Asymmetric Synthesis of the C(33) – C(37) Fragment of Amphotericin B

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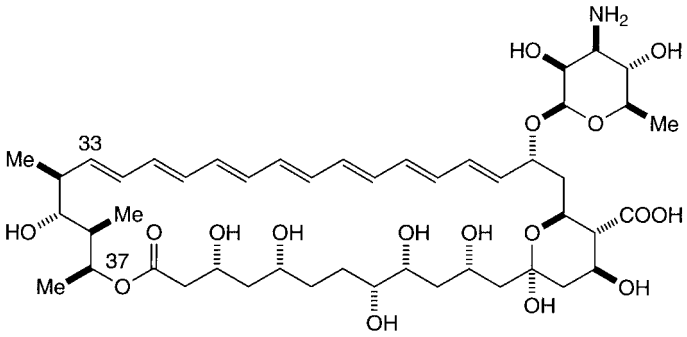
We have devised an expeditious, efficient, asymmetric synthesis of the C(33) – C(37) fragment of amphotericin B that proceeds in 14 steps and 16% overall yield from tiglic aldehyde ((*E*)-2-methylbut-2-enal) with complete stereocontrol. The route described herein relies on the application of recently developed methods in catalytic asymmetric synthesis for stereocontrol through enantio- and diastereoselective functionalization of a substituted sorbate derivative.

Introduction. – Amphotericin B (AmB, **1**) is one of the most prominent members of the polyene macrolide antibiotics that shows significant pharmacological activity [1]. Indeed, in this regard, AmB serves as the drug of choice in the clinic for antifungal chemotherapy in life-threatening infections, although it is poorly tolerated and elicits adverse side effects [2]. With a rising number of fungal infections resistant to extant remedies, the development of analogs with improved therapeutic profiles has become increasingly necessary. Additionally, because the mechanism of action of amphotericin's antifungal activity and its toxicity to the host are not yet fully understood, efficient synthesis strategies allow access to active structures that serve as designed probes, providing insight into the mode of action of these remarkable natural products (for reviews, see [3]).



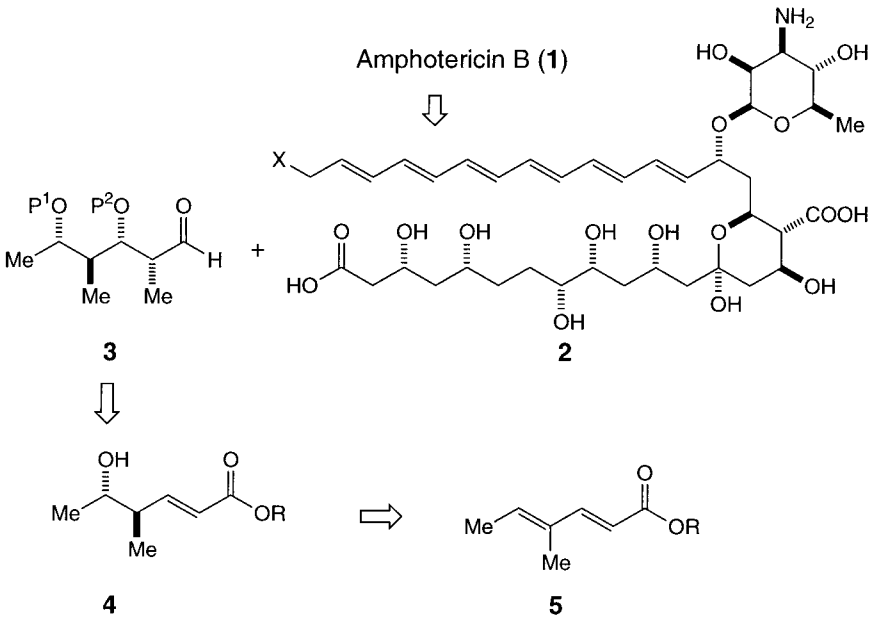
Amphotericin B (**1**)

A number of synthetic studies aimed at the preparation of amphotericin B (**1**) have been documented [4]. Although notable in their own right, in general, the strategies employed are not amenable to analog synthesis, as the approaches are carefully tailored specifically to provide the fragments for amphotericin B (**1**). We have been interested in crafting a general, flexible synthesis strategy to the polyene macrolide antibiotics

that could provide access to designed analogs incorporating added functionality, less functionality, as well as displaying various stereochemical permutations. Moreover, because of our interest in crafting a synthetic strategy that affords preparatively useful quantities of such analogs, we have focused on the application of modern methods for catalytic asymmetric synthesis for the preparation of the amphotericin subunits (for a recent, highly convergent synthesis of the C(1)–C(13) polyol fragment, see [5]). Herein, we document an asymmetric synthesis of the C(33)–C(37) subunit of amphotericin B (**1**)[1]) in 14 steps and 16% overall yield from commercially available tiglic aldehyde ((*E*)-2-methylbut-2-enal). Importantly, the synthesis is not only amenable to the large-scale preparation of the C(33)–C(37) subunit but to the preparation of designed analogs possessing alternate relative stereochemical relationships.

The C(33)–C(37) fragment **3** of amphotericin B represents a strategically important substructure for any general, convergent strategy for the synthesis of this polyene macrolide antibiotic (*Scheme 1*). It is the subunit that serves as a lynchpin between the polyol and polyene sectors of the natural product. In this respect, it can be chemically excised from the macrolide following ozonolytic cleavage of the polyene and saponification of the ensuing ester. Because of our interest in crafting a modular synthesis strategy to amphotericin B (**1**) [5], a plan that relies on the use of this fragment demands its expeditious preparation. The incorporation of the C(33)–C(37)

Scheme 1. *Retrosynthetic Analysis of Amphotericin B*



[1]) Throughout the text of the manuscript, amphotericin numbering scheme is employed in referring to the C-atoms of fragment **3**.

fragment or its congeners into an advanced intermediate in the synthesis plan can be readily envisioned through olefination and esterification reactions by independent operation on either the C(33) aldehyde or the C(37) secondary alcohol.

The juxtaposition of Me and OH groups along the C(33)–C(37) C-chain is synthetically suggestive of a strategy employing the aldol-addition reaction or its closely related transformations. An inherent feature of any plan that relies on iterative aldol-addition reactions to install the requisite functional groups with appropriate configuration is the accompanying transformations that must be employed to effect oxidation-state adjustment and auxiliary removal. This is exacerbated by the fact that the aldol-addition reaction is a transformation that incorporates C_2 fragments piecemeal on a growing C-chain (for a recent development in aldol-addition chemistry that involves C_4 acetoacetate fragments, see [6]). We envisioned that a strategy that commences with the C(33)–C(37) C-framework in the form of hexadienoate **5** and proceeds by asymmetric functionalization of the olefinic functionality (*i.e.*, **5** → **4**) would be strategically beneficial (*Scheme 1*). Moreover, given the phenomenal advances in catalytic asymmetric olefin functionalization reactions, such a strategy would be efficient as well as amenable to analog synthesis. The details of the successful implementation of such a plan is described below (for other approaches to the C(33)–C(37) fragment, see [7]).

Results and Discussion. – Treatment of the known Me-substituted derivative of ethyl sorbate (**6**) [8][2]) to catalytic, asymmetric dihydroxylation conditions of *Sharpless* [9] (5 mol-% dihydroquinidine 1,4-phthalazinediyl diether ($(DHQD)_2$-PHAL), 1 mol-% $K_2OsO_4 \cdot 2\ H_2O$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$) in *t*-BuOH/H_2O 1:1 at 0° over 48 h furnished diol **7** in 68% yield and 99% ee (*Scheme 2*) (for an excellent review of the asymmetric dihydroxylation reaction, see [10]). The enantiomeric excess could be readily determined by HPLC analysis of the reaction products on a *Chiralcel OD-H* column[3]). The well-known ease with which this reaction can be conducted allowed the preparation of this key starting material in preparatively useful quantities. It is important to note that the conditions employed for the enantioselective dihydroxylation reaction are that employed for tetrasubstituted alkenes (special conditions have been reported for the dihydroxylation reaction of tetrasubstituted alkenes [11]). When the standard conditions for dienoates and trienoates were employed, the yield along with the enantioselectivity were diminished. Chemoselective mesylation of the secondary alcohol in **7** afforded **8** (93%), which, upon treatment with base (NaH, MeCN), underwent subsequent ring closure to provide epoxide **9** in 92% yield.

Reductive opening of the C(35)/C(36) epoxide with correct incorporation of the C(36) stereogenic center was effected by the Pd-catalyzed stereospecific allylic reduction methodology of *Tsuji* and co-workers [12] (*Scheme 3*). Thus, when **9** was treated with 2.5 mol-% $[Pd_2(dba)_3] \cdot CHCl_3$ (dba = dibenzylideneacetone = 1,5-diphenylpenta-1,4-dien-3-one) and Bu_3P in the presence of HCO_2H/Et_3N (THF, 3 h, 23°)

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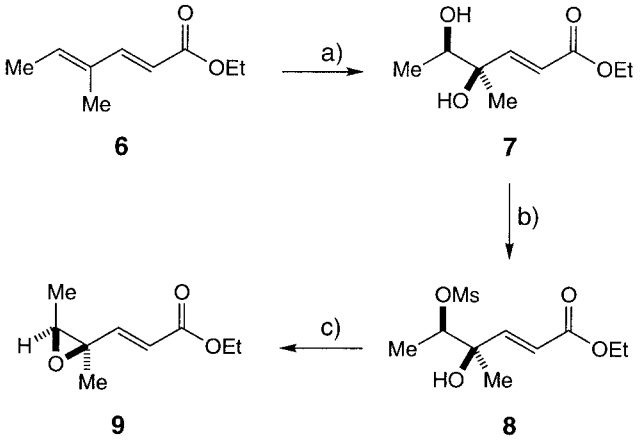
[2]) Ethyl sorbate derivative **6** was conveniently prepared from tiglic aldehyde *via* a *Horner-Wadsworth-Emmons* condensation reaction as described in [8].

[3]) The use of the pseudoenantiomer ligand, hydroquinine 1,4-phthalazinediyl diether ($(DHQ)_2$-PHAL), resulted in the opposite enantiomer, albeit in somewhat lower yield (50%) and ee (97%).

Scheme 2



a) $(DHQD)_2$-PHAL (5 mol-%), $K_2OsO_4 \cdot 2\,H_2O$ (1 mol-%), K_2CO_3 (3 equiv.), $K_3Fe(CN)_6$ (3 equiv.), $MeSO_2NH_2$ (3 equiv.), *t*-BuOH/H_2O 1:1, 0°, 48 h; 68%, >99% ee. *b*) MsCl (2 equiv.), pyridine (2 equiv.), CH_2Cl_2, 0°, 48 h; 93%. *c*) NaH (1.2 equiv.), MeCN, 0–23°, 3 h, 92%.

secondary alcohol **10** was isolated in 93% yield as a single stereoisomer, as determined by ^{1}H-NMR spectroscopy[4]). Installation of the C(35)–OH moiety could be carried out by treatment of **10** with PhCHO in the presence of *t*-BuOK (THF, 0°) to afford **11** in 82% yield [13]. This benzylidene acetal was isolated as a single diastereoisomer, as evidenced by its ^{1}H-NMR spectrum. The coupling constants ($J = 3.5$, 8.6, and 10.0 Hz) associated with the resonance corresponding to the CH proton at C(35) (δ 3.99) are consistent with the configuration shown and parallel in magnitude to those documented in the study of *Evans*. Numerous procedures have been reported for the removal of benzylidene acetals involving acidic hydrolysis (for selected examples, see [14]). Our attempts to effect hydrolysis of **11** under acidic conditions were met with only limited success, as the reactions were observed to be slow and led to the formation of unidentified by-products. After some experimentation, we found that Pd-catalyzed hydrogenolysis of the acetal group proved optimal. Thus, when **11** was subjected to hydrogenolysis, a mixture of products consisting of *ca*. 30% lactone **12** and 70% of the corresponding acyclic dihydroxy ester was isolated. Because of our interest in securing lactone **12** for subsequent elaboration, this mixture was subjected without purification to acidic conditions (2.5 mol-% F_3CCO_2H in MeCN, 23°, 12 h), whereupon lactone **12** was isolated in 92% overall yield (two steps). The final stereogenic center C(34) was incorporated by the alkylation method involving β-alkoxy lactone enolates reported by *Seebach et al.* [14c]. In the experiment, exposure of a solution (THF/hexamethylphosphoric triamide (HMPA)) of **12** to 2.5 equiv. of lithium diisopropylamide (LDA) followed by addition of excess MeI proceeded in 80% yield to give fully substituted

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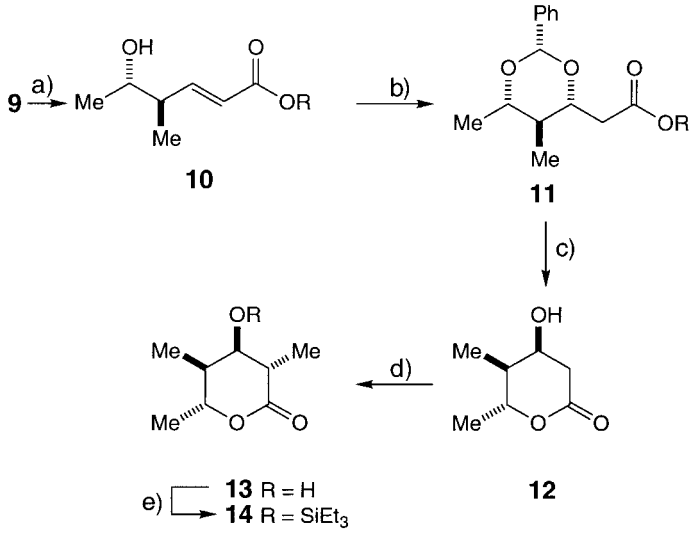
[4]) A small amount (<5%) of an unidentified contaminating by-product could be observed. Although its separation and purification from the mixture containing the principal product proved untenable, its presence did not have an adverse effect on the subsequent synthetic step, where it ceased to be a contaminant of product **10**.

lactone **13** as a single diastereoisomer as evidenced by analysis of the ^{1}H-NMR spectrum. The coupling constants associated with the resonance of the CH protons at C(34) ($J = 7.6$ and 2.6 Hz) are consistent with the configuration shown, as predicted from the extensive studies of this transformation. Following treatment of **13** with Et_3SiOTf (2,6-di-(*tert*-butyl)-4-methylpyridine, CH_2Cl_2, $-40°$, 2 h), **14** was isolated in 99% yield.

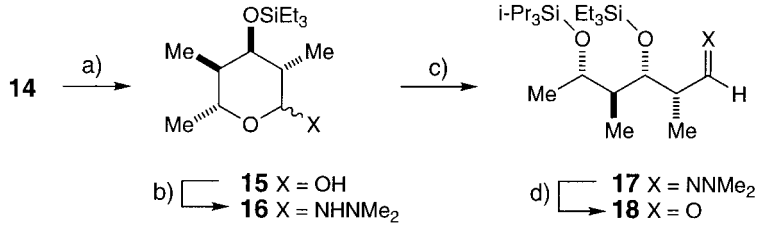
Scheme 3



a) $[Pd_2(dba)_3] \cdot CHCl_3$ (2.5 mol-%), Bu_3P, HOOH, Et_3N, THF, 23°, 3 h, 93%, >95%, de. *b*) PhCHO, *t*-BuOK, THF, 0°, 1 h; 82%. *c*) *i*) $Pd(OH)_2$, H_2 (atm), EtOH, 23°, 24 h; *ii*) TFA/MeCN (2.5%), 23°, 12 h, 92%. *d*) LDA, MeI, HMPA/THF, −78°, 16 h; 80%; >95% de. *e*) 2,6-di(*tert*-butyl)-4-methylpyridine, Et_3SiOTf ($Tf = CF_3SO_2$), CH_2Cl_2, −40°, 2 h, 99%.

Having completed the installation of the key functionality and attendant stereogenic centers of the C(33) – C(37) subunit, we proceeded to adjust the oxidation state at C(33) so as to enable the fragment to serve as a coupling partner for the polyene of amphotericin B. In this respect, reduction of lactone **14** with diisobutylaluminium hydride (DIBAL-H) gave lactol **15** in 93% yield, as a mixture of anomers (*ca.* 2:1; *Scheme 4*). This lactol proved reluctant to undergo ring opening to provide access to the corresponding aldehyde for subsequent synthetic elaboration. In this respect, highly substituted lactols have been shown to have a strong preference to remain in the cyclic form at the expense of the open acyclic isomer. Indeed, increasing substitution on the ring typically increases the preference for the cyclic lactol form [15]. To favor ring opening, **15** was first treated with *N*,*N*-dimethylhydrazine, whereupon hydrazine **16** was isolated in 92% yield. The corresponding acyclic hydrazone could only be accessed following treatment of **16** with $(i\text{-}Pr)_3SiOTf$ in pyridine (23°, 3 h). The choice of pyridine as solvent proved crucial, because, in this reaction solvent, the ring-opened form of hydrazine **16** is kinetically accessible, permitting derivatization of the liberated alcohol at C(37) as the corresponding silyl ether [16]. Ozonolytic cleavage of hydrazone **17** furnished the desired aldehyde **18** in good yield as a single isomer, without any observed accompanying epimerization at C(34).

Scheme 4



a) DIBAL-H (2 equiv.), THF, – 78°, 2 h; 93%. *b*) H_2NNMe_2 (6 equiv.), $TsOH \cdot H_2O$ (20 mol-%), EtOH, reflux, 12 h, 92%. *c*) $(i\text{-}Pr)_3SiOTf$ (3 equiv.), pyridine, 0–23°, 3 h, 92%. *d*) *i*) O_3, CH_2Cl_2, – 78°; *ii*) Me_2S, 71%.

Conclusion. – We have documented an expeditious, efficient, asymmetric synthesis of the C(33)–C(37) fragment of amphotericin B that proceeds in 14 steps and 16% overall yield from tiglic aldehyde with complete stereocontrol. In comparison to other syntheses of this fragment that have been reported, the route described herein applies recently developed methods in catalytic asymmetric synthesis to install three of the four stereogenic centers of the subunit. Moreover, by utilizing such methods, it should be possible to readily access analogs of amphotericin in preparatively useful quantities. Efforts are currently underway along these avenues, and will be reported as results become available.

Experimental Part

General. With the following exceptions, all reagents and solvents were purchased from commercial suppliers and used without further purification: *ethyl (*E,E*)-4-methylhexa-2,4-dienoate* (**6**) was synthesized according to the procedure of *Shing* and *Yang* [8]; MsCl and Bu_3P was distilled before use; pyridine and Et_3N were distilled from KOH; PhCHO was freshly distilled before use; MeI was filtered through a plug of basic alumina in order to remove acidic impurities; HMPA was freshly distilled from CaH_2; 2,6-di(*tert*-butyl)-4-methylpyridine was filtered through a plug of silica gel. Silica gel (230–400 mesh) for column chromatography (CC) as well as corresponding TLC plates were purchased from *Merck*. Unless noted otherwise, all experiments were performed under N_2 atmosphere using oven-dried glassware and dry solvents (CH_2Cl_2, MeCN, and THF were passed through a column of actived alumina). Solvents for chromatography were distilled before use. The expressions 'evaporation of solvent(s)' refer to the use of a rotatory evaporator at reduced pressure at 30°. M.p.: *Büchi 510* melting-point apparatus; uncorrected. Optical rotation: *Jasco DIP-1000* digital polarimeter. IR Spectra: *Perkin-Elmer Spectrum-RX-1 FT-IR* spectrophotometer. NMR Spectra: *Varian Mercury-300* instrument. Microanalyses were performed by Mikroelementaranalytisches Laboratorium, ETH-Zürich.

*Ethyl (*2E,4R,5R*)-4,5-Dihydroxy-4-methylhex-2-enoate* (**7**). To a suspension of $(DHQD)_2$-PHAL (0.390 g, 0.500 mmol, 5.00 mol-%), $K_3Fe(CN)_6$ (9.88 g, 30.0 mmol), K_2CO_3 (4.15 g, 30.0 mmol), $MeSO_2NH_2$ (2.85 g, 30.0 mmol), and $K_2OsO_4 \cdot 2\,H_2O$ (37 mg, 0.1 mmol, 1 mol-%) in a suspension of *t*-BuOH (50 ml) and deionized water (50 ml) at 0° was added, in one portion, *ethyl (*E,E*)-4-methylhexa-2,4-dienoate* (**6**) [8] (1.54 g, 10.0 mmol). After stirring at 0° for 48 h, the reaction was quenched by the slow, portionwise addition of Na_2SO_3 (15.2 g). The mixture was allowed to reach r.t., whereupon it was transferred to a separatory funnel with the aid of AcOEt (200 ml). Brine (100 ml) was added. The org. phase was separated, and the aq. phase was extracted further with AcOEt (3 × 50 ml). The collected org. phases were washed with brine (100 ml) before drying ($MgSO_4$). After evaporation of the solvents, the residue was purified by CC (silica gel; AcOEt/hexane 0–50%) to yield **7** (1.28 g, 6.81 mmol, 68%). A clear viscous oil. $[\alpha]_D^{24} = -6.3$ ($c = 0.98$, CH_2Cl_2). IR (neat) 3442, 2982, 1703, 1656, 1370, 1308, 1284, 1191. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.96 (*d*, *J* = 15.6, 1 H); 6.12 (*d*, *J* = 15.9, 1 H); 4.19 (*q*, *J* = 7.2, 2 H); 3.72 (*q*, *J* = 6.2, 1 H); 2.34 (*s*, OH); 2.14 (br. *d*, OH); 1.29 (*t*, *J* = 7.2, 3 H); 1.26 (*s*, 3 H); 1.18 (*d*, *J* = 6.2, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 166.7 (*s*); 152.0 (*d*); 120.7 (*d*); 75.5 (*s*); 72.6 (*d*); 60.6 (*t*); 21.8 (*q*); 16.9 (*q*); 14.2 (*q*). Anal. calc. for $C_9H_{16}O_4$: C 57.43, H 8.57; found: C 57.45, H 8.74. The ee was determined by HPLC

analysis (*Chiralcel OD-H* column, 8% i-PrOH/hexane, 0.8 ml/min, t_R 7.1 min) to be >99% by comparison with the *ent*-diol sample (t_R 9.4 min) prepared with the pseudoenantiomeric ligand $(DHQ)_2$-PHAL.

*Ethyl (2*E*,4*R*,5*R*)-4-Hydroxy-5-[(methylsulfonyl)oxy]-4-methylhex-2-enoate* (**8**). Compound **7** (1.27 g, 6.75 mmol) was dissolved in dry CH_2Cl_2 (7 ml) under N_2, and pyridine (1.07 g, 13.5 mmol) was added. Upon cooling the soln. to 0°, MsCl (1.55 g, 13.5 mmol) was added dropwise during 10 min, and the mixture was allowed to stir until the consumption of starting material was complete as judged by TLC (20% AcOEt/CH_2Cl_2), typically 48 h. The mixture was transferred to a separatory funnel with the aid of CH_2Cl_2 (90 ml), and the soln. was extracted consecutively with 1M aq. HCl (30 ml), H_2O (20 ml), and sat. aq. $NaHCO_3$ soln. (30 ml) before drying ($MgSO_4$) the org. phase. After evaporation of the solvents, the residue was purified by CC (silica gel; AcOEt/CH_2Cl_2 (0–50%) to yield **8** (1.67 g, 6.27 mmol, 93%). A clear viscous oil. $[\alpha]_D^{29} = -5.1$ ($c = 0.80$, CH_2Cl_2). IR (neat) 3502, 2987, 1716, 1351, 1176, 921. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.91 (*d*, $J = 15.6$, 1 H); 6.18 (*d*, $J = 15.9$, 1 H); 4.68 (*d*, $J = 6.2$, 1 H); 4.21 (*q*, $J = 7.2$, 2 H); 3.04 (*s*, 3 H); 2.45 (br. *s*, OH); 1.43 (*d*, $J = 6.5$, 3 H); 1.38 (*s*, 3 H); 1.30 (*t*, $J = 7.2$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 166.2 (*s*); 149.2 (*d*); 121.8 (*d*); 83.4 (*d*); 74.4 (*s*); 60.8 (*t*); 38.8 (*q*); 23.1 (*q*); 16.4 (*q*); 14.2 (*q*). Anal. calc. for $C_{10}H_{18}O_6S$: C 45.10, H 6.81; found: C 44.90, H 6.72.

*Ethyl (*E*)-3-[(2*S*,3*S*)-2,3-Dimethyloxiran-2-yl]prop-2-enoate* (**9**). NaH (190 mg, 7.50 mmol) was suspended in dry MeCN (18 ml) under N_2. The suspension was cooled to 0°, and a soln. of **8** (1.665 g, 7.50 mmol) in dry MeCN (10 ml) was added dropwise over 10 min. The flask containing methanesulfonate was rinsed with MeCN (2×2 ml). After 1 h at 0°, the ice-bath was removed, and the mixture was allowed to reach r.t. The mixture was stirred until the consumption of starting material was complete as judged by TLC (20% AcOEt/hexane), typically 3 h, whereupon the mixture was poured onto ice (60 g). Upon melting of the ice, the mixture was transferred to a separatory funnel with the aid of CH_2Cl_2 (30 ml). The org. phase was separated, and the aq. phase was extracted further with CH_2Cl_2 (3×30 ml). The collected org. phases were washed with brine (70 ml) before drying ($MgSO_4$). Evaporation of the solvents gave **9** (0.974 g, 5.72 mmol, 92%). A colorless, relatively volatile oil (avoid high vacuum). $[\alpha]_D^{24} = -80.3$ ($c = 1.06$, CH_2Cl_2). IR (neat) 2983, 1720, 1303, 1258, 1178. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.87 (*d*, $J = 15.6$, 1 H); 6.01 (*d*, $J = 15.9$, 1 H); 4.21 (*q*, $J = 7.2$, 2 H); 3.11 (*q*, $J = 5.6$, 1 H); 1.46 (*s*, 3 H); 1.30 (*t*, $J = 7.2$, 3 H); 1.25 (*d*, $J = 5.6$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 165.9 (*s*); 145.4 (*d*); 123.7 (*d*); 62.4 (*d*); 60.5 (*t*); 59.6 (*s*); 21.2 (*q*); 14.2 (*q*); 13.8 (*q*). Anal. calc. for $C_9H_{14}O_3$: C 63.51, H 8.29; found: C 63.49, H 8.28.

The reaction should not be allowed to proceed longer than necessary: a destructive process sets in when the starting material has been consumed as evidenced by coloring of the reaction mixture and a lower yield.

*Ethyl (2*E*,4*R*,5*S*)-5-Hydroxy-4-methylhex-2-enoate* (**10**). $[Pd_2(dba)_3] \cdot CHCl_3$ (148 mg, 0.143 mmol, 5 mol-% Pd) was suspended in dry THF (6 ml) under N_2. Bu_3P (54 µl, 0.215 mmol, 3.8 mol-%) was added, followed by a soln. of HCOOH (1.08 ml, 28.6 mmol) and Et_3N (1.60 ml, 11.4 mmol) in dry THF (12 ml). After 5 min, a soln. of **9** (0.974 g, 5.72 mmol) in dry THF (15 ml) was added. The flask containing the epoxide was rinsed with THF (2×1.5 ml). The intense red color of the mixture gradually faded, and a yellowish soln. was obtained. The mixture was stirred until the consumption of starting material was complete as monitored by TLC (20% AcOEt/hexane), typically 2–3 h; at this point the initial intensely red color could be observed. The reaction was quenched with H_2O (40 ml), whereupon it was transferred to a separatory funnel with the aid of AcOEt (40 ml). The org. phase was separated, and the aq. phase was extracted further with AcOEt (2×20 ml). The collected org. phases were washed with brine (which precipitates the catalyst from the org. phase) before drying ($MgSO_4$). After separation of the solvents, the residue was purified by CC (silica gel; AcOEt/hexane 0–50%), to yield **10** (0.909 g, 5.28 mmol, 92%). A colorless oil. $[\alpha]_D^{29} = +31.2$ ($c = 1.39$, CH_2Cl_2). IR (neat) 3441, 2976, 1719, 1702, 1651, 1274, 1187. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.93 (*d*, $J = 15.9$, 8.4, 1 H); 5.87 (*dd*, $J = 15.6$, 1.1, 1 H); 4.19 (*q*, $J = 7.2$, 2 H); 3.74 (*dq*, $J = 6.2$, 6.2, 1 H); 2.34 (*m*, 1 H); 1.91 (br. *s*, OH); 1.29 (*t*, $J = 7.2$, 3 H); 1.19 (*d*, $J = 6.2$, 3 H); 1.08 (*d*, $J = 6.9$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 166.6 (*s*); 150.5 (*d*); 122.2 (*d*); 70.7 (*d*); 60.4 (*t*); 44.1 (*d*); 20.6 (*q*); 15.4 (*q*); 14.2 (*q*). Anal. calc. for $C_9H_{16}O_3$: C 62.77, H 9.36; found: C 62.67, H 9.34.

*Ethyl 2-[(4*S*,5*R*,6*R*)-5,6-Dimethyl-2-phenyl-1,3-dioxan-4-yl]acetate* (**11**). Compound **10** (0.889 g, 5.16 mmol) was dissolved in dry THF (50 ml) under N_2. Upon cooling to 0°, PhCHO (0.59 ml, 5.8 mmol) was added, followed by *t*-BuOK (59 mg, 0.53 mmol). The now yellow soln. was stirred for 20 min., whereupon another portion of PhCHO and *t*-BuOK was added. After further 20 min, a last portion of PhCHO and *t*-BuOK was added, and, 20 min after the last addition, the reaction was quenched with a sat., aq. NH_4Cl soln. (50 ml). Upon warming to r.t., the mixture was transferred to a separatory funnel with the aid of AcOEt. The org. phase was separated, and the aq. phase was extracted further with AcOEt (3×25 ml). The collected org. phases were washed with brine before drying ($MgSO_4$). After evaporation of the solvents, the residue was purified by CC (silica gel; AcOEt/hexane 0–12%) to yield **11** (1.18 g, 4.24 mmol, 82%). A colorless, nice-smelling oil. $[\alpha]_D^{29} =$

+63.6 ($c = 1.21$, CH_2Cl_2). IR (neat) 2978, 1737, 1182, 1144, 1029. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.50–7.45 (*m*, 2 H); 7.38–7.28 (*m*, 3 H); 5.60 (*s*, 1 H); 4.17 (*q*, $J = 7.2$, 2 H); 3.99 (*ddd*, $J = 3.5, 8.6, 10.0$, 1 H); 3.62 (*dq*, $J = 9.6, 6.2$, 1 H); 2.70 (*dd*, $J = 3.6, 15.4$, 1 H); 2.55 (*dd*, $J = 8.2, 15.5$, 1 H); 1.57–1.43 (*m*, 1 H); 1.34 (*d*, $J = 5.9$, 3 H); 1.26 (*t*, $J = 7.2$, 3 H); 0.87 (*d*, $J = 6.9$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 171.4 (*s*); 138.5 (*s*); 128.6 (*d*); 128.1 (*d*); 126.1 (*d*); 100.2 (*d*); 78.9 (*d*); 78.4 (*d*); 60.6 (*t*); 40.6 (*d*); 39.0 (*t*); 19.4 (*q*); 14.2 (*q*); 12.4 (*q*). Anal. calc. for $C_{16}H_{22}O_4$: C 69.04, H 7.97; found: C 68.94, H 7.81.

*(4*S*,5*S*,6*S*)-3,4,5,6-Tetrahydro-4-hydroxy-5,6-dimethyl-2*H*-pyran-2-one* (**12**). Compound **11** (0.609 g, 2.19 mmol) was dissolved in abs. EtOH (22 ml), and $Pd(OH)_2$ (20% on C; 0.233 g, 0.219 mmol) was added. H_2 was bubbled through the suspension for 5 min, whereupon the system was kept under an H_2 atmosphere. After *ca.* 8 h and 16 h H_2, was again bubbled through the suspension during a few min. in order to reactivate the catalyst. After a total of 24 h under H_2 atmosphere, N_2 was bubbled through the suspension in order to deactivate the catalyst before it was filtered off through a pad of *Celite*. The filter cake was thoroughly washed with EtOH. After evaporation of the solvent, the crude product was redissolved in MeCN (20 ml) and cooled to 0°. CF_3COOH (0.50 ml) was added dropwise over 5 min., whereupon the ice-bath was removed. After stirring for 12 h at amb. temp., silica gel (3 g) was added, and the solvents were evaporated. The impregnated silica gel was put on top of a column packed with silica gel, and the product was eluted with AcOEt/CH_2Cl_2 0–70%: **12** (0.295 g, 2.05 mmol, 93%). A flaky, white solid. M.p. 95–96°. $[\alpha]_D^{24} = -29.0$ ($c = 0.89$, CH_2Cl_2). IR (KBr) 3549, 3413, 2985, 2903, 1690, 1638, 1618, 1238, 1048. ^{1}H-NMR ($CDCl_3$, 300 MHz): 4.52 (*dq*, $J = 10.4, 6.4$, 1 H); 4.07–4.04 (*m*, 1 H); 2.71–2.68 (*m*, 2 H); 2.20 (br. *s*, OH); 1.71 (*ddq*, $J = 10.3, 2.2, 6.8$, 1 H); 1.37 (*d*, $J = 6.5$, 3 H); 1.07 (*d*, $J = 6.8$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 170.8 (*s*); 77.3 (*d*); 67.6 (*d*); 39.5 (*t*); 39.2 (*d*); 19.9 (*q*); 13.6 (*q*). Anal. calc. for $C_7H_{12}O_3$: C 58.32, H 8.39; found: C 58.34, H 8.43.

*(3*R*,4*R*,5*S*,6*S*)-3,4,5,6-Tetrahydro-4-hydroxy-3,5,6-trimethyl-2*H*-pyran-2-one* (**13**). A soln. of LDA was prepared from (i-Pr)$_2$NH (1.06 ml, 7.6 mmol) and BuLi (2.1M in hexane; 3.6 ml, 7.6 mmol) in dry THF (10 ml) at −60°. A soln. of **12** (0.448 g, 3.11 mmol) in dry THF (10 ml) and HMPA (3.8 ml) was added dropwise during 50 min; the flask containing the lactone was rinsed with dry THF (3.5 + 3 ml). After stirring at −60° for 1.5 h, the mixture was cooled in an dry ice-EtOH bath and BuLi (2.1M in hexane; 3.0 ml, 6.2 mmol) was added dropwise during 20 min. After stirring for further 45 min, MeI (2.65 g, 18.7 mmol) was added in one portion. After 16 h, the reaction was quenched dropwise (5 min) with a soln. of AcOH (0.83 ml, 14.5 mmol) in dry THF (4 ml), rinsing with dry THF (2 × 0.5 ml). After 30 min., the temp. was increased to −20°, and H_2O (25 ml) was added. After 30 min., the cooling bath was removed, and the mixture was allowed to reach amb. temp. and transferred to a separatory funnel with the aid of CH_2Cl_2 (50 ml). The org. phase was separated, and the aq. phase was extracted further with CH_2Cl_2 (3 × 25 ml). The collected org. phases were dried ($MgSO_4$). After evaporation of the solvents, the residue was purified by CC (silica gel; Et_2O/hexane 0–100%) to yield **13** (0.394 g, 2.49 mmol, 80%). White, shiny crystals. M.p. 117–118°. $[\alpha]_D^{29} = -28.8$ ($c = 0.93$, CH_2Cl_2). IR (KBr) 3394, 2981, 1696, 1390, 1240, 1099. ^{1}H-NMR ($CDCl_3$, 300 MHz): 4.46 (*dq*, $J = 9.9, 6.4$, 1 H); 3.72–3.70 (*m*, 1 H); 2.67 (*dq*, $J = 3.9, 7.4$, 1 H); 2.37 (br. *s*, OH); 1.88–1.76 (*m*, 1 H); 1.35 (*d*, $J = 6.5$, 3 H); 1.30 (*d*, $J = 7.5$, 3 H); 1.05 (*d*, $J = 7.2$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 174.5 (*s*); 76.8 (*d*); 73.2 (*d*); 43.5 (*d*); 37.2 (*d*); 19.6 (*q*); 15.9 (*q*); 12.6 (*q*). Anal. calc. for $C_8H_{14}O_3$: C 60.74, H 8.92; found: C 60.71, H 8.99.

*(3*R*,4*R*,5*R*,6*S*)-3,4,5,6-Tetrahydro-3,5,6-trimethyl-4-(triethylsilyloxy)-2*H*-pyran-2-one* (**14**). Compound **13** (0.396 g, 2.50 mmol) was dissolved in dry CH_2Cl_2 (12 ml) under N_2. Upon cooling to −40°, 2,6-di(*tert*-butyl)-4-methylpyridine (1.03 g, 5.00 mmol) was added, followed by the dropwise (5 min) addition of Et_3SiOTf (0.71 ml, 3.1 mmol). The mixture was stirred until the consumption of starting material was complete as judged by TLC (20% AcOEt/hexane), typically 2 h, whereupon the reaction was quenched by the addition of H_2O (10 ml). After allowing the mixture to reach r.t., it was transferred to a separatory funnel with the aid of CH_2Cl_2 (100 ml) and extracted consecutively with aq. 1M HCl (2 × 30 ml), H_2O (30 ml), and sat., aq. $NaHCO_3$ soln. (50 ml) before it was dried ($MgSO_4$). After evaporaton of the solvents, the residue was purified by CC (silica gel; AcOEt/hexane 0–25%) to yield **14** (0.673 g, 2.47 mmol, 99%). A viscous, colorless oil, which solidified upon standing to white shiny crystals. M.p. 56–57°. $[\alpha]_D^{29} = +1.0$ ($c = 0.94$, CH_2Cl_2). IR (KBr) 3549, 3476, 3401, 2979, 2954, 2878, 1725, 1236, 1100, 1054. ^{1}H-NMR ($CDCl_3$, 300 MHz): 4.46 (*dq*, $J = 10.0, 6.5$, 1 H); 3.66 (*dd*, $J = 2.5, 2.5$, 1 H); 2.64 (*dq*, $J = 2.6, 7.6$, 1 H); 1.79 (*m*, 1 H); 1.34 (*d*, $J = 6.5$, 3 H); 1.27 (*d*, $J = 7.5$, 3 H); 0.99 (*d*, $J = 6.8$, 3 H); 0.95 (*t*, $J = 7.9$, 9 H); 0.61 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 174.4 (*s*); 77.3 (*d*); 74.5 (*d*); 44.3 (*d*); 36.1 (*d*); 19.8 (*q*); 16.6 (*q*); 13.8 (*q*); 6.8 (*q*); 4.9 (*t*). Anal. calc. for $C_{14}H_{28}O_3Si$: C 61.72, H 10.36; found: C 61.73, H 10.25.

*(3*R*,4*R*,5*R*,6*S*)-3,4,5,6-Tetrahydro-3,5,6-trimethyl-4-(triethylsilyloxy)-2*H*-pyran-2-ol* (**15**). Compound **14** (0.673 g, 2.47 mmol) was dissolved in dry THF (12 ml) under N_2. Upon cooling the soln. in a dry ice-EtOH bath, DIBAL-H (1.0M in THF, 5.0 ml, 5.0 mmol) was added dropwise over 15 min. After 2 h, the consumption of

starting material was complete as judged by TLC (5% AcOEt/CH_2Cl_2), and the reaction was quenched with a sat., aq. solution of *Rochelle*'s salt (1 ml); an additional 20 ml was added after the initial quench. Upon reaching r.t., the mixture was stirred vigorously overnight, whereupon it was transferred to a separatory funnel with the aid of AcOEt (40 ml). The org. phase was separated, and the aq. phase was extracted further with AcOEt (3 × 25 ml); the collected org. phases were dried ($MgSO_4$). Upon evaporation of the solvents, the residue was purified by CC (silica gel; AcOEt/hexane 0–25%) to yield **15** (0.633 g, 2.31 mmol, 93%), as a mixture of anomers (*ca.* 2:1). A viscous, colorless oil. $[\alpha]_D^{28} = -8.6$ ($c = 1.03$, CH_2Cl_2). IR (neat) 3488, 2960, 2911, 2878, 1459, 1070, 1052, 1034, 1004. ^{1}H-NMR ($CDCl_3$, 300 MHz): 5.55 (*d*, *J* = 10.6, 0.8 H); 5.19 (*dd*, *J* = 6.7, 2.3, 0.2 H); 4.85 (*d*, *J* = 10.9, 0.8 H); 3.95 (*m*, 0.8 H); 3.73–3.61 (*m*, 1.2 H); 2.72 (*d*, *J* = 6.5, 0.2 H); 2.13–1.89 (*m*, 1 H); 1.75–1.48 (*m*, 1 H); 1.20 (*d*, *J* = 6.2, 2.4 H); 1.17 (*d*, *J* = 6.2, 0.6 H); 1.11–0.91 (*m*, 12 H); 0.87 (*d*, *J* = 6.8, 2.4 H); 0.81 (*d*, *J* = 6.8, 0.6 H); 0.71–0.55 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 96.8 (*d*); 93.6 (*d*); 76.6 (*d*); 76.5 (*d*); 72.0 (*d*); 64.5 (*d*); 41.6 (*d*); 40.0 (*d*); 36.4 (*d*); 36.0 (*d*); 19.3 (*q*); 19.3 (*q*); 15.0 (*q*); 14.6 (*q*); 13.7 (*q*); 9.0 (*q*); 6.9 (*q*); 6.8 (*q*); 5.0 (*t*); 4.8 (*t*). Anal. calc. for $C_{14}H_{30}O_3Si$: C 61.26, H 11.02; found: C 61.07, H 10.90.

*(3*R*,4*R*,5*R*,6*S*)-3,4,5,6-Tetrahydro-2-(2,2-dimethylhydrazino)-3,5,6-trimethyl-4-(triethylsilyloxy)-2*H*-pyran* (**16**). Compound **15** (0.633 g, 2.31 mmol) was dissolved in abs. EtOH (17 ml). *N,N*-dimethylhydrazine (1.05 ml, 13.8 mmol) was added, followed by $TsOH \cdot H_2O$ (88 mg, 0.46 mmol, 20 mol-%), and the mixture was heated to reflux under N_2. After 12 h at reflux, the mixture was allowed to cool, and, upon reaching r.t. silica gel (4 g) was added, and the solvents were evaporated. The impregnated silica gel was put on top of a column packed with silica gel, and the products were eluted with Et_2O/hexane 0–50%. Apart from **16** (0.622 g, 1.96 mmol, 85%), which was obtained as a faintly yellow oil, also some starting material **15** (50 mg, 0.18 mmol, 7.9%) could be recovered for recycling; this raised the effective yield to 92%. Longer reaction times led to diminished yields and the appearance of by-products. $[\alpha]_D^{29} = -26.7$ ($c = 1.32$, CH_2Cl_2). IR (neat) 2957, 2906, 2878, 2806, 2765, 1072, 1042. ^{1}H-NMR ($CDCl_3$, 300 MHz): 4.76 (*d*, *J* = 2.5, 0.78 H); 4.45 (br. *s*, 0.22 H); 3.80–3.44 (*m*, 2 H); 2.51 (*s*, 4.68 H); 2.46 (*s*, 1.32 H); 1.92–1.66 (*m*, 1 H); 1.66–1.30 (*m*, 1 H); 1.20–0.70 (*m*, 18 H); 0.70–0.50 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz); major isomer: 86.9 (*d*); 76.9 (*d*); 71.9 (*d*); 50.1 (*q*); 40.7 (*d*); 36.8 (*d*); 19.6 (*q*); 13.9 (*q*); 10.2 (*q*); 7.0 (*q*); 5.0 (*t*); minor isomer: 90.4 (*d*); 75.2 (*d*); 63.7 (*d*); 50.0 (*q*), 39.0 (*d*), 36.4 (*d*); 19.1 (*q*); 16.6 (*q*); 14.4 (*q*); 7.0 (*q*); 4.9 (*t*). Anal. calc. for $C_{16}H_{36}N_2O_2Si$: C 60.71, H 11.46, N 8.85; found: C 60.80, H 11.51, N 8.86.

*(2*R*,3*S*,4*R*,5*R*)-2,4-Dimethyl-3-(triethylsilyloxy)-5-(triisopropylsilyloxy)hexanal Dimethylhydrazone* (**17**). Compound **16** (120 mg, 0.379 mmol) was cooled to 0° under N_2. Dry pyridine (3.6 ml) was added, and, after allowing some time for recooling, $(i\text{-}Pr)_3SiOTf$ (0.31 ml, 0.38 mmol) was added dropwise over 5 min. After stirring at 0° for 1 h, the ice-bath was removed and the stirring continued until the consumption of starting material was complete as judged by TLC (10% AcOEt/hexane, 50% AcOEt/hexane), typically 3 h. The mixture was transferred to a bigger flask with the aid of CH_2Cl_2, and silica gel (1 g) and cyclohexane (60 ml) were added. After evaporation of the solvents, the impregnated silica gel was put on top of a pre-packed column, and the product was eluted with an AcOEt/hexane gradient (0–10%). The product co-eluted to some extent with $(i\text{-}Pr)_3SiOH$, but subjecting the product to heat (60°) under high vacuum left pure **17** (167 mg, 0.353 mmol, 93%). Colorless oil. $[\alpha]_D^{29} = -16.1$ ($c = 1.57$, CH_2Cl_2). IR (neat) 2958, 2868, 1109, 1095, 1012. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.59 (*d*, *J* = 5.9, 1 H); 4.22 (*dq*, *J* = 3.7, 6.2, 1 H); 3.61 (*dd*, *J* = 2.5, 9.0, 1 H); 2.74 (*s*, 6 H); 2.64–2.40 (*m*, 1 H); 2.00–1.85 (*m*, 1 H); 1.14–1.00 (*m*, 27 H); 0.95 (*t*, *J* = 7.9, 9 H); 0.83 (*d*, *J* = 6.9, 3 H); 0.66–0.50 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 142.0 (*d*); 77.4 (*d*); 67.6 (*d*); 43.8 (*d*); 43.2 (*q*); 40.3 (*d*); 18.2 (*d*); 17.6 (*q*); 12.4 (*q*); 11.8 (*q*); 9.4 (*q*); 7.1 (*q*); 5.6 (*t*). Anal. calc. for $C_{25}H_{56}N_2O_2Si_2$: C 63.50, H 11.94, N 5.92; found: C 63.56, H 11.93, N 5.80.

*(2*S*,3*R*,4*S*,5*R*)-2,4-Dimethyl-3-(triethylsilyloxy)-5-(triisopropylsilyloxy)hexanal* (**18**). Compound **17** (167 mg, 0.353 mmol) was dissolved in dry CH_2Cl_2 (10 ml) under N_2, and the soln. was cooled in a dry ice-EtOH bath to −72°. The mixture was ozonolyzed, until the soln. adopted a blueish color, whereupon N_2 was bubbled through the soln. during 20 min. Me_2S (0.60 ml) was added dropwise during 10 min, and the mixture was allowed to slowly reach r.t. After stirring overnight, silica gel (0.5 g) was added, and the solvents were evaporated. The impregnated silica gel was put on top of a pre-packed column, and the product was eluted with CH_2Cl_2/hexane 0–50%: **18** (101 mg, 0.251 mmol, 71%). A colorless oil. $[\alpha]_D^{24} = -22.6$ ($c = 1.01$, CH_2Cl_2). IR (neat) 2944, 2868, 1733, 1464, 1100, 1029, 1014. ^{1}H-NMR ($CDCl_3$, 300 MHz): 9.74 (*s*, 1 H); 4.30–4.00 (*m*, 2 H); 2.49 (*dq*, *J* = 1.9, 7.0, 1 H); 1.99–1.87 (*m*, 1 H); 1.16–1.00 (*m*, 27 H); 0.92 (*t*, *J* = 7.9, 9 H); 0.83 (*d*, *J* = 6.9, 3 H); 0.62–0.48 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 205.4 (*d*); 72.8 (*d*); 67.7 (*d*); 50.4 (*d*); 44.3 (*d*); 18.1 (*q*); 17.9 (*q*); 12.5 (*d*); 9.7 (*q*); 7.0 (*q*); 6.8 (*q*); 5.4 (*t*). Anal. calc. for $C_{23}H_{50}O_3Si_2$: C 64.12, H 11.70; found: C 64.29, H 11.79.

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