Primary and Secondary Allyltitanium(IV) Reagents in Aldehyde Allylation II: Application to an Enantioselective Preparation of a C1-C7 Fragment of Spiramycin

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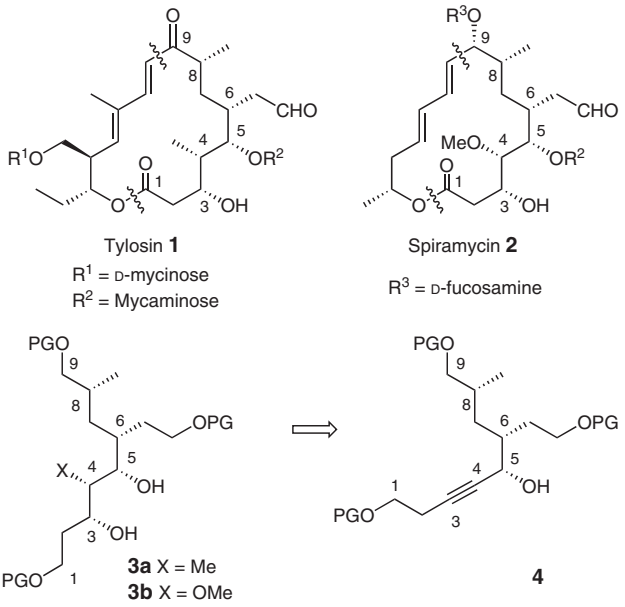
Abstract: A synthetic approach to the eastern part of spiramycin, an important antibiotic compound, is described. Introduction of the side chain was first envisaged through a Hoppe aldehyde allylation. This reaction was carried out between an optically pure aldehyde **32** and a (±)-γ-alkoxy allyltitanium(IV) species derived from a primary γ-alkoxy allyl (diisopropyl)carbamate. Under kinetic resolution conditions, the *anti-Cram* compound **35** was obtained in an 80:20 mixture, with the *Cram* isomer **34**, in 81% yield. Employing the optically pure (*S*)-γ-alkoxy allyl (diisopropyl)carbamate **36**, the corresponding (*R*)-γ-alkoxy allyltitanium (*R*)-**'Ti'-III** was generated under *n*-BuLi·TMEDA/Ti(O*i*-Pr)$_4$ conditions, that reacted with aldehyde **32** in double stereodifferentiation to deliver the expected *Cram* compound **40** in 80% yield (95% de). This latter corresponded to the C1-C7 fragment of spiramycin.

Key words: spiramycin, synthesis, Hoppe allylation, secondary allyltitanium reagent, double stereodifferentiation

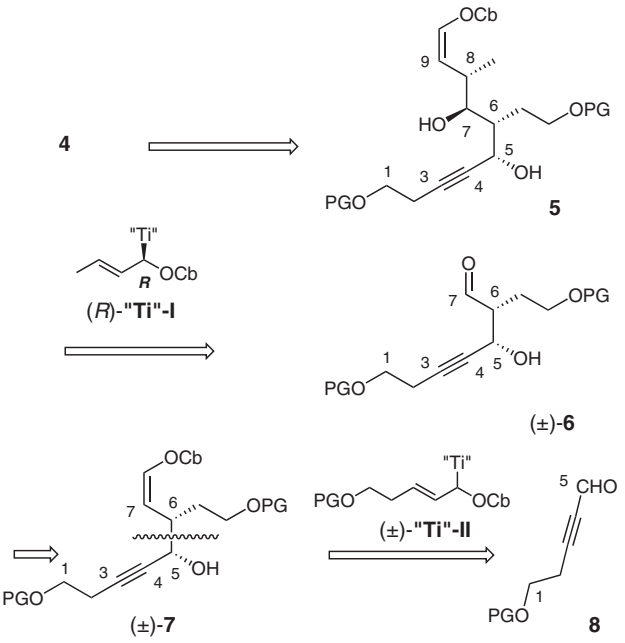
In the course of total synthesis of 14- and 16-membered macrolide antibiotics we were interested in the preparation of tylosin (**1**) [1] and spiramycin (**2**),[2] two components of the important erythromycin family[3] (Scheme 1).

In a precedent study we described a synthetic approach to the C1-C9 eastern part **3a** of tylosin (**1**),[4] based on sequential Hoppe aldehyde allylation reactions. We now focus on spiramycin (**2**), for which only one total synthesis has been reported.[5] As the C1-C9 portions of tylosin (**1**) and spiramycin (**2**) are quite similar, we first tried to develop a common strategy for the construction of **3a** and **3b**.

In our retrosynthetic approaches of tylosin (**1**) and spiramycin (**2**), the key intermediate acetylenic compound **4** could be a hub for synthesis of eastern parts **3a** and **3b** as well as analogues, and may arise from a Hoppe allylation[6] of aldehyde (±)-**6** with the optically active crotyltitane (*R*)-**'Ti'-I** (Scheme 2). A Barton deoxygenation at the C-7 position[7] was envisaged to transform **5** into **4** for the last step of the sequence. On the other hand, precursor (±)-**7** of aldehyde (±)-**6** could result from another allylation reaction between aldehyde **8** and the γ-alkoxy allyltitanium **'Ti'-II** in a Hoppe-like reaction.



Scheme 1



Scheme 2

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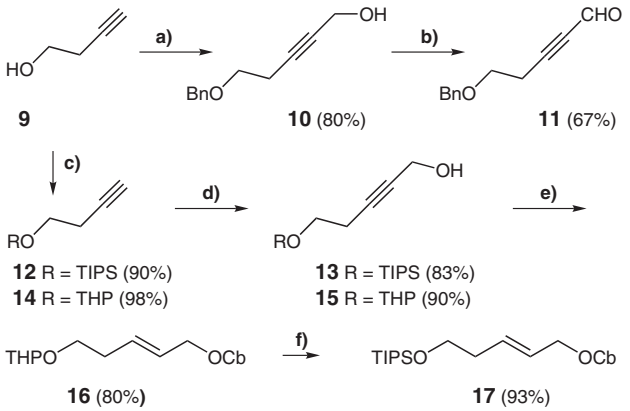
We decided to employ racemic γ-alkoxy allyltitanium (±)-**'Ti'-II** for the allylation of aldehyde **8**, leading to racemic vinyl carbamate (±)-**7** in a large scale. An optically active product will result from the second allylation of the racemic aldehyde (±)-**6** with crotyltitane (*R*)-**'Ti'-I**.

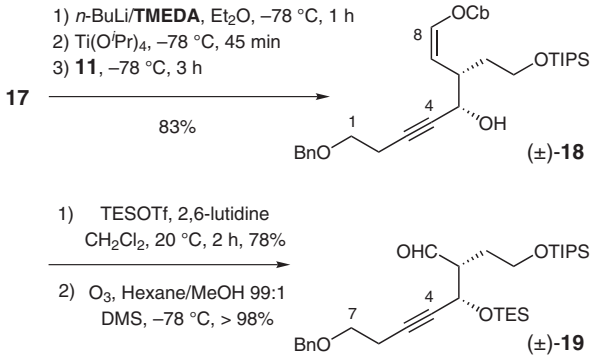
For this purpose, preparation of aldehyde **11** was effected in 54% overall yield for three steps from but-3-ynol (**9**) (Scheme 3): protection of the primary alcohol as a benzyl ether was followed by an homologation into a pentynediol derivative (**10**, 80% yield), and an oxidation step (67% yield).



Scheme 3 Reagents and conditions: **a**) i. NaH, BnBr, NaI cat., THF–Et_2O (1:1), 20 °C, 8 h. ii. *n*-BuLi, THF, HCHO, –78 °C, then 20 °C, 5 h; **b**) IBX, DMSO, 20 °C, 4 h; **c**) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 20 °C, 2 h → **12**, DHP, 10 N HCl, 20 °C, 2 h → **14**; **d**) *n*-BuLi, THF, HCHO, –78 °C, then 20 °C, 5 h, **12** → **13**, **14** → **15**; **e**) i. **15**, 1 M $LiAlH_4$, Et_2O, reflux, 2.5 h. ii. NaH, THF, $N(i\text{-}Pr)_2C(O)Cl$, 20 °C, 5 h; **f**) i. Amberlyst 15, MeOH, 20 °C, 4 h. ii. TIPSOTf, 2,6-lutidine, CH_2Cl_2, 20 °C, 3 h.

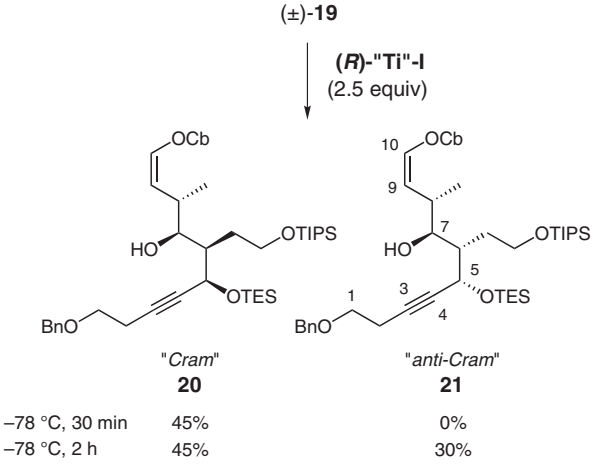
For the synthesis of γ-alkoxy carbamate **17**, the alcohol function of but-3-ynol was first protected as a triisopropylsilyl ether to furnish **12** (TIPS, 90% yield). However, after a homologation step of **12** (*n*-BuLi, THF, HCHO, –78 °C, → **13**, 88% yield), reduction of the propargyl alcohol **13** into the corresponding (*E*)-allylic alcohol did not give satisfying results, and we were forced to use the tetrahydropyranyl ether **14**. Thus, homologation of **14** (90% yield) following by $LiAlH_4$ reduction of the resulting propargylic alcohol **15** and carbamoylation led to the expected *E*-allyl carbamate **16** in 80% yield from **15**. Because of the unpractical use of the THP group in synthesis, two supplementary steps were carried out to prepare allyl carbamate **17** from the THP analogue **16** (93% overall yield).

Having in our hands the required γ-alkoxycarbamate **17**, we were able to realise the allylation of aldehyde **11**. Treatment of **17** under classical conditions, [*n*-BuLi/TMEDA/Et_2O, –78 °C, 1 h; $Ti(Oi\text{-}Pr)_4$, –78 °C, 3 h; **11**, –78 °C, 3 h] furnished the racemic allylic alcohol (±)-**18** in 83% as a single diastereomer (Scheme 4). This reaction was carried out on a 50 g scale. Before the second allylation reaction, the secondary alcohol was protected as a triethylsilyl ether (TES, 78%), then ozonolysis under the given conditions [O_3, hexane–MeOH, 99:1, Me_2S, –78 °C, 98%] gave the expected aldehyde (±)-**19** in 76% yield (Scheme 4).



Scheme 4

This compound was then reacted with 2.5 equivalents of the optically active crotyltitane (*R*)-**'Ti'-I** at –78 °C for 30 minutes, and only one diastereomer **20** was isolated in 45% yield (Scheme 5). This *Cram* isomer could be considered as the 'matched' compound. Interestingly when the reaction was kept at –78 °C for 2 hours, both the two 'matched' and 'mismatched' derivatives **20** and **21** were produced in 45 and 30% yield, respectively.

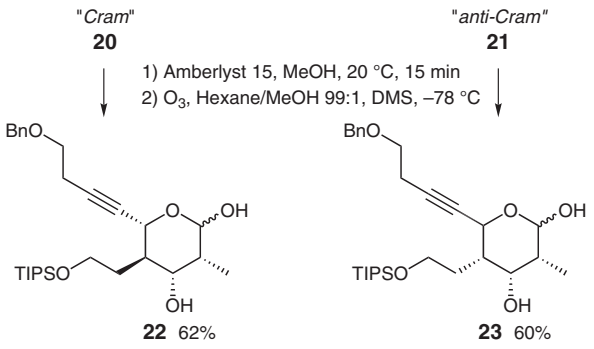


Scheme 5

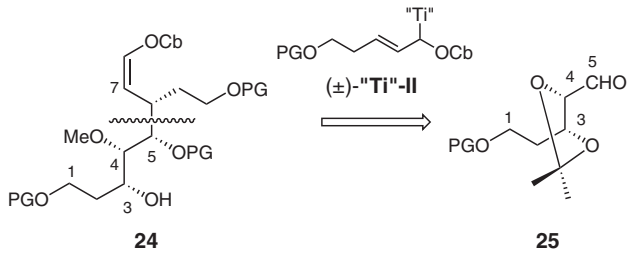
Structural proof of **20** and **21** was deduced from NMR analysis of the corresponding lactols **22** and **23** obtained after deprotection of the C5 TES ether and ozonolysis of the C9–C10 double bond (Scheme 6).

Although the 'mismatched' derivative **21** was prepared in good yield, the C1-C9 fragments **3a** and **3b** of tylosin (**1**) and spiramycin (**2**) could not be synthesised by this route, several difficulties arose linked to instability of compound **21** during triple bond transformation.

So we focused on a specific approach to the C1-C7 portion **24** of spiramycin (**2**), and decided to investigate a kinetic resolution of racemic γ-alkoxytitane (±)-**'Ti'-II** by optically active aldehyde **25**, which is already functionalized at C3 and C4 (Scheme 7).



Scheme 6



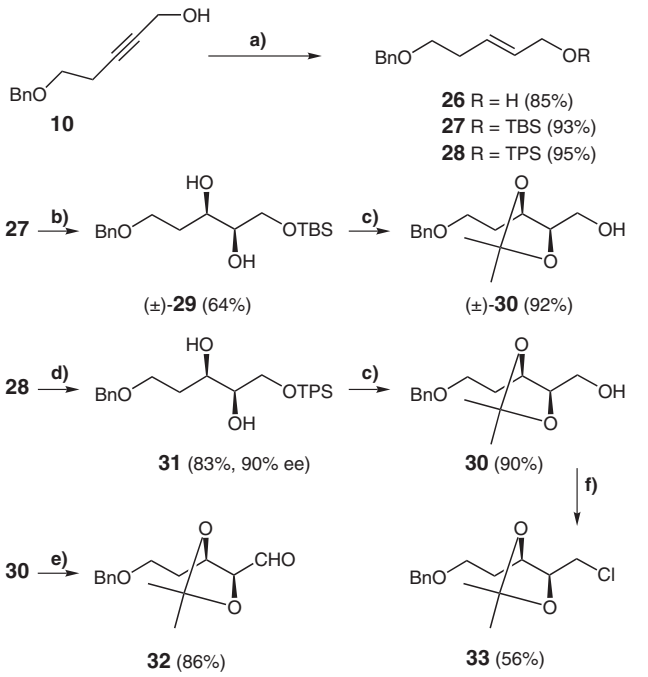
Scheme 7

Reduction of monoprotected pentynediol **10** with $LiAlH_4$ in Et_2O gave the (*E*)-allylic alcohol **26** in 85% yield (Scheme 8). Both *tert*-butyldimethylsilyl (TBS) and *tert*-butyldiphenylsilyl (TPS) ethers **27** and **28** were prepared in 93 and 95% yields, respectively. At this stage, a dihydroxylation reaction was performed on the TBS derivative **27** using OsO_4/NMO in acetone–water to give the racemic diol (±)-**29** in 64% yield. The corresponding ketal (±)-**30** was then prepared in 92% yield.

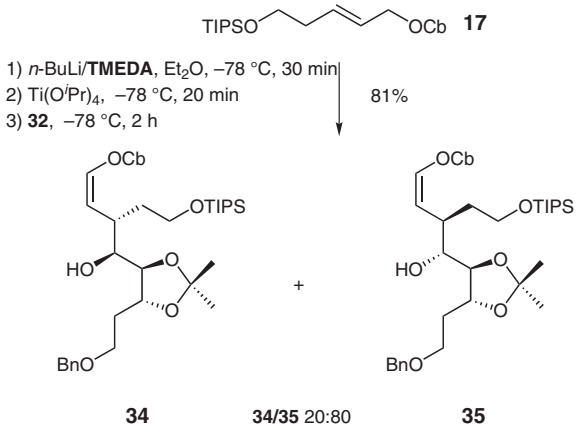
Under Sharpless conditions, using AD-Mix-β,[8] optically active diol **31** was obtained in 83% yield and 90% ee from the TIPS derivative **28**. The enantiomeric excess was measured by NMR analysis of the corresponding ketal **30** using Europium salt shifts. Absolute configuration of **30** was proved by comparison of the optical rotations of the chloro derivative **33** prepared from **30**, and from **26** as earlier described in the literature.[9]

After oxidation of alcohol **30** ($Py{\cdot}SO_3$, DMSO, 20 °C, 1 h, 86%), the resulting aldehyde **32** was reacted with the racemic γ-allyltitanium prepared from carbamate **17** (Scheme 9). The reaction was kept at –78 °C for 2 hours and led, in 81% yield, to a 20:80 mixture of the two diastereomers **34** and **35**. This kinetic resolution led to a major isomer **35** that presented the inverse expected configurations at C5 and C6 centres.[10]

In order to improve and to reverse the diastereoselectivity in this reaction, we turned our attention to the results published by Hoppe about secondary crotylcarbamates.[11] In this work it was established that metallation of secondary crotyl carbamates could be effected without racemisation. Transmetallation with $Ti(O\textit{i}\text{-}Pr)_4$ then delivered a reactive optically pure crotyltitanium intermediate able to promote aldehyde allylation in a good enantiomeric excess.



Scheme 8 Reagents and conditions: **a**) i. 1 M $LiAlH_4$, Et_2O, reflux, 2.5 h, → **26**. ii. **26**, TBSCl, imidazole, CH_2Cl_2, 20 °C, 1 h, → **27**; **26**, TPSCl, imidazole, CH_2Cl_2, 20 °C, 1 h, → **28**; **b**) **27**, cat. OsO_4, NMO, acetone–H_2O (60:40); **c**) i. 2,2-DMP, PTSA, 2 h. ii. TBAF, THF, 20 °C, 1 h; **d**) **28** Sharpless AD-Mix-β; **e**) $Py{\cdot}SO_3$, DMSO, Et_3N, 20 °C, 1 h; **f**) PPh_3, CCl_4, CH_2Cl_2, 20 °C, 8 h.

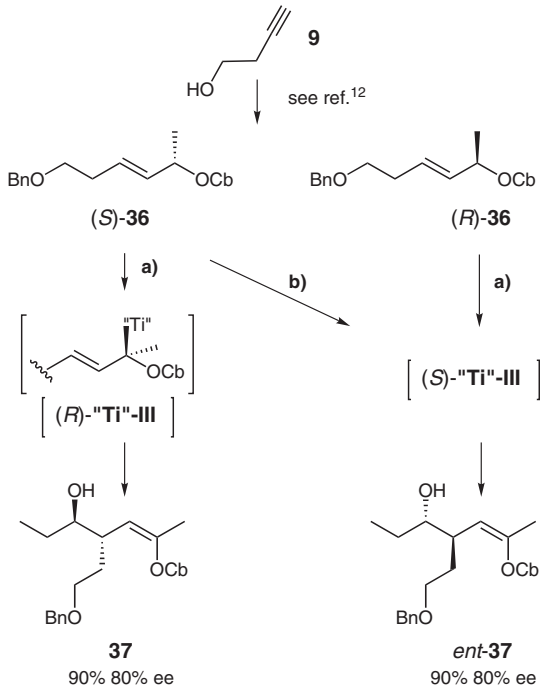


Scheme 9

In the course of our synthetic approaches of tylosin (**1**) and spiramycin (**2**) we exploited the potentiality of optically pure γ-alkoxy allyltitanium **'Ti'-III** derived from secondary allyl carbamates (*R*)- and (*S*)-**36**.

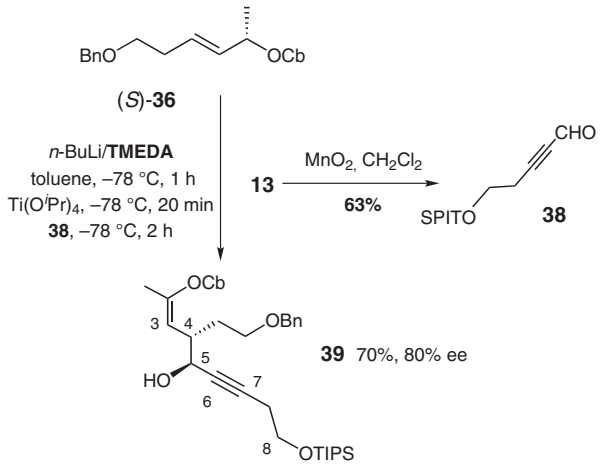
At the outcome of the study,[12] we were able to prepare homoallylic alcohols **37** and *ent*-**37** from either (*R*)-**36** or (*S*)-**36** in 90% yield and 80% ee, depending of experimental conditions used. Employing *n*-BuLi/TMEDA, and starting from the (*R*)- or (*S*)-**36** allyl carbamate, the resulting stable lithio derivative then underwent a transmetallation with $Ti(O\textit{i}\text{-}Pr)_4$ to deliver the (*S*)-**'Ti'-III** or (*R*)-**'Ti'-III** titanium intermediate responsible for the formation of *ent*-**37** or **37**. In contrast, when *n*-BuLi/(–)-sparteine con-

ditions were used, transmetallation with Ti(O*i*-Pr)$_4$ occurred with inversion of configuration and starting from the (*S*)-**36** allyl carbamate, allylation led to the *ent*-**37** derivative (90% yield, 88% ee) (Scheme 10).



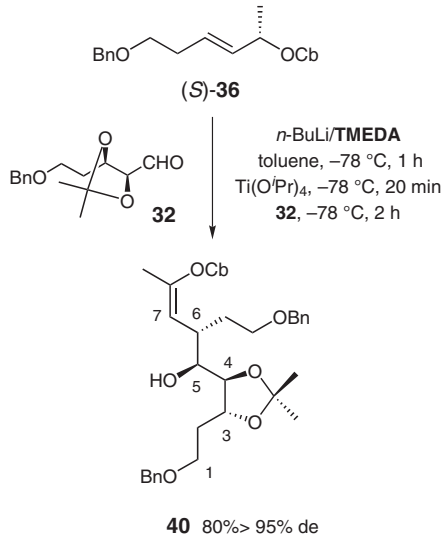
Scheme 10 Reagents and conditions: **a)** *n*-BuLi/**TMEDA**, toluene, –78 °C, 1 h, Ti(O*i*-Pr)$_4$, –78 °C, 20 min, propanal –78 °C, 2h; **b)** *n*-BuLi/**(–)-sparteine**, toluene, –78 °C, 1 h, Ti(O*i*-Pr)$_4$, –78 °C, 20 min, propanal –78 °C, 2 h.

With optically active γ-alkoxy carbamates (*R*)- and (*S*)-**36** now available, we turned to our common synthetic approach to eastern parts **3a** and **3b** of tylosin (**1**) and spiramycin (**2**) from acetylenic aldehyde **38** and the (*S*)-**36** carbamate (See Scheme 3). Conducted under *n*-BuLi/TMEDA/Ti(O*i*-Pr)$_4$ conditions, this reaction led, via a (*R*)-**'Ti'-III** intermediate, to the allylic alcohol **39** as a single diastereomer in 70% yield and 80% ee (Scheme 11).



Scheme 11

In another application of this strategy, optically active aldehyde **32**, prepared earlier, was submitted to the reaction of the optically active (*R*)-**'Ti'-III** allyltitanium, derived from (*S*)-**36** under *n*-BuLi/TMEDA/Ti(O*i*-Pr)$_4$ conditions. This expected aldehyde allylation, carried out under double stereodifferentiation, gave access to compound **40** as the only diastereomer in 80% chemical yield and 95% de (Scheme 12).



Scheme 12

In this work, an efficient synthesis of a C1-C7 fragment **40** of spiramycin (**2**) was achieved with total stereocontrol of C5 and C6 centres using optically active secondary γ-oxygenated allyl carbamates. These compounds generate optically active secondary γ-alkoxy allyltitanium reagents that react with aldehydes with a good enantiomeric excess (80%) under simple asymmetric induction, but also with a total diastereocontrol in the case of double stereodifferentiation.

For general introduction to the experimental part, see Ref.[12]

5-(Benzyloxy)pent-2-yn-1-ol (10)

To a suspension of NaH (60% in oil, 13.7 g, 342 mmol, 1.2 equiv) in anhyd THF (120 mL) at 0 °C was slowly added a solution of but-3-yn-1-ol (**9**; 20 g, 285 mmol) in Et_2O (120 mL). The resulting solution was stirred for 20 min at 20 °C and freshly distilled benzyl bromide (37.3 g, 313.5 mmol, 1.1 equiv) in anhyd THF (60 mL) was added along with NaI (500 mg). After stirring for 8 h at 20 °C, the mixture was treated at 0 °C with 1 M aq HCl (75 mL) and extracted with Et_2O. The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The oily residue was purified by distillation to give the 4-(benzyloxy)butyne as a colourless oil (42.9 g, 94%); bp 83 °C/2 mbar.

4-(Benzyloxy)butyne

IR (CCl_4): 3329, 3040, 2216 cm^{-1}.

^{1}H NMR (270 MHz): δ = 2.01 (t, *J* = 2.5 Hz, 1 H, H-1), 2.55 (td, *J* = 7.0, 2.5 Hz, 2 H, CH_2-3), 3.62 (t, *J* = 7.0 Hz, 2 H, CH_2-4), 4.56 (s, 2 H, PhC*H*$_2$), 7.21–7.42 (m, 5 H, C_6H_5).

^{13}C NMR (67.8 MHz): δ = 19.7 (CH_2-3), 65.2 (CH_2-4), 68.9 (≡CH-

1), 73.2 (Ph*C*H$_2$), 81.1 (≡C-2), 127.4 (2 CH, C$_6$H$_5$), 128.2 (2 CH, C$_6$H$_5$), 128.5 (CH, C$_6$H$_5$), 138.6 (C, C$_6$H$_5$).

MS (CI, NH$_3$): *m*/*z* = 161 (MH$^+$).

To a solution of 4-(benzyloxy)butyne (17 g, 106 mmol) in anhyd THF (120 mL) at –78 °C was slowly added *n*-BuLi (1.6 M in hexane, 73 mL, 116 mmol, 1.1 equiv). After stirring for 15 min, the temperature was then allowed to reach 0 °C and a stream of formaldehyde, obtained by depolymerisation of dried paraformaldehyde (11.1 g, 119 mmol, 1.1 equiv) at 200 °C, was blown on the surface of the anion solution. After stirring for 5 h at 20 °C, 1 M aq HCl (50 mL) was added. After extraction with Et$_2$O, drying (Na$_2$SO$_4$) and filtration, the solvent was removed under reduced pressure. The crude oil was purified by flash chromatography on silica gel (hexane–EtOAc, 70:30) to give **10** as a colourless oil (17.0 g, 85%).

10

IR (CCl$_4$): 3650, 3470, 3040, 2280, 2220 cm^{-1}.

^{1}H NMR (200 MHz): δ = 1.82 (t, *J* = 3.0 Hz, 1 H, OH), 2.55 (tt, *J* = 7.0, 2.5 Hz, 2 H, CH$_2$-4), 3.58 (dt, *J* = 3.0, 2.5 Hz, 2 H, CH$_2$-1), 4.26 (t, *J* = 7.0 Hz, 2 H, CH$_2$-5), 4.58 (s, 2 H, PhC*H*$_2$), 7.2–7.4 (m, 5 H, C$_6$H$_5$).

^{13}C NMR (50.3 MHz): δ = 19.7 (CH$_2$-4), 50.6 (CH$_2$-1), 67.9 (CH$_2$-5), 72.5 (Ph*C*H$_2$), 79.4 and 82.3 (C≡C), 127.3 (3 CH, C$_6$H$_5$), 128.0 (2 CH, C$_6$H$_5$), 137.7 (C, C$_6$H$_5$).

MS (CI, NH$_3$): *m*/*z* = 191 (MH$^+$).

Anal Calcd for C$_{12}$H$_{14}$O$_2$: C, 75.76; H, 7.42. Found: C, 75.83; H, 7.56.

5-(Benzyloxy)pent-2-yn-1-al (11)

Method A; Using Iodoxybenzoic Acid (IBX): To a solution of **10** (1.5 g, 7.9 mmol) in anhyd DMSO (15 mL) at 20 °C was slowly added a solution of IBX (3.31 g, 12 mmol, 1.5 equiv) in anhyd DMSO (20 mL). After stirring for 4 h, H$_2$O (20 mL) was added and the reaction mixture was filtered on a pad of Celite. After extraction with Et$_2$O, washing with NaHCO$_3$, drying (Na$_2$SO$_4$) and filtration, the solvent was removed under reduced pressure. The crude oil was purified by flash chromatography on silica gel (hexane–EtOAc, 70:30) to give the aldehyde **11** as a colourless to pale yellow oil (995 mg, 67%).

Method B, Using MnO$_2$: To a solution of **10** (3 g, 15.8 mmol) in CH$_2$Cl$_2$ (30 mL) was added portionwise MnO$_2$ (6.9 g, 79 mmol, 5 equiv) until the starting material had completely disappeared. After stirring for 4 h, the reaction mixture was filtered on a pad of Celite and the solvent was removed under reduced pressure. The crude oil was purified by flash chromatography on silica gel (hexane–EtOAc, 70:30) to give **11** as a colourless to pale yellow oil (1.9 g, 67%).

IR (CCl$_4$): 2200, 1730 cm^{-1}.

^{1}H NMR (200 MHz): δ = 2.74 (t, *J* = 7.0 Hz, 2 H, CH$_2$-4), 3.62 (t, *J* = 7.0 Hz, 2 H, CH$_2$-5), 4.57 (s, 2 H, PhC*H*$_2$), 7.2–7.4 (m, 5 H, C$_6$H$_5$), 9.18 (s, 1 H, H-1).

^{13}C NMR (50.3 MHz): δ = 20.7 (CH$_2$-4), 67.1 (CH$_2$-5), 72.5 (Ph*C*H$_2$), 82.2 and 95.5 (C≡C), 127.7 (3 CH, C$_6$H$_5$), 128.4 (2 CH, C$_6$H$_5$), 137.8 (C, C$_6$H$_5$), 175.8 (C-1).

MS (CI, NH$_3$): *m*/*z* = 189 (MH$^+$).

Anal Calcd for C$_{12}$H$_{12}$O$_2$: C, 76.57; H, 6.43. Found: C, 76.63; H, 6.52.

4-[(Triisopropylsilyl)oxy]butyne (12)

To a solution of commercial but-3-yn-1-ol (**9**; 5 g, 5.4 mL, 71.3 mmol) in anhyd CH$_2$Cl$_2$ (60 mL) at 0 °C were added 2,6-lutidine (24.8 mL, 214 mmol, 3 equiv) and TIPSOTf (21.6 mL, 78.4 mmol, 1.1 equiv). After stirring for 2 h at 20 °C, the reaction mixture was treated with 2 M aq HCl (70 mL) and extracted with Et$_2$O. The organic layer was washed with aq 2 M HCl (70 mL), brine, dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure. The residue was purified by distillation to give the title compound **12** as a colourless oil (14.5 g, 90%); bp 71 °C/0.1 mbar.

IR (CCl$_4$): 2110 cm^{-1}.

^{1}H NMR (270 MHz): δ = 1.07 {m, 21 H, 3 CH and 6 CH$_3$, Si[CH(CH$_3$)$_2$]$_3$}, 1.97 (t, *J* = 2.6 Hz, 1 H, ≡CH-1), 2.45 (td, *J* = 7.3, 2.6 Hz, 2 H, CH$_2$-3), 3.83 (t, *J* = 7.3 Hz, 2 H, CH$_2$-4).

^{13}C NMR (67.8 MHz): δ = 12.2 {3 CH, Si[*C*H(CH$_3$)$_2$]$_3$}, 18.2 {6 CH$_3$, Si[CH(*C*H$_3$)$_2$]$_3$}, 23.4 (CH$_2$-3), 62.3 (CH$_2$-4), 80.2 and 81.7 (C≡CH).

MS (CI, NH$_3$): *m*/*z* = 227 (MH$^+$).

Anal Calcd for C$_{13}$H$_{26}$OSi: C, 68.96; H, 11.57. Found: C, 69.05; H, 11.63.

5-[(Triisopropylsilyl)oxy]pent-2-yn-1-ol (13)

To a solution of **12** (8 g, 35.4 mmol) in anhyd THF (100 mL) at –78 °C was slowly added *n*-BuLi (2.5M in hexane, 15.6 mL, 38.9 mmol, 1.1 equiv). After stirring for 15 min, the temperature was then allowed to reach 0 °C and a stream of formaldehyde, obtained by depolymerisation of dried paraformaldehyde (3.71 g, 38.9 mmol, 1.1 equiv) at 200 °C, was blown on the surface of the anion solution. After stirring for 5 h at 20 °C, 1 M aq HCl (50 mL) was added. After extraction with Et$_2$O, drying (Na$_2$SO$_4$) and filtration, the solvent was removed under reduced pressure. The crude oil was purified by flash chromatography on silica gel (hexane–EtOAc, 70:30) to give the alcohol **13** as a pale yellow oil (7.52 g, 83%).

IR (CCl$_4$): 3333, 2227 cm^{-1}.

^{1}H NMR (270 MHz): δ = 1.07 {m, 21 H, 3 CH and 6 CH$_3$, Si[CH(CH$_3$)$_2$]$_3$}, 1.62 (s, 1 H, OH), 2.36 (tt, *J* = 7.3, 2.2 Hz, 2 H, CH$_2$-4), 3.82 (t, *J* = 7.3 Hz, 2 H, CH$_2$-5), 4.24 (t, *J* = 2.2 Hz, 2 H, CH$_2$-1).

^{13}C NMR (67.8 MHz): δ = 12.2 {3 CH, Si[*C*H(CH$_3$)$_2$]$_3$}, 18.2 {6 CH$_3$, Si[CH(*C*H$_3$)$_2$]$_3$}, 23.4 (CH$_2$-4), 51.5 (CH$_2$-1), 60.8 (CH$_2$-5), 79.8 and 83.5 (C≡C).

MS (CI, NH$_3$): *m*/*z* = 274 (MH$^+$ + 17), 257 (MH$^+$).

Anal Calcd for C$_{14}$H$_{28}$O$_2$Si: C, 65.57; H, 11.00. Found: C, 65.68; H, 11.13.

4-[(2-Tetrahydropyranyl)oxy]butyne (14)

To a solution of 3,4-dihydro-2*H*-pyran (25 g, 27 mL, 297 mmol, 1.1 equiv) in 10 N aq HCl (0.3 mL) was added but-3-yn-1-ol (**9**; 18.9 g, 20.4 mL, 270 mmol) keeping the temperature at 50 °C. After completion of the addition, the solution was stirred for 2.5 h at 20 °C. The mixture was diluted with Et$_2$O at r.t. and the Et$_2$O layer was washed with a sat. aq NaHCO$_3$ (2 ×). The Et$_2$O phase was dried (Na$_2$SO$_4$), filtered, and the solvent was removed under reduced pressure. The crude oil was purified by distillation to furnish the title compound **14** as a colourless oil (40.74 g, 98%).; bp 70 °C/2 mbar.

IR (CCl$_4$): 2110 cm^{-1}.

^{1}H NMR (200 MHz): δ = 1.42–1.88 (m, 6 H, CH$_2$-3′ + CH$_2$-4′+ H$_2$-5′), 1.94 (t, *J* = 2.5 Hz, 1 H, ≡CH-1), 2.45 (td, *J* = 7.0, 2.5 Hz, 2 H, CH$_2$-3), 3.45, 3.7 (2 m, 2 H, CH$_2$-4), 3.45–3.77 (m, 1 H, Ha-6′), 3.77–3.94 (m, 1 H, Hb-6′), 4.6 (t, *J* = 3.5 Hz, 1 H, H-2′).

^{13}C NMR (50.3 MHz): δ = 19.3 (CH$_2$-5′), 19.9 (CH$_2$-3), 25.3 (CH$_2$-4′), 30.4 (CH$_2$-3′), 62.1 (CH$_2$-6′), 65.4 (CH$_2$-4), 69.1 (≡CH-1), 81.3 (≡C-2), 98.7 (CH-2′).

MS (CI, NH$_3$): *m*/*z* = 172 (MH$^+$ + 17), 155 (MH$^+$).

Anal Calcd for C$_9$H$_{14}$O$_2$: C, 70.10; H, 9.15. Found: C, 70.24; H, 9.21.

5-[(2-Tetrahydropyranyl)oxy]pent-2-yn-1-ol (15)

To a solution of **14** (22 g, 143 mmol) in anhyd THF (150 mL) at –78 °C was slowly added *n*-BuLi (1.6 M in hexane, 96.5 mL, 154.5 mmol, 1.08 equiv). After stirring for 15 min, the temperature was then allowed to reach 0 °C and a stream of formaldehyde, obtained by depolymerisation of dried paraformaldehyde (1.6 g, 157 mmol, 1.1 equiv) at 200 °C, was blown on the surface of the anion solution. After stirring for 5 h at 20 °C, 1 M aq HCl (50 mL) was added. After extraction with Et_2O, drying (Na_2SO_4) and filtration, the solvent was removed under reduced pressure. The crude oil was purified by flash chromatography on silica gel (hexane–EtOAc, 70:30) to give **15** as a colourless oil (23.6 g, 90%).

IR (CCl_4): 3610, 3420, 2110 cm^{-1}.

^1H NMR (200 MHz): δ = 1.40–1.89 (m, 6 H, CH_2-3′ + CH_2-4′ + CH_2-5′), 2.48 (m, 2 H, CH_2-4), 2.49 (br s, 1 H, OH), 3.45, 3.74 (2 m, 2 H, CH_2-5), 3.57–3.74 (m, 1 H, Ha-6′), 3.75–3.90 (m, 1 H, Hb-6′), 4.17 (m, 2 H, CH_2-1), 4.57 (t, *J* = 3.5 Hz, 1 H, CH-2′).

^{13}C NMR (50.3 MHz): δ = 19.3 (CH_2-5′), 20.1 (CH_2-4), 25.3 (CH_2-4′), 30.4 (CH_2-3′), 51.0 CH_2-1), 62.2 (CH_2-6′), 65.6 (CH_2-5), 79.5 and 82.9 (C≡C), 98.7 (CH-2′).

MS (CI, NH_3): *m*/*z* = 185 (MH^+).

Anal Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.23; H, 8.77.

(2*E*)-1-{[(*N*,*N*-Diisopropyl)carbamoyl]oxy}-5-[2-(tetrahydropyranyl)oxy]pent-2-ene (16)

To a solution of alcohol **15** (15.2 g, 83 mmol) in anhyd Et_2O (85 mL) at 0 °C was slowly added a 1 M solution of $LiAlH_4$ in THF (108 mL, 108 mmol, 1.3 equiv). The reaction mixture was placed in a preheated bath and refluxed for 2.5 h. The solution was then cooled to 0 °C, and carefully and successively treated with H_2O (28 mL), a 7.5 M aq solution of NaOH (14 mL), and H_2O (28 mL). The precipitate was filtered, washed with Et_2O and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane–EtOAc, 50:50) to give (2*E*)-5-[(2-tetrahydropyranyl)oxy]pent-2-en-1-ol as a colourless oil (13.6 g, 88%).

(2*E*)-5-[(2-Tetrahydropyranyl)oxy]pent-2-en-1-ol

IR (CCl_4): 3600, 3440 cm^{-1}.

^1H NMR (200 MHz): δ = 1.40–1.97 (m, 6 H, CH_2-3′ + CH_2-4′ + CH_2-5′), 2.35 (m, 2 H, CH_2-4), 3.40, 3.71 (2 m, 2 H, CH_2-5), 3.48 (m, 1 H, CHa-6′), 3.76 (m, 1 H, CHb-6′), 4.07 (m, 2 H, CH_2-1), 4.54 (t, *J* = 3.5 Hz, 1 H, CH-2′), 5.55–5.76 (m, 2 H, CH=CH).

^{13}C NMR (50.3 MHz): δ = 19.6 (CH_2-5′), 25.4 (CH_2-4′), 30.6 (CH_2-3′), 32.5 (CH_2-4), 62.3 (CH_2-6′), 63.5 (CH_2-1), 66.8 (CH_2-5), 98.8 (CH-2′), 129.1 and 131.0 (CH=CH).

MS (CI, NH_3): *m*/*z* = 187 (MH^+).

To a suspension of NaH (60% in oil, 3.87 g, 96.8 mmol, 1.2 equiv) in anhyd THF (40 mL) at 0 °C, was slowly added a solution of (2*E*)-5-[(2-tetrahydropyranyl)oxy]pent-2-en-1-ol (15 g, 80.6 mmol) in THF (40 mL). The resulting solution was stirred for 20 min at 20 °C and a solution of diisopropylcarbamoyl chloride (15.84 g, 96.8 mmol, 1.2 equiv) in anhyd THF (60 mL) was added. After stirring for 5 h at 20 °C, the mixture was treated at 0 °C with 1 M aq HCl (50 mL) and extracted with Et_2O. The combined organic phases were then washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The oily residue was purified by flash chromatography on silica gel (hexane–EtOAc, 80:20), or distillation, to give the title compound **16** as a colourless oil (22.7 g, 90%); bp 160 °C/2 mbar.

16

IR (CCl_4): 1670 cm^{-1}.

^1H NMR (200 MHz): δ = 1.20 {d, *J* = 7.0 Hz, 12 H, 4 CH_3, N[CH(CH_3)$_2$]$_2$}, 1.44–1.95 (m, 6 H, 3 CH_2, CH_2-3′ + CH_2-4′ + CH_2-5′), 2.43 (q, *J* = 7.0 Hz, 2 H, CH_2-4), 3.42, 3.60 (2 m, 2 H, Ha-5 + Ha-6′), 3.69–4.05 {m, 4 H, N[CH(CH_3)$_2$]$_2$ + Hb-5 + Hb-6′}, 4.56 (d, *J* = 5.0 Hz, 2 H, H_2-1), 4.62 (m, 1 H, H-2′), 5.65 (dt, *J* = 16.0, 5.0 Hz, 1 H, =CH-2), 5.79 (dt, *J* = 16.0, 5.0 Hz, 1 H, =CH-3).

^{13}C NMR (50.3 MHz): δ = 19.3 (CH_2-5′), 20.8 {4 CH_3, N[CH(CH_3)$_2$]$_2$}, 25.3 (CH_2-4′), 30.5 (CH_2-3′), 32.5 (CH_2-4), 45.6 {2 CH, N[CH(CH_3)$_2$]$_2$}, 62.0 (CH_2-6′), 64.9 (CH_2-1), 66.5 (CH_2-5), 98.5 (CH-2′), 126.8 (=CH-2), 130.7 (=CH-3), 155.3 (C=O).

MS (CI, NH_3): *m*/*z* = 331 (MH^+ + 17), 314 (MH^+).

Anal. Calcd for $C_{17}H_{31}O_4N$: C, 65.14; H, 9.97; N, 4.47. Found: C, 65.17; H, 9.95; N, 4.52.

(2*E*)-1-{[(*N*,*N*-Diisopropyl)carbamoyl]oxy}-5-{[triisopropylsilyl)]oxy}pent-2-ene (17)

To a solution of **16** (12.4 g, 39 mmol) in MeOH (100 mL) was added Amberlyst 15. After stirring for 4 h at r.t., the reaction mixture was filtered and the solvent was removed under reduced pressure. The crude oily residue was purified by flash chromatography on silica gel (hexane–EtOAc, 60:40) to give (2*E*)-1-{[(*N*,*N*-diisopropyl)carbamoyl]oxy}pent-2-en-5-ol as a colourless oil (8.6 g, 98%).

(2*E*)-1-{[(*N*,*N*-Diisopropyl)carbamoyl]oxy}pent-2-en-5-ol

IR (CCl_4): 3630, 1660 cm^{-1}.

^1H NMR (200 MHz): δ = 1.18 {d, *J* = 6.5 Hz, 12 H, 4 CH_3, N[CH(CH_3)$_2$]$_2$}, 2.10 (br s, 1 H, OH), 2.17 (q, *J* = 6.0 Hz, 2 H, CH_2-4), 3.64, (t, *J* = 6.0 Hz, 2 H, CH_2-5), 3.73, 3.98 {m, 2 H, N[CH(CH_3)$_2$]$_2$}, 4.51 (d, *J* = 5.0 Hz, 2 H, CH_2-1), 5.68 (m, 2 H, CH=CH).

^{13}C NMR (50.3 MHz): δ = 21.0 {4 CH_3, N[CH(CH_3)$_2$]$_2$}, 35.6 (CH_2-4), 45.8 {2 CH, N[CH(CH_3)$_2$]$_2$}, 61.6 (CH_2-5), 64.9 (CH_2-1), 128.4 and 130.4 (CH=CH), 155.4 (C=O).

MS (CI, NH_3): *m*/*z* = 230 (MH^+).

To a solution of (2*E*)-1-{[(*N*,*N*-diisopropyl)carbamoyl]oxy}pent-2-en-5-ol (15 g, 65.5 mmol) in anhyd CH_2Cl_2 (100 mL) at 0 °C were added 2,6 lutidine (22.8 mL, 196.5 mmol, 3 equiv) and TIPSOTf (19.8 mL, 72 mmol, 1.1 equiv). After stirring for 3 h at 20 °C, the reaction mixture was treated with 2 M aq HCl (60 mL) and extracted with Et_2O. The organic layer was washed with aq 2 M HCl (60 mL), brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane–EtOAc, 90:10) to give the title compound **17** as a colourless oil (23.95 g, 95%).

17

IR (CCl_4): 1670 cm^{-1}.

^1H NMR (200 MHz): δ = 1.04 {m, 21 H, 3 CH + 6 CH_3, Si[CH(CH_3)$_2$]$_3$}, 1.19 {d, *J* = 6.5 Hz, 12 H, 4 CH_3, N[CH(CH_3)$_2$]$_2$}, 2.29 (q, *J* = 6.0 Hz, 2 H, CH_2-4), 3.73 (t, *J* = 6.0 Hz, 2 H, CH_2-5), 3.90 {m, 2 H, N[CH(CH_3)$_2$]$_2$}, 4.52 (d, *J* = 6.0 Hz, 2 H, CH_2-1), 5.64 (dt, *J* = 16.0, 6.0 Hz, 1 H, CH=C*H*, H-2), 5.78 (dt, *J* = 16.0, 6.0 Hz, 1 H, C*H*=CH, H-3).

^{13}C NMR (50.3 MHz): δ = 12.3 {3 CH, Si[CH(CH_3)$_3$]$_3$}, 17.7 {6 CH_3, Si[CH(CH_3)$_3$]$_3$}, 21.0 {4 CH_3, N[CH(CH_3)$_2$]$_2$}, 36.1 (CH_2-4), 45.8 {2 CH, N[CH(CH_3)$_2$]$_2$}, 63.0 (CH_2-5), 65.3 (CH_2-1), 126.9 (=CH-2), 131.3 (=CH-3), 155.5 (C=O).

MS (CI, NH_3): *m*/*z* = 386 (MH^+).

Anal. Calcd for $C_{21}H_{43}O_3NSi$: C, 65.40; H, 11.24; N, 3.63. Found: C, 65.43; H, 11.28; N, 3.62.

(7*Z*,5*S,6*S**)-1-Benzyloxy-8-{[(*N*,*N*-diisopropyl)carbamoyl]oxy}-5-hydroxy-6-{2-[(triisopropylsilyl)oxy]ethyl}oct-7-ene-3-yne [(±)-18]**

To a solution of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, 34.5 mL, 229 mmol, 2.2 equiv) in anhyd Et_2O (150 mL) at –78 °C, under argon, was added *n*-BuLi (1.6 M in hexane, 143 mL, 229 mmol, 2.2 equiv). After stirring for 1 h at –78 °C, a solution of the allyl carbamate **17** (40 g, 104 mmol, 1.1 equiv) in anhyd Et_2O (100 mL), was slowly added. After stirring for 1 h at –78 °C, Ti(O*i*-Pr)$_4$ (74 mL, 260 mmol, 2.5 equiv) was rapidly added and the reaction mixture was stirred for 45 min at –78 °C (transmetallation time). Then, the acetylenic aldehyde **11** (17.8 g, 94.5 mmol) diluted in anhyd Et_2O (50 mL) was added. The reaction mixture was stirred for 3 h at –78 °C and quenched by transferring to a vigorously stirring mixture of aq 3 M HCl (150 mL) and Et_2O (100 mL) at –20 °C. The temperature was allowed to reach 20 °C and the resulting solution was eventually filtered on a pad of Celite to remove titanium salts and extracted with Et_2O. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane–EtOAc, 80:20), to give the title compound (±)-**18** as a yellow oil (45.0 g, 83%).

IR (CCl_4): 3646, 3396, 2948, 1710 cm^{-1}.

^{1}H NMR (400 MHz): δ = 1.06 {m, 21 H, 3 CH + 6 CH_3, Si[CH(CH_3)$_2$]$_3$}, 1.15 {d, *J* = 6.5 Hz, 12 H, 4 CH_3, N[(CH(CH_3)$_2$]$_2$}, 1.50–1.70 (m, 1 H, Ha-1′), 1.97–2.15 (m, 1 H, Hb-1′), 2.51 (td, *J* = 7.0, 3.0 Hz, 2 H, CH_2-2), 2.78–2.93 (m, 1 H, H-6), 3.58 (t, *J* = 7.0 Hz, 2 H, CH_2-1), 3.62–3.88 (m, 2 H, OH, Ha-2′), 3.70–3.88 [m, 2 H, Hb-2′ + NC*H*(CH_3)$_2$], 4.0–4.10 [m, 1 H, NC*H*(CH_3)$_2$], 4.31–4.40 (m, 1 H, H-5), 4.51 (s, 2 H, PhH_2O), 4.67 (dd, *J* = 6.0, 9.0 Hz, 1 H, C*H*=CH, H-7), 7.06 (d, *J* = 6.0 Hz, 1 H, CH=C*H*OCb, H-8), 7.2–7.4 (m, 5 H, C_6H_5).

^{13}C NMR (100.6 MHz): δ = 11.7 {3 CH, Si[*C*H(CH_3)$_2$]$_3$}, 17.7 {6 CH_3, Si[CH(*C*H_3)$_2$]$_3$}, 20.0 (CH_2-2), 20.1 and 21.2 {4 CH_3, N[CH(*C*H_3)$_2$]$_2$}, 34.1 (CH_2-1′), 40.7 (CH-6), 45.8 and 45.9 {2 CH, N[C*H*(CH_3)$_2$]$_2$}, 62.0 (CH_2-2′), 65.1 (CH-5), 68.3 (CH_2-1), 72.7 (Ph*C*H$_2$), 82.8 and 84.6 (C≡C), 110.3 (=CH-7), 127.4 (3 CH, C_6H_5), 128.2 (2 CH, C_6H_5), 131.3 (=CH-8), 136.0 (C, C_6H_5), 152.1 (C-1).

MS (CI, NH_3): *m*/*z* = 574 (MH^+).

Anal Calcd for $C_{33}H_{55}NO_5Si$: C, 69.07; H, 9.66; N, 2.44. Found: C, 69.14; H, 9.72; N, 2.48

(2*R*,3*S*)-7-Benzyloxy-3-[(triethylsilyl)oxy]-2-{2-[(triisopropylsilyl)oxy]ethyl}hept-4-ynal [(±)-19]

To a solution of alcohol (±)-**18** (8.7 g, 15.2 mmol) in anhyd CH_2Cl_2 (80 mL) at 0 °C were added 2,6-lutidine (5.3 mL, 45.6 mmol, 3 equiv) and TESOTf (3.8 mL, 16.7 mmol, 1.1 equiv). After stirring for 2 h at 20 °C, the reaction mixture was treated with 1 M aq HCl (60 mL) and extracted with Et_2O. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane–EtOAc, 90:10) to give the corresponding triethylsilyloxy derivative (8.14 g, 78%).

Triethylsilyloxy Derivative of 18

IR (CCl_4): 2963, 1711 cm^{-1}.

^{1}H NMR (400 MHz): δ = 0.55–0.63 [m, 6 H, 3 CH_2, Si(CH_2CH$_3$)$_3$], 0.89–1.02 [m, 9 H, 3 CH_3, Si(CH$_2$CH_3)$_3$], 1.04 {m, 21 H, 3 CH + 6 CH_3, Si[CH(CH_3)$_2$]$_3$}, 1.23 {d, *J* = 6.5 Hz, 12 H, 4 CH_3, N[CH(CH_3)$_2$]$_2$}, 1.50–1.68 (m, 1 H, Ha-1′), 1.91–2.10 (m, 1 H, Hb-1′), 2.50 (td, *J* = 7.0, 3.0 Hz, 2 H, CH_2-2), 2.78–2.85 (m, 1 H, H-6), 3.58 (t, *J* = 7.0 Hz, 2 H, CH_2-1), 3.62–3.88 [m, 2 H, NC*H*(CH_3)$_2$ + Ha-2′), 3.75–4.05 [m, 2 H, Hb-2′ + NC*H*(CH_3)$_2$], 4.30–4.35 (m, 1 H, H-5), 4.52 (s, 2 H, PhCH_2), 4.62 (dd, *J* = 6.0, 9.0 Hz, 1 H, =CH-7), 7.08 (d, *J* = 6.0 Hz, 1 H, =CH-8), 7.2–7.4 (m, 5 H, C_6H_5).

^{13}C NMR (100.6 MHz): δ = 4.7 [3 CH_2, Si(CH_2CH$_3$)$_3$], 6.7 [3 CH_3, Si(CH$_2$CH_3)$_3$], 11.9 {3 CH, Si[C*H*(CH_3)$_2$]$_3$}, 17.9 {6 CH_3, Si[CH(CH_3)$_2$]$_3$}, 20.2 (CH_2-2), 20.3 and 21.4 {4 CH_3, N[CH(CH_3)$_2$]$_2$}, 33.2 (CH_2-1′), 39.6 (CH-6), 45.8 and 46.4 {2 CH, N[C*H*(CH_3)$_2$]$_2$}, 61.9 (CH_2-2′), 65.5 (CH-5), 68.5 (CH_2-1), 72.9 (Ph*C*H$_2$), 81.1 and 81.7 (C≡C), 110.6 (=CH-7), 127.6 (3 CH, C_6H_5), 128.3 (2 CH, C_6H_5), 136.2 (=CH-8), 138.0 (C, C_6H_5), 152.5 (C=O).

MS (CI, NH_3): *m*/*z* = 688 (MH^+).

Ozone was bubbled into a solution of the above prepared carbamate (5.28 g, 7.7 mmol) in hexane–MeOH (99:1, 200 mL) at –78 °C until the solution turned light blue. Me_2S (20 mL) was added at –78 °C, and the mixture was allowed to warm to r.t. and stirred for 4 h. The solvent was partially removed under reduced pressure and the solution was washed with H_2O. The organic layer was dried (Na_2SO_4), filtered and evaporated to give the aldehyde (±)-**19** as a pale yellow oil (4.18 g, quant.).

19

IR (CCl_4): 2962, 2870, 1728 cm^{-1}.

^{1}H NMR (400 MHz): δ = 0.55–0.63 [m, 6 H, 3 CH_2, Si(CH_2CH$_3$)$_3$], 0.88–1.02 [m, 9 H, 3 CH_3, Si(CH$_2$CH_3)$_3$], 1.04 {m, 21 H, 3 CH + 6 CH_3, Si[CH(CH_3)$_2$]$_3$}, 1.81–1.85 (m, 1 H, Ha-1′), 1.93–2.08 (m, 1 H, Hb-1′), 2.53 (td, *J* = 7.0, 2.0 Hz, 2 H, CH_2-6), 2.63–2.72 (m, 1 H, H-2), 3.57 (t, *J* = 7.0 Hz, 2 H, CH_2-7), 3.81–3.88 (m, 2 H, CH_2-2′), 4.50 (s, 2 H, PhCH_2), 4.70 (dt, *J* = 6.0, 2.0 Hz, 1 H, H-3), 7.3–7.4 (m, 5 H, C_6H_5), 9.01 (d, *J* = 2.0 Hz, 1 H, H-1).

^{13}C NMR (100.6 MHz): δ = 4.8 [3 CH_2, Si(*C*H$_2$CH$_3$)$_3$], 6.8 [3 CH_3, Si(CH$_2$*C*H$_3$)$_3$], 11.9 {3 CH, Si[*C*H(CH$_3$)$_2$]$_3$}, 18.0 {6 CH_3, Si[CH(*C*H$_3$)$_2$]$_3$}, 20.2 (CH_2-6), 29.6 (CH_2-1′), 55.8 (CH-2), 61.2 (CH_2-2′), 62.8 (CH-3), 68.3 (CH_2-7), 73.0 (Ph*C*H$_2$), 80.5 and 83.7 (C≡C), 127.7 (3 CH, C_6H_5), 128.4 (2 CH, C_6H_5), 138.0 (C, C_6H_5), 203.6 (C=O).

MS (CI, NH_3): *m*/*z* = 547 (MH^+).

Anal Calcd for $C_{31}H_{54}O_4Si_2$: C, 68.08; H, 9.95. Found: C, 68.21; H, 10.11.

(9*Z*,5*R*,6*R*,7*S*,8*S*)-1-Benzyloxy-10-[(*N*,*N*-diisopropylcarbamoyl)oxy]-7-hydroxy-8-methyl-5- [(triethylsilyl)oxy]-6-{-2-[(triisopropylsilyl)oxy]ethyl}dec-9-ene-3-yne (Cram-20) and (9*Z*,5*S*,6*S*,7*S*,8*S*)-1-Benzyloxy-10-[(*N*,*N*-diisopropylcarbamoyl)oxy]-7-hydroxy-8-methyl-5- [(triethylsilyl)oxy]-6-{-2-[(triisopropylsilyl)oxy]ethyl}dec-9-ene-3-yne (*anti*-Cram-21)

To a rapidly stirred solution of the crotyl carbamate (900 mg, 4.52 mmol, 2.5 equiv) and (–)-sparteine (1.10 g, 4.7 mmol, 2.6 equiv) in pentane (6.4 mL) and cyclohexane (0.75 mL) at –78 °C was added a solution of *n*-BuLi (1.6 M in hexane, 2.93 mL, 4.7 mmol, 2.6 equiv). White crystals appeared after 10 min. After allowing 3 h for crystallisation at –78 °C, a precooled (–78 °C, 30 min) solution of Ti(O*i*-Pr)$_4$ (4.05 mL, 13.5 mmol, 6.5 equiv) in pentane (10 mL) was quickly added via cannula to the reaction mixture of lithio carbamate which became limpid and turned red. After 20 min at –78 °C, aldehyde (±)-**19** (990 mg, 1.81 mmol) in pentane (4 mL) was added to the red solution. The mixture was stirred for 2 h at –78 °C and quenched by transferring to a vigorously stirred mixture of 1 M aq HCl (25 mL) and Et_2O at 0 °C. The temperature was allowed to reach 20 °C, eventually filtered to remove titanium salts and extracted with Et_2O. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by two successive flash chromatography on silica gel (hexane–EtOAc, 80:20), to give the title compounds **Cram-20** (606 mg, 45%) and ***anti*-Cram-21** (404 mg, 30%) as colourless oils.

Cram-20

$[\alpha]_D$ +10.8 (*c* = 1.6, MeOH).

IR (CCl_4): 3607, 2965, 2870, 1700 cm^{-1}.

^1H NMR (400 MHz): δ = 0.55–0.63 [m, 6 H, 3 CH_2, Si(CH_2CH_3)$_3$], 0.88–1.02 [m, 9 H, 3 CH_3, Si(CH_2CH_3)$_3$], 1.03 (d, *J* = 7.0 Hz, 3 H, CH_3-8), 1.04 {m, 21 H, 3 CH + 6 CH_3, Si[CH(CH_3)$_2$]$_3$}, 1.25 {d, *J* = 6.5 Hz, 12 H, 4 CH_3, N[CH(CH_3)$_2$]$_2$}, 1.81–1.85 (m, 3 H, CH_2-1′ + H-6), 2.51 (td, *J* = 7.0, 3.0 Hz, 2 H, CH_2-2), 2.86 (m, 1 H, H-8), 3.56 (t, *J* = 7.0 Hz, 2 H, CH_2-1), 3.70 [m, 2 H, Ha-2′ + NC*H*(CH_3)$_2$], 3.85 (m, 2 H, Hb-2′ + H-7), 4.10 [m, 1 H, NC*H*(CH_3)$_2$], 4.5 (s, 2 H, PhCH_2), 4.58 (m, 1 H, H-5), 4.84 (dd, *J* = 6.5, 9.5 Hz, 1 H, =CH-9), 7.12 (d, *J* = 6.5 Hz, 1 H, =CH-10), 7.3–7.4 (m, 5 H, C_6H_5).

^{13}C NMR (100.6 MHz): δ = 4.6 [3 CH_2, Si(*C*H_2CH_3)$_3$], 6.8 [3 CH_3, Si(CH_2*C*H_3)$_3$], 11.9 {3 CH, Si[*C*H(CH_3)$_2$]$_3$}, 18.0 (CH_3-8), 18.1 {6 CH_3, Si[CH(*C*H_3)$_2$]$_3$}, 20.1 (CH_2-2), 20.4 and 21.2 {4 CH_3, N[CH(*C*H_3)$_2$]$_2$}, 28.2 (CH_2-1′), 33.4 (CH-8), 44.3 (CH-6), 45.3 and 46.4 {2 CH, N[*C*H(CH_3)$_2$]$_2$}, 62.3 (CH_2-2′), 64.7 (CH-5), 68.5 (CH_2-1), 73.0 (Ph*C*H_2), 75.4 (CH-7), 81.3 and 82.4 (C≡C), 113.4 (=CH-9), 127.7 (3 CH, C_6H_5), 128.4 (2 CH, C_6H_5), 135.2 (=CH-10), 138.0 (C, C_6H_5), 152.9 (C=O).

MS (CI, NH_3): *m*/*z* = 747 (MH^+).

Anal Calcd for $C_{42}H_{75}NO_6Si_2$: C, 67.60; H, 10.13; N, 1.88. Found: C, 67.75; H, 10.31; N, 1.75

anti-Cram-21

$[\alpha]_D$ –15.1 (*c* = 1.6, MeOH).

IR (CCl_4): 3607, 2965, 2870, 1700 cm^{-1}.

^1H NMR (400 MHz): δ = 0.55–0.63 [m, 6 H, 3 CH_2, Si(*C*H_2CH_3)$_3$], 0.88–1.02 [m, 9 H, 3 CH_3, Si(CH_2*C*H_3)$_3$], 1.03 (d, *J* = 7.0 Hz, 3 H, CH_3-8), 1.04 {m, 21 H, 3 CH + 6 CH_3, Si[CH(CH_3)$_2$]$_3$}, 1.25 {d, *J* = 6.5 Hz, 12 H, 4 CH_3, N[CH(*C*H_3)$_2$]$_2$}, 1.60–1.90 (m, 3 H, CH_2-1′ + H-6), 2.45 (td, *J* = 7.0, 3.0 Hz, 2 H, CH_2-2), 2.95 (m, 1 H, H-8), 3.50 (t, *J* = 7.0 Hz, 2 H, CH_2-1), 3.60–4.1 [m, 5 H, H_2-2′ + N[C*H*(CH_3)$_2$]$_2$ + H-7), 4.48 (s, 2 H, PhCH_2), 4.72 (m, 1 H, H-5), 4.85 (dd, *J* = 6.0, 9.0 Hz, 1 H, =CH-9), 7.08 (d, *J* = 6.0 Hz, 1 H, =CH-10), 7.3–7.4 (m, 5 H, C_6H_5).

^{13}C NMR (100.6 MHz): δ = 5.0 [3 CH_2, Si(*C*H_2CH_3)$_3$], 6.9 [3 CH_3, Si(CH_2*C*H_3)$_3$], 12.2 {3 CH, Si[*C*H(CH_3)$_2$]$_3$}, 18.2 (CH_3-8), 18.8 {6 CH_3, Si[CH(*C*H_3)$_2$]$_3$}, 20.4 (CH_2-2), 20.5 and 21.2 {4 CH_3, N[CH(*C*H_3)$_2$]$_2$}, 31.4 (CH_2-1′), 33.9 (CH-8), 45.2 (CH-6), 45.3 and 46.4 {2 CH, N[*C*H(CH_3)$_2$]$_2$}, 61.9 (CH_2-2′), 64.5 (CH-5), 68.6 (CH_2-1), 73.1 (Ph*C*H_2), 76.3 (CH-7), 82.2 and 83.5 (C≡C), 112.3 (=CH-9), 127.8 (3 CH, C_6H_5), 128.5 (2 CH, C_6H_5), 138.3 (=CH-10), 139.5 (C, C_6H_5), 153.0 (C=O).

MS (CI, NH_3): *m*/*z* = 747 (MH^+).

Anal Calcd for $C_{42}H_{75}NO_6Si_2$: C, 67.60; H, 10.13; N, 1.88. Found: C, 67.73; H, 10.34; N, 1.82

(6*S*,5*S*,2*R*,3*R*,5*RS*)- and (6*R*,5*R*,2*R*,3*R*,5*RS*)-6-[4-(Benzyloxy)but-1-ynyl]-3-methyl-5-{2-[triisopropylsilyl)oxy]ethyl}tetrahydropyran-2,5-diol (22 and 23)

The numbers given to lactols correspond to the respective precursor aldehydes.

To a solution of Cram-**20** or *anti*-Cram-**21** (500 mg, 0.67 mmol) in MeOH (10 mL) was added Amberlyst 15. After 15 min, the solution was filtered and concentrated under reduced pressure. The crude oil was chromatographed on silica gel (hexane–EtOAc, 70:30) to give the corresponding diol in 71% (300 mg) or in 87% yield (368 mg), respectively, as colourless oils.

(9*Z*,5*R*,6*R*,7*S*,8*S*)-Cram Diol Isomer

$[\alpha]_D$ –15.2 (*c* = 1.2, MeOH).

IR (CCl_4): 3607, 3523, 2947, 2871, 1710 cm^{-1}.

^1H NMR (400 MHz): δ = 0.95 (d, *J* = 7.0 Hz, 3 H, CH_3-8), 1.04 {m, 21 H, 3 CH + 6 CH_3, Si[CH(CH_3)$_2$]$_3$}, 1.25 {d, *J* = 6.5 Hz, 12 H, 4 CH_3, N[CH(C*H*$_3$)$_2$]$_2$}, 1.60–2.1 (m, 3 H, CH_2-1′ + H-6), 2.55 (td, *J* = 7.0, 3.0 Hz, 2 H, CH_2-2), 2.85 (m, 1 H, H-8), 3.57 (t, *J* = 7.0 Hz, 2 H, CH_2-1), 3.70–4.2 {m, 5 H, CH_2-2′ + N[C*H*(CH_3)$_2$]$_2$ + H-7}, 4.52 (s, 2 H, PhCH_2), 4.60 (m, 1 H, H-5), 4.65 (dd, *J* = 6.0, 9.0 Hz, 1 H, H-9), 7.10 (d, *J* = 6.0 Hz, 1 H, H-10), 7.30–7.40 (m, 5 H, C_6H_5).

^{13}C NMR (100.6 MHz): δ = 11.9 {3 CH, Si[*C*H(CH_3)$_2$]$_3$}, 17.1 (CH_3-3′), 17.9 {6 CH_3, Si[CH(*C*H_3)$_2$]$_3$}, 20.2 (CH_2-2), 20.4 and 21.2 {4 CH_3, N[CH(*C*H_3)$_2$]$_2$}, 26.9 (CH_2-1′), 34.1 (CH-8), 43.7 (CH-6), 46.8 and 47.8 {2 CH, N[*C*H(CH_3)$_2$]$_2$}, 61.7 (CH_2-2′), 64.2 (CH-5), 68.5 (CH_2-1), 72.9 (Ph*C*H_2), 76.1 (CH-7), 78.5 and 81.8 (C≡C), 113.2 (CH-9), 127.7 (3 CH, C_6H_5), 128.4 (2 CH, C_6H_5), 138.3 (CH-10). C, C_6H_5 and C=O were not observed.

MS (CI, NH_3): *m*/*z* = 632 (MH^+).

(9*Z*,5*S*,6*S*,7*S*,8*S*)-*anti*-Cram Diol Isomer

$[\alpha]_D$ –5.3 (*c* = 1.7, MeOH).

IR (CCl_4): 3607, 3403, 2948, 2870, 1711 cm^{-1}.

^1H NMR (400 MHz): δ = 1.03 (d, *J* = 7.0 Hz, 3 H, CH_3-8), 1.04 {m, 21 H, 3 CH + 6 CH_3, Si[CH(CH_3)$_2$]$_3$}, 1.25 {d, *J* = 6.5 Hz, 12 H, 4 CH_3, N[CH(C*H*$_3$)$_2$]$_2$}, 1.68 (m, 1 H, H_a-1′), 1.92 (m, 1 H, H_b-1′), 2.01 (m, 1 H, H-6), 2.36 (s, 1 H, OH), 2.52 (td, *J* = 7.0, 3.0 Hz, 2 H, CH_2-2), 3.04 (m, 1 H, H-8), 3.50 (m, 1 H, H-7), 3.57 (t, *J* = 7.0 Hz, 2 H, CH_2-1), 3.69 (m, 1 H, CH_a-2′), 3.80 and 4.08 {2 m, 2 H, N[C*H*(CH_3)$_2$]$_2$}, 3.83 (m, 1 H, H_b-2′), 4.55 (s, 2 H, PhCH_2), 4.71 (m, 1 H, H-5), 4.81 (dd, *J* = 9.0, 6.0 Hz, 1 H, H-9), 7.09 (d, *J* = 6.0 Hz, 1 H, H-10), 7.30–7.40 (m, 5 H, C_6H_5).

^{13}C NMR (100.6 MHz): δ = 11.8 {3 CH, Si[*C*H(CH_3)$_2$]$_3$}, 17.9 {6 CH_3, Si[CH(*C*H_3)$_2$]$_3$}, 18.2 (CH_3-3′), 20.2 (CH_2-2), 20.4 and 21.2 {4 CH_3, N[CH(*C*H_3)$_2$]$_2$}, 31.5 (CH_2-1′), 33.6 (CH-8), 45.3 and 46.4 {2 CH, N[*C*H(CH_3)$_2$]$_2$}, 46.0 (CH-6), 62.4 (CH_2-2′), 62.9 (CH-5), 68.4 (CH_2-1), 73.0 (Ph*C*H_2), 76.9 (CH-7), 81.9 and 83.1 (C≡C), 111.6 (CH-9), 127.7 (3 CH, C_6H_5), 128.3 (2 CH, C_6H_5), 138.3 (CH-10). C, C_6H_5 and C=O were not observed.

MS (CI, NH_3): *m*/*z* = 632 (MH^+).

Ozone was bubbled into a solution of the above Cram diol (2 g, 3.17 mmol) or *anti*-Cram diol (500 mg, 0.79 mmol) in hexane–MeOH (99:1, 50 mL) at –78 °C until the solution turned light blue. Me_2S (10 mL) was added at –78 °C, and the mixture was allowed to warm to r.t. and stirred for 6 h. The solvents were partially removed under reduced pressure and the organic solution was washed with H_2O. The organic layer was dried (Na_2SO_4), filtered, and evaporated to give the title compound **22** (274 mg, 71%) or **23** (1.29 g, 84%).

Lactol 22, Major Epimer (Cram Isomer)

$[\alpha]_D$ –1.5 (*c* = 1.6, MeOH).

IR (CCl_4): 3632, 3421, 2949, 2871 cm^{-1}.

^1H NMR (400 MHz): δ = 1.04 {m, 21 H, 3 CH + 6 CH_3, Si[CH(CH_3)$_2$]$_3$}, 1.10 (d, *J* = 7.0 Hz, 3 H, CH_3-8), 1.55 (m, 1 H, H_a-1′), 1.75 (m, 1 H, H-6), 1.95 (m, 1 H, H_b-1′), 2.18 (m, 1 H, H-8), 2.53 (td, *J* = 7.0, 3.0 Hz, 2 H, CH_2-2), 3.55 (t, *J* = 7.0 Hz, 2 H, CH_2-1), 3.70 and 3.87 (2 m, 4 H, CH_2-2′, H-7, OH), 4.40 (d, *J* = 11.0 Hz, 1 H, H-5), 4.50 (s, 2 H, PhCH_2), 4.55 (s, 1 H, OH), 5.15 (s, 1 H, H-9), 7.43 (s, 5 H, C_6H_5).

^{13}C NMR (100.6 MHz): δ = 10.5 (CH_3-8), 11.8 {3 CH, Si[*C*H(CH_3)$_3$]}, 17.8 {Si[CH(*C*H_3)$_2$]$_3$}, 20.2 (CH_2-2), 33.1 (CH_2-1′), 38.0 (CH-8), 43.3 (CH-6), 62.8 (CH_2-1), 64.0 (CH-5), 68.2 (CH_2-2′), 68.8 (CH-7), 72.9 (Ph*C*H_2), 79.4 and 82.2 (C≡C), 97.4 (CH-9), 127.5, 127.6, 128.3 (5 CH, C_6H_5), 137.9 (C, C_6H_5).

MS (CI, NH_3): *m*/*z* = 491 (MH^+).

Anal Calcd for $C_{28}H_{46}O_5Si$: C, 68.53; H, 9.45. Found: C, 68.61; H, 9.53.

Lactol 23, Major Epimer (*anti*-Cram Isomer)
$[\alpha]_D$ +9.0 (*c* = 1.5, MeOH).

IR (CCl_4): 3607, 3488, 2949, 2871 cm^{-1}.

^1H NMR (400 MHz): δ = 1.07 {m, 21 H, 3 CH + 6 CH_3, $Si[CH(CH_3)_2]_3$}, 1.15 (d, *J* = 6.0 Hz, 3 H, CH_3-8), 1.50–2.00 (m, 4 H, CH_2-1′ + H-6 + H-8), 2.51 (td, *J* = 7.0, 3.0 Hz, 2 H, CH_2-2), 3.60 (t, *J* = 7.0 Hz, 2 H, CH_2-1), 3.75 (m, 1 H, H_a-2′), 3.87 (m, 1 H, H_b-2′), 4.00 (s, 1 H, OH), 4.25 (s, 1 H, H-7), 4.52 (s, 2 H, $PhCH_2$), 4.65 (d, *J* = 11.0 Hz, 1 H, H-5), 4.97 (s, 1 H, H-9), 7.33 (s, 5 H, C_6H_5).

^{13}C NMR (100.6 MHz): δ = 11.8 (CH_3-8), 13.7 {3 CH, $Si[CH(CH_3)_2]_3$}, 17.9 {$Si[CH(CH_3)_2]_3$}, 20.2 (CH_2-2), 31.4 (CH_2-1′), 38.5 (CH-8), 45.3 (CH-6), 58.9 (CH-5), 62.0 (CH_2-2′), 68.2 (CH_2-1), 70.5 (CH-7), 72.9 ($PhCH_2$), 79.4 and 82.2 (C≡C), 97.4 (CH-9), 127.5, 127.6, 128.3 (5 CH, C_6H_5), 137.9 (C, C_6H_5).

MS (CI, NH_3): *m*/*z* = 491 (MH^+).

Anal Calcd for $C_{28}H_{46}O_5Si$: C, 68.53; H, 9.45. Found: C, 68.67; H, 9.49.

(2*E*)-5-(Benzyloxy)pent-2-en-1-ol (26)
To a solution of alcohol **10** (26 g, 136 mmol) in anhyd Et_2O (150 mL) at 0 °C was slowly added a 1 M solution of $LiAlH_4$ in THF (150 mL, 150 mmol, 1.1 equiv). The mixture was placed in a preheated bath and refluxed for 2.5 h. The solution was then cooled to 0 °C, and carefully and successively treated with H_2O (52 mL), 10 M aq NaOH (12.4 mL), and H_2O (24.8 mL). The precipitate was filtered and washed with Et_2O. The filtrate was concentrated under reduced pressure and purified by flash chromatography on silica gel (cyclohexane–EtOAc, 50:50) to give the title compound **26** as a colourless oil (22.3 g, 85%).

IR (CCl_4): 3385, 2857, 1495, 1361, 1092, 735, 696 cm^{-1}.

^1H NMR (200 MHz): δ = 1.40 (s, 1 H, OH), 2.30 (q, *J* = 6.5 Hz, 2 H, CH_2-4), 3.45 (t, *J* = 6.5 Hz, 2 H, CH_2-5), 4.03 (m, 2 H, CH_2-1), 4.45 (s, 2 H, $PhCH_2$), 5.58–5.73 (m, 2 H, CH=CH), 7.36 (m, 5 H, C_6H_5).

^{13}C NMR (50.8 MHz): δ = 32.5 (CH_2-4), 62.7 (CH_2-1), 69.5 (CH_2-5), 72.6 ($PhCH_2$), 127.5, 127.6, 128.1, 128.2 (6 CH, 5 C_6H_5 + =CH-2), 131.2 (=CH-3), 138.1 (C, C_6H_5).

MS (CI, NH_3): *m*/*z* = 193 (MH^+).

(2*E*)-5-(Benzyloxy)-1-[(*tert*-butyldimethylsilyl)oxy]pent-2-ene (27)
To a solution of alcohol **26** (3 g, 15.5 mmol) in anhyd CH_2Cl_2 (25 mL) at 0 °C were added imidazole (1.6 g, 23.3 mmol, 1.5 equiv) and TBSCl (2.6 g, 17.1 mmol, 1.1 equiv). After stirring for 1 h at 20 °C, the reaction mixture was treated with 1 M aq HCl (25 mL) and extracted with Et_2O. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane–EtOAc, 95:5) to give the title compound **27** as a colourless oil (4.43 g, 93%).

^1H NMR (200 MHz): δ = 0.00 [s, 6 H, 2 CH_3, $Si(CH_3)_2$], 0.80–0.9 [s, 9 H, 3 CH_3, $SiC(CH_3)_3$] 1.8 (q, *J* = 6.5 Hz, 2 H, CH_2-4), 3.50–3.70 (m, 4 H, CH_2-1 + CH_2-5), 4.50 (s, 2 H, $PhCH_2$), 5.73 (m, 2 H, CH=CH), 7.37 (m, 5 H, C_6H_5).

^{13}C NMR (50.3 MHz): δ = 4.7 [$Si(CH_3)_2$], 18.2 [$SiC(CH_3)_3$], 25.9 [$SiC(CH_3)_3$], 33.5 (CH_2-4), 67.8 (CH_2-1), 70.4 (CH_2-5), 73.2 ($PhCH_2$), 127.7 and 128.4 (6 CH, 5 C_6H_5 + =CH-2), 129.5 (=CH-3), 138.1 (C, C_6H_5).

MS (CI, NH_3): *m*/*z* = 307 (MH^+).

Anal Calcd for $C_{18}H_{30}O_2Si$: C, 70.53; H, 9.87. Found: C, 70.67; H, 9.94.

(2*E*)-5-(Benzyloxy)-1-[(*tert*-butyldiphenylsilyl)oxy]pent-2-ene (28)
To a solution of alcohol **26** (22 g, 114 mmol) in anhyd CH_2Cl_2 (200 mL) was added imidazole (11.64 g, 171 mmol, 1.5 equiv) and TPSCl (29.64 mL, 114 mmol, 1 equiv). The mixture was stirred for 1 h at r.t. and then quenched at 0 °C with 1 M aq HCl (75 mL). The resulting mixture was extracted with Et_2O. The combined organic layers were washed with brine and concentrated under reduced pressure. The crude oil was purified by flash chromatography on silica gel (cyclohexane–EtOAc, 95:5) to give the title compound **28** as a colourless oil (46.5 g, 95%).

^1H NMR (200 MHz): δ = 0.85 [s, 9 H, 3 CH_3, $SiC(CH_3)_3$], 2.34 (q, *J* = 7.0 Hz, 2 H, CH_2-4), 3.50 (t, *J* = 7.0 Hz, 2 H, CH_2-5), 4.21 (m, 2 H, CH_2-1), 4.52 (s, 2 H, $PhCH_2O$), 5.52–5.69 (m, 2 H, CH=CH), 7.32 (m, 4 H, C_6H_5), 7.43 (m, 11 H, C_6H_5).

^{13}C NMR (50.8 MHz): δ = 19.2 [$SiC(CH_3)_3$], 25.8 [3 CH_3, $SiC(CH_3)_3$], 30.9 (CH_2-4), 64.4 (CH_2-1), 70.3 (CH_2-5), 73.0 ($PhCH_2O$), 127.4, 127.7, 128.5, 128.1, 129.3 129.7 (16 CH, C_6H_5 + =CH-2), 132.4 (=CH-3), 137.2 (C, C_6H_5). C, C_6H_5–Si was not observed.

MS (CI, NH_3): *m*/*z* = 431 (MH^+).

Anal Calcd for $C_{28}H_{34}O_2Si$: C, 78.09; H, 7.96. Found: C, 78.18; H, 8.12.

(2*R,3*R**)-5-(Benzyloxy)-1-[(*tert*-butyldimethylsilyl)oxy]pentane-2,3-diol (29)**
Racemic (±)-29
To a solution of NMO (1.53 g, 13 mmol, 2 equiv) in a mixture of acetone and H_2O (60 mL, 60:40) was added a catalytic amount of OsO_4 (165 mg, 0.65 mmol, 0.1 equiv) and compound **27** (2 g, 6.52 mmol). The resulting solution was stirred until all the starting material was consumed, and quenched by the addition of aq 1 M HCl (30 mL). The mixture was extracted with EtOAc. The organic layers were washed with brine, filtered and concentrated under reduced pressure. The crude oil was purified by flash chromatography to give the title compound (±)-**29** (1.42 g, 64%).

Optically Active 29
A 100 mL round-bottomed flask equipped with a magnetic stirrer was charged with *tert*-butyl alcohol (32 mL, 5 mL/mmol), H_2O (32 mL, 5 mL/mmol), AD-Mix-β (9.13 g, 1.4 g/mmol) and methanesulfonamide (620 mg, 95 mg/mmol). The mixture was stirred at r.t. until both phases were clear, and then cooled to 0 °C, whereupon the inorganic salts partially precipitated. Compound **27** was added (2 g, 6.5 mmol) and the heterogeneous slurry was stirred vigorously at 0 °C until the starting material was consumed. The reaction was quenched at 0 °C by addition of Na_2SO_3 (9.75 g, 1.5 g/mmol) and then warmed to r.t. and stirred for 1 h. The mixture was extracted several times with EtOAc. The combined organic layers were washed with aq 2 M KOH, dried ($MgSO_4$) and concentrated under reduced pressure. The crude diol was purified by flash chromatography on silica gel (cyclohexane–EtOAc, 60:40) to give the title compound **29** (1.78 g, 80% yield, 60% ee).

IR (CCl_4): 3438, 2928, 2856, 1251, 1095, 834, 776, 696 cm^{-1}.

^1H NMR (200 MHz): δ = 0.05 [s, 6 H, 2 CH_3, $Si(CH_3)_2$], 0.85 [s, 9 H, 3 CH_3, $SiC(CH_3)_3$], 1.55–1.84 (m, 2 H, CH_2-4), 2.72 (d, *J* = 5.7 Hz, 1 H, OH), 3.04 (d, *J* = 5.7 Hz, 1 H, OH), 3.38 (m, 1 H, CH-2), 3.50–3.60 (m, 4 H, CH_2-1 + CH_2-5), 3.64 (m, 1 H, H-3), 4.40 (s, 2 H, $PhCH_2$), 7.30 (m, 5 H, C_6H_5).

^{13}C NMR (50.3 MHz): δ = – 4.90 [2 CH_3, $Si(CH_3)_2$], 18.2 [3 CH_3, $SiC(CH_3)_3$], 25.9 [3 CH_3, $SiC(CH_3)_3$], 33.5 (CH_2-4), 65.3 (CH_2-1), 67.9 (CH, C-2 or C-3), 70.4 (CH_2-5), 73.2 ($PhCH_2$), 73.4 (CH, C-3 or C-2), 127.7, 128.4 (5 CH, C_6H_5), 138.1 (C, C_6H_5).

MS (CI, NH_3): *m*/*z* = 341 (MH^+).

Anal Calcd for $C_{18}H_{32}O_4Si$: C, 63.49; H, 9.47. Found: C, 63.54; H, 9.52.

(2*R,3*R**)-5-(Benzyloxy)-2,3-[(isopropylidene)dioxy]pentan-1-ol [(±)-30]**

To a solution of diol (±)-**29** (1.5 g, 4.4 mmol) in CH_2Cl_2 (15 mL) was added 2,2-dimethoxypropane (6.55 mL, 53 mmol, 12 equiv) and a catalytic amount of PPTS (10% w/w, 150 mg). The solution was stirred for 2 h and quenched with H_2O (15 mL). The reaction mixture was extracted with Et_2O. The combined organic layers were washed with aq sat. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude oil was then purified by flash chromatography on silica gel (hexane–EtOAc, 90:10) to give (2*R*,3*R*)-5-(benzyloxy)-2,3-[(isopropylidene)dioxy]-1-[(*tert*-butyldimethylsilyl)oxy]pentane (1.54 g, 92%).

(2*R*,3*R*)-5-(Benzyloxy)-2,3-[(isopropylidene)dioxy]-1-[(*tert*-butyldimethylsilyl)oxy]pentane

IR (CCl_4): 2929, 2857, 1367, 1251, 1087, 834, 776, 696 cm^{-1}.

^1H NMR (200 MHz): δ = 0.05 [s, 6 H, 2 CH_3, $Si(CH_3)_2$], 0.84 {s, 9 H, 3 CH_3, $Si[C(CH_3)_3]$}, 1.30 [s, 3 H, CH_3, $OC(CH_3)_2O$], 1.32 [s, 3 H, CH_3, $OC(CH_3)_2O$], 1.60–2.00 (m, 2 H,CH_2-4), 3.61 (t, *J* = 7.6 Hz, 2 H, CH_2-5), 3.64 (dd, *J* = 13.5, 3.5 Hz, 1 H, H_a-1), 3.70–3.80 (m, 2 H, H-2 + H_b-1), 4.03 (dt, *J* = 8.5, 5.0 Hz, 1 H, H-3), 4.42 (s, 2 H, PhCH_2), 7.28 (m, 5 H, C_6H_5).

^{13}C NMR (50.8 MHz): δ = –5.5 [2 CH_3, $Si(CH_3)_2$], 18.2 [Si*C*$(CH_3)_3$] 25.8 [3 CH_3, $SiC(CH_3)_3$], 26.9 and 27.3 [$OC(CH_3)_2O$], 33.6 (CH_2-4), 63.4 (CH_2-1), 67.1 (CH_2-5), 72.8 (Ph*C*H_2), 75.7 (CH-3), 81.2 (CH-2), 108.4 [O*C*$(CH_3)_2O$], 127.4, 128.2 (5 CH, C_6H_5), 138.4 (C, C_6H_5).

MS (CI, NH_3): *m*/*z* = 381 (MH^+).

(±)-30

To a solution of the (±)-(2*R*,3*R*)-5-(benzyloxy)-2,3-[(isopropylidene)dioxy]-1-[(*tert*-butyldimethylsilyl)oxy]pentane (1 g, 2.63 mmol) in THF (10 mL) was added an 1 M solution of TBAF in THF (5.26 mL, 5.26 mmol, 2 equiv). The resulting solution was stirred for 1 h at 20 °C, quenched with H_2O (10 mL) and extracted with Et_2O. The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The oily residue was purified by flash chromatography on silica gel (hexane–EtOAc, 70:30) to give the title compound (±)-**30** as a colourless oil (695 mg, quant.).

IR (CCl_4): 3448, 2985, 2869, 1369, 1087, 736, 697 cm^{-1}.

^1H NMR (400 MHz): δ = 1.43 and 1.42 [2 s, 6 H, 2 CH_3, $OC(CH_3)_2O$], 1.94 (q, *J* = 6.6 Hz, 2 H, CH_2-4), 3.60–3.70 (m, 3 H, CH_2-5 + H_a-1), 3.70 (m, 1 H, H-2), 3.79 (dd, *J* = 15.3, 3.6 Hz, 1 H, H_b-1), 3.84 (m, 1 H, H-2), 4.04 (dt, *J* = 8.1, 6.6 Hz, 1 H, H-3), 4.53 (s, 2 H, PhCH_2O), 7.30 (m, 5 H, C_6H_5).

^{13}C NMR (100.6 MHz): δ = 26.9, 27.2 [2 CH_3, $OC(CH_3)_2O$], 33.2 (CH_2-4), 61.9 (CH_2-1), 66.9 (CH_2-5), 73.0 (Ph*C*H_2), 74.7 (CH-3), 81.3 (CH-2), 108.5 [O*C*$(CH_3)_2O$], 126.6, 127.4, 127.6, (5 CH, C_6H_5), 138.6 (C, C_6H_5).

MS (CI, NH_3): *m*/*z* = 267 (MH^+).

(2*R*,3*R*)-5-(Benzyloxy)-1-[(*tert*-butyldiphenylsilyl)oxy]pentane-2,3-diol (31)

A 1 L round-bottomed flask equipped with a magnetic stirrer was charged with *tert*-butyl alcohol (244 mL, 5 mL/mmol), H_2O (244 mL, 5 mL/mmol), AD-Mix-β (68.32 g, 1.4 g/mmol) and methanesulfonamide (4.64 g, 95 mg/mmol). The mixture was stirred at r.t. until both phases were clear, and then cooled to 0 °C, whereupon the inorganic salts partially precipitated. Compound **28** was added (21 g, 48.8 mmol) and the heterogeneous slurry was stirred vigorously at 0 °C until the starting material was consumed. The reaction was quenched at 0 °C by addition of Na_2SO_3 (73.2 g, 1.5 g/mmol) and then warmed to r.t. and stirred for 1 h. The mixture was extracted several times with EtOAc. The combined organic layers were washed with aq 2 M KOH, dried ($MgSO_4$) and concentrated under reduced pressure. The crude diol was purified by flash chromatography on silica gel (cyclohexane–EtOAc, 60:40) to give the title compound **31** (18.8 g, 83% yield, 90% ee); $[\alpha]_D$ +21.3 (*c* = 0.61, MeOH).

IR (CCl_4): 3436, 2929, 2856, 1427, 1108, 698 cm^{-1}.

^1H NMR (400 MHz): δ = 1.10 [s, 9 H, 3 CH_3, $SiC(CH_3)_3$], 1.82 (m, 1 H, H_a-4), 1.92 (m, 1 H, H_b-4), 3.61 (dt, *J* = 8.9, 6.0 Hz, 1 H, H-2), 3.69 (m, 2 H, CH_2-5), 3.81 (2dd, *J* = 10.3, 6.0 Hz and *J* = 10.3 Hz, 6.0 Hz, 2 H, CH_2-1), 3.96 (dt, *J* = 8.9, 3.6 Hz, 1 H, H-3), 4.53 (s, 2 H, PhCH_2), 7.30–7.45 (m, 11 H, C_6H_5), 7.9 (m, 4 H, C_6H_5).

^{13}C NMR (100.6 MHz): δ = 19.1 [Si*C*$(CH_3)_3$], 26.8 [3 CH_3, $SiC(CH_3)_3$], 33.4 (CH_2-4), 65.8 (CH_2-1), 67.8 (CH_2-5), 70.1 (CH-2), 73.2 (Ph*C*H_2), 73.8 (CH-3), 132.8, 132.9, 137.9 (3 C, C_6H_5), 127.5, 127.6, 127.7, 128.4, 129.8, 135.4 (15 CH, C_6H_5).

MS (CI, NH_3): *m*/*z* = 465 (MH^+).

Anal Calcd for $C_{28}H_{36}O_4Si$: C, 72.37; H, 7.81. Found: C, 72.42; H, 7.92.

(2*R*,3*R*)-5-(Benzyloxy)-2,3-[(isopropylidene)dioxy]pentan-1-ol (30)

To a solution of diol **31** (8 g, 17.2 mmol) in CH_2Cl_2 (80 mL) was added 2,2-dimethoxypropane (25.5 mL, 206 mmol, 12 equiv) and a catalytic amount of PPTS (5% w/w, 400 mg). The mixture was stirred for 2 h and then quenched with H_2O (80 mL). The mixture was extracted with Et_2O. The combined organic layers were washed with aq sat. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude oil was then purified by flash chromatography on silica gel (hexane–EtOAc, 95:5) to give (2*R*,3*R*)-5-(benzyloxy)-2,3-[(isopropylidene)dioxy]-1-[(*tert*-butyldiphenylsilyl)oxy]pentane (7.8 g, 90%).

(2*R*,3*R*)-5-(Benzyloxy)-2,3-[(isopropylidene)dioxy]-1-[(*tert*-butyldiphenylsilyl)oxy]pentane

$[\alpha]_D$ +19.2 (*c* = 1.25, MeOH).

^1H NMR (200 MHz): δ = 0.84 [s, 9 H, 3 CH_3, $SiC(CH_3)_3$], 1.30 [s, 3 H, CH_3, $OC(CH_3)_2O$], 1.32 [s, 3 H, CH_3, $OC(CH_3)_2O$], 1.60–2.00 (m, 2 H, CH_2-4), 3.61 (t, *J* = 7.6 Hz, 2 H, CH_2-5), 3.64 (dd, *J* = 15.0, 3.5 Hz, 1 H, H_a-1), 3.71–3.80 (m, 2 H, H-2 + H_b-1), 4.04 (dt, *J* = 8.5, 5.0 Hz, 1 H, H-3), 4.42 (s, 2 H, PhCH_2), 7.28 (m, 4 H, C_6H_5), 7.41 (m, 11 H, C_6H_5).

^{13}C NMR (50.8 MHz): δ = 19.3 [Si*C*$(CH_3)_3$], 25.8 [3 CH_3, $SiC(CH_3)_3$], 26.9 and 27.3 [$OC(CH_3)_2O$], 33.4 (CH_2-4), 63.5 (CH_2-5), 67.1 (CH_2-1), 72.8 (Ph*C*H_2), 75.7 (CH-3), 81.2 (CH-2), 108.4 [O*C*$(CH_3)_2O$], 127.5, 127.6, 128.1, 128.2 (15 CH, C_6H_5), 138.4 (C, C_6H_5). C, C_6H_5–Si not observed.

MS (CI, NH_3): *m*/*z* = 505 (MH^+).

To a solution of the (2*R*,3*R*)-5-(benzyloxy)-2,3-[(isopropylidene)dioxy]-1-[(*tert*-butyldiphenylsilyl)oxy]pentane (7 g, 13.9 mmol) in THF (50 mL) was added an 1 M solution of TBAF in THF (27.8 mL, 27.8 mmol, 2 equiv). The resulting solution was stirred for 1 h at 20 °C, quenched with H_2O (20 mL) and extracted with Et_2O. The combined organic phases were then washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The oily residue was purified by flash chromatography on silica gel (hexane–EtOAc, 70:30) to give the title compound **30** as a colourless oil (3.69 g, quant.).

30

$[\alpha]_D$ +17.4 (*c* = 0.75, MeOH).

IR (CCl_4): 3448, 2985, 2869, 1369, 1087, 736, 697 cm^{-1}.

^1H NMR (400 MHz): δ = 1.43 and 1.42 [2 s, 6 H, 2 CH_3, $OC(CH_3)_2O$], 1.94 (q, *J* = 6.6 Hz, 2 H, CH_2-4), 3.60–3.70 (m, 3 H, CH_2-5 + H_a-1), 3.70 (m, 1 H, H-2), 3.79 (dd, *J* = 15.3, 3.6 Hz, 1 H, H_b-1), 3.84 (m, 1 H, H-2), 4.04 (dt, *J* = 8.1, 6.6 Hz, 1 H, H-3), 4.53 (s, 2 H, PhCH_2), 7.30 (m, 5 H, C_6H_5).

^{13}C NMR (100.6 MHz): δ = 26.9, 27.2 [2 CH_3, $OC(CH_3)_2O$], 33.2 (CH_2-4), 61.9 (CH_2-1), 66.9 (CH_2-5), 73.0 (PhCH_2O), 74.7 (CH-3), 81.3 (CH-2), 108.5 [$OC(CH_3)_2O$], 126.6, 127.4, 127.6, (5 CH, C_6H_5), 138.6 (C, C_6H_5).

MS (CI, NH_3): *m*/*z* = 267 (MH^+).

Anal Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.68; H, 8.41.

(2*R*,3*R*)-5-(Benzyloxy)-2,3-[(isopropylidene)dioxy]pentanal (32)

To a solution of alcohol **30** (2.67 g, 10.1 mmol) in anhyd DMSO (40 mL) was added Et_3N (9.9 mL, 71 mmol, 7 equiv). The resulting mixture was cooled to 0 °C and a solution of pyridine sulfur trioxide complex (4.84 g, 30.4 mmol, 3 equiv) in DMSO (25 mL) was slowly added. The solution was allowed to warm to r.t. and after 1 h quenched with ice. The resulting solution was extracted with Et_2O and the combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The oily residue was purified by flash chromatography on silica gel (hexane–EtOAc, 70:30) to give the title compound **32** as a pale yellow oil (2.30 g, 86%).

IR (CCl_4): 2985, 2926, 1735, 1086, 735, 697 cm^{-1}.

^1H NMR (200 MHz): δ = 1.38 [s, 3 H, CH_3, $OC(CH_3)_2O$], 1.48 [s, 3 H, CH_3, $OC(CH_3)_2O$], 2.03 (q, *J* = 6.0 Hz, 2 H, CH_2-4), 3.50 (t, *J* = 6.0 Hz, 2 H, CH_2-5), 4.11 (dd, *J* = 9.0, 1.0 Hz, 1 H, H-2), 4.23 (dt, *J* = 9.0, 6.0 Hz, 1 H, H-3), 4.52 (s, 2 H, PhCH_2), 7.31 (m, 5 H, C_6H_5), 9.64 (d, *J* = 1.0 Hz, 1 H, H-1).

MS (CI, NH_3): *m*/*z* = 265 (MH^+).

Anal Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.22; H, 7.71.

(2*R*,3*R*)-5-(Benzyloxy)-1-chloro-2,3-[(isopropylidene)dioxy]pentane (33) from Allylic Alcohol 26

To a solution of *N*-chlorosuccinimide (3.9 g, 29 mmol, 2 equiv) in anhyd CH_2Cl_2 (75 mL) was added Me_2S (2.15 mL, 2 equiv) at 0 °C. After stirring for 1 h at 0 °C, the mixture was cooled to –20 °C and a solution of the allylic alcohol **26** (2.8 g, 14.5 mmol, 1 equiv) in CH_2Cl_2 (25 mL) was added dropwise over a period of 15 min. After stirring for 30 min a 0 °C, the mixture was allowed to warm slowly to r.t. and stirred at this temperature for 1 h. Then, H_2O (35 mL) was added and the organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (cyclohexane–EtOAc, 90:10) led to (2*E*)-5-(benzyloxy)-1-chloropent-2-ene as a colourless oil (2.68 g, 88%).

(2*E*)-5-(Benzyloxy)-1-chloropent-2-ene

IR (CCl_4): 1453, 1363, 1251 cm^{-1}.

^1H NMR (270 MHz): δ = 2.39 (dt, *J* = 6.6, 6.5 Hz, 2 H, CH_2-4), 3.51 (t, *J* = 6.6 Hz, 2 H, CH_2-5), 4.04 (d, *J* = 6.7 Hz, 2 H, CH_2-1), 4.51 (s, 2 H, PhCH_2O), 5.60–5.90 (m, 2 H, CH=CH), 7.26–7.35 (m, 5 H, C_6H_5).

^{13}C NMR (67.8 MHz): δ = 32.6 (CH_2-4), 45.2 (CH_2-1), 69.3 (CH_2-5), 72.9 (PhCH_2O), 127.7 and 128.4 (6 CH, 5 C_6H_5 + =CH-3), 132.3 (=CH-2), 138.0 (C, C_6H_5).

MS (CI, NH_3): *m*/*z* = 210 (MH^+).

A 1 L round-bottomed flask equipped with a magnetic stirrer was charged with *tert*-butyl alcohol (50 mL, 5 mL/mmol), H_2O (50 mL, 5 mL/mmol), AD-Mix-β (13.4 g, 1.4 g/mmol) and methanesulfonamide (910 mg, 95 mg/mmol). The mixture was stirred at r.t. until both phases were clear, and then cooled to 0 °C, whereupon the inorganic salts partially precipitated. The (2*E*)-5-(benzyloxy)-1-chloropent-2-ene was added (2 g, 9.6 mmol) and the heterogeneous slurry was stirred vigorously at 0 °C until all the starting material was consumed. The reaction was quenched at 0 °C by addition of Na_2SO_3 (14.4 g, 1.5 g/mmol) and then warmed to r.t., and stirred for 1 h. The mixture was extracted several times with EtOAc. The combined organic layers were washed with aq 2 M KOH, dried ($MgSO_4$) and concentrated under reduced pressure. The crude diol which was purified by flash chromatography on silica gel (cyclohexane–EtOAc, 60:40) to give (2*R*,3*R*)-5-(benzyloxy)-1-chloropentane-2,3-diol (2.06 g, 89%).

(2*R*,3*R*)-5-(Benzyloxy)-1-chloropentane-2,3-diol

$[\alpha]_D$ –12.3 (*c* = 2.0, MeOH) {Lit.[9] $[\alpha]_D$ –13 (*c* = 2.0, CH_2Cl_2) (ee = 96%)}.

IR (CCl_4): 3430, 1455, 1100, 850 cm^{-1}.

^1H NMR (400 MHz): δ = 1.73–1.82 (m, 1 H, H_a-4), 1.92–2.07 (m, 1 H, H_b-4), 3.02 (s, 1 H, OH), 3.27 (s, 1 H, OH), 3.56–3.76 (m, 5 H, CH_2-1, CH_2-5, H-3), 3.97–4.02 (m, 1 H, H-2), 4.53 (s, 2 H, PhCH_2O), 7.27–7.38 (m, 5 H, C_6H_5).

^{13}C NMR (67.8 MHz): δ = 33.2 (CH_2-4), 45.9 (CH_2-1), 68.5 (CH_2-5), 70.7 (CH-3), 73.5 (PhCH_2O), 74.0 (CH-2), 127.7 and 128.6 (5 CH, C_6H_5), 137.6 (C, C_6H_5).

MS (CI, NH_3): *m*/*z* = 245 (MH^+).

To a solution of (2*R*,3*R*)-5-(benzyloxy)-1-chloropentane-2,3-diol (0.20 g, 0.82 mmol) in CH_2Cl_2 (10 mL) was added 2,2-dimethoxypropane (1.21 mL, 9.8 mmol, 12 equiv) and a catalytic amount of PPTS (20 mg). The solution was stirred for 2 h and was quenched with H_2O (10 mL). The reaction mixture was extracted with Et_2O, the organic layers were washed with aq sat. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude oil was purified by flash chromatography on silica gel (cyclohexane–EtOAc, 95:5) to give the title compound **33** (150 mg, 65%).

33

$[\alpha]_D$ +31.4 (*c* = 0.93, MeOH).

^1H NMR (200 MHz): δ = 1.0 [m, 6 H, 2 CH_3, $OC(CH_3)_2O$], 1.90 (m, 2 H, CH_2-4), 3.50 (m, 4 H, CH_2-1, CH_2-5), 3.95 (m, 2 H, CH-2, H-3), 4.45 (s, 2 H, PhCH_2), 7.25 (m, 5 H, C_6H_5).

^{13}C NMR (50.3 MHz): δ = 27.0, 27.4 [2 CH_3, $OC(CH_3)_2O$], 33.7 (CH_2-4), 44.2 (CH_2-1), 66.9 (CH_2-5), 73.1 (PhCH_2), 76.8 (CH-3), 80.4 (C-2), 109.2 [$OC(CH_3)_2O$], 127.5 (2 CH, C_6H_5), 127.7 (2 CH, C-Ar), 128.3 (CH, C_6H_5), 138.4 (C, C_6H_5).

MS (CI, NH_3): *m*/*z* = 285 (MH^+).

Anal Calcd for $C_{15}H_{21}ClO_3$: C, 63.26; H, 7.43. Found: C, 63.31; H, 7.55.

(2*R*,3*R*)-5-(Benzyloxy)-1-chloro-2,3-[(isopropylidene)dioxy]pentane (33) from Acetonide 30

To a solution of acetonide **30** (0.20 g, 0.75 mmol) in CH_2Cl_2 (10 mL) was added Ph_3P (245 mg, 9.0 mmol, 1.2 equiv) and CCl_4 (140 mg, 9.0 mmol, 1.2 equiv). The mixture was stirred for 8 h, quenched with pentane (10 mL) and H_2O (10 mL). The resulting mixture was filtered and extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude oil was purified by flash chromatography on silica gel (cyclohexane–EtOAc, 95:5) to give the title compound **33** (120 mg, 56%); $[\alpha]_D$ +30.1 (*c* = 0.83, MeOH). For spectral data, see above.

(7*Z*,3*R*,4*S*,5*S*,6*S*)- and (7*Z*,3*R*,4*S*,5*R*,6*R*)-1-(Benzyloxy)-5-hydroxy-3,4-[(isopropylidene)dioxy]-6-{[(triisopropylsilyl)oxy]ethyl}oct-7-ene (34 and 35)

To a solution of TMEDA (6.21 mL, 41.1 mmol, 5.1 equiv) in anhyd Et_2O (50 mL) at –78 °C, under argon, was added *n*-BuLi (1.6 M in hexane, 25.7 mL, 41.1 mmol, 5.1 equiv). After stirring for 30 min at –78 °C, a solution of the allyl carbamate **17** (7.2 g, 20 mmol, 2.5 equiv) in anhyd Et_2O (50 mL), was slowly added. After stirring for 40 min at –78 °C, Ti(O*i*-Pr)$_4$ (18 mL, 60 mmol, 7.5 equiv) was rapidly added and the reaction mixture was stirred for 20 min at –78 °C (transmetallation time). Then, the aldehyde **32** (2.13 g, 8.07 mmol) diluted in anhyd Et_2O (10 mL) was added. The mixture was stirred for 2 h at –78 °C and quenched by transferring to a vigorously stirred mixture of aq 3 M HCl (100 mL) and Et_2O (100 mL) at 0 °C. The temperature was allowed to reach 20 °C and the resulting solution was eventually filtered on a pad of Celite to removed titanium salts and extracted with Et_2O. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane–EtOAc, 80:20) to give a 20:80 mixture of compounds **34** and **35** as a pale yellow oil (4.3 g, 81%).

IR (CCl_4): 3490, 2929, 2865, 1704, 1061, 732 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (two diastereomers, minor isomer underlined) = 1.10 {m, 21 H, 3 CH + 6 CH_3, Si[CH(C*H*$_3$)$_2$]$_3$}, 1.20 {m, 12 H, 4 CH_3, N[(CH(C*H*$_3$)$_2$]$_2$}, 1.25, 1.30 and 1.32, 1.40 [2 s, 6 H, 2 CH_3, OC(C*H*$_3$)$_2$O], 1.50–2.0 (m, 4 H, CH_2-2 + CH_2-1′), 2.10 and 2.60 (m, 1 H, H-6), 3.50–4.10 {2 m, 9 H, CH_2-1 + CH_2-2′ + H-3 + H-4 + H-5 + N[(C*H*(CH$_3$)$_2$]$_2$}, 4.59 and 4.60 (s, 2 H, PhC*H*$_2$), 4.70 (dd, *J* = 10.0, 7.0 Hz, 1 H, =CH-7), 7.1 (d, *J* = 7.0 Hz, 1 H, =CH-8), 7.30 (m, 5 H, C_6H_5).

^{1}H NMR (400 MHz, DMSO-d_6): δ (two diastereomers, minor isomer underlined) = 1.10 {m, 21 H, 3 CH + 6 CH_3, Si[CH(C*H*$_3$)$_2$]$_3$}, 1.20 {m, 12 H, 4 CH_3, N[(CH(C*H*$_3$)$_2$]$_2$}, 1.25, 1.26 and 1.34, 1.36 [2 s, 6 H, 2 CH_3, OC(C*H*$_3$)$_2$O], 1.64 (m, 2 H, CH_2-2), 1.74 (m, 2 H, CH_2-1′), 2.05 (m, 1 H, H-6), 3.32–3.68 (2 m, 6 H, CH_2-1 + CH_2-2′ + H-3 + H-4), 4.00 (m, 1 H, H-5), 3.75–4.00 {m, 2 H, N[(C*H*(CH$_3$)$_2$]$_2$}, 4.46 and 4.47 (s, 2 H, PhC*H*$_2$O), 4.70 and 4.82 (dd, *J* = 8.9, 6.5 Hz, 1 H, =CH-7), 4.97 (d, *J* = 6.6 Hz, 1 H, OH), 6.86 and 6.95 (d, *J* = 6.5 Hz, 1 H, =CH-8), 7.30 (m, 5 H, C_6H_5).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ (two diastereomers, minor isomer underlined) = 11.9 {3 CH, Si[*C*H(CH$_3$)$_2$]$_3$}, 17.9 {6 CH_3, Si[CH(*C*H$_3$)$_2$]$_3$}, 21.0 {4 CH_3, N[(CH(*C*H$_3$)$_2$]$_2$}, 27.0 and 27.2 [2 CH_3, OC(*C*H$_3$)$_2$O], 36.6 (2 CH_2, C-2 + C-1′), 36.0 and 36.5 (CH-6), 45.7 {2 CH, N[(*C*H(CH$_3$)$_2$]$_2$}, 61.6 (CH_2-2′), 67.2 (CH_2-1), 73.3 (Ph*C*H$_2$), 75.2 and 75.7 (CH-3), 78.4 and 71.7 (CH-5), 80.6 and 81.4 (CH-4), 81.6 (CH-4), 109.9 [O*C*(CH$_3$)$_2$O], 110.5 (=CH-7), 128.3, 128.7 (5 CH, C_6H_5), 138.3 (C, C_6H_5), 138.6 (=CH-8), 155.2 (C=O).

MS (CI, NH_3): *m*/*z* = 650 (MH^+).

Anal Calcd for $C_{36}H_{63}NO_7Si$: C, 66.52; H, 9.77; N, 2.15. Found: C, 66.63; H, 9.83; N, 2.12.

5-[(Triisopropyl)oxy]pent-2-yn-1-al (38)

To a solution of **13** (3 g, 12 mmol) in CH_2Cl_2 (15 mL) was added portionwise MnO_2 (5.1 g, 58.5 mmol, 5 equiv) until all the starting material was completely consumed. After stirring for 2 h, the reaction mixture was filtered on a pad of Celite and the solvent was removed under reduced pressure. The crude oil (81% yield by ^{1}H NMR, before chromatography) was purified by flash chromatography on silica gel (hexane–EtOAc, 70:30) to give **38** as a colourless to pale yellow oil (1.9 g, 63%).

IR (KBr): 2204, 1670 cm^{-1}.

^{1}H NMR (270 MHz): δ = 1.08 {m, 21 H, 3 CH and 6 CH_3, Si[CH(CH$_3$)$_2$]$_3$}, 2.64 (td, *J* = 6.8, 1.0 Hz, 2 H, CH_2-4), 3.90 (t, *J* = 6.8 Hz, 2 H, CH_2-5), 9.18 (d, *J* = 1.0 Hz, 1 H, H-1).

^{13}C NMR (67.8 MHz): δ = 12.0 {3 CH, Si[*C*H(CH$_3$)$_2$]$_3$}, 18.0 {6 CH_3, Si[CH(*C*H$_3$)$_2$]$_3$}, 23.7 (CH_2-4), 61.0 (CH_2-5), 82.4 and 96.3 (C≡C), 177.1 (C-1).

MS (CI, NH_3): *m*/*z* = 272 (MH^+ + NH_3), 255 (MH^+).

Anal Calcd for $C_{14}H_{26}O_2Si$: C, 66.09; H, 10.30. Found: C, 66.13; H, 10.38.

(2*Z*,4*S,5*R**)- and (2*Z*,4*S*,5*R*)-4-[2-(Benzyloxy)ethyl]-2-{[(*N*,*N*-diisopropyl)carbamoyl]oxy}-5-hydroxy-9-[(triisopropylsilyl)oxy]non-2-ene-6-yne [(±)-39] and [(2*Z*,4*S*,5*R*)-39]**

Racemic Compound (±)-39

To a solution of (±)-**36** (2.48 g, 7.5 mmol) at –78 °C in anhyd Et_2O (30 mL) and TMEDA (2.25 mL, 15.0 mmol, 2.0 equiv) was slowly added *n*-BuLi (1.6M in hexane, 9.3 mL, 15 mmol, 2.0 equiv). After stirring for 1 h at –78 °C, Ti(O*i*-Pr)$_4$ (6.7 mL, 22 mmol, 3 equiv) was rapidly added and the reaction mixture was stirred for 20 min at –78 °C (transmetallation time). Then, a solution of **38** (1.9 g, 7.5 mmol, 1 equiv) in Et_2O (10 mL) was added. The mixture was stirred for 2 h at –78 °C and quenched by transferring to a vigorously stirred mixture of aq 3 M HCl (30 mL) and Et_2O (30 mL) at 0 °C. The temperature was allowed to reach 20 °C and the resulting solution was eventually filtered on a pad of Celite to remove titanium salts and extracted with Et_2O. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane–EtOAc, 70:30), to give the title compound (±)-**39** as a pale yellow oil (3.2 g, 72%).

Optically Active Compound 39

To a solution of the optically active allyl carbamate (*S*)-**36** (1.0 g, 3.02 mmol) in anhyd pentane–cyclohexane (20 mL/2 mL) and TMEDA (1.0 mL, 6.05 mmol, 2.0 equiv) at –78 °C was slowly added *n*-BuLi (1.6 M in hexane, 3.8 mL, 6.05 mmol, 2.0 equiv). After stirring for 1 h 15 min to 1 h 30 min at –78 °C, precooled Ti(O*i*-Pr)$_4$ (5.5 mL, 18.1 mmol, 3 equiv) at –78 °C in anhyd pentane (15 mL) was rapidly added via cannula and the reaction mixture was stirred for 30 min at –78 °C (transmetallation time). Then, a solution of **38** (880 mg, 3.0 mmol, 1 equiv) in pentane (5.0 mL) was added. The mixture was stirred for 2 h at –78 °C and quenched by transferring to a vigorously stirring mixture of aq 3 M HCl (30 mL) and Et_2O (30 mL) at 0 °C. The temperature was allowed to reach 20 °C and the resulting solution was eventually filtered on a pad of Celite to remove titanium salts and extracted with Et_2O. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane–EtOAc, 70:30), to give **39** as a pale yellow oil (1.26 g, 70% yield, ee = 80%).

^{1}H NMR (400 MHz): δ = 1.05 {m, 21 H, 3 CH and 6 CH_3, Si[CH(CH$_3$)$_2$]$_3$}, 1.21 {d, *J* = 7.2 Hz, 12 H, 4 CH_3, N[CH(CH$_3$)$_2$]$_2$}, 1.53 (m, 1 H, H$_a$-1′), 1.89 (s, 3 H, CH_3-1), 2.11 (m, 1 H, H$_b$-1′), 2.46 (2 td, *J* = 7.4, 1.9 Hz, 2 H, CH_2-8), 2.62 (m, 1 H, H-4), 3.45 (m, 1 H, H$_a$-2′), 3.52 (m, 1 H, H$_b$-2′), 3.75 {br m, 1 H, N[C*H*(CH$_3$)$_2$]$_2$}, 3.78 (t, *J* = 7.4 Hz, 2 H, CH_2-9), 4.03 {br m, 1 H, N[(C*H*(CH$_3$)$_2$]$_2$}, 4.15 (dt, *J* = 5.9, 1.9 Hz, 1 H, H-5), 4.47 (d, *J* = 11.8 Hz, 1 H, PhC*H*$_2$), 4.52 (d, *J* = 11.8 Hz, 1 H, PhC*H*$_2$), 4.85 (d, *J* = 10.3 Hz, 1 H, =CH-3), 7.37 (m, 5 H, C_6H_5).

^{13}C NMR (100.6 MHz): δ = 11.8 {3 CH, Si[*C*H(CH$_3$)$_2$]$_3$}, 18.1 {3 CH_3, Si[CH(*C*H$_3$)$_2$]$_3$}, 20.1 (CH_3-1), 20.4 and 22.1 {4 CH_3, N[CH(*C*H$_3$)$_2$]$_2$}, 23.2 (CH_2-8), 31.2 (CH_2-1′), 41.3 (CH-4), 45.9 and 47.0 {2 CH, N[C*H*(CH$_3$)$_2$]$_2$}, 62.3 (CH_2-9), 65.7 (CH-5), 68.7 (CH_2-2′), 72.9 (Ph*C*H$_2$), 81.4 (≡C-7), 82.4 (≡C-6), 117.1 (=CH-3), 127.5 (2 CH, C_6H_5), 127.7 (2 CH, C_6H_5), 128.3 (CH-7′), 138.4 (C, C_6H_5), 147.5 (C-2), 153.7 (C=O).

Anal Calcd for $C_{34}H_{57}NO_5Si$: C, 69.46; H, 9.77; N, 2.38. Found: C, 69.51; H, 9.89; N, 2.42.

(2*Z*,3*R*,4*S*,5*S*,6*S*)-1-(Benzyloxy)-3,4-[(isopropylidene)dioxy]-5-hydroxy-6-[2-(benzyloxy)ethyl]-8-{[(*N*,*N*-diisopropyl)carbamoyl]oxy}non-7-ene (40)

To a solution of (*S*)-allyl carbamate (*S*)-**36** (1.0 g, 3.0 mmol) in anhyd pentane–cyclohexane (10 mL/1.0 mL), was added TMEDA (0.90 mL, 6.0 mmol, 2.0 equiv). The solution was cooled at –78 °C, and after 15 min, *n*-BuLi (1.6M in hexane, 3.8 mL, 6.0 mmol, 2.0 equiv) was slowly added. After stirring for 1 h at –78 °C, a precooled solution of Ti(O*i*-Pr)$_4$ (2.7 mL, 9.0 mmol, 3 equiv) in pentane (10 mL) at –78 °C was rapidly added via cannula and the reaction mixture was stirred for 20 min at –78 °C (transmetallation time). Then, aldehyde **32** (800 mg, 3.0 mmol, 1 equiv) diluted in pentane–Et_2O (8.0 mL/2.5 mL) was added. The mixture was stirred for 2 h at –78 °C and quenched by transferring to a vigorously stirred mixture of aq 3 M HCl (3 M, 20 mL) and Et_2O (20 mL) at 0 °C. The temperature was allowed to reach 20 °C and the resulting solution was eventually filtered on a pad of Celite to remove titanium salts and extracted with Et_2O. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane–EtOAc, 70:30) to give **40** as a single diastereomer; pale yellow oil; yield: 1.4 g (80%).

^{1}H NMR (400 MHz): δ = 1.22 {m, 12 H, 4 CH_3, N[CH(CH_3)$_2$]$_2$}, 1.36 [s, 6 H, 2 CH_3, OC(CH_3)$_2$O], 1.47 and 1.90 (2 m, 4 H, CH_2-1′ and CH_2-2), 1.90 (s, 3 H, CH_3-9), 2.65 (m, 1 H, H-6), 3.33 (dd, *J* = 7.6, 2.0 Hz, 1 H, H-5), 3.46 (m, 2 H, CH_2-1), 3.58 (m, 2 H, CH_2-2′), 3.74 (dd, *J* = 8.0, 2.0 Hz, 1 H, H-4), 3.80 [m, 1 H, NC*H*(CH$_3$)$_2$], 4.05 [m, 1 H, NC*H*(CH$_3$)$_2$], 4.22 (m, 1 H, H-3), 4.50 and 4.47 (2 s, 4 H, 2 PhCH_2), 4.92 (d, *J* = 11.1 Hz, 1 H, =CH-7), 7.30–7.37 (2 s, 10 H, C_6H_5).

^{13}C NMR (100.6 MHz): δ = 20.1 (CH_3-9), 20.5 and 21.4 {4 CH_3 N[CH(*C*H$_3$)$_2$]$_2$}, 26.7 and 26.8 [2 CH_3, OC(*C*H$_3$)$_2$O], 31.2 (CH_2-1′), 33.0 (CH_2-2), 37.0 (CH-6), 46.3 and 46.6 {2 CH, N[*C*H(CH$_3$)$_2$]$_2$}, 68.6 (CH_2-1), 67.4 (CH_2-2′), 71.4 (CH-5), 72.8 and 72.9 (2 CH_2, 2 Ph*C*H$_2$), 74.5 (CH-3), 80.9 (CH-4), 108.3 [O*C*(CH$_3$)$_2$O], 117.5 (=CH-7), 127.3, 127.6, 128.2 (10 CH, C_6H_5), 138.4 and 138.6 (2 C, C_6H_5), 146.8 (C-8), 153.5 (C=O).

MS (CI, NH_3): *m*/*z* = 598 (MH^+).

Anal Calcd for $C_{35}H_{51}NO_7$: C, 70.32; H, 8.60; N, 2.34. Found: C, 70.48; H, 8.79; N, 2.46.

References

(1) (a) Tatsuta, K.; Amemiya, Y.; Kanemura, Y.; Takahashi, H.; Kinoshita, M. *Tetrahedron Lett.* **1982**, *23*, 3375. (b) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2031. (c) Masamune, S.; Lu, L. D.-L.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *J. Am. Chem. Soc.* **1982**, *104*, 5523. (d) Grieco, P. A.; Inanaga, J.; Lin, N. H.; Yanami, T. *J. Am. Chem. Soc.* **1982**, *104*, 578. (e) Tanaka, T.; Oikawa, Y.; Hamada, T.; Yonemitsu, O. *Chem. Pharm. Bull.* **1987**, *35*, 2219.

(2) (a) Omura, S.; Sano, H.; Sunazuka, T. *J. Antimicrob. Chemother.* **1985**, *16 Suppl. A*, 1. (b) Omura, S.; Sano, H.; Inoue, M.; Yamashita, K.; Okachi, R. *J. Antibiot.* **1983**, *36*, 1336. (c) Tsuchiya, M.; Hamada, H.; Takeuchi, T.; Umewaza, H.; Yamamoto, K.; Tanaka, H.; Kiyoshima, K.; Mori, S.; Okamoto, R. *J. Antibiot.* **1982**, *35*, 661.

(3) (a) Kirst, H. A. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lucas, G.; Ohno, M., Eds.; Springer Verlag: Berlin, **1990**, 39. (b) In *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: New York, **1984**. (c) Kirst, H. A. *J. Antimicrob. Chemother.* **1991**, *28*, 787.

(4) (a) Berque, I.; Razon, P.; Le Ménez, P.; Aniès, C.; Pancrazi, A.; Ardisson, J. *Synlett* **1998**, 1129. (b) Berque, I.; Razon, P.; Le Ménez, P.; Pancrazi, A.; Ardisson, J. *Synlett* **1998**, 1135. (c) Berque, I.; Razon, P.; Le Ménez, P.; Mahuteau, J.; Férézou, J. P.; Pancrazi, A.; Ardisson, J. *J. Org. Chem.* **1999**, *64*, 373.

(5) (a) Oddon, G.; Uguen, D. *Tetrahedron* **1997**, *38*, 4407. (b) Oddon, G.; Uguen, D. *Tetrahedron Lett.* **1997**, *38*, 4411. (c) Breuilles, P.; Oddon, G.; Uguen, D. *Tetrahedron Lett.* **1997**, *38*, 6607. (d) Oddon, G.; Uguen, D.; De Cain, A.; Fischer, J. *Tetrahedron Lett.* **1998**, *39*, 1149. (e) Oddon, G.; Uguen, D. *Tetrahedron Lett.* **1998**, *39*, 1153. (f) Oddon, G.; Uguen, D. *Tetrahedron Lett.* **1998**, *39*, 1157. (g) For the synthesis of the eastern part of spiramycin, see: Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *Tetrahedron Lett.* **1979**, *25*, 2327. (h) See also: Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 1222. (i) See also: Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1981**, *103*, 1224. (j) See also: Tatsuta, K.; Amemiya, Y.; Maniwa, S.; Kinoshita, M. *Tetrahedron Lett.* **1980**, *21*, 2837. (k) See also: Wuts, P. M. G.; Bigelow, S. S. *J. Org. Chem.* **1988**, *53*, 5023.

(6) (a) Hoppe, D.; Zschage, O. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 69. (b) Zschage, O.; Hoppe, D. *Tetrahedron* **1992**, *48*, 5657. (c) Zschage, O.; Hoppe, D. *Tetrahedron* **1992**, *48*, 8389. (d) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282. (e) Hoppe, D.; Paulsen, H. *Tetrahedron* **1992**, *48*, 5667. (f) Férézou, J.-P.; Julia, M.; Li, Y.; Liu, L. W.; Pancrazi, A. *Bull. Soc. Chim. Fr.* **1995**, *132*, 428. (g) Smith, N. D.; Kocienski, P. J.; Street, S. D. A. *Synthesis* **1996**, 652.

(7) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1754.

(8) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(9) Maier, M. E.; Hermann, C. *Tetrahedron* **2000**, *56*, 557.

(10) The structure of **36** was established by comparison of its ^{1}H and ^{13}C NMR spectra with those of compound **46**. Analysis of ^{1}H and ^{13}C NMR spectra was supported by 2D experiments.

(11) (a) From racemic secondary crotyl carbamate, see: Zschage, O.; Schwark, J.-A.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 296. (b) See also: Zschage, O.; Schwark, J.-A.; Krämer, T.; Hoppe, D. *Tetrahedron* **1992**, *48*, 8377. (c) From optically active secondary crotyl carbamates, see: Hoppe, D.; Krämer, T. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 160. (d) See also: Hoppe, D.; Krämer, T. *Tetrahedron Lett.* **1987**, *28*, 5149. (e) See also: Hoppe, D.; Schwark, J.-R. *Synthesis* **1990**, 291. (f) See also: Zschage, O.; Hoppe, D. *Tetrahedron* **1992**, *48*, 8389.

(12) Razon, P.; Dhulut, S.; Bezzenine-Lafollée, S.; Courtieu, J.; Pancrazi, A.; Ardisson, J. *Synthesis* **2004**, preceding paper.