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SYNTHESIS OF THE CYCLOBUTANE MOIETY OF PROVIDENCIN

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Abstract –A short and stereoselective synthesis of the protected cyclobutane diol moiety of the natural compound providencin is reported. Key step is the chemo- and stereoselective hydroboration of the silyl-enol ether obtained from commercially available bicyclo[3.2.0]hept-6-en-2-one.

INTRODUCTION

Quite recently, the diterpene providencin ((+)-**1**)[1] was isolated from the gorgonian octocoral *Pseudopterogorgia kallos*, featuring an uncommon furyl cyclobutane ring system. The synthesis of highly functionalized cyclobutanes still represents a challenge for synthetic chemists, as substituents and functional groups attached to the cyclobutane ring are highly congested and the ring-geometry forces them into a fully eclipsed conformation[2]. The cyclobutane ring in **1** is *trans*-fused to the 13-membered macrocycle. Furthermore it exhibits an *exo*-methylene group with an allylic alcohol. In our retrosynthetic analysis we planned to introduce this allylic alcohol *via* an α-hydroxylation of commercially available non-racemic bicyclo[3.2.0]cyclo-hept-6-en-2-one (**3**) (Figure 1).

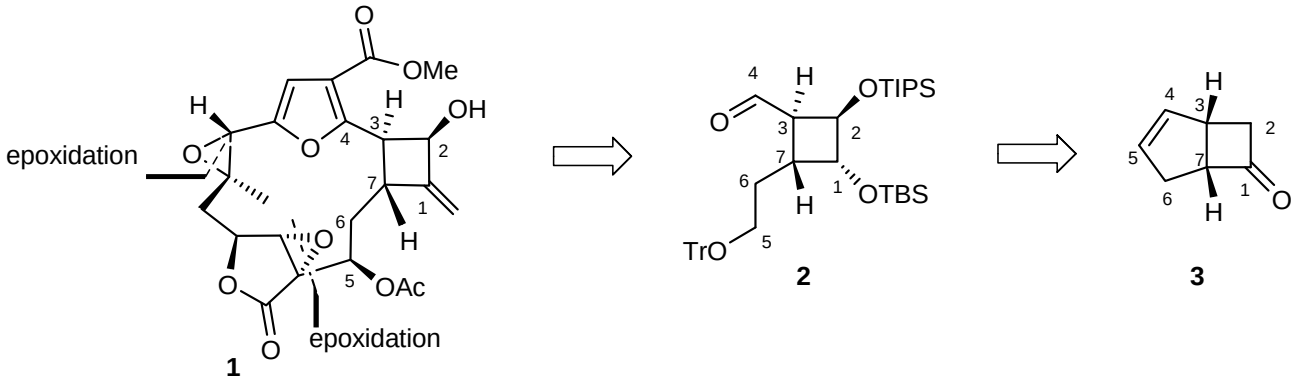
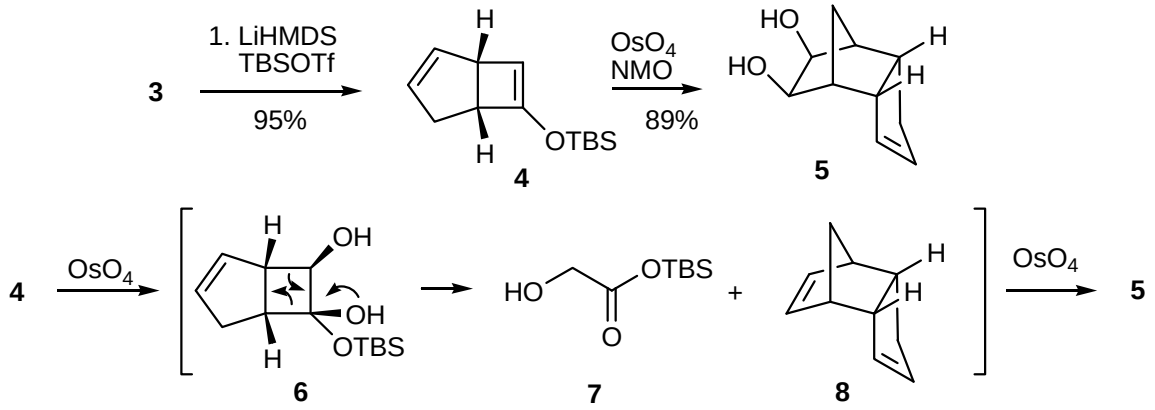


Figure 1. Retrosynthetic considerations

The use of **3** has the big advantage to provide us, not only the cyclobutanone ring, but to give after ozonolysis, two differentiable carbon appendages of suitable length for further elaboration. The *cis*-stereochemistry of the two carbon chains originates from bicycle **3** and was to be inverted to the desired *trans*-relation as shown in figure 1. In our current studies, racemic **3** was used to keep costs low.

RESULTS AND DISCUSSION

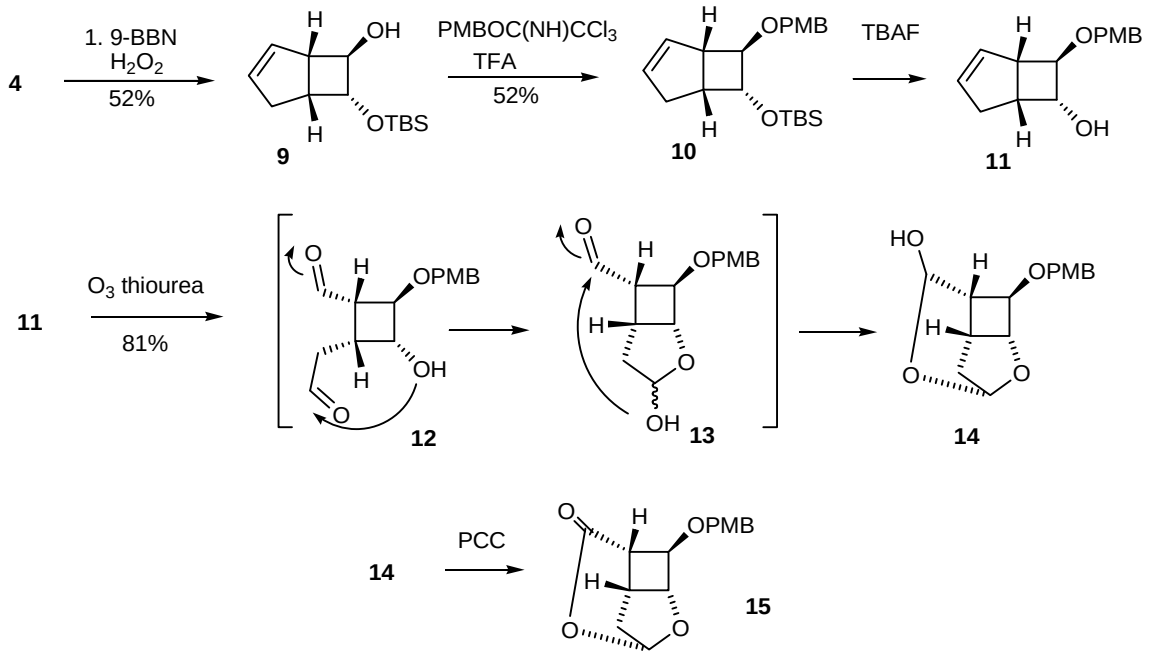
We tried various methods for the α-hydroxylation of bicyclic structure **3**.[3,4] Unfortunately we either got decomposition of starting material, or unwanted side products. For instance, after converting **3** into the silyl enol ether **4**, reaction with osmium tetroxide did not lead to α-hydroxylation. Instead compound **5** was isolated, obviously resulting from a sequential dihydroxylation retro-[2+2]–cycloaddition to give glycolic ester **7** and cyclopentadiene, which immediately undergoes Diels-Alder dimerization (**8**) /dihydroxylation to **5** (Scheme 1).



Scheme 1. Osmylation of **4** unexpectedly leads to **5**

As we could not introduce the hydroxyl group by α-hydroxylation, we tried a hydroboration of **4** with 9-BBN. To our delight, the desired diol **9** was formed in 52% yield (Scheme 2). The reaction not only established a *trans*-configuration of the diol, but also allowed complete differentiation of the two hydroxy-groups, as the former enol ether was converted to a TBS-protected alcohol and the free hydroxy group was protected as PMB ether **10**.

Next we aimed for cleaving the cyclopentene ring and inverting the configuration at C-3. To differentiate the two aldehyde functions resulting from ozonolysis we removed the TBS group to obtain **11** and hoped for an intramolecular lactol formation to give **13** from di-aldehyde **12**. However, the lactol OH function in **13** immediately added to the second aldehyde group to give **14** instead (Scheme 2).



Scheme 2. Formation of cage lactol **15**

This result is a nice illustration for the ease of transannular reactions in this bicyclic system. For further differentiation of the two acetals, we converted lactol **14** with PCC to lactone **15** in 35% yield. To corroborate the structure of **14** we performed an analogous sequence with dichloro-compound **16** (Scheme 3). In this case, lactol **17** crystallized nicely and we were able to confirm the cage structure via single crystal diffraction (Figure 2).

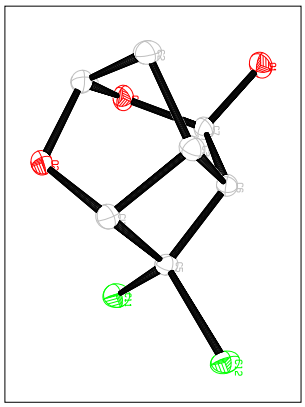
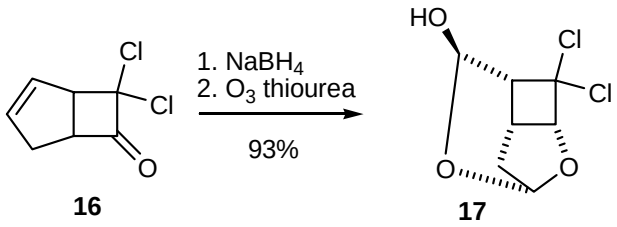
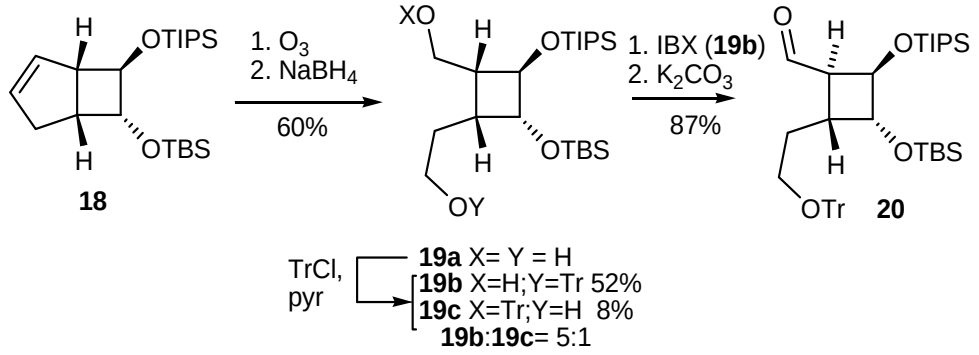


Figure 2. Crystal structure of compound **17**



Scheme 3. Synthesis of crystalline compound **17**

To avoid the low yielding oxidation of **14** we decided to prevent the double acetalization of **13** and used the doubly silylated diol **18** in the ozonolysis step.



Scheme 4. Synthesis of providencin fragment **20**

This time we used a reductive work up to get diol **19a**. To our delight we found that mono-tritylation furnished **19b** and **19c** with 5:1 regioselectivity, The regioisomers were easily separated by column chromatography. Oxidation of **19b** to the aldehyde and base catalyzed isomerization to the *trans* isomer **20** proceeded smoothly in 92% yield with 9:1 diastereomeric excess (Scheme 4). Evidence for this isomerization has been found in the ^{1}H NMR spectrum. The signal of the aldehyde-H changes its position from 9.67 to 9.74 ppm. By detritylation with formic acid, **19c** could be recycled to **19a** so that no material was lost.

In conclusion we have developed a stereoselective and short approach to the tetrasubstituted cyclobutane moiety of providencin **1**.

EXPERIMENTAL

Analytical data of key intermediates:

Compound **4** (Bicyclo[3.2.0]hepta-2,6-dien-6-yloxy) (*tert*-butyl)dimethylsilane):

To a solution of **3** (1.00 g, 9.24 mmol, 1eq.) in dry THF (40 mL) at -78 °C was slowly added TBSOTf (6.4 mL, 27.7 mmol, 3eq.). To this mixture at -78 °C was rapidly added LiHMDS (1M in hexane, 46 mL, 46 mmol, 5eq.). The reaction mixture was stirred for 1 h at -78 °C, and then quenched with saturated aqueous NH_4Cl solution and extracted two times with Et_2O (100 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude product was filtered over silica gel with (hexane/EtOAc 20:1 and 5% Et_3N) and was then further purified *via* a bulb to bulb distillation to yield 95% 1.95 g of pure **4**.

^{1}H-NMR: δ 5.90-5.85 (m, 1H), 5.62-5.57 (m, 1H), 4.99 (s, 1H), 3.51-3.44 (m, 1H), 3.25-3.20 (m, 1H), 2.46-2.17 (m, 2H), 0.95 (s, 9H), 0.19 (s, 6H). ^{13}C-NMR: δ 134.97, 130.52, 111.52, 49.09, 45.52, 30.77, 26.04, -4.17, -4.33. HRMS (EI) *m/z* calcd for $C_{13}H_{22}OSi$ 222.3987, found 222.3982.

Compound **5** (4,7-Methano-1*H*-indene-5,6-diol, 3a,4,5,6,7,7a-hexahydro-, (3aα,4β,5α,6α,7β,7aα):
To a solution of **4** (743 mg, 3.3 mmol, 1eq.) in *t*BuOH: H_2O (1:1, 30 mL) at 0 °C was added OsO_4 (4 mg, 0.016 mmol, 0.5mol%) and *N*-morpholine-*N*-oxide (390 mg, 3.3 mmol, 1eq.). The reaction mixture was stirred for 20 h, quenched with an aqueous sodium thiosulfate solution, and extracted two times with Et_2O (50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvents were removed under reduced pressure. Crude **5** was purified by chromatography (silica gel, hexane/ EtOAc 1:1) to yield 488 mg 89% of pure **5**.
^{1}H-NMR: δ 5.45-5.37 (m, 2H), 3.61 (d, *J* = 5.38 Hz, 1H), 3.52 (d, *J* = 5.56 Hz, 1H), 2.94-2.88 (m, 1H), 2.69-2.59 (m, 2H OH broad), 2.42-2.35 (m, 1H), 2.15-2.06 (m, 3H), 1.92 (d, *J* = 4.29 Hz, 1H), 1.70-1.67 (m, 1H), 116-1.12 (m, 1H). ^{13}C-NMR: δ 131.33, 131.13, 71.81, 70.19, 51.29, 48.47, 46.87, 40.92, 35.35, 32.35. HRMS (EI) *m/z* calcd for $C_{10}H_{14}O_2$ 166.2170, found 166.2178.

Compound **9** (7-(*tert*-Butyldimethylsilyloxy)bicyclo[3.2.0]hept-3-en-6-ol):
To a solution of **4** (743 mg, 3.3 mmol, 1eq.) in dry THF (7 mL) at 0 °C was added 9-BBN (0.5 M in THF 6.6 mL, 1eq.). The reaction mixture was warmed to rt and stirred for 14 h. The reaction was quenched with 0.5M NaOH (3 mL) and H_20_2 (30%, 1 mL), diluted with brine and extracted two times with Et_2O (50 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed under vacuum. Crude **9** was purified by flash column chromatography (hexane/EtOAc 3:1) to yield 412 mg 52% of pure **9**.
^{1}H-NMR: δ 5.79-5.72 (m, 2H), 4.11 (dd, *J* = 8.96, 4.92 Hz, 1H), 3.59-3.56 (m, 1H), 2.96-2.88 (m, 1H), 2.67-2.60 (m, 2H), 2.25-2.17 (m, 1H), 0.83 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H). ^{13}C-NMR: δ 134.46, 131.79, 84.38, 74.59, 49.47, 37.69, 26.24, -4.47. (HRMS (EI) *m/z* calcd for $C_{13}H_{24}O_2Si$ 240.4140, found 240.4133.

Compound **10 (***tert*-Butyl(-7-(4-methoxybenzyloxy)bicyclo[3.2.0]hept-2-en-6-yloxy)dimethylsilane):
To a solution of alcohol **9** (2.1 g, 8.7 mmol, 1eq.) in dry DCM (10 mL) was added a solution of Bundles reagent (5 g, 17.5 mmol, 2eq.) in hexane (30 mL) and cooled to 0 °C. Then 20 mg of camphorsulfonic acid were added and the reaction mixture was stirred over night. The reaction was quenched with saturated aqueous $NaHCO_3$ solution, and extracted two times with Et_2O (100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure and crude **10** was purified by column chromatography (silica gel, hexane/EtOAc 7:1) to yield 1.63 g 52% of pure **10**.
^{1}H-NMR: δ 7.30-7.26 (m, 2H), 6.92-6.88 (m, 2H), 5.83-5.79 (m, 1H), 5.76-5.71 (m, 1H), 4.44 (s, 2H), 3.83 (s, 3H), 3.49-3.45 (m, 1H), 3.09-2.96 (m, 1H), 2.81-2.69 (m, 2H), 2.38-2.24 (m, 1H), 0.94 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H). ^{13}C-NMR: δ 159.71, 134.31, 131.75, 129.82, 129.61, 114.27, 91.22, 74.59,

73.18, 55.86, 49.47, 37.69, 26.24, 18.43, -4.51. HRMS (EI) *m/z* calcd for $C_{21}H_{32}O_3Si$ 360.5625, found 360.5620.

Compound **14** 2-(4-Methoxybenzyl)oxy-4,9-dioxatricyclo[3.2.2.$0^{3,7}$]nonan-8-ol:
Ozone was bubbled through a solution of **11** (219 mg, 0.89 mmol, 1eq.) in CH_2Cl_2/MeOH 4:1 (5 mL) at -78 °C for 10 min. To remove unreacted ozone, air was subsequently bubbled through the reaction mixture at the same temperature for 5 min. Then thiourea (71 mg, 0.93 mmol, 1.05 eq.) was added and the reaction was warmed to rt. The solid was filtered off, the solvents were removed under reduced pressure and crude **14** was submitted to flash column chromatography (silica gel, hexane/EtOAc 2:1) to yield 200 mg 81% of pure **14**.
^{1}H-NMR: δ 7.30-7.21 (m, 2H), 6.90-6.82 (m, 2H), 5.67-5.54 (m, 1H), 5.17 (s, 1H), 4.63-4.35 (m, 3H), 3.78 (s, 3H), 3.51-3.22 (m, 1H), 3.06-2.91 (m, 1H), 2.75-2.69 (m, 1H), 2.64-2.55 (m, 1H), 1.55-1.45 (m, 1H). HRMS (EI) *m/z* calcd for $C_{15}H_{18}O_5$ 278.3004, found 278.2999.

Compound **15** 2-(4-Methoxybenzyl)oxy-4,9-dioxatricyclo[3.2.2.$0^{3,7}$]nonan-3-one
Lactol **14** (200 mg, 0.72 mmol, 1eq.) was dissolved in dry CH_2Cl_2 (12 mL) at 0 °C. The PCC (170 mg, 0.8 mmol, 1.2 eq.) was added. After 30 minutes another portion of PCC (240 mg, 1.21 mmol, 1.7 eq.) was added and a last portion of PCC (240 mg, 1.21 mmol, 1.7 eq.) was added after 2 h. The reaction was then stirred for 24 h, quenched with saturated aqueous $NaHCO_3$ solution, and extracted two times with Et_2O (50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure and crude **15** was purified by column chromatography (silica gel, hexane/EtOAc 2:1) to yield 70 mg 35% of pure **15**.
^{1}H-NMR: δ 7.32-7.26 (m, 2H), 6.94-6.89 (m, 2H), 5.99 (dd, *J* = 3.08, 1.03 Hz, 1H), 4.62-4.46 (m, 3H), 3.93 (s, 1H), 3.83 (s, 3H), 3.66-3.59 (m, 1H), 3.28-3.24 (m, 1H), 2.11-2.04 (m, 1H), 2.00-1.91 (s, 1H). HRMS (EI) *m/z* calcd for $C_{15}H_{16}O_5$ 276.2845, found 276.2855.

Compound **17 (**5,5-Dichloro-2,9-dioxatricyclo[3.2.2.$0^{3,7}$]nonan-3-ol):
See procedure for compound **14.**
^{1}H-NMR: δ 5.70 (dd, *J* = 3.48, 0.50 Hz, 1H), 5.41 (s, 1H), 4.76-4.73 (m, 1H), 3.62-3.58 (m, 1H), 3.26-3.22 (s, 1H OH, broad), 3.19 (ddd, *J* = 7.39, 4.47, 1.57 Hz, 1H), 2.78 (d, *J* = 12.28 Hz, 1H), 1.70 (ddd, *J* = 12.14, 4.16, 4.16 Hz, 1H) ^{13}C-NMR: δ 101.60, 90.31, 88.38, 82.36, 56.06, 35.22, 31.26. HRMS (EI) *m/z* calcd for $C_7H_8Cl_2O_3$ 211.0426, found 211.0420.

Compound **19a** ((3-(*tert*-Butyldimethylsilyloxy)-2-(triisopropylsilyloxy)-4-(2-(trityloxy)ethyl)-cyclobutyl)methanol):

Ozone was bubbled through a solution of **18** (385 mg, 1.0 mmol, 1eq.) in DCM/MeOH 4:1 (7 mL) at -78 °C for 10 min. To remove unreacted ozone air was bubbled through the reaction mixture at the same temperature for 5 min. Then $NaBH_4$ (71 mg, 2.0 mmol, 2 eq.) were added and the reaction was warmed to rt. The reaction was then stirred for 2 h, quenched with saturated aqueous NH_4Cl solution, and extracted two times with Et_2O (50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure and crude **19a** (330 mg, 0.76 mmol, 1eq.) was directly used in the next step. **19a** was dissolved in dry DCM (15 mL) cooled to 0 °C and pyridine (250µl, 2.28 mmol, 3eq.) were added at that temperature. To this solution was added dropwise trityl chloride in dry DCM (2 mL) and the reaction was stirred over night. The mixture was quenched with brine and extracted two times with Et_2O (50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure and crude product was purified by flash column chromatography (silica gel, hexane/EtOAc 7:1) to yield 267 mg 52% of **19b** and 41 mg 8% of **19c** 35% of pure **15**.

^{1}H-NMR: δ 7.54-7.25 (m, 15H), 4.00-3.62 (m, 4H), 3.37-3.14 (m, 2H), 2.34 (ddd, *J* = 16.9, 8.79, 4.23 Hz, 1H), 2.08-1.94 (m, 2H), 1.76-1.61 (m, 1H), 1.69 (s, broad 1H), 1.12 (s, 21H), 0.95 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H). HRMS (EI) *m/z* calcd for $C_{41}H_{62}O_4Si_2$ 675.0996, found 675.0989.

Compound **20** (3-(*tert*-Butyldimethylsilyloxy)-2-(triisopropylsilyloxy)-4-(2-(trityloxy)ethyl)cyclobutane-carbaldehyde):

Alcohol **19b** (175 mg, 0.26 mmol, 1eq.) was dissolved in EtOAc (3 mL) and IBX (218 mg, 0.78 mmol, 3eq.) was added. The suspension was refluxed for 2 h, and then cooled to rt and the solid was filtered off. The organic layer was concentrated, re-dissolved in MeOH (10 mL) and K_2CO_3 (361 mg, 2.6 mmol, 10eq.) was added to the solution. The reaction was stirred for 1.5 h, diluted with Et_2O, the solids filtered off, and extracted with saturated aqueous NH_4Cl solution. The combined organic layers were washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure and crude **20** was purified by flash column chromatography (silica gel, hexane/EtOAc 7:1) to yield 152 mg 87% of pure **20**.

^{1}H-NMR: δ 9.74 (t, *J* = 1.37 Hz, 1H), 4.13-4.05 (m, 1H), 3.77-3.71 (m, 1H), 3.53 (dd, *J* = 9.50, 4.23 Hz, 1H), 3.17-3.05 (m, 1H), 2.86 (t, *J* = 10.16 Hz, 1H), 2.46-2.18 (m, 2H), 1.02 (s, 21H), 0.89 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H). HRMS (EI) *m/z* calcd for $C_{22}H_{45}O_3Si_2$ 413.7619, found 413.7611.

Crystal Data of Compound **17**.

Symmetry cell setting monoclinic, symmetry space group P21, a =5.9039(2), b= 10.8209(4), c= 6.4507(2), alpha =90.00, beta =90.510(2), gamma = 90.00, V = 412.09(2), Z = 2, density calc = 1.710, T = 373 K, diffrn radiation wavelength 0.71073 ,diffrn radiation type MoKα, graphite, diffrn reflns number 15712, diffrn reflns av R equivalents 0.0202, diffrn reflns av_sigmaI/netI 0.0128, diffrn reflns limit h min 8,

diffrn reflns limit h max 8, diffrn reflns limit k min -15, diffrn reflns limit k max 15, diffrn reflns limit l min 9, diffrn reflns limit l max 9, diffrn reflns heta min 3.16, diffrn reflns theta max 30.02, reflns number total 2409, reflns number gt 2379, reflns threshold expression >2sigma(I), computing structure solution SHELXS-97 (Sheldrick, 1990),' computing structure refinement SHELXL-97 (Sheldrick, 1997).'
Refinement of F^2^ against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2^, conventional R-factors R are based on F, with F set to zero for negative F^2^. The threshold expression of F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2^ are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger. Refine ls number reflns 2409, refine, ls number parameters 111, refine ls number restraints 1, refine ls R factor all 0.0161, refine ls R factor gt 0.0158, refine ls wR factor ref 0.0427, refine ls wR _factor gt 0.0424, refine ls goodness of fit ref 1.069.
Abbreviations: TBSOf: *tert*Butyldimethylsilyltriflate, LiHMDS: lithium hexamethyldisilazide, DCM: dichloromethane, PCC: pyridinium chlorochromate, IBX: *o*-iodoxybenzoxy acid.

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