Synthesis of Pederic Acid and Related Model Studies

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{[2-(Trimethylsilyl)ethoxy]methyl} (SEM)-protected pederic acid **16** was prepared by deriving the stereogenic center at C(7) from mannitol and those at C(2) and C(3) (mycalamide numbering) from *trans*-2,3-dimethyloxirane. Routes to pederamides involving a late oxygenation at C(7) were explored.

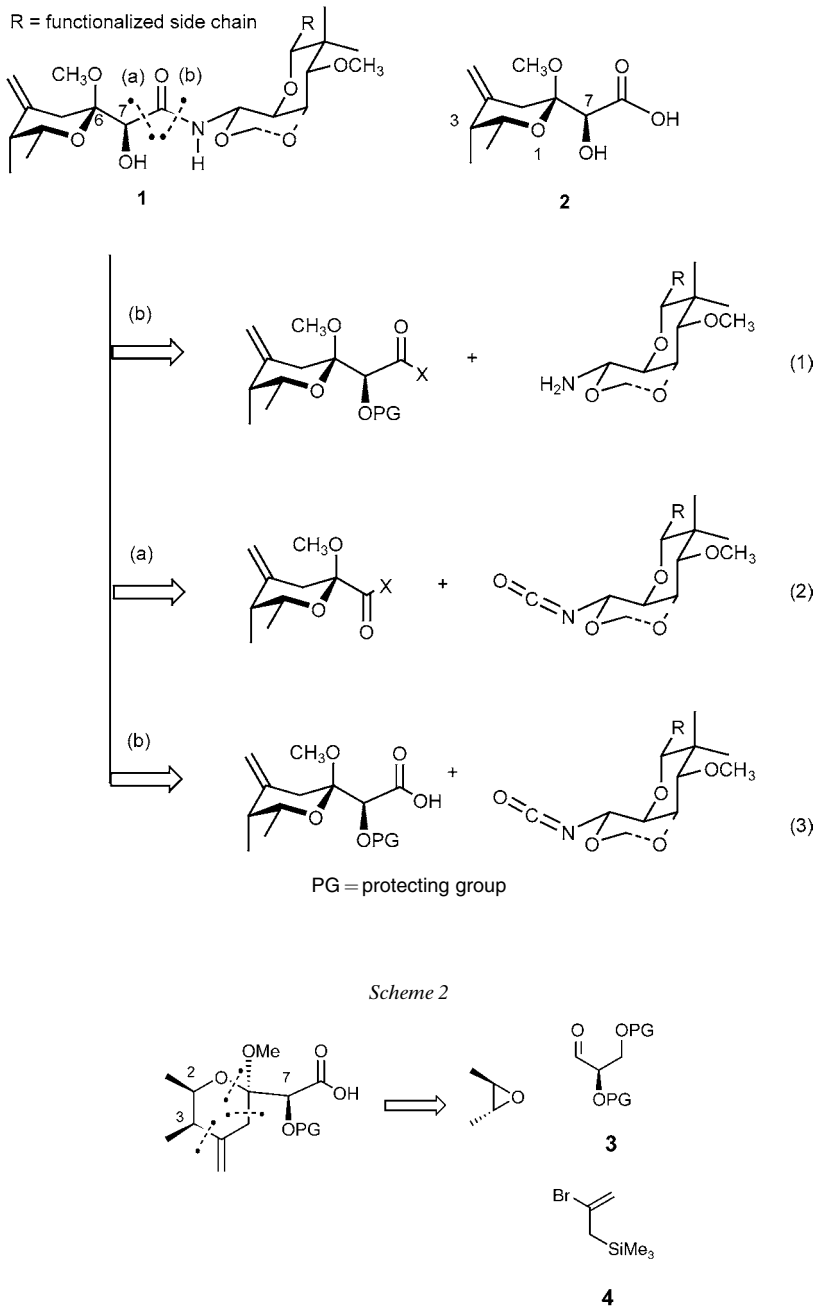
Introduction. – The pederins [1], theopederins [2], mycalamides [3], and onnamides [4] are all amides of type **1** of pederic acid (=(α*S*,2*R*,5*R*,6*R*)-tetrahydro-α-hydroxy-2-methoxy-5,6-dimethyl-4-methylene-2*H*-pyran-2-acetic acid; **2**). In previous syntheses (mycalamides [5][6], pederin [7–10]) of members of these classes of compounds, the two parts of the target molecules were joined by formation of the amide bond *b* (*cf. Eqn. 1* in *Scheme 1*). We were interested in a different approach [11], in which bond *a* is formed, requiring the right-hand building block to carry an isocyanate function. The polarity of this functional group was to be reversed by transformation to a lithiated carbamate, which should then be coupled with a norpederic acid derivative (*cf. Eqn. 2*). While this approach worked fine with model isocyanates [11], it failed when applied to a more elaborate isocyanate [12] that would have led to a fully functionalized mycalamide. In continuing our efforts, we wanted nevertheless to retain the approach *via* an isocyanate and considered forming bond *b* by a decarboxylative coupling of a protected pederic acid to isocyanates (*cf. Eqn. 3*) [13]. To apply this reaction to a synthesis of pederin or the mycalamides, we needed a reliable route to suitable protected pederic acid derivatives.

Several syntheses of pederic acid and derivatives have been reported over the last 25 years [7][14–19]. Except for two syntheses [18][19], establishment of the stereogenic center at C(7) (mycalamide numbering) required extra steps, such as oxidation to a ketone and reduction with variable stereoselectivity. Therefore, we opted to derive this stereogenic center from a chiral building block. Second, the previously used [15–17] import of the stereogenic centers at C(2) and C(3) (mycalamide numbering) from enantiomerically pure *trans*-2,3-dimethyloxirane appeared highly advantageous. This led us to the synthons *trans*-2,3-dimethyloxirane, **3**, and **4** (*Scheme 2*).

We describe in the following a synthesis of the SEM-protected pederic acid **16** along these lines (SEM = [2-(trimethylsilyl)ethoxy]methyl).

Synthesis of Pederic Acid from Chiral Precursors. – The glyceraldehyde building block **3** was prepared from 1,3:4,6-di-*O*-benzylidene-D-mannitol (**5**) [20] (*Scheme 3*). SEM Protection led to **6** in 92–99% yield, hydrogenation of which gave the tetrol **7** (98%). The primary-alcohol functions were protected as (*tert*-butyl)dimethylsilyl

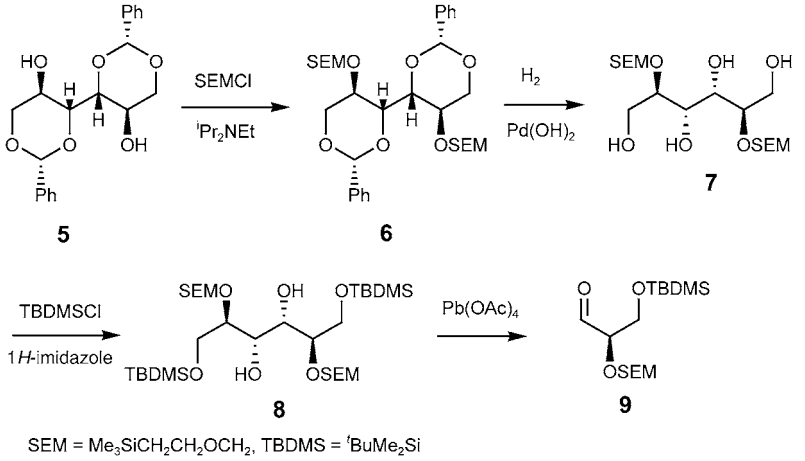
Scheme 1



Scheme 2

(TBDMS) ethers to give **8** (99%). Diol **8** was then cleaved by lead tetraacetate to give aldehyde **9**. In view of its tendency to racemize, the aldehyde was not purified but used as obtained.

Scheme 3



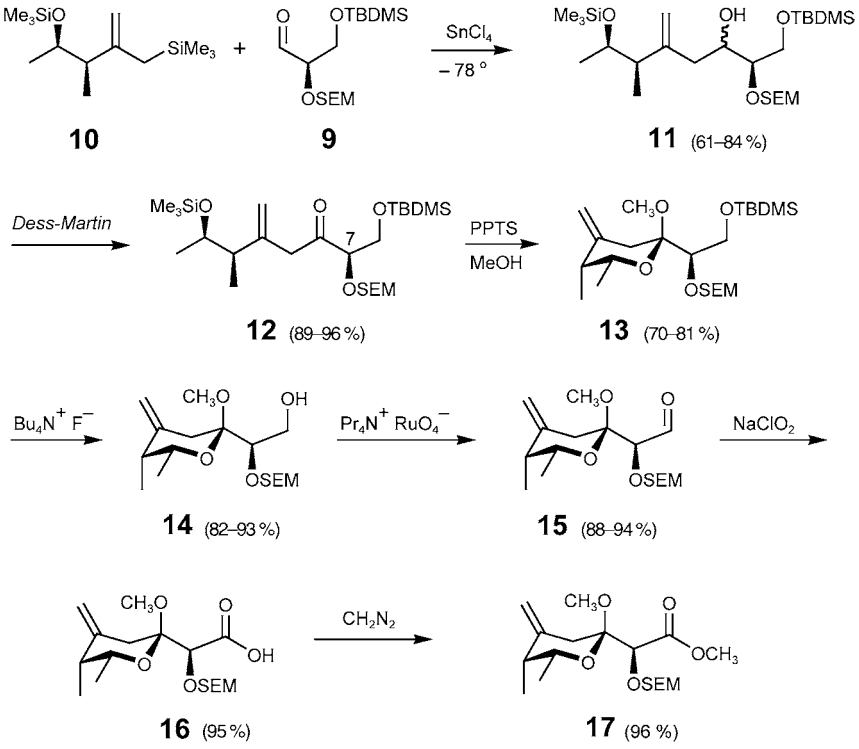
SEM = $Me_3SiCH_2CH_2OCH_2$, TBDMS = $^{t}BuMe_2Si$

The other building block, **10** (*Scheme 4*), was prepared [11] from *trans*-2,3-dimethyloxirane and **4** according to the *Kocienski* protocol [17]. In our hands, the $SnCl_4$-mediated reaction of **10** with aldehyde **9** turned out to be capricious in that variable amounts of a by-product arose, probably the product of an ene reaction [21]. The reaction became well-behaved when conditions were chosen that initiated the transmetallation of the allylsilane to an allyltrichlorostannane (*i.e.*, premixing of the allylsilane with $SnCl_4$) [22]. This way, the adduct **11** was obtained in 61–84% yield. One diastereoisomer at the new stereogenic center predominated by 10:1, but this was irrelevant because this stereogenic centre was given up in the next step by *Dess–Martin* oxidation [23] to ketone **12**. With ketone **12** in hand, the tetrahydro-2*H*-pyran ring was closed by pyridinium toluenesulfonate (PPTS) catalyzed acetalization to give **13**. This reaction had a bonus effect: Frequently, the starting ketone **12** was contaminated by small amounts of the 7-epimer due to partial racemization of **9**. This epimeric ketone did not form an acetal under these conditions and could be removed at this stage. Thus, the diastereoisomerically pure product **13** was obtained. To elaborate C(8) to a carboxylic acid, the TBDMS group was cleaved by the action of Bu_4NF. *Ley* oxidation [24] of the resulting primary alcohol **14** led to aldehyde **15**. To avoid epimerization of **15**, the latter was subjected as obtained to *Pinnick* oxidation in the *Smith* variant [25]. The resulting acid **16** is 'acid labile' [17][18] and not stable on storage, but it could be characterized as the methyl ester **17**.

The protected pederic acid **16** could, as expected, readily be coupled [13] with the model isocyanate **18** [11] (→**19**), but similar coupling with an isocyanate **20** [12] corresponding to the right half of mycalamide B failed (*Scheme 5*).

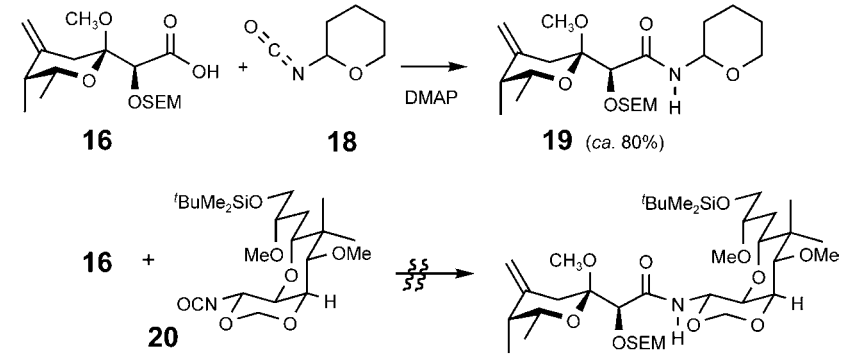
Difficulties in forming an amide bond in this series (bond *b*, *Scheme 1*) had been noted by others [6][10] and ascribed to the highly crowded situation around the reaction center. In the past, this has forced previous workers to adopt approaches in

Scheme 4



SEM = $Me_3SiCH_2CH_2OCH_2$, TBDMS = $^tBuMe_2Si$

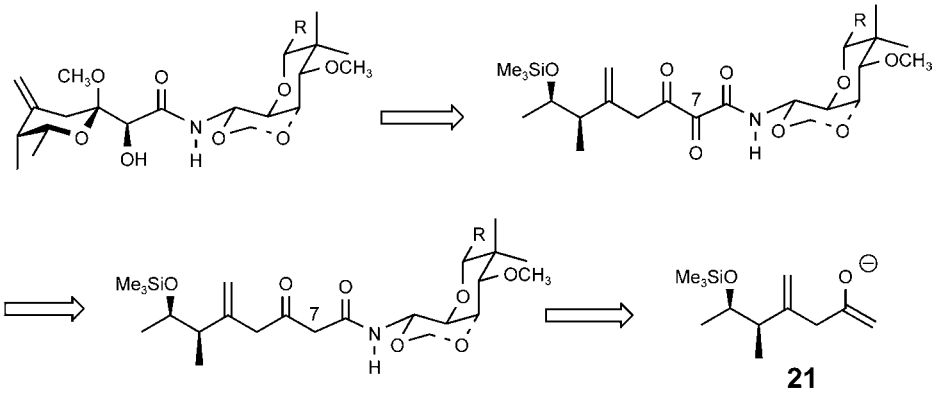
Scheme 5



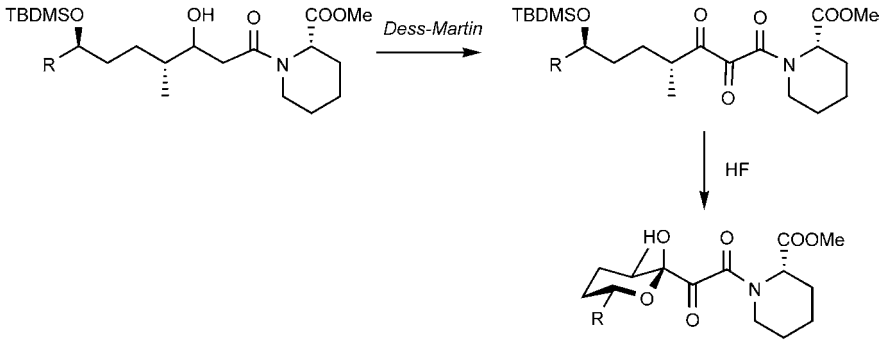
which C(8) and C(7) were attached first to the right-hand part *via* an amide bond, followed by subsequent elaboration of the pederic acid moiety [6][8].

Other Approaches to Pederic Acid. – While the above described synthesis of the protected pederic acid **16** is high yielding and viable, it is rather pedestrian given the many protective-group interconversions involved. For this reason, we started to evaluate other approaches to pederic acid, *e.g.*, those that would introduce the oxygenation at C(7) late in the synthesis sequence. This would also reduce the steric congestion around the amide bond if we were to attach a slimmed-down pederic acid core to the isocyanate prior to complete elaboration of the pederic acid part. This led us to explore the *retro*-synthesis given in *Scheme 6*. This plan was inspired by a sequence of steps in the synthesis of rapamycin by *Smith* and co-workers [26] (see *Scheme 7*). To evaluate this route, we focussed on the generation of the enolate **21**. Obviously it cannot be generated from the methyl ketone by deprotonation, as this would lead to the conjugated enolate.

Scheme 6

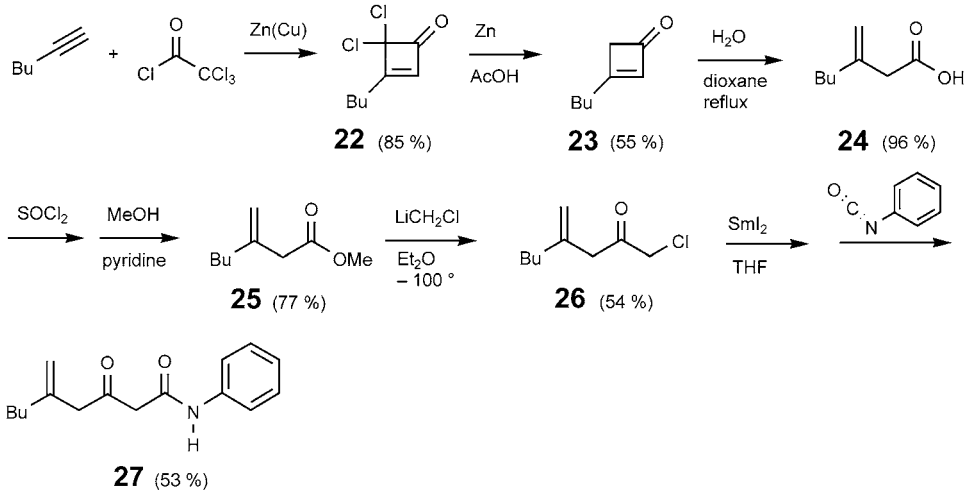


Scheme 7



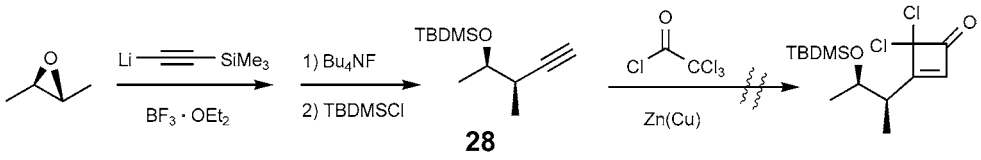
We, therefore, envisaged a Cl-atom (*cf.* **26**) as the locator for the enolate double bond to be generated. The viability of this approach was tested in the following model series (see *Scheme 8*). The dichlorocyclobutenone **22** and, in turn, the cyclobutenone **23** were generated by standard procedures [27][28]. The ring opening to the carboxylic acid **24** could be performed in a noncatalyzed fashion [29] by simply heating **23** to reflux in aqueous dioxane. The acid **24** was converted to the methyl ester **25**. Reaction of the latter with chloromethyllithium [30] led to the desired **26** (we did not probe whether this α-chloro ketone could also be obtained [31] by addition of chloromethyllithium to the cyclobutenone **23**). The α-chloro ketone **26** was then subjected to SmI_2-mediated enolate formation [32], followed by *in situ* coupling to phenyl isocyanate to give **27**.

Scheme 8



Encouraged by these results, we turned to alkyne **28** (*Scheme 9*). Though it was readily prepared, we were unable to effect the addition of dichloroketene to this alkyne. This is the more disturbing as a successful addition of dichloroketene to the probably more hindered (*tert*-butyl)acetylene has been reported [33].

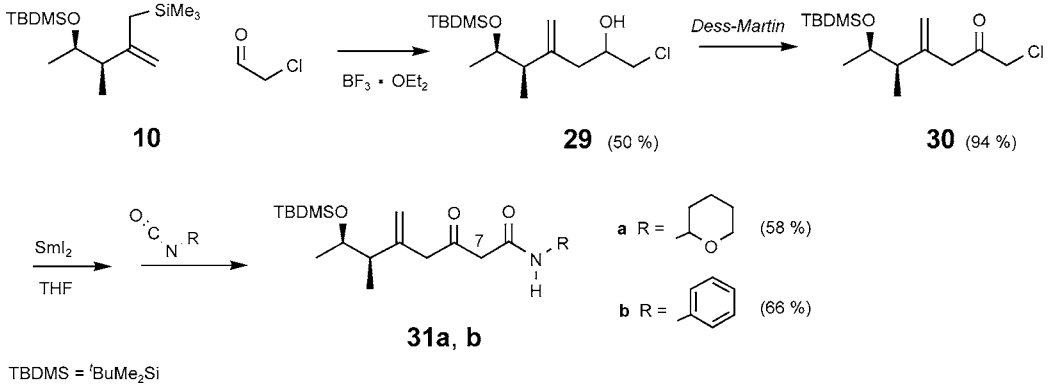
Scheme 9



TBDMS = ^{t}BuMe$_2$Si

We then used another option to access the desired α-chloro ketone **30** (*Scheme 10*). To this end, the allylsilane **10** was allowed to react with freshly generated [34] chloroacetaldehyde. The resulting chlorohydrin **29** could be oxidized to α-chloro ketone **30** without isomerization of the C=C bond. As before, SmI_2-mediated enolate

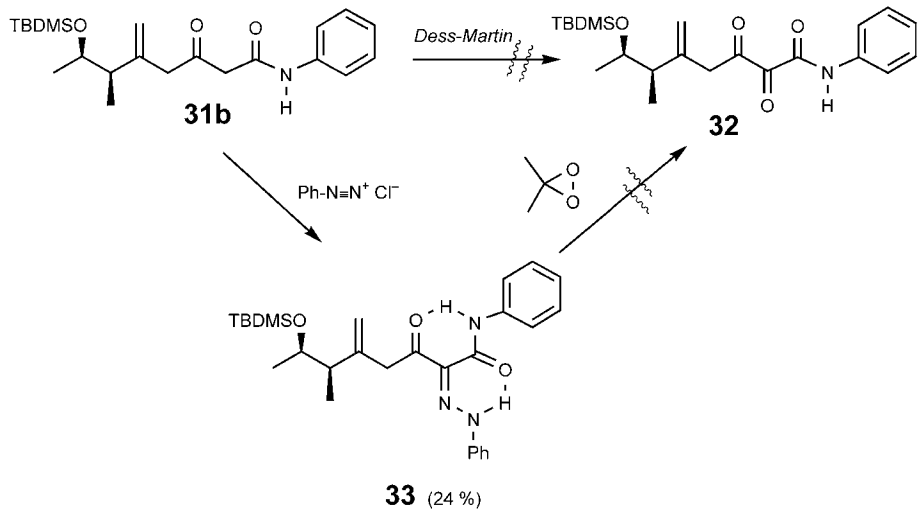
Scheme 10



formation coupled with *in situ* trapping by isocyanates gave the ketoamides **31** in acceptable yields.

We then focussed on the oxygenation at C(7) of **31** (*Scheme 11*). We were disappointed that the *Dess-Martin* oxidation of **31b** did not provide the expected [26] vicinal tricarbonyl compound **32** despite varied attempts. We then embarked on a slight detour by generating the phenylhydrazone **33** from **31b** by coupling with phenyldiazonium chloride. Attempts of oxidative cleavage [35] of **33**, be it with sodium periodate, hydroxyl-tosyloxy-iodobenzene (*Kosers* reagent), or dimethyldioxirane, did, however, not lead to the desired vicinal tricarbonyl compound **32**.

Scheme 11



Thus, what was planned as a quick foray to reach pederic acid turned out to develop into a siege, for which we no longer had the time nor resources. We, thus, concluded our efforts having secured the above described route to the protected pederic acid **16** from D-mannitol and *trans*-2,3-dimethyloxirane.

We would like to thank the *Deutsche Forschungsgemeinschaft* for support of this study. We are grateful to the *Fonds der Chemischen Industrie* for granting a *Kekulé Fellowship* to *A. C. S.* Finally, special thanks go to the *Alexander v. Humboldt Foundation* for a fellowship to *M. K.*

Experimental Part

General. Boiling range of petroleum ether 40–60°. pH 7 Buffer: $NaH_2PO_4 \cdot 2\ H_2O$ (56.2 g) and $Na_2HPO_4 \cdot 4\ H_2O$ (213.6 g) filled up to 1 l with H_2O. All quoted temp. are uncorrected. Flash chromatography (FC): silica gel *SI 60* (40–63 μm), *E. Merck KGaA*, Darmstadt. NMR Spectra: *Bruker ARX-200*, *AC-300*, *WH-400*, *AMX-500*; δ in ppm rel. to Me_4Si, *J* in Hz.

1. *1,3:4,6-Di*-O-*benzylidene-2,5-bis*-O-*{[2-(trimethylsilyl)ethoxy]methyl}*-D-*mannitol* (**6**). $^iPr_2NEt$ (2.35 ml, 13.2 mol) was added to a suspension of 1,3:4,6-di-*O*-benzylidene-D-mannitol (**5**) [20] (790 mg, 2.20 mmol) in CH_2Cl_2 (26 ml). A soln. of [2-(chloromethoxy)ethyl]trimethylsilane (2.20 g, 13.2 mmol) in CH_2Cl_2 (5 ml) was added dropwise at 0° with stirring. After stirring for 3 d at room temp., the soln. was evaporated and the residue purified by FC (petroleum ether/^{t}BuOMe 5:1): **6** (1.25 g, 92%). Colorless solid. M.p. 45°. $[\alpha]_D^{20} = +29.7$ ($c = 1.33$, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.51–7.47 (*m*, 5 H); 7.37–7.32 (*m*, 5 H); 5.49 (*s*, 2 H); 4.79 (*d*, $J = 9.9$, 2 H); 4.66 (*d*, $J = 9.9$, 2 H); 4.49–4.44 (*m*, 2 H); 4.10–4.00 (*m*, 2 H); 3.69–3.44 (*m*, 8 H); 0.98–0.88 (*m*, 4 H); 0.01 (*s*, 18 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 137.7 (2 C); 128.8 (2 C); 128.2 (4 C); 125.9 (4 C); 101.0 (2 C); 95.3 (2 C); 77.1 (2 C); 70.4 (2 C); 66.6 (2 C); 65.6 (2 C); 18.0 (2 C); −1.3 (6 C). Anal. calc. for $C_{32}H_{50}O_8Si_2$ (618.92): C 62.10, H 8.15; found: C 61.83, H 8.25.

2. *2,5-Bis*-O-*{[2-(trimethylsilyl)ethoxy]methyl}*-D-*mannitol* (**7**). A mixture of 20% $Pd(OH)_2$/C (*ca.* 10 mg) and **6** (640 mg, 1.03 mmol) in EtOH (34 ml) was degassed and subsequently stirred for 12 h under 1 bar of H_2. The suspension was filtered over a pad of 'Kielselgur', the filtrate evaporated, and the residue subjected to FC (AcOEt): **7** (450 mg, 98%). Colorless solid. M.p. 71–72°. $[\alpha]_D^{20} = +18.9$ ($c = 1.19$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 4.81 (*d*, $J = 6.8$, 2 H); 4.74 (*d*, $J = 6.8$, 2 H); 3.85–3.82 (*m*, 4 H); 3.72–3.68 (*m*, 4 H); 3.60 (*t*, $J = 8.3$, 4 H); 0.94 (*t*, $J = 8.3$, 4 H); −0.57 (*s*, 18 H); signals of OH not detected. ^{13}C-NMR (75 MHz, $CDCl_3$): 95.9 (2 C); 81.2 (2 C); 69.6 (2 C); 66.3 (2 C); 63.3 (2 C); 18.1 (2 C); −1.4 (6 C). Anal. calc. for $C_{18}H_{42}O_8Si_2$ (442.70): C 48.84, H 9.56; found: C 48.60, H 9.62.

3. *1,6-Bis*-O-*[(*tert*-butyl)dimethylsilyl]-2,5-bis*-O-*{[2-(trimethylsilyl)ethoxy]methyl}*-D-*mannitol* (**8**). At 0°, 1*H*-imidazole (449 mg, 6.60 mmol) was added to a soln. of **7** (730 mg, 1.65 mmol) in CH_2Cl_2 (60 ml). After the 1*H*-imidazole had dissolved, (*tert*-butyl)chlorodimethylsilane (50% in hexane; 1.99 g, 6.60 mmol) was added dropwise. The mixture was stirred for 12 h at r.t. MeOH (2 ml) was added, the mixture evaporated, and the residue submitted to FC (petroleum ether/^{t}BuOMe 5:1 containing 1% of Et_3N): **8** (1.10 g, 99%). Colorless oil. $[\alpha]_D^{20} = -18.5$ ($c = 1.62$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 4.81 (*d*, $J = 6.6$, 2 H); 4.76 (*d*, $J = 6.6$, 2 H); 3.93 (*dd*, $J = 10.1$, $J = 4.0$, 2 H); 3.84 (*dd*, $J = 6.9$, $J = 5.1$, 2 H); 3.78–3.71 (*m*, 2 H); 3.70–3.46 (*m*, 8 H); 0.90–0.87 (*m*, 4 H); 0.88 (*s*, 18 H); 0.06 (*s*, 12 H); 0.01 (*s*, 18 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 95.8 (2 C); 78.8 (2 C); 69.6 (2 C); 65.7 (2 C); 64.4 (2 C); 25.7 (6 C); 18.3 (2 C); 18.1 (2 C); −1.5 (6 C); −5.5 (4 C). Anal. calc. for $C_{30}H_{70}O_8Si_4$ (671.22): C 53.68, H 10.51; found: C 53.44, H 10.67.

4. *(2*R*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-2-{[2-(trimethylsilyl)ethoxy]methoxy}propanal* (**9**). $NaHCO_3$ (227 mg, 2.70 mmol) and $Pb(OAc)_4$ (460 mg, 1.04 mmol) were added at −78° immediately after each other to a soln. of **8** (606 mg, 0.90 mmol) in CH_2Cl_2 (55 ml). The mixture was stirred for 20 min at −78° and filtered over a pad of 'Kieselgur'. The 'Kieselgur' was washed with CH_2Cl_2 (30 ml) and the combined filtrate dried (K_2CO_3) and evaporated. Hexane (20 ml) was added and the mixture evaporated (removal of residual AcOH). This process was repeated once: crude **9** (587 mg, 97%) which was used immediately. $[\alpha]_D^{20} = +6.1$ ($c = 3.45$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 9.69 (*d*, $J = 1.3$, 1 H); 4.80 (*s*, 2 H); 4.02 (*td*, $J_t = 4.9$, $J_d = 1.3$, 1 H); 3.91 (*d*, $J = 4.9$, 2 H); 3.76–3.58 (*m*, 2 H); 0.88–0.86 (*m*, 2 H); 0.86 (*s*, 9 H); 0.05 (*s*, 6 H); 0.01 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 202.2; 95.0; 82.5; 78.8; 69.6; 25.8 (3 C); 18.2; 18.0; −1.5 (3 C); −5.5 (2 C).

5. *(2*R*,3*RS*,6*R*,7*R*)-1-{[(*tert*-Butyl)dimethylsilyl]oxy}-6-methyl-5-methylidene-2-{[2-(trimethylsilyl)ethoxy]methoxy}-7-[(trimethylsilyl)oxy]octan-3-ol* (**11**). Three solns. were prepared separately and were stirred individually over 4-Å molecular sieves at −78°: aldehyde **9** (560 mg, 1.67 mmol) in CH_2Cl_2 (12 ml), $SnCl_4$

(0.249 ml, 2.12 mmol) in CH_2Cl_2 (6 ml), and allylsilane **10** [11] (550 mg, 2.12 mmol) in CH_2Cl_2 (15 ml). The $SnCl_4$ soln. was transferred *via* canula into that of **10** and stirring was continued for 15 min at $-78°$. Then the soln. of **9** was transferred *via* canula into the mixture. Et_3N (1.63 ml, 11.7 mmol) was added dropwise, and stirring was continued for 2 min at $-78°$. Aq. sat. $NaHCO_3$ soln. (12 ml) was added, the mixture allowed to reach r.t., the aq. layer extracted with CH_2Cl_2 (3×20 ml), the combined org. layer washed with brine (10 ml), dried (Na_2SO_4), and evaporated, and the residue subjected to FC (petroleum ether/^{t}BuOMe 10:1 containing 1% of Et_3N): **11** (diastereoisomer mixture; 530 mg, 61%). Yellowish oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.92 (br. *s*, 1 H); 4.86 (br. *s*, 1 H); 4.81 (*d*, *J* = 6.9, 1 H); 4.73 (*d*, *J* = 6.9, 1 H); 3.82–3.61 (*m*, 1 H); 3.74–3.68 (*m*, 4 H); 3.56–3.54 (*m*, 1 H); 2.59 (*d*, *J* = 5.4, 1 H); 2.32–2.07 (*m*, 4 H); 1.10 (*d*, *J* = 6.0, 3 H); 1.03 (*d*, *J* = 6.8, 3 H); 0.95–0.88 (*m*, 2 H); 0.88 (*s*, 9 H); 0.09 (*s*, 9 H); 0.05 (*s*, 6 H); 0.00 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 149.3; 112.1; 95.3; 79.5; 71.6; 69.4; 65.6; 63.2; 47.6; 40.1; 25.8 (3 C); 22.0; 18.2; 18.1; 16.9; 0.3 (3 C); −1.4 (3 C); −5.5 (2 C). Anal. calc. for $C_{25}H_{56}O_5Si_3$ (508.96): C 56.64, H 11.09; found: C 56.84, H 10.97.

6. *(2*R*,6*R*,7*R*)-1-[[(*tert*-Butyl)dimethylsilyl]oxy]-6-methyl-5-methylidene-2-[[2-(trimethylsilyl)ethoxy]methoxy]-7-[(trimethylsilyl)oxy]octan-3-one* (**12**). *Dess–Martin* periodinane [36] (234 mg, 0.55 mmol) was added to a soln. of **11** (125 mg, 0.240 mmol) in CH_2Cl_2 (10 ml). After stirring for 1 h, the mixture was filtered over a column with 'Kieselgur', which was eluted with CH_2Cl_2 (120 ml). The eluates were evaporated: **12** (120 mg, 96%). Slightly yellowish oil. $[\alpha]_D^{20} = +11.5$ ($c = 1.04$, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): 4.86 (*d*, *J* = 6.9, 1 H); 4.70 (*d*, *J* = 6.9, 1 H); 4.79 (br. *s*, 1 H); 4.76 (br. *s*, 1 H); 3.92–3.84 (*m*, 1 H); 3.73–3.59 (*m*, 4 H); 3.45–3.26 (*m*, 1 H); 2.11–2.02 (*m*, 3 H); 1.09 (*d*, *J* = 6.1, 3 H); 1.02 (*d*, *J* = 7.1, 3 H); 0.93–0.90 (*m*, 2 H); 0.87 (*s*, 9 H); 0.08 (*s*, 6 H); 0.06 (*s*, 9 H); 0.00 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 199.1; 147.0; 114.5; 94.8; 83.8; 70.9; 65.7; 65.0; 47.6; 26.0 (3 C); 22.8; 18.5; 18.1; 17.8; 15.4; 0.3 (6 C); −1.3 (2 C).

7. *(2*R*,5*R*,6*R*)-2-{(1*R*)-2-[[(*tert*-Butyl)dimethylsilyl]oxy]-1-{[(2-trimethylsilyl)ethoxy]methoxy}ethyl}tetrahydro-2-methoxy-5,6-dimethyl-4-methylidene-2*H*-pyran* (**13**). Pyridinium *p*-toluenesulfonate (*ca.* 5 mg) was added to a soln. of **12** (124 mg, 0.239 mmol) in MeOH (10 ml). After stirring for 45 min, sat. aq. $NaHCO_3$ soln. (5 ml) was added, the aq. layer extracted with ^{t}BuOMe (3×10 ml), the combined org. layer washed with brine (10 ml), dried (Na_2SO_4), and evaporated, and the residue subjected to FC (petroleum ether/^{t}BuOMe 3:1 containing 1% of Et_3N): **13** (79 mg, 71%). Colorless oil. $[\alpha]_D^{20} = +30.3$ ($c = 1.42$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 4.89 (*d*, *J* = 6.8, 1 H); 4.81–4.76 (*m*, 2 H); 4.67 (*dd*, *J* = 9.0, 1.8, 1 H); 3.97 (*dd*, *J* = 10.6, 2.4, 1 H); 3.87–3.56 (*m*, 5 H); 3.19 (*s*, 3 H); 2.37 (*d*, *J* = 14.5, 1 H); 2.22 (*d*, *J* = 14.5, 1 H); 2.17 (*dd*, *J* = 7.0, 2.4, 1 H); 1.09 (*d*, *J* = 6.5, 3 H); 0.96 (*d*, *J* = 7.0, 3 H); 0.93–0.87 (*m*, 2 H); 0.89 (*s*, 9 H); 0.05 (*s*, 6 H); 0.01 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 147.5; 109.2; 100.2; 94.8; 76.4; 68.3; 65.2; 64.5; 47.8; 41.5; 33.8; 27.0 (3 C); 18.2; 17.8; 17.6; 12.0; −1.4 (3 C); −5.4 (2 C). Anal. calc. for $C_{23}H_{48}O_5Si_2$ (460.80): C 59.95, H 10.50; found: C 59.60, H 10.31.

8. *(α*S*,2*R*,5*R*,6*R*)-Tetrahydro-2-methoxy-5,6-dimethyl-4-methylidene*-N-*(tetrahydro-2*H*-pyran-2-yl)-α-[[2-(trimethylsilyl)ethoxy]methoxy]-2*H*-pyran-2-acetamide* (**19**). A soln. of 1M Bu_4NF in THF (0.66 ml, 0.66 mmol) was added at 0° to a soln. of **13** (160 mg, 0.347 mmol) in THF (7 ml). After stirring for 4 h, the soln. was evaporated and the residue subjected to FC (petroleum ether/^{t}BuOMe 2:1 containing 1% of Et_3N): *(α*R*,2*R*,5*R*,6*R*)-tetrahydro-2-methoxy-5,6-dimethyl-4-methylene-α-[[2-(trimethylsilyl)ethoxy]methoxy]-2*H*-pyran-2-ethanol* (**14**; 100 mg, 82%). Yellowish oil. $[\alpha]_D^{20} = +40.1$ ($c = 2.58$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 4.82 (*dd*, *J* = 4.6, 2.4, 2 H); 4.7 (*dd*, *J* = 7.1, 2.4, 2 H); 3.89–3.80 (*m*, 3 H); 3.74 (*dd*, *J* = 8.9, 7.6, 1 H); 3.65–3.57 (*m*, 2 H); 3.41–3.30 (*m*, 2 H); 3.19 (*s*, 3 H); 2.38–2.33 (*m*, 1 H); 2.21–2.17 (*m*, 1 H); 1.10 (*d*, *J* = 6.5, 3 H); 0.97 (*d*, *J* = 7.1, 3 H); 0.94–0.84 (*m*, 2 H); 0.01 (s, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 146.6; 109.8; 101.0; 95.3; 78.4; 68.8; 65.8; 62.9; 47.8; 41.4; 33.0; 18.1; 17.7; 11.9; −1.4 (3 C).

Tetrapropylammonium perruthenate (7 mg, 0.018 mmol) was added to a soln. of **14** (51 mg, 0.15 mmol) and *N*-methylmorpholine *N*-oxide (34 mg, 0.29 mmol) in CH_2Cl_2 (6 ml) containing 4-A molecular sieves (*ca.* 5 mg). After stirring for 50 min, the mixture was filtered over 'Kieselgur' followed by washing with CH_2Cl_2 (30 ml). The soln. was evaporated and the resulting aldehyde **15** (50 mg, 94%) taken up in ^{t}BuOH (3.5 ml) and 2-methylbut-2-ene (0.9 ml). A soln. of sodium chlorite (1.38 mg, 1.90 mmol) and of sodium dihydrogen phosphate dihydrate (187 mg, 1.20 mmol) in H_2O (2 ml) was added. After stirring vigorously for 20 min, the aq. layer was extracted with ^{t}BuOMe (3×15 ml), the combined org. layer dried (Na_2SO_4) and evaporated, hexane (10 ml) added, and the mixture evaporated (removal of residual ^{t}BuOH). This process was repeated once. The resulting crude acid **16** (50 mg, 95%) was used immediately.

Acid **16** (40 mg, 0.11 mmol) and isocyanate **18** [11] (14 mg, 0.10 mmol) were dissolved at 0° in CH_2Cl_2 (3 ml). *N*,*N*-Dimethylpyridin-4-amine (*ca.* 5 mg) was added. After stirring 30 min at 0° and 3 h at r.t., the mixture was evaporated and the residue subjected to FC (petroleum ether/^{t}BuOMe 1:3 containing 1% of Et_3N): diastereoisomerically pure **19** (18 mg) followed by a mixture of diastereoisomeric amides (18 mg, total 80%). **19** (unassigned rel. configuration at the aminal C-atom): ^{1}H-NMR (200 MHz, $CDCl_3$): 5.08 (*d*, *J* = 3.4, 1 H); 4.80

(*d*, *J* = 2.0, 1 H); 4.76 (br. *s*, 1 H); 4.69 (*d*, *J* = 10.6, 1 H); 4.72 (*d*, *J* = 10.6, 1 H); 4.36–4.09 (*m*, 2 H); 3.85–3.40 (*m*, 5 H); 3.21 (*s*, 3 H); 2.90–2.80 (*m*, 1 H); 2.30–2.10 (*m*, 2 H); 1.33–0.80 (*m*, 8 H); 1.08 (*d*, *J* = 6.4, 3 H); 0.90 (*d*, *J* = 7.2, 3 H); 0.06 (*s*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 170.5; 146.9; 109.5; 100.2; 94.4; 77.7; 74.4; 69.0; 65.9; 60.8; 48.1; 41.6; 32.7; 29.7; 25.4; 22.8; 18.0; 17.6; 11.6; −1.4 (3 C). HR-FAB-MS: 443.2669 ($C_{22}H_{41}NO_6Si^+$; calc. 443.2703).

9. *(αS,2R,5R,6R)-Tetrahydro-2-methoxy-5,6-dimethyl-4-methylidene-α-[[2-(trimethylsilyl)ethoxy]methoxy]-2H-pyran-2-acetic Acid Methyl Ester* (**17**). In another experiment, acid **16** was generated as above from aldehyde **15** (35 mg, 0.10 mmol) and dissolved in Et_2O. A soln. of diazomethane (*ca.* 5 mmol) in Et_2O (*ca.* 5 ml) was added at 0°. After stirring for 30 min at 0°, sat. aq. NH_4Cl soln. (*ca.* 1 ml) was added. After the yellow color had disappeared, the aq. layer was extracted with Et_2O (2 × 5 ml), the combined org. layer washed with brine (5 ml), dried (Na_2SO_4), and evaporated, and the residue subjected to FC (petroleum ether/^{t}BuOMe): **17** (36 mg, 96%). Colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.01 (*s*, 9 H); 0.85–0.90 (*m*, 5 H; including a *d*, *J* = 6.99, at 0.89, 3 H); 1.07 (*d*, *J* = 6.84, 3 H); 2.15 (*dq*, *J* = 6.97, 2.48, 1 H); 2.26 (*d*, *J* = 14.73, 1 H); 2.87 (*ddd*, *J* = 14.74, 2.18, 2.18, 1 H); 3.21 (*s*, 3 H); 3.56–3.64 (*m*, 2 H); 3.73 (*s*, 3 H); 3.81 (*dq*, *J* = 6.53, 2.58, 1 H); 4.37 (*s*, 1 H); 4.64–4.72 (*m*, 3 H; including a *dd*, *J* = 2.11, 2.11, at 4.70, 1 H, and an *AB* system, J_A = 4.67, J_B = 4.72, J_{AB} = 7.04, 2 H); 4.79 (*dd*; *J* = 2.04, 2.04, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): −1.48; 11.51; 17.65; 18.02; 32.68; 41.54; 48.06; 51.81; 65.87; 69.01; 74.75; 94.51; 100.06; 109.45; 146.76; 170.93.

10. *3-Methylideneheptanoic Acid* (**24**). Cyclobutenone **23** [28] (158 mg, 1.20 mmol) was dissolved in H_2O (1.5 ml) to which had been added a few drops of 1,4-dioxane. The soln. was heated to reflux for 12 h. The pH was adjusted to 3 by addition of a few drops of 1M HCl. The mixture was extracted with CH_2Cl_2 (3 × 6 ml) and the combined org. layer dried (Na_2SO_4) and evaporated: **24** (166 mg, 96%). Yellowish liquid. ^{1}H-NMR (300 MHz, $CDCl_3$; see [37]): 10.71 (br. *s*, 1 H); 4.72 (2*d*, *J* = 1.2, 2 H); 3.06 (*s*, 2 H); 2.17–2.09 (*m*, 2 H); 1.50–1.24 (*m*, 4 H); 0.89 (*t*, *J* = 7.2, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 178.3; 142.0; 113.9; 41.7; 35.5; 29.5; 22.2; 13.9.

11. *Methyl 3-Methylideneheptanoate* (**25**). A soln. of **24** (644 mg, 4.22 mmol) in $SOCl_2$ (*ca.* 3 ml) was stirred for 15 h at r.t. Evaporation of the excess of $SOCl_2$ gave the crude acyl chloride as a colorless oil (617 mg). The latter was added at −20° to a soln. of pyridine (3 ml) in MeOH (5 ml). After stirring for 3 h at r.t., H_2O and Et_2O (4 ml) were added. The aq. layer was extracted with Et_2O (3 × 10 ml), the combined org. layer washed with brine (10 ml), dried (Na_2SO_4), and evaporated: **25** (510 mg, 77%). Colorless oil which was purified by distillation (75°/1 Torr) before the next step. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.92 (*d*, *J* = 1.3, 1 H); 4.88 (*d*, *J* = 0.8, 1 H); 3.69 (*s*, 3 H); 3.05 (br. *d*, *J* = 0.8, 2 H); 2.09 (br. *t*, *J* = 7.3, 2 H); 1.37 (*m*, 4 H); 0.9 (br. *t*, *J* = 7.3, 3 H).

12. *1-Chloro-4-methylidenoctan-2-one* (**26**). To a soln. of chloroiodomethane (0.33 ml, 4.48 mmol) in THF/Et_2O 1:1 (40 ml), at −100°, 1.6M BuLi in hexane (1.4 ml, 2.24 mmol) was added. After stirring for 1 h at −100°, **25** (100 mg, 0.640 mmol) was added at −100°, and the mixture was allowed to reach −78° during 1 h. The mixture was poured into sat. aq. NH_4Cl soln. (100 ml), the aq. layer extracted with Et_2O (3 × 10 ml), the combined org. layer washed with brine (10 ml), dried ($MgSO_4$), and evaporated, and the residue subjected to FC (pentane/^{t}BuOMe 30:1): **26** (60 mg, 54%). Colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.98 (*d*, *J* = 1.5, 1 H); 4.89 (*d*, *J* = 1.0, 1 H); 4.15 (*s*, 2 H); 3.29 (*s*, 2 H); 2.04 (*t*, *J* = 7.6, 2 H); 1.36 (*m*, 4 H); 0.90 (*t*, *J* = 6.9, 3 H).

13. *5-Methyliden-3-oxo-*N*-phenylnonanamide* (**27**). At 0°, 0.1M SmI_2 in THF (4.6 ml, 0.46 mmol) was added to a soln. of **26** (20 mg, 0.115 mmol) and phenyl isocyanate (15 µl, 0.137 mmol) in dry THF (2 ml). After stirring for 3 h at 0°, aq. $NaHCO_3$ soln. (15 ml) was added, the aq. layer extracted with Et_2O (3 × 3 ml), the combined org. layer washed with brine (10 ml), dried ($MgSO_4$), and evaporated, and the residue subjected to FC (pentane/^{t}BuOMe 4:1 → pentane/AcOEt 4:1): **27** (16 mg, 53%). Colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 9.13 (br. *s*, 1 H); 7.55 (*d*, *J* = 9.0, 2 H); 7.33 (*t*, *J* = 7.8, 2 H); 7.18–7.08 (*m*, 1 H); 5.04 (*d*, *J* = 1.3, 1 H); 4.92 (*d*, *J* = 0.8, 1 H); 3.62 (*s*, 2 H); 3.26 (*s*, 2 H); 2.05 (*t*, *J* = 7.4, 2 H); 1.50–1.20 (*m*, 4 H); 0.90 (*t*, *J* = 7.4, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 206.0; 163.3; 141.9; 137.5; 129.0 (2 C); 124.6; 120.1 (2 C); 115.2; 51.8; 47.8; 35.9; 29.6; 22.3; 13.9.

14. rel-*(tert-Butyl)[[(1R,2R)-1,2-dimethylbut-3-ynyl]oxy]dimethylsilane* (**28**). At −78°, 1.6M BuLi in hexane (12.8 ml, 20.8 mmol) was added to a soln. of ethynyltrimethylsilane (2.04 g, 20.8 mmol) in THF (60 ml). After stirring for 10 min, $BF_3 \cdot OEt_2$ (2.95 g, 20.8 mmol) and racemic *trans*-2,3-dimethyloxirane (1.24 ml, 13.9 mmol) was added at −78°. After stirring for 1.5 h at −78°, sat. aq. NH_4Cl soln. (50 ml) was added, the aq. layer extracted with Et_2O (3 × 40 ml), and the combined org. layer washed with brine (50 ml), dried ($MgSO_4$), and evaporated (removal of residual Et_2O). The remaining crude THF soln. was used for the next step.

At 0°, 1.0M Bu_4NF in THF (14 ml, 14 mmol) was added to the above THF soln. After stirring for 30 min at r.t., the reaction was quenched by addition of H_2O (3 drops). The mixture was filtered with Et_2O through a pad of SiO_2, the filtrate carefully evaporated, the residual liquid taken up in DMF (20 ml), and 1*H*-imidazole (2.43 g, 35.8 mmol) added at 0°. After dissolution of the 1*H*-imidazole, ^{t}BuMe$_2$SiCl (50 wt-% in toluene; 5.4 g, 18 mmol)

was added dropwise. The mixture was stirred for 1 h at 75°. H_2O (10 ml) was added, the aq. layer extracted with Et_2O (4 × 40 ml), the combined org. layer dried ($MgSO_4$) and evaporated, and the residue distilled at 40–50°/1 Torr): **28** (1.08 g, 37% over 3 steps). Colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.61 (*dq*, *J* = 6.7, 6.3, 1 H); 2.32 (*ddq*, *J* = 7.0, 7.0, 2.3, 1 H); 2.06 (*d*, *J* = 2.3, 1 H); 1.25 (*d*, *J* = 6.0, 3 H); 1.17 (*d*, *J* = 6.8, 3 H); 0.89 (*s*, 9 H); 0.06 (*s*, 6 H).

15. *rel-(5*R,*6*R*)-6-{[(*tert-*Butyl)dimethylsilyl]oxy}-1-chloro-5-methyl-4-methylideneheptan-2-one* (**30**). $BF_3 \cdot OEt_2$ (1.7 ml, 13 mmol) was added at 0° to a soln. of freshly distilled chloroacetaldehyde [34] (0.76 ml, 13 mmol) and the allylsilane **10** (2.0 g, 6.7 mmol) in CH_2Cl_2 (100 ml). After stirring for 3 h at 0°, aq. $NaHCO_3$ soln. (20 ml) was added, the aq. layer extracted with CH_2Cl_2 (3 × 20 ml), the combined org. layer dried ($MgSO_4$) and evaporated, and the residue filtered with pentane/Et_2O 9:1 over a SiO_2 column: alcohol **29** as a colorless oil (1.03 g, 50%).

Dess–Martin periodinane [23] (400 mg, 1.21 mmol) was added at r.t. to a soln. of alcohol **29** (140 mg, 0.453 mmol) in wet CH_2Cl_2 (20 ml). After stirring for 1 h, the mixture was filtered over a pad of *Celite* and washed with CH_2Cl_2. The eluents were washed with aq. $NaHCO_3$ soln. (2 × 20 ml), dried ($MgSO_4$), and evaporated, and the residue was subjected to FC (pentane/Et_2O 10:1): **30** (130 mg, 94%). Colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.00 (br. *s*, 1 H); 4.95 (br. *d*, *J* = 1.0, 1 H); 4.14 (*s*, 2 H); 3.72 (*dq*, *J* = 6.0, 5.9, 1 H); 3.43 (*dd*, *J* = 15.5, 1.0, 1 H); 3.33 (*dd*, *J* = 15.5, 0.4, 1 H); 2.18 (*dq*, *J* = 6.5, 6.0, 1 H); 1.06 (*d*, *J* = 6.0, 3 H); 1.03 (*d*, *J* = 6.5, 3 H); 0.87 (*s*, 9 H); 0.04 (*s*, 3 H); 0.03 (*s*, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 199.8; 144.5; 115.2; 71.1; 47.2; 46.7; 33.5; 25.8; 20.9; 18.0; 15.5; −4.5; −4.9.

16. rel-*(6*R,*7*R*)-7-{[(*tert-*Butyl)dimethylsilyl]oxy}-6-methyl-5-methyliden-3-oxo*-N-*(tetrahydro-2*H*-pyran-2-yl)octanamide* (**31a**). At 0°, 0.1M SmI_2 in THF (39 ml, 3.9 mmol) was added to a mixture of **30** (400 mg, 1.30 mmol), tetrahydro-2-isocyanato-2*H*-pyran (133 mg, 1.04 mmol) and 4-Å molecular sieves (500 mg) in dry THF (5 ml). After stirring at r.t. for 3 h, sat. aq. NH_4Cl soln. (*ca.* 50 ml) was added, the aq. layer extracted with AcOEt (3 × 20 ml), the combined org. layer was dried ($MgSO_4$) and evaporated, and the residue subjected to FC (pentane/AcOEt 3:2): **31a** (240 mg, 58%). Colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.65 (br. *d*, *J* = 5.0, 1 H); 5.11 (br. *t*, *J* = 9.1, 2.1, 1 H); 4.99 (br. *s*, 1 H); 4.92 (br. *s*, 1 H); 3.97–3.91 (br. *d*, 1 H); 3.68 (*dq*, *J* = 6.1, 6.0, 1 H); 3.64–3.50 (*m*, 1 H); 3.44 (br. *s*, 2 H); 3.28 (br. *d*, *J* = 5.0, 2 H); 2.12 (*dq*, *J* = 6.7, 6.1, 1 H); 1.91–1.74 (*m*, 2 H); 1.58–1.40 (*m*, 4 H); 1.03 (*d*, *J* = 5.8, 3 H); 1.00 (*d*, *J* = 7.0, 3 H); 0.85 (*s*, 9 H); 0.02 (*s*, 3 H); 0.00 (*s*, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 205.6; 165.6; 144.6; 116.1; 77.8; 71.6; 67.5; 52.0; 48.0; 47.2; 31.6; 26.3; 25.4; 23.0; 21.4; 18.5; 16.1; −4.0; −4.4.

17. rel-*(6*R,*7*R*)-7-{[(*tert-*Butyl)dimethylsilyl]oxy}-6-methyl-5-methyliden-3-oxo*-N-*phenyloctanamide* (**31b**). As described for **31a**, with 0.1M SmI_2 in THF (49 ml, 4.9 mmol), **30** (500 mg, 1.63 mmol), phenyl isocyanate (291 mg, 2.44 mmol), 4-Å molecular sieves (500 mg), and THF (5 ml) for 5 h. FC (pentane/Et_2O 4:1 → 2:1) furnished **31b** (418 mg, 66%). Colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 9.19 (br. *s*, 1 H); 7.54 (*d*, *J* = 7.8, 2 H); 7.31 (*t*, *J* = 7.9, 2 H); 7.11 (*t*, *J* = 7.3, 1 H); 5.04 (*s*, 1 H); 4.98 (*s*, 1 H); 3.71 (*dq*, *J* = 5.9, 5.9, 1 H); 3.60 (*s*, 2 H); 3.41 (*d*, *J* = 15.0, 1 H); 3.31 (*d*, *J* = 15.0, 1 H); 2.16 (*dq*, *J* = 6.6, 6.6, 1 H); 1.02 (*d*, *J* = 6.3, 3 H); 1.00 (*d*, *J* = 7.3, 3 H); 0.88 (*s*, 9 H); 0.05 (*s*, 3 H); 0.03 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 206.2; 163.5; 144.2; 137.6; 129.0 (2 C); 124.6; 120.2 (2 C); 115.9; 71.4; 65.9; 51.8; 48.1; 46.8; 25.9; 20.9; 15.7; −4.3; −4.7.

18. rel-*(6*R,*7*R*)-7-{[(*tert-*Butyl)dimethylsilyl]oxy}-6-methyl-5-methyliden-3-oxo*-N-*phenyl-2-(phenylhydrazono)octanamide* (**33**). At 0°, 3-methyl-1-(nitrosooxy)butane was added dropwise to a suspension of aniline hydrochloride (20 mg) in AcOH (0.1 ml) until a clear soln. resulted. After stirring for 30 min, Et_2O (2 ml) was added, and the resulting white solid was washed with additional Et_2O (3 × 2 ml). The salt was suspended in EtOH (1 ml) and a soln. of **31b** (17 mg, 0.048 mmol) in EtOH (0.3 ml) was added at 0°, followed by 0.5M AcONa in H_2O (0.1 ml, 0.048 mmol) at 0°. After stirring for 1 h, H_2O (2 ml) was added, the aq. layer extracted with Et_2O (4 × 2 ml), dried ($MgSO_4$), and evaporated, and the residue subjected to FC (pentane/Et_2O 8:1 → 2:1): **33** (14 mg, 24%), besides recovered **31b** (8 mg, 47%). **33**: Colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 14.83 (br. *s*, 1 H); 11.52 (br. *s*, 1 H); 7.65–7.62 (*m*, 2 H); 7.42–7.34 (*m*, 6 H); 7.22–7.13 (*m*, 2 H); 5.02 (br. *s*, 1 H); 4.98 (br. *s*, 1 H); 3.86–3.78 (*m*, 3 H); 2.28 (*dq*, *J* = 6.6, 6.6, 1 H); 1.13 (*d*, *J* = 5.6, 3 H); 1.11 (*d*, *J* = 6.6, 3 H); 0.87 (*s*, 9 H); 0.05 (*s*, 3 H); 0.04 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 199.5; 163.0; 146.4; 141.5; 136.9; 129.4; 128.8; 125.5; 125.2; 124.6; 120.7; 115.8; 115.5; 114.1; 71.1; 47.2; 44.2; 25.6; 21.2; 17.9; 15.7; −4.5; −5.0.

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