 60%) was recovered.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69–1.81 (m, 4 H), 1.92–2.00 (m, 4 H), 2.11 (dd, *J* = 7.5 Hz, *J* = 14.9 Hz, 2 H), 3.17 (t, *J* = 6.9 Hz, 2 H), 3.92–4.02 (m, 4 H), 5.37 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 6.55 (t), 21.18 (t), 28.72 (t), 31.24 (t), 33.53 (t), 38.05 (t), 64.68 (t), 106.67 (s), 122.94 (d), 143.49 (s)

MS (EI): *m*/*z* (%) = 308 ([M$^+$], 12), 280 (44), 265 (4), 252 (17), 181 (72), 153 (12), 139 (14), 126 (100), 99 (12), 79 (10); 53 (6).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{17}IO_2$: 308.0273, found: 308.0266.

IR (neat): 2940 (s), 2878 (s), 2360 (s), 2342 (s), 1669 (m), 1438 (m), 1355 (m), 1219 (s), 1186 (s), 1095 (s), 933 (s) cm^{-1}.

(1*S*,2*R*,3*S*,5*R*)-(2-Methoxymethyl-6,6-dimethylbicyclo[3.1.1]hept-3-yl)dimethylprop-2-ynylsilane (19)
An argon flushed Schlenk tube was charged with **17**[15] (240 mg, 0.79 mmol) and cooled to 0 °C. Neat Br_2 (82 μL, 1.59 mmol) was added in one portion and the mixture was stirred for 1 h. After cooling the mixture to –10 °C, a freshly prepared solution of 0.5 M allenylmagnesium bromide[20] in Et_2O (16 mL, 7.9 mmol) was slowly added. The mixture was allowed to come to r.t. within 1 h and was quenched with crushed ice and sat. aq NH_4Cl solution (10 mL). The aqueous layer was extracted with pentane (3 × 30 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (pentane–Et_2O, 100:1) to yield the pure propargylic silane **19** (180 mg, 86%) as a colorless liquid; $[\alpha]_D^{20}$ +34.0 (*c* = 1.60, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.14 (s, 3 H), 0.15 (s, 3 H), 0.75 (d, *J* = 9.7 Hz, 1 H), 0.93 (ddd, *J* = 7.0 Hz, *J* = 8.4 Hz, *J* = 11.2 Hz, 1 H), 1.05 (s, 3 H), 1.19 (s, 3 H), 1.54 (d, *J* = 2.9 Hz, 2 H), 1.76 (ddd, *J* = 2.8 Hz, *J* = 7.0 Hz, *J* = 13.4 Hz, 1 H), 1.84 (t, *J* = 2.9 Hz, 1 H), 1.91 (sept, *J* = 3.0 Hz, 1 H), 2.01–2.08 (m, 1 H), 2.15 (dt, *J* = 2.0 Hz, *J* = 6.9 Hz, 1 H), 2.18–2.24 (m, 1 H), 2.27–2.33 (m, 1 H), 3.15 (dd, *J* = 4.1 Hz, *J* = 9.4 Hz, 1 H), 3.31 (s, 3 H), 3.43 (t, *J* = 9.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.41 (q), –5.12 (q), 4.24 (t), 15.52 (d), 22.84 (q), 27.84 (q), 27.92 (t), 31.82 (t), 38.85 (s), 41.17 (d), 42.46 (d), 42.68 (d), 58.73 (q), 67.04 (d), 77.20 (t), 82.65 (s).

MS (EI): *m*/*z* (%) = 264 ([M$^+$], 1), 225 (38), 219 (8), 163 (8), 97 (40), 89 (100), 79 (6), 69 (8), 59 (10).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{28}OSi$: 264.1909, found: 264.1907.

IR (neat): 3315 (m), 2900 (s), 2116 (w), 1457 (m), 1250 (s), 1116 (s), 837 (s), 629 (m) cm^{-1}.

(1*S*,2*R*,3*S*,5*R*)-(3-Iodoprop-2-ynyl)-(2-methoxymethyl-6,6-dimethylbicyclo[3.1.1]hept-3-yl)dimethylsilane (20)
To a solution of **19** (58 mg, 0.22 mmol) in anhyd THF (3 mL) at –78 °C was added a solution of 1.6 M BuLi in hexane (200 μL, 0.33 mmol). After stirring for 1 h at this temperature, solid I_2 (95 mg, 0.37 mmol) was added at –20 °C. The violet solution was allowed to reach r.t. within 1 h whereupon solid $Na_2S_2O_3$ was added. The resulting colorless slurry was filtered through a short path column of Celite (pentane–Et_2O, 1:1). Removal of the solvent in vacuo and purification of the residue by flash chromatography on silica gel (pentane–Et_2O, 30:1) yielded the pure iodide **20** (82 mg, 95%) as a colorless oil; $[\alpha]_D^{20}$ +30.5 (*c* = 3.09, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.13 (s, 3 H), 0.14 (s, 3 H), 0.74 (d, *J* = 9.7 Hz, 1 H), 0.91 (ddd, *J* = 7.0 Hz, *J* = 8.4 Hz, *J* = 11.2 Hz, 1 H), 1.05 (s, 3 H), 1.19 (s, 3 H), 1.74 (s, 2 H), 1.75 (ddd, *J* = 2.8 Hz, *J* = 7.0 Hz, *J* = 13.4 Hz, 1 H), 1.91 (sept, *J* = 3.0 Hz, 1 H), 2.00–2.07 (m, 1 H), 2.12–2.16 (m, 1 H), 2.17–2.22 (m, 1 H), 2.26–2.33 (m, 1 H), 3.13 (dd, *J* = 4.1 Hz, *J* = 9.4 Hz, 1 H), 3.30 (s, 3 H), 3.42 (t, *J* = 9.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.47 (q), –5.22 (q), 6.89 (t), 15.60 (d), 22.55 (q), 27.55 (q), 27.68 (t), 31.56 (t), 38.54 (s), 40.93 (d), 42.32 (d), 42.42 (d), 58.42 (q), 77.00 (t), 91.92 (s) (one acetylenic carbon atom not detected).

MS (EI): *m*/*z* (%) = 390 ([M$^+$], 1), 225 (16), 167 (24), 135 (26), 105 (12), 97 (34), 93 (22), 91 (32), 89 (100), 77 (18), 59 (12).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{27}IOSi$: 390.0876, found: 390.0883.

IR (neat): 3314 (w), 2900 (s), 2362 (s), 2342 (s), 1457 (m), 1250 (s), 1115 (s), 836 (s) cm^{-1}.

(1*S*,2*R*,3*S*,5*R*)-[6-(1,4-Dioxaspiro[4.5]dec-6-en-7-yl)hex-2-ynyl]-(2-methoxymethyl-6,6-dimethylbicyclo[3.1.1]hept-3-yl)dimethylsilane (22)
An argon flushed Schlenk tube was charged with freshly prepared Rieke zinc[19] (203 mg, 3.1 mmol) and anhyd THF (3 mL). A solution of **16** (96 mg, 0.31 mmol) in anhyd THF (1 mL) was added to the resulting fine black zinc dispersion and the mixture was heated 2 h at 50 °C. Complete insertion of zinc had occurred as indicated by TLC analysis of reaction aliquots. The excess of zinc was allowed to settle and a clear solution of the zinc reagent was ready for use. The zinc reagent was transferred via cannula to a solution of CuCN

(28 mg, 0.31 mmol) and LiCl (26 mg, 0.62 mmol) in anhyd THF (2 mL) at –20 °C and stirred for 20 min. The slightly green solution of **21** obtained, was cooled to –78 °C and the iodoalkyne **20** (60 mg, 0.15 mmol) in anhyd THF (1 ml) was slowly added. The reaction was allowed to warm to r.t. within 12 h. Finally the mixture was diluted with pentane (20 mL) and filtered through a short path of silica gel. Removal of the solvent in vacuo and purification of the residue by flash chromatography on silica gel (pentane–Et_2O, 5:1) yielded the pure silane **22** (41 mg, 60%) as a colorless oil; $[\alpha]_D^{20}$ +24.0 (*c* = 2.48, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.11 (s, 3 H), 0.12 (s, 3 H), 0.76 (d, *J* = 9.7 Hz, 1 H), 0.86–0.94 (m, 2 H), 1.05 (s, 3 H), 1.19 (s, 3 H), 1.48 (t, *J* = 2.6 Hz, 2 H), 1.60 (qui, *J* = 7.4 Hz, 2 H), 1.74–1.79 (m, 4 H), 1.90 (sept, *J* = 2.8 Hz, 1 H), 1.96–2.04 (m, 4 H), 2.07–2.11 (m, 2 H), 2.12–2.18 (m, 2 H), 2.19–2.24 (m, 1 H), 2.26–2.32 (m, 1 H), 3.13–3.15 (m, 1 H), 3.30 (s, 3 H), 3.42 (t, *J* = 9.7 Hz, 1 H), 3.92–4.01 (m, 4 H), 5.34 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.23 (q), –4.97 (q), 4.37 (t), 15.70 (d), 18.73 (t), 20.98 (t), 22.82 (q), 27.07 (t), 27.86 (q), 27.98 (t), 28.52 (t), 31.83 (t), 33.36 (t), 36.44 (t), 38.86 (s), 41.27 (d), 42.50 (d), 42.73 (d), 58.67 (q), 64.36 (t), 77.21 (t), 77.75 (s), 78.58 (s), 106.60 (s), 121.88 (d), 144.72 (s).

MS (EI): *m*/*z* (%) = 444 ([M^+], 1), 226 (8), 225 (42), 167 (26), 135 (8), 91 (12), 89 (100), 75 (8).

HRMS (EI): *m*/*z* calcd for $C_{27}H_{44}O_3Si$: 444.3060, found: 444.3065.

IR (neat): 2942 (s), 2363 (w), 2342 (w), 1671 (m), 1456 (s), 1248 (s), 1099 (s), 1077 (s), 943 (s), 835 (s) cm^{-1}.

Cyclization of 7 to 8-Vinylidene-1,4-dioxadispiro[4.1.4.3]tetradecane (2) with Et_2AlCl

Et_2AlCl (1.0 M solution in hexanes, 400 μL, 0.4 mmol) was added dropwise to a stirred and cooled solution (–95 °C) of propargylic silane **7** (41 mg, 0.1 mmol) in anhyd CH_2Cl_2 (10 mL). The solution was allowed to warm up to r.t. over a period of 10 h. The mixture was quenched with sat. aq $NaHCO_3$ solution (2 mL) and the resulting slurry was filtered through a short path of silica gel (pentane–Et_2O, 1:1). Removal of the solvent in vacuo and purification of the residue by flash chromatography on silica gel (pentane–Et_2O, 10:1) afforded the spiroketal **2** (16 mg, 0.073 mmol, 73%, 25% ee) as a colorless oil. The determination of the enantiomeric excess of **2** was performed on a 12 m × 0.25 mm (i.d.) fused silica capillary column, containing immobilized octakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin, 120 °C, 1 bar hydrogen.[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18–1.27 (m, 2 H), 1.42–1.50 (m, 1 H), 1.54–1.83 (m, 9 H), 2.37–2.44 (m, 2 H), 3.87–3.95 (m, 4 H), 4.74 (dt, *J* = 1.0 Hz, *J* = 4.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.10 (t), 24.37 (t), 30.11 (t), 34.91 (t), 36.07 (t), 36.53 (t), 44.13 (t), 46.67 (s), 63.71 (t), 64.47 (t), 77.92 (t), 109.54 (s), 113.31 (s), 201.92 (s).

MS (EI): *m*/*z* (%) = 220 ([M^+], 8), 205 (15), 192 (100), 177 (37), 136 (26), 119 (22), 99 (58), 91 (38).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{20}O_2$: 220.1463, found: 220.1463.

IR (neat): 2938 (s), 2871 (s), 1955 (m), 1729 (m), 1448 (m), 1172 (s), 1090 (s), 948 (s), 845 (s) cm^{-1}.

Cyclization of 7 with Titanium Tetrachloride

$TiCl_4$ (1.0 M solution in CH_2Cl_2, 690 μL, 0.69 mmol) was added dropwise to a stirred and cooled solution (–95 °C) of propargylic silane **7** (70 mg, 0.17 mmol) in anhyd CH_2Cl_2 (10 mL). The solution was allowed to warm up to r.t. over a period of 10 h. The mixture was quenched with sat. aq $NaHCO_3$ solution (2 mL) and the resulting slurry was filtered through a short path of silica gel (pentane–Et_2O, 1:1). Removal of the solvent in vacuo and purification of the residue by flash chromatography on silica gel (pentane–Et_2O, 10:1) afforded the spiroketal **2** (27 mg, 0.12 mmol, 71%, 42% ee) as a colorless oil. The determination of the enantiomeric excess of **2** was performed on a 12 m × 0.25 mm (i.d.) fused silica capillary column, containing immobilized octakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin, 120 °C, 1 bar hydrogen.[10] The analytical data were identical with those reported above.

Cyclization of 12 to 1-Vinylidenespiro[4.5]decan-7-one (13) with Diethylaluminum Chloride

Et_2AlCl (1.0 M solution in hexanes, 300 μL, 0.3 mmol) was added dropwise to a stirred and cooled solution (–95 °C) of **12** (170 mg, 0.297 mmol) in anhyd CH_2Cl_2 (10 mL). The solution was allowed to warm up to r.t. over a period of 10 h. The mixture was quenched with sat. aq $NaHCO_3$ solution and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (pentane–Et_2O, 30:1) to afford the spiroketone **13** (42 mg, 0.238 mmol, 80%, 4% ee) as a colorless oil. The determination of the enantiomeric excess of **13** was performed on a 12 m × 0.25 mm (i.d.) fused silica capillary column, containing immobilized octakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin, 120 °C, 1 bar hydrogen.[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42–1.54 (m, 2 H), 1.59–1.76 (m, 6 H), 1.93–2.00 (m, 1 H), 2.19–2.23 (m, 2 H), 2.29 (t, *J* = 13.8 Hz, 1 H), 2.37–2.43 (m, 2 H), 4.73 (dt, *J* = 0.6 Hz, *J* = 4.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.95 (t), 23.68 (t), 30.33 (t), 35.82 (t), 37.63 (t), 41.03 (t), 49.27 (s), 52.32 (t), 78.64 (t), 110.82 (s), 202.31 (s), 211.39 (s).

MS (EI): *m*/*z* (%) = 176 ([M^+], 29), 134 (58), 119 (43), 105 (56), 91 (100), 84 (57), 79 (59), 50 (60), 41 (57), 39 (63).

HRMS (EI): *m*/*z* calcd for $C_{12}H_{16}O$: 176.1201, found: 176.1206.

IR (neat): 2953 (s), 2872 (s), 1956 (s), 1713 (s), 1446 (m) cm^{-1}.

Cyclization of 22 to the Spiroketal 2 with Et_2AlCl

Using the same reaction and workup conditions as reported for the cyclization of compound **7**, treatment of **22** (52 mg, 0.117 mmol) with Et_2AlCl (1.0 M solution in hexanes, 234 μL, 0.234 mmol) afforded the spiroketal **2** (20 mg, 0.09 mmol, 77%, 8% ee) as a colorless oil. The determination of the enantiomeric excess of **2** was performed on a 12 m × 0.25 mm (i.d.) fused silica capillary column, containing immobilized octakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin, 120 °C, 1 bar hydrogen.[10] The analytical data were identical with those reported above.

Cyclization of 22 to the Spiroketal 2 with $TiCl_4$

Using the same reaction and workup conditions as reported for the cyclization of compound **7**, treatment of **22** (45 mg, 0.1 mmol) with $TiCl_4$ (1.0 M solution in CH_2Cl_2, 200 μL, 0.2 mmol) afforded spiroketal **2** (17 mg, 0.077 mmol, 76%, 51% ee) as a colorless oil. The determination of the enantiomeric excess of **2** was performed on a 12 m × 0.25 mm (i.d.) fused silica capillary column, containing immobilized octakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin, 120 °C, 1 bar hydrogen.[10] The analytical data were identical with those reported above.

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(17) X-ray analysis of compound **17**: $C_{19}H_{30}OSi$, M = 302.52, orthorhombic, space group $P2_12_12_1$, a = 10.1154(6) Å, b = 13.3330(10) Å, c = 14.0385(3) Å, U = 1839.35(19) Å^3, Z = 4, D = 1.061 Mgm^{-3}, F(000) = 664, μ (MoK_α) = 0.122 mm^{-1}, max/min transmission 1.00/0.58, colorless plate 0.52 × 0.16 × 0.05 mm, T = 173(2) K. Siemens SMART CCD system with MoK_α X-radiation (λ = 0.71073 Å) and graphite monochromator, 12366 reflections over a range of 2.11° < θ < 28.16°, absorption correction with the SADABS routine. *Structure refinement:* Anisotropic on F^2 (program SHELXL-93. G. M. Sheldrick, University of Göttingen). H atoms riding or as rigid methyl groups; $R1$ = 0.0607 (conventional) and $wR2$ = 0.1317 (all data), with goodness of fit = 0.991 for 195 refined parameters. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre under the number 6974. Copies may be obtained without charge from: CCDC, Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223/336 033; E-mail: deposit@ccdc.cam.ac.uk).
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