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Stereochemistry of intramolecular Diels–Alder furan (IMDAF) reactions of furyl-substituted chiral ethanolamides

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This paper describes the stereoselective outcome of the intramolecular Diels–Alder furan (IMDAF) reaction of substituted (2*S*,3*S*)-ethanolamides **9**–**13**, which were synthesised from a furyl substituted cyanohydrin. The latter was obtained from 2-furaldehyde with high enantioselectivity by an oxynitrilase catalysed addition of hydrogen cyanide. The stereochemistry of the IMDAF products was shown to be dependent on the size of the ethanolamide substituents R. Small substituents (H, Me, CN) gave exclusively *exo*-cycloaddition, whereas more bulky ones (Ph, Et) gave both *exo*- and *endo*-addition, the larger phenyl substituent giving a high *endo*–*exo*-ratio.

Introduction

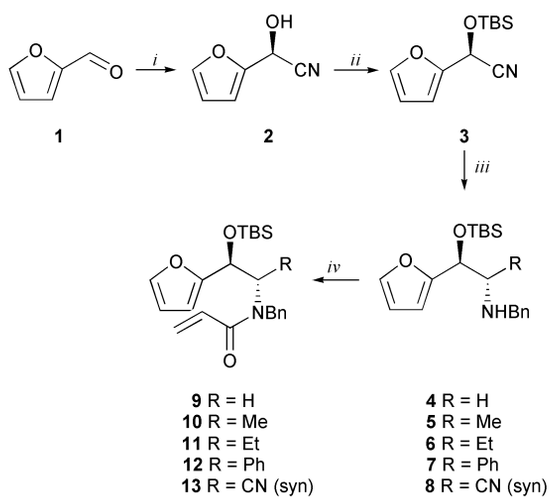
Cyanohydrins have proved to be versatile starting compounds in organic synthesis, due to the large number of transformations that they can undergo.[1] Transformations at the hydroxyl function and at the nitrile position provide, *e.g.*: α-hydroxy esters,[2] ethanolamines,[3–5] and aziridines.[6] Less attention has been directed to transformation of the cyanohydrin side chain. So far, the side chains have been subjected to oxidation,[7] ring closure,[8] and chirality transfer reactions.[9] The presence of unsaturation in the cyanohydrin side chains makes them interesting starting materials for the synthesis of complex ring systems *via* an intramolecular Diels–Alder reaction. The use of furans in Diels–Alder reactions is of special interest, since the oxygen bridge obtained after cyclisation can be opened for further manipulation.[10] Marchionni and Vogel synthesised highly substituted ring systems using the furan Diels–Alder reaction.[11] Padwa *et al.* demonstrated the utility of amine-substituted furan rings in the IMDAF reaction by synthesis of the biologically active compound dendrobine.[12] Cauwberghs and de Clercq applied the IMDAF reaction for the synthesis of periplanone B.[13] There has been only one report on the IMDAF reaction of 2-furylamides.[14] However, no clear information was presented on the stereochemistry of the cycloaddition product.

Here we describe the synthesis of several ethanolamides containing a furyl side chain and their subsequent use in the IMDAF reaction. Special attention is paid to the influence of the ethanolamide substitutient R on the stereochemical outcome of the IMDAF reaction.

Results and discussion

2-Furaldehyde (**1**) was converted into its corresponding (*S*)-cyanohydrin **2** with high conversion and *ee* (98%) by (*R*)-oxynitrilase[15] (E.C. 4.1.2.10), as present in defatted almond meal (Scheme 1).[16] Protection with TBSCl in the presence of imidazole in DMF[17] afforded **3** in 88% yield from **1**.

For the conversion of the nitrile function of **3** into ethanolamine **4** a reduction–transimination–reduction sequence was applied.[5] The cyano group was reduced to the imine by DIBAL-H at low temperature. Addition of methanol provided the free imine, which was subjected to a transimination reaction with benzylamine. The resulting secondary imine was further reduced with sodium borohydride to provide ethanolamine **4**. The acryloyl function was introduced by stirring crude **4** with freshly distilled acryloyl chloride in a dichloromethane–water biphasic solvent system, using sodium carbonate as the base, to provide **9**.[18]



Scheme 1 *Reagents and conditions: i.* (*R*)-Oxynitrilase, HCN, methyl *tert*-butyl ether (MTBE), pH 5.5, 4 °C.; *ii.* TBSCl (1.2 eq.), imidazole (2.4 eq.), DMF, 0 °C to rt; *iii. R = H*: 1. DIBAL-H (1.2 eq.), Et_2O, −70 °C to −20 °C; 2. MeOH, −70 °C; 3. $BnNH_2$, MeOH, −70 °C to −20 °C; 4. $NaBH_4$ (2 eq.), −70 °C to rt; *R = Me, Et, Ph*: 1. RMgX (1.2 eq.), Et_2O, reflux; 2. MeOH, −20 °C; 3. $BnNH_2$, MeOH, −70 °C to −20 °C; 4. $NaBH_4$ (2 eq.), −70 °C to rt; *R = CN*: 1. DIBAL-H (1.2 eq.), Et_2O, −70 °C to −20 °C; 2. MeOH, −70 °C; 3. $BnNH_2$, MeOH, −70 °C to −20 °C; 4. NaCN (3.8 eq.), NH_4Br (3.8 eq.), MeOH, −70 °C to rt; *iv*. Acryloylchloride (1.1 eq.), Na_2CO_3 (1.2 eq.), CH_2Cl_2, H_2O.

The methyl, ethyl, and phenyl groups were introduced by a Grignard addition–transimination–reduction reaction as previously described.[4] The appropriate Grignard reagent was added to protected cyanohydrin **3** in diethyl ether and the mixture was refluxed for one hour. After addition of methanol, introduction of the benzyl group was accomplished by transimination. Stereoselective reduction of the resulting secondary imine with sodium borohydride gave ethanolamines **5**–**7** with high *anti*-selectivity (Table 1).[19] The acryloyl group was introduced as described above, yielding ethanolamides **10**–**12**.

Introduction of the cyano group was performed as in the synthesis of β-hydroxy-α-amino acids described by Zandbergen *et al.*[20] After DIBAL-H reduction of the protected cyanohydrin and introduction of the benzyl function, the nitrile group was introduced stereoselectively by addition of *in situ* formed

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Table 1 Ethanolamines (**4**–**8**) and ethanolamides (**9**–**13**)

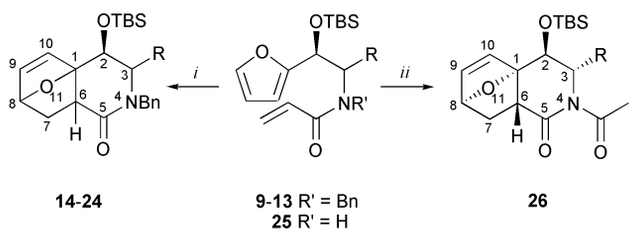
R	*syn* : *anti* (**4**–**8**)[a]	Yield (%) (**9**–**13**)[b]
H	—	30
Me	8 : 92	80
Et	8 : 92	29
Ph	14 : 86	72
CN	93 : 7	48

[a] Based on NMR data of crude product. [b] From **3** (%).

hydrogen cyanide to the imine, giving **8**. Introduction of the acryloyl group provided **13**.

NMR spectra of crude **13** revealed formation of a small amount of cyclised product **24** (8%). Except for ethanolamide **13** no spontaneous cycloaddition had occurred. The results of the synthesis of compounds **9**–**13** are presented in Table 1.

Next, the substituted furyl-ethanolamides (**9**–**13**) were applied in the IMDAF reaction using elevated temperatures.[21] Refluxing in toluene provided a cleaner reaction with higher yields than refluxing in xylene. Non-benzylated **25** was studied to investigate the outcome of the IMDAF reaction of a furyl-ethanolamide in refluxing acetic anhydride (Scheme 2).[21] The results, however, showed no improvement.



Scheme 2 *Reagents: i.* Toluene, reflux; *ii.* Acetic acid anhydride, reflux.

As depicted in Scheme 3, four different stereoisomers can be formed: *endo* or *exo* with the oxygen bridge at the same side of the molecule as the silyloxy function (*syn*), or at the opposite side (*anti*). In most cases the IMDAF reaction showed high stereoselectivity (Table 2). ^{1}H-NMR coupling constants between H-6, H-7, and H-8 were used to investigate if *exo*- or *endo*-addition had occurred. *Exo*-coupling could be correlated with literature values for comparable compounds.[22] Typical coupling constants are depicted in Fig. 1.

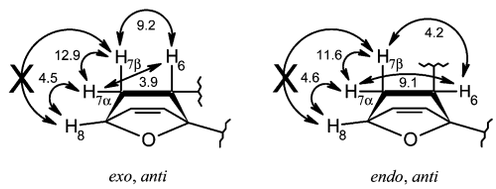
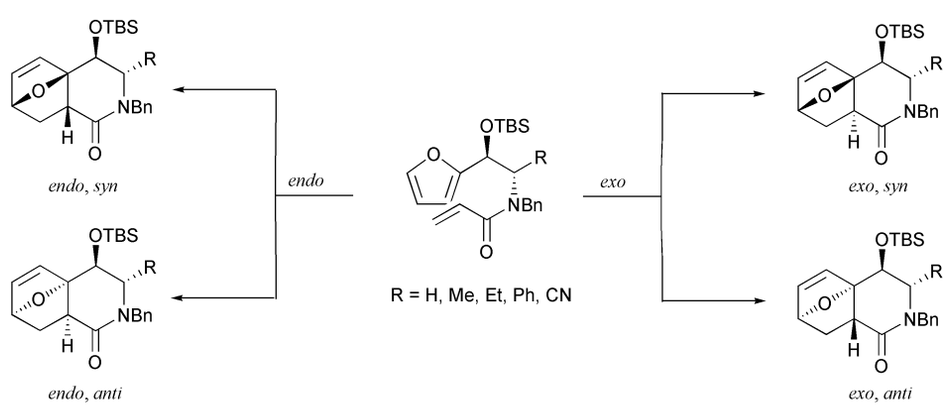


Fig. 1

Formation of the *exo* product was deduced from the coupling of H-7β. Since the dihedral angle between H-7β and H-8 in both the *exo* and the *endo* addition product is close to 90° ($J \sim 0$ Hz), the only visible coupling of H-7β other than with H-7α will be, in both instances, with H-6. A large coupling constant (9.2 Hz; Fig. 1) shows H-6 and H-7β to be present at the same side of the molecule, thus indicating *exo* addition. *Endo* cyclisation leads to significantly smaller coupling between H-7β and H-6 ($J \sim 4$ Hz).

These findings were supported by NOESY experiments. Interaction between H-6 and H-10 indicated that these atoms were present at the same side of the molecule, which is typical for *exo*-addition. The NOESY experiments were also used to determine whether *syn*- or *anti*-addition had taken place. (*Exo*, *anti*)-addition showed a clear correlation between H-6 and the *tert*-butyl group of the TBS group. This indicated that H-6 and the silylated hydroxyl function were situated at the same side of the ring system. Furthermore, no interaction between the alkyl function with H-6 was observed, such as found for (*exo*, *syn*)-addition product **19**. In the latter case coupling between H-2 and H-6 was observed as well. (*Endo*, *anti*)-addition showed correlation between H-2 and H-6, as well as between H-6 and the alkyl side chain (compunds **18** and **22**).

The structure of **15**, as determined by NMR, was confirmed by X-ray analysis. As shown in Fig. 2, the oxygen bridge and H-6 are situated on opposite sides of the molecule (*exo*). Also, the silyloxy substituent and the oxygen bridge (O-11) are found on opposite sides (*anti*). The lactam ring adopted a half-chair conformation, with H-3β occupying an equatorial position.



Scheme 3 Possible diastereoisomers of the IMDAF reaction products.

Table 2 Product ratio[a] of the IMDAF reactions

Ethanolamide	R	*exo* : *anti*	*exo* : *syn*	*endo* : *anti*	*exo* : *syn*
9	H	1	—	—	—
10	Me	1	—	—	—
13	CN	1	—	—	—
11	Et	2	1	1	—
12	Ph	1	—	5	—

[a] Based on isolated yields. Ratio for R = Et also based on NMR data.

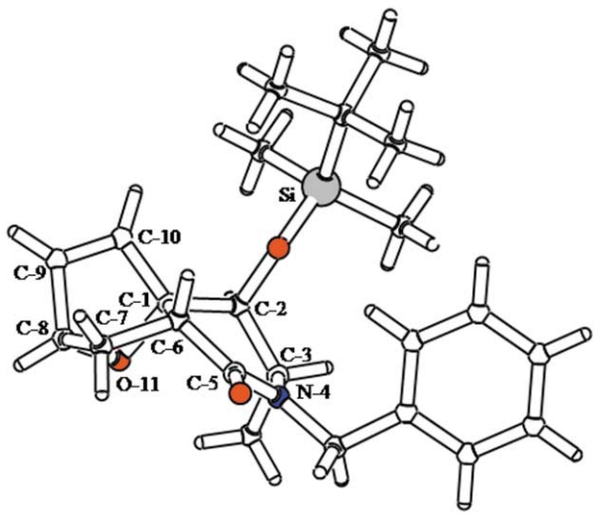


Fig. 2 Crystal structure of compound **15**.[23]

Due to the presence of a small amount of the *syn*-diastereoisomer in ethanolamides **10**, **11**, and **12**, a small amount of cyclisation product resulting from these isomers was found. In all three cases (**16**, **20**, **23**) only the (*exo*, *anti*)-diastereoisomer was observed. In these cases a NOESY correlation was observed between H-6, H-10, and the alkyl side chain.

An overview of all stereoisomers obtained is presented in Table 3.

In conclusion, we have shown that, starting from achiral 2-furfural, complex ring systems can be obtained in a limited number of steps. The IMDAF reaction occurred with high stereoselectivity when small substituents R (hydrogen, methyl, nitrile) were present. *Exo* products were exclusively formed, with the oxygen bridge and the protected hydroxyl function at opposite sides of the ring system (*exo*, *anti*). The general preference for *exo*-cyclisation is in agreement with literature data for comparable compounds carrying distinct tethers.[24] With the larger phenyl group, however, *endo*-cycloaddition was favoured. Ethyl-substitution seemed to be at the turning point between a preference for *exo*- or *endo*-addition, providing a mixture of three compounds in a ratio of 2 : 1 : 1. The IMDAF reactions resulting from the presence of a small amount of diastereoisomer in the ethanolamines gave exclusively (*exo*, *anti*)-stereoisomers.

Thus, depending on the size of the substituent R in the (2′-furyl)-ethanolamides, IMDAF cyclisation yielded either the *exo*- or the *endo*-product with high stereoselectivity, generally with the oxygen bridge and the silyloxy function on opposite sides of the ring system.

Finally, it is to be noted that in only five synthetic steps five chiral centres were introduced.

Experimental

Column chromatography was performed on Baker Silica Gel (0.063–0.200 mm). For TLC analysis, Schleicher and Schuell F1500/LS 254 silica plates were used. Spots were visualised with ultraviolet light, potassium permanganate spray (solution of $KMnO_4$ (5%) and $NaHCO_3$ (0.5%) in water) or by molybdene spray (solution of conc. sulfuric acid (10 mL) and $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (2.5 g) in 90 mL of water) and heating. ^{1}H NMR and ^{13}C NMR were recorded with a Bruker AC 200 or a Bruker DRX-400 instrument. NOESY and COSY experiments were obtained with a Bruker DRX-400 instrument (Mixing time: 1 s). Tetramethylsilane was used as internal standard; δ in ppm, J in Hz. Infrared spectra were obtained with a Perkin-Elmer FT-IR Paragon 1000 spectrometer equipped with a Golden Gate Diamond ATR, using reflectance technique (neat, 4000–300 cm^{-1}, res. 4 cm^{-1}). Melting points were determined with a Büchi melting point apparatus and are uncorrected. Enantiomeric purity was determined by HPLC using a Daicel Chiralcel OD column; with hexane–2-propyl alcohol (99.75 : 0.25, v/v) as eluent. Optical rotations were measured with a Propol automatic polarimeter, at the sodium D line (λ = 589 nm) in units of 10^{-1} deg cm^2 g^{-1}. High resolution mass spectroscopy was performed on a Finnigan MAT 900 instrument equipped with an Electrospray interface (ESI). Other masses were recorded with a Perkin-Elmer Sciex API 165 with ion spray interface.

(*S*)-2-(2′-Furyl)-2-hydroxyacetonitrile (2)

A suspension of 30 g almond meal in 45 mL of 0.10 M citric acid buffer pH 5.5, 19.2 g of freshly distilled 2-furaldehyde **1** (200 mmol) and 50 mL of MTBE was stirred at 4 °C. A freshly prepared solution of HCN in MTBE was added dropwise. This HCN solution was prepared by extracting a mixture of 440 mmol NaCN (2.2 eq.) in 400 mL of H_2O (acidified to pH 5.5 with AcOH), three times with 175 mL of MTBE. The resulting mixture was allowed to stir over the weekend, filtered, and dried with $MgSO_4$. The solvent was evaporated to yield crude **2** (26.1 g). *Ee* 99% (HPLC; determined as TBDPS ether). δ_H ($CDCl_3$) 3.54 (1 H, br s, O*H*), 5.55 (1 H, s, *H-2*), 6.44 (1 H, dd, *J* 1.8 and 3.3, *H-4′*), 6.61 (1 H, d, *J* 3.3, *H-3′*) and 7.49 (1 H, d, *J* 1.8, *H-5′*); δ_C ($CDCl_3$) 56.4 (*C-2*), 109.8, 110.6 (*C-3′*, *C-4′*), 116.9 (*C-1*), 143.9 (*C-5′*) and 147.3 (*C-2′*).

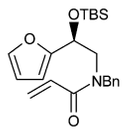
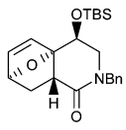
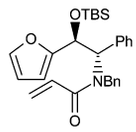
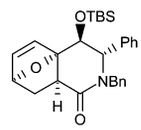
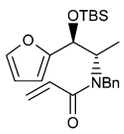
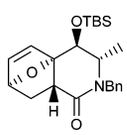
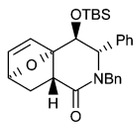
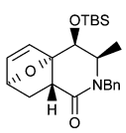
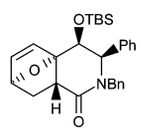
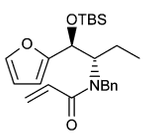
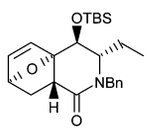
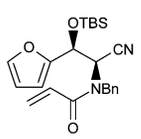
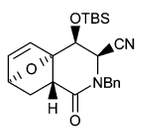
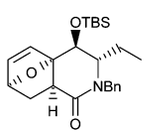
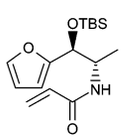
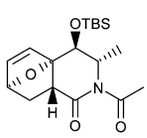
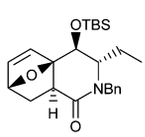
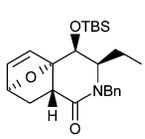
(*S*)-2-(2′-Furyl)-2-*O*-(*tert*-butyldimethylsilyl)acetonitrile (3)

To a solution of 36 g of *tert*-butyldimethylsilylchloride (240 mmol; 1.2 eq.) in 250 mL of DMF was added 32.7 g of imidazole (480 mmol; 2.4 eq.). After 15 minutes the crude cyanohydrin **2** was added and the mixture was allowed to warm to rt overnight. Then water and diethyl ether were added and the layers separated. The organic phase was washed with water and brine, dried ($MgSO_4$) and the solvent was evaporated. The resulting oil was distilled under reduced pressure (96 °C, 150 Pa) to yield **3** (41.6 g, 88%) as a colourless oil. $[\alpha]_D^{20} = +18.9$ (c = 5, $CHCl_3$); ν (cm^{-1}) 1500, 1473, 1464, 1254, 1146, 1070, 1014, 1006, 834, 779 and 740; δ_H ($CDCl_3$) 0.14, 0.16 (2 × 3 H, 2 × s, 2 × C*H*$_3$Si), 0.92 (9 H, s, (C*H*$_3$)$_3$C), 5.56 (1 H, s, *H-2*), 6.40 (1 H, dd, *J* 1.8 and 3.3, *H-4′*), 6.61 (1 H, d, *J* 0.7 and 3.3, *H-3′*) and 7.49 (1 H, d, *J* 0.7 and 1.8, *H-5′*); δ_C ($CDCl_3$) −5.4 (2 × *C*H$_3$Si), 18.0 ((CH$_3$)$_3$*C*), 25.3 ((*C*H$_3$)$_3$C), 57.9 (*C-2*), 109.3, 110.6 (*C-3′*, *C-4′*), 117.1 (*C-1*), 143.6 (*C-5′*) and 148.3 (*C-2′*).

(*S*)-2-*N*-Benzyl-1-(2′-furyl)-1-*O*-(*tert*-butyldimethylsilyl)ethane (4)

To a solution (−70 °C) of 2.37 g of **3** (10 mmol) in 50 mL of diethyl ether was added 12 mmol of DIBAL-H (12 mL of a 1 M solution in hexanes; 1.2 eq.) and the mixture was allowed to warm to −20 °C. Subsequently, 20 mL of MeOH was added dropwise at −70 °C, followed by a solution of 4.4 mL of $BnNH_2$ in 10 mL of methanol. After warming up to −20 °C, 20 mmol of $NaBH_4$ (0.76 g, 2 eq.) was added at −70 °C and the solution was allowed to rise to rt overnight. Diethyl ether was added and the organic layer was washed two times with 1 M $KHSO_4$ and once with 1 M NaOH and brine. After drying with $MgSO_4$, the solvent was evaporated. The crude product (2.2 g) was used without purification in the next step. δ_H ($CDCl_3$) −0.08, 0.06 (2 × 3 H, 2 × s, 2 × Si–C*H*$_3$), 0.87 (9 H, s, C(C*H*$_3$)$_3$), 2.87 (1 H, dd, *J* 4.8 and 12.1, *H-2*), 3.02 (1 H, dd, *J* 7.7 and 12.1, *H-2*), 3.82 (2 H, s, C*H*$_2$ Bn), 4.88 (1 H, dd, *J* 4.8 and 7.7, *H-1*), 6.21–6.33 (2 H, m, *H-3′*, *H-4′*) and 7.20–7.40 (6 H, m, *H-5′*, C*H* Ph); δ_C ($CDCl_3$) −5.4, −5.2 (2 × Si–*C*H$_3$), 17.9 (*C*(CH$_3$)$_3$), 25.5 (C(*C*H$_3$)$_3$), 53.2, 54.0 (*C-2*, *C*H$_2$Ph), 67.8 (*C-1*), 106.3, 109.9 (*C-3′*, *C-4′*), 126.6, 127.7, 128.1 (*C*H Ph), 140.0 (C_q Ph), 141.3 (*C-5′*) and 155.4 (*C-2′*).

Table 3

Entry	Ethanolamide	Product	Yield (%)[a]	Entry	Ethanolamide	Product	Yield (%)[a]
1	 **9**	 *exo*, *anti* **14**	90	**4**	 **12**	 *endo*, *anti* **21**	42
2	 **10**	 *exo*, *anti* **15**	74			 *exo*, *anti* **22**	8
		 *exo*, *anti* **16**	10[b]			 *exo*, *anti* **23**	11[b]
3	 **11**	 *exo*, *anti* **17**	42	**5**	 **13**	 *exo*, *anti* **24**	87
		 *endo*, *anti* **18**	20	**6**	 **25**	 *exo*, *anti* **26**	47
		 *exo*, *syn* **19**	22				
		 *exo*, *anti* **20**	7[b]				

[a] After purification by column chromatography. [b] Due to the presence of a small amount of *syn*-isomer in the starting material.

General procedure for Grignard–transimination–reduction reaction

To 10 mmol of **3** in 15 mL of dry diethyl ether was added dropwise 12 mmol of the respective Grignard reagent in a total volume of 15 mL of dry diethyl ether. The mixture was refluxed for one hour, cooled to −20 °C, and 10 mL of MeOH was added dropwise. After cooling the mixture to −70 °C a solution of 4.4 mL of $BnNH_2$ in 10 mL of methanol was added dropwise followed by warming the solution to −20 °C. Subsequently, 20 mmol of $NaBH_4$ (0.76 g, 2 eq.) was added at −70 °C and allowed to warm to rt overnight. Diethyl ether was added and the organic layer was washed two times with 1 M $KHSO_4$, 1 M NaOH and brine. After drying with $MgSO_4$, the solvent was evaporated. The crude product was used without purification in the next step.

(1*S*,2*S*)-2-*N*-Benzyl-1-(2′-furyl)-1-*O*-(*tert*-butyldimethylsilyl)-propane (5)

Yellow oil (3.1 g). δ_H ($CDCl_3$) −0.11, 0.05 (2 × 3 H, 2 × s, 2 × Si–C*H*$_3$), 0.88 (9 H, s, C(C*H*$_3$)$_3$), 1.12 (3 H, d, *J* 6.2, *H-3*), 3.00 (1 H, q, *J* 6.2, *H-2*), 3.82 (2 H, AB, *J* 13.5, C*H*$_2$ Bn), 4.88 (1 H, dd, *J* 4.8 and 7.7, *H-1*), 6.25 (1 H, d, *J* 3.3, *H-3′*), 6.33 (1 H, dd, *J* 1.8 and 3.3, *H-4′*), 7.21–7.32 (5 H, m, C*H* Ph) and 7.36 (1 H, dd, *J* 0.7 and 1.8, *H-5′*); δ_C ($CDCl_3$) −5.5, −5.3 (2 × Si–*C*H$_3$), 15.9 (*C-3*), 17.8 (*C*(CH$_3$)$_3$), 25.5 (C(*C*H$_3$)$_3$), 50.9 (*C*H$_2$Ph), 56.4 (*C-2*), 73.9 (*C-1*), 107.0, 109.8 (*C-3′*, *C-4′*), 126.5, 127.6, 128.0 (*C*H Ph), 140.3 (C_q Ph), 141.1 (*C-5′*) and 155.2 (*C-2′*).

(1*S*,2*S*)-2-*N*-Benzyl-1-(2′-furyl)-1-*O*-(*tert*-butyldimethylsilyl)-butane (6)

Dark brown oil (2.2 g). δ_H ($CDCl_3$) −0.14, 0.05 (2 × 3 H, 2 × s, 2 × Si–C*H*$_3$), 0.88 (9 H, s, C(C*H*$_3$)$_3$), 0.91 (3 H, dd, *J* 3.3 and 7.6,

H-4), 1.38–1.78 (2 H, m, *C-3*), 2.82 (1 H, m, *H-2*), 3.69 (2 H, AB, *J* 13.2, CH_2 Bn), 4.70 (1 H, d, *J* 5.9, *H-1*), 6.26 (1 H, d, *J* 3.3, *H-3′*), 6.34 (1 H, dd, *J* 1.8 and 3.3, *H-4′*) and 7.20–7.40 (5 H, m, C*H* Ph, *H-5′*); δ_C ($CDCl_3$) −5.5, −5.3 (2 × Si–CH_3), 9.8 (*C-4*), 17.8 ($C(CH_3)_3$), 22.7 (*C-3*), 25.5 ($C(CH_3)_3$), 51.5 (CH_2Ph), 62.3 (*C-2*), 70.2 (*C-1*), 107.2, 109.9 (*C-3′*, *C-4′*), 126.4, 127.8, 127.9 (*C*H Ph), 140.6 (C_q Ph), 141.0 (*C-5′*) and 155.3 (*C-2′*).

(1*S*,2*S*)-2-*N*-Benzyl-1-(2′-furyl)-1-*O*-(*tert*-butyldimethylsilyl)-2-phenylethane (7)

After the addition of benzylamine in methanol the temperature was allowed to rise to room temperature before cooling to −70 °C. Yellow oil (3.8 g). δ_H ($CDCl_3$) −0.30, −0.27 (2 × 3 H, 2 × s, 2 × Si–CH_3), 0.68 (9 H, s, $C(CH_3)_3$), 3.54 (2 H, AB, *J* 13.5, CH_2 Bn), 3.95 (1 H, d, *J* 7.7, *H-2*), 4.70 (1 H, d, *J* 7.7, *H-1*), 6.21 (1 H, d, *J* 2.9, *H-3′*), 6.33 (1 H, dd, *J* 1.8 and 2.9, *H-4′*) and 7.09–7.43 (11 H, m, C*H* Ph, *H-5′*); δ_C ($CDCl_3$) −5.8, −5.6 (2 × Si–CH_3), 17.8 ($C(CH_3)_3$), 25.4 ($C(CH_3)_3$), 50.8 (CH_2Ph), 66.3 (*C-2*), 72.8 (*C-1*), 107.9, 109.9 (*C-3′*, *C-4′*), 126.5, 127.1, 127.7, 127.8, 128.0, 128.5 (*C*H Ph), 140.0, 140.0 (C_q Ph), 141.6 (*C-5′*) and 154.6 (*C-2′*).

(1*S*,2*R*)-2-*N*-Benzyl-3-(2′-furyl)-3-*O*-(*tert*-butyldimethylsilyl)-propionitrile (8)

To a solution (−70 °C) of **3** (10 mmol, 2.37 g) in 50 mL of diethyl ether was added 12 mmol of DIBAL-H (12 mL of 1 M in hexanes; 1.2 eq.), which was slowly warmed to −20 °C. 20 mL of MeOH was added dropwise at −70 °C, followed by a solution of 4.4 mL of $BnNH_2$ in 10 mL of methanol. After raising the temperature to −20 °C and subsequent cooling, a solution of 3.75 g of NH_4Br and 1.86 g of NaCN in 30 mL of MeOH was added dropwise at −70 °C and the solution was allowed to warm to rt overnight. Diethyl ether was added and the organic layer was washed two times with 1 M $KHSO_4$, 1 M NaOH and brine. After drying with $MgSO_4$, the solvent was evaporated to provide the crude product as a yellow oil (2.7 g), which was used without purification in the next step. δ_H ($CDCl_3$) −0.04, 0.12 (2 × 3 H, 2 × s, 2 × Si–CH_3), 0.91 (9 H, s, $C(CH_3)_3$), 3.00 (1 H, q, *J* 6.2), 3.83 (1 H, m, *H-2*), 3.96 (2 H, AB, *J* 13.1, CH_2 Bn), 4.98 (1 H, d, *J* 4.4, *H-3*), 6.39 (1 H, dd, *J* 1.8 and 3.3, *H-4′*), 6.47 (1 H, d, *J* 3.3, *H-3′*), 7.20–7.37 (5 H, m, C*H* Ph) and 7.40 (1 H, dd, *J* 0.73 and 1.83, *H-5′*); δ_C ($CDCl_3$) −5.8, −5.6 (2 × Si–CH_3), 17.6 ($C(CH_3)_3$), 25.2 ($C(CH_3)_3$), 50.4 (CH_2Ph), 54.4 (*C-2*), 68.5 (*C-3*), 108.2, 110.1 (*C-3′*, *C-4′*), 117.7 (*C*N), 126.9, 127.6, 128.0 (*C*H Ph), 137.6 (C_q Ph), 141.7 (*C-5′*) and 151.9 (*C-2′*).

General procedure for aminoacylation

To a vigorously stirred solution of crude ethanolamine (**4**–**8**) and 1.2 eq. of Na_2CO_3 in 4 mL of CH_2Cl_2 and 2 mL of water per mmol of ethanolamine, was added dropwise 1.1 eq. freshly distilled acryloylchloride. The mixture was allowed to stir overnight and the layers were separated. The water layer was extracted once with CH_2Cl_2. The combined organic layers were washed with a 10% Na_2CO_3 solution and brine, dried with $MgSO_4$ and the solvent was evaporated. The products were purified by column chromatography (pet. ether (40–60)–EtOAc 90 : 10). Yields determined from **3**.

(*S*)-2-*N*-Acryloyl-2-*N*-benzyl-1-(2′-furyl)-1-*O*-(*tert*-butyldimethylsilyl)ethane (9)

(Two rotamers, 1 : 1). Yellowish oil (1.2 g, 30%). $[\alpha]_D^{20}$ = −24.0 (*c* = 1, $CHCl_3$); *ν* (cm^{-1}) 1652, 1616, 1442, 1250, 1220, 1082, 938, 831, 778, 731 and 697; δ_H ($CDCl_3$) −0.11, −0.07, 0.00, 0.06 (6 H, 4 × s, 2 × Si–CH_3), 0.85, 0.88 (9 H, 2 × s, $C(CH_3)_3$), 3.48 (0.5 H, dd, *J* 4.8 and 15.7, H-2), 3.51 (0.5 H, dd, *J* 5.1 and 13.2, *H-2*), 3.73 (0.5 H, dd, *J* 8.4 and 15.7, *H-2*), 3.81 (0.5 H, dd, *J* 8.0 and 13.2, *H-2*), 4.57 (1 H, AB, *J* 17.2, CH_2Ph), 4.7 (1 H, AB, *J* 15.0, CH_2Ph), 4.81 (0.5 H, dd, *J* 4.8 and 8.4, *H-1*), 5.22 (0.5 H, dd, *J* 5.1 and 8.0, *H-1*), 5.66 (0.5 H, dd, *J* 2.9 and 9.5, CH=CH_2), 5.70 (0.5 H, dd, *J* 2.4 and 10.2, CH=CH_2), 6.20 (0.5 H, d, *J* 3.3, *H-3′*), 6.23 (0.5 H, d, *J* 3.3, *H-3′*), 6.31 (1 H, dd, *J* 1.8 and 3.3, *H-4′*), 6.39 (1 H, dd, *J* 3.3 and 16.8, *H-4′*), 6.53 (0.5 H, dd, *J* 9.5 and 16.8, CH=CH_2), 6.72 (0.5 H, dd, *J* 10.2 and 16.8, CH=CH_2) and 7.09–7.37 (7 H, m, C*H*=CH_2, C*H* Ph, *H-5′*); δ_C ($CDCl_3$) −5.6 (2 × Si–CH_3), 17.7 ($C(CH_3)_3$), 25.4 ($C(CH_3)_3$), 49.1, 51.9, 52.3, 52.6 (*C-2*, CH_2Ph), 66.0, 66.9 (*C-1*), 106.8, 107.1, 109.8, 110.0 (*C-3′*, *C-4′*), 125.9, 127.0, 127.1, 127.3, 127.5, 127.8, 128.2, 128.4 (*C*H Ph, CH_2=*C*H), 127.7, 128.1 (CH_2=CH), 136.6, 137.2 (C_q Ph), 141.5, 141.6 (*C-5′*), 153.5, 154.4 (*C-2′*) and 166.5, 166.6 (*C*ON); MS (ESI) *m*/*z* 408.1 (M + Na^+ requires 408.6).

(1*S*,2*S*)-2-*N*-Acryloyl-2-*N*-benzyl-1-(2′-furyl)-1-*O*-(*tert*-butyldimethylsilyl)propane (10)

Yellow oil (3.2 g, 80%). $[\alpha]_D^{20}$ = −14.8 (*c* = 1, $CHCl_3$); *ν* (cm^{-1}) 1651, 1615, 1422, 1251, 1073, 1006, 857, 835, 777, 728 and 696; δ_H ($CDCl_3$) −0.06, 0.02 (2 × 3 H, 2 × s, 2 × Si–CH_3), 0.88 (9 H, s, $C(CH_3)_3$), 1.28 (3 H, d, *J* 6.8, CH_3), 4.16–4.81 (3 H, m, *H-2*, CH_2Ph), 5.27 (1 H, d, *J* 6.6, *H-1*), 5.57 (1 H, dd, *J* 4.8 and 8.0, CH=CH_2), 6.20–6.35 (3 H, m, CH=CH_2, *H-3′*, *H-4′*) and 7.05–7.37 (7 H, m, C*H*=CH_2,C*H* Ph, *H-5′*); δ_C ($CDCl_3$) −5.7 (2 × Si–CH_3), 12.9 (*C*H_3), 17.5 ($C(CH_3)_3$), 25.2 ($C(CH_3)_3$), 50.1 (CH_2Ph), 57.2 (*C-2*), 69.3 (*C-1*), 106.7, 109.5 (*C-3′*, *C-4′*), 125.5, 126.6, 128.1, 128.4 (*C*H Ph, CH_2=*C*H), 127.4 (CH_2=CH), 137.4 (C_q Ph), 140.8 (*C-5′*), 154.4 (*C-2′*) and 166.4 (*C*ON); MS (ESI) *m*/*z* 422.6 (M + Na^+ requires 422.2).

(1*S*,2*S*)-2-*N*-Acryloyl-2-*N*-benzyl-1-(2′-furyl)-1-*O*-(*tert*-butyldimethylsilyl)butane (11)

Yellow oil (1.2 g, 29%). $[\alpha]_D^{20}$ = 3.14 (*c* = 1, $CHCl_3$); *ν* (cm^{-1}) 1649, 1614, 1436, 1421, 1250, 1069, 857, 836, 777, 727 and 698; δ_H ($CDCl_3$) −0.19, −0.01 (2 × 3 H, 2 × s, 2 × Si–CH_3), 0.84 (9 H, s, $C(CH_3)_3$), 0.70 (3 H, t, *J* 7.5, CH_2CH_3), 1.84–2.21 (2 H, m, CH_2CH$_3$), 4.19–4.80 (4 H, m, *H-1*, *H-2*, CH_2Ph), 5.59 (1 H, dd, *J* 4.6 and 7.7, CH=CH_2), 6.26 (1 H, dd, *J* 0.7 and 3.3, *H-3′*), 6.31 (1 H, dd, *J* 1.8 and 3.3, *H-4′*), 6.34–6.58 (1 H, m, CH=CH_2), 7.01–7.30 (6 H, m, C*H*=CH_2, C*H* Ph) and 7.32 (1 H, dd, *J* 0.7 and 1.8, *H-5′*); δ_C ($CDCl_3$) −5.5 (2 × Si–CH_3), 11.7 (CH_2CH_3), 17.8 ($C(CH_3)_3$), 21.7 (CH_2CH_3), 25.5 ($C(CH_3)_3$), 44.6 (CH_2Ph), 64.3 (*C-2*), 69.4(*C-1*), 107.4, 110.1 (*C-3′*, *C-4′*), 126.7, 127.9, 128.2, 128.8 (*C*H Ph, CH_2=*C*H), 137.2, (C_q Ph), 141.0 (*C-5′*), 154.7 (*C-2′*) and 167.1 (*C*ON); MS (ESI) *m*/*z* 436.4 (M + Na^+ requires 436.2).

(1*S*,2*S*)-2-*N*-Acryloyl-2-*N*-benzyl-1-(2′-furyl)-2-phenyl-1-*O*-(*tert*-butyldimethylsilyl)ethane (12)

Yellowish solid (3.3 g, 72%). Mp 86–88 °C; $[\alpha]_D^{20}$ = −37.1 (*c* = 1, $CHCl_3$); *ν* (cm^{-1}) 1652, 1615, 1436, 1420, 1250, 1223, 1074, 854, 836, 778, 751, 731 and 698; δ_H ($CDCl_3$) −0.12, 0.04 (2 × 3 H, 2 × s, 2 × Si–CH_3), 0.84 (9 H, s, $C(CH_3)_3$), 4.64 (2 H, AB, *J* 17.7, CH_2Ph), 5.12 (1 H, d, *J* 7.3, *H-1*), 5.41 (1 H, d, *J* 7.3, *H-2*), 5.60–5.74 (1 H, m, CH=CH_2), 6.33 (1 H, dd, *J* 1.8 and 3.3, *H-3′*), 6.35–6.46 (2 H, m, CH=CH_2, *H-4′*) and 7.13–7.42 (7 H, m, C*H*=CH_2, C*H* Ph, *H-5′*); δ_C ($CDCl_3$) −5.9, −5.7 (2 × Si–CH_3), 17.5 ($C(CH_3)_3$), 25.2 ($C(CH_3)_3$), 51.3 (CH_2Ph), 67.4 (*C-2*), 68.0 (*C-1*), 107.7, 109.8 (*C-3′*, *C-4′*), 126.0, 126.8, 127.3, 127.7, 128.1, 129.1, 129.9 (*C*H Ph, CH_2=*C*H), 127.9 (CH_2=CH), 136.4, 138.6 (C_q Ph), 141.1 (*C-5′*), 154.1 (*C-2′*) and 167.2 (*C*ON); MS (ESI) *m*/*z* 484.4 (M + Na^+ requires 484.7).

(1*S*,2*R*)-2-*N*-Acryloyl-2-*N*-benzyl-3-(2′-furyl)-3-*O*-(*tert*-butyldimethylsilyl)propionitrile (13)

Colourless oil (48%). $[\alpha]_D^{20}$ = −22.6 (*c* = 1, $CHCl_3$); *ν* (cm^{-1}) 1660, 1621, 1418, 1240, 1207, 1094, 838, 780, 732 and 696;

δ_H ($CDCl_3$) −0.11, 0.06 (2 × 3 H, 2 × s, 2 × Si–CH_3), 0.86 (9 H, s, C(CH_3)$_3$), 4.64 (2 H, AB, *J* 17.90, CH_2Ph), 5.15 (1 H, d, *J* 7.0, *H-2*), 5.41 (1 H, d, *J* 7.0, *H-3*), 5.72 (1 H, dd, *J* 2.9 and 8.0, CH=CH_2), 6.37 (1 H, dd, *J* 1.8 and 3.3, *H-3′*), 6.38–6.46 (2 H, m, CH=CH_2, *H-4′*), 7.18–7.39 (6 H, m, C*H*=CH_2, C*H* Ph) and 7.41 (1 H, dd, *J* 0.7 and 1.8, *H-5′*); δ_C ($CDCl_3$) −5.7 (2 × Si–CH_3), 17.5 (*C*(CH_3)$_3$), 25.2 (C(*C*H_3)$_3$), 52.0 (*C*H_2Ph), 53.3 (*C-2*), 66.8 (*C-3*), 109.5, 110.3 (*C-3′*, *C-4′*), 114.7 (*C*N), 125.8, 126.5, 127.5, 128.6 (*C*H Ph, CH_2=*C*H), 130.0 (*C*H_2=CH), 135.7 (C_q Ph), 142.6 (*C-5′*), 150.8 (*C-2′*) and 166.4 (*C*ON); MS (ESI) *m/z* 433.1 (M + Na^+ requires 433.6).

General procedure for intramolecular Diels–Alder reaction

Ethanolamides **9**–**13** (2 mmol) were dissolved in 10 mL of dry toluene. The mixtures were refluxed overnight and the solvent evaporated. The crude compounds were purified by column chromatography (pet. ether (40–60)–EtOAc 90 : 10 ⟶ 75 : 25). Compounds **17** and **18** could not be separated and the yields were calculated using NMR (combined yield: 0.52 g).

(1*S*,2*S*,6*R*,8*S*)-4-Benzyl-2-*O*-(*tert*-butyldimethylsilyl)-11-oxa-4-aza-tricyclo[6.2.1.0^{1,6}]undec-9-en-5-one (14)

White solid (0.69 g, 90%). Mp 95 °C; $[\alpha]_D^{20}$ = −57.4 (*c* = 1, $CHCl_3$); *v* (cm^{-1}) 1622, 1472, 1455, 1361, 1250, 1114, 1061, 971, 939, 832, 779, 748, 700, 663 and 590; δ_H ($CDCl_3$) −0.18, 0.02 (2 × 3 H, 2 × s, 2 × Si–CH_3), 0.81 (9 H, s, C(CH_3)$_3$), 1.93 (1 H, dd, *J* 9.2 and 12.9, *H-7β*), 2.09 (1 H, dd, *J* 4.3 and 12.9, *H-7α*), 2.54 (1 H, dd, *J* 3.9 and 9.2, *H-6*), 3.18 (1 H, dd, *J* 3.1 and 13.0, *H-3*), 3.49 (1 H, dd, *J* 2.6 and 13.0, *H-3*), 4.18 (1 H, t, *J* 2.7, *H-2*), 4.24 (1 H, d, *J* 14.7, C*H* Bn), 4.92 (1 H, d, *J* 14.7, C*H* Bn), 4.97 (1 H, d, *J* 4.5, *H-8*), 6.32 (1 H, d, *J* 5.8, *H-10*), 6.39 (1 H, dd, *J* 1.2 and 5.8, *H-9*) and 7.21–7.29 (5 H, m, C*H* Ph); δ_C ($CDCl_3$) −5.3, −4.8 (2 × Si–*C*H_3), 17.7 (*C*(CH_3)$_3$), 25.5 (C(*C*H_3)$_3$), 32.1 (*C-7*), 40.8 (*C-6*), 49.7 (*C*H_2Ph), 50.4 (*C-3*), 65.0 (*C-2*), 78.4 (*C-8*), 88.7 (*C-1*), 127.2, 128.1, 128.4 (*C*H Ph), 134.1 (*C-10*), 136.8 (C_q Ph), 137.2 (*C-9*) and 171.2 (*C-5*); HRMS (ESI) *m/z* 386.2062 (M + H^+ requires 386.2151).

(1*S*,2*S*,3*S*,6*R*,8*S*)-4-Benzyl-2-*O*-(*tert*-butyldimethylsilyl)-3-methyl-11-oxa-4-aza-tricyclo[6.2.1.0^{1,6}]undec-9-en-5-one (15)

White solid (0.59 g, 74%). Mp 117 °C; $[\alpha]_D^{20}$ = −102.9 (*c* = 1, $CHCl_3$); *v* (cm^{-1}) 1622, 1472, 1452, 1361, 1250, 1074, 1060, 964, 839, 780, 730, 701, 620 and 588; δ_H ($CDCl_3$) −0.26, 0.04 (2 × 3 H, 2 × s, 2 × Si–CH_3), 0.78 (9 H, s, C(CH_3)$_3$), 1.31 (3 H, d, *J* 7.1, CHCH_3), 1.94 (1 H, dd, *J* 9.2 and 11.9, *H-7β*), 2.09 (1 H, dd, *J* 4.4 and 11.9, *H-7α*), 2.57 (1 H, dd, *J* 4.1 and 9.2, *H-6*), 3.45 (1 H, dq, *J* 1.8 and 7.1, *H-3*), 3.83 (1 H, d, *J* 15.0, C*H* Bn), 4.09 (1 H, d, *J* 1.8, *H-2*), 4.97 (1 H, dd, *J* 1.6 and 4.5, *H-8*), 5.50 (1 H, d, *J* 15.0, C*H* Bn), 6.31 (1 H, d, *J* 5.8, *H-10*), 6.35 (1 H, dd, *J* 1.6 and 5.8, *H-9*) and 7.19–7.28 (5 H, m, C*H* Ph); δ_C ($CDCl_3$) −5.6, −4.9 (2 × Si–*C*H_3), 16.2 (*C*H_3C-3), 17.4 (*C*(CH_3)$_3$), 25.3 (C(*C*H_3)$_3$), 32.1 (*C-7*), 40.0 (*C-6*), 46.5 (*C*H_2Ph), 57.6 (*C-3*), 68.6 (*C-2*), 78.5 (*C-8*), 88.2 (*C-1*), 126.8, 127.8, 128.1 (*C*H Ph), 135.4 (*C-10*), 136.1 (*C-9*), 137.0 (C_q Ph) and 170.8 (*C-5*); HRMS (ESI) *m/z* 400.2198 (M + H^+ requires 400.2307).

Crystal structure determination of compound 15

Single crystals suitable for X-ray analysis† were obtained as colourless needles by recrystallisation from dichloromethane and hexane. The reflection intensities were measured on a four-circle Enraf-Nonius CAD-4 diffractometer using graphite-monochromated MoKα radiation (λ = 0.71073 Å). The cell dimensions were determined using 24 independent reflections. Intensities were corrected for Lorentz and polarisation effects. Absorption correction was not applied. The positions of heavy atoms were determined from a Patterson map (DIFDIF).[25] The atomic scattering factors were taken from the International Tables for X-ray Crystallography.[26] The remainder of the non-hydrogen atoms was located in subsequent difference Fourier syntheses. Full-matrix least-squares refinement on *F* using XTAL3.4 set of programs[27] with the function minimised being $\Sigma w(|F_o|-|F_c|)^2$ with $w = 1/\sigma^2$ (*F*). Positional refinement of the non-hydrogen atoms, anisotropic for the non-hydrogen atoms, fixed isotropic thermal parameters of 0.08 Å^2 for the hydrogens, which were placed at the distance of 0.95 Å from their parent atoms. Geometric calculations and molecular graphics were performed with the PLATON package.[23]

Crystal data. $C_{23}H_{33}NO_3Si$, *M* = 399.22, orthorhombic, *a* = 19.214(6), *b* = 16.341(4), *c* = 7.1838(9) Å, *U* = 2255.5(9) Å^3, *T* = 145 K, space group *P*2(1)2(1)2(1) (no. 19), *Z* = 4, μ(MoK_α) = 0.126 mm^{-1}, 5389 reflections measured, observed data [$I > 2.0\sigma(I)$] 3287, reflections used 3129, *R* = 0.042, *wR* = 0.045, *S* = 2.04.

(1*S*,2*S*,3*R*,6*R*,8*S*)-4-Benzyl-2-*O*-(*tert*-butyldimethylsilyl)-3-methyl-11-oxa-4-aza-tricyclo[6.2.1.0^{1,6}]undec-9-en-5-one (16)

Colourless oil (80 mg, 10%). $[\alpha]_D^{20}$ = 29.8 (*c* = 1, $CHCl_3$); *v* (cm^{-1}) 1659, 1466, 1449, 1435, 1255, 1226, 1121, 1059, 1029, 995, 954, 836, 778, 701 and 588; δ_H ($CDCl_3$) −0.18, −0.10 (2 × 3 H, 2 × s, 2 × Si–CH_3), 0.80 (9 H, s, C(CH_3)$_3$), 1.24 (3 H, d, *J* 7.0, CHCH_3), 1.69 (1 H, dd, *J* 9.9 and 13.0, *H-7β*), 2.49 (1 H, dd, *J* 4.4 and 13.0, *H-7α*), 2.52 (1 H, dd, *J* 4.4 and 9.9, *H-6*), 3.40 (1 H, dq, *J* 5.6 and 7.0, *H-3*), 3.97 (1 H, d, *J* 5.6, *H-2*), 3.99 (1 H, d, *J* 14.7, C*H* Bn), 4.97 (1 H, dd, *J* 1.6 and 4.2, *H-8*), 5.23 (1 H, d, *J* 14.7, C*H* Bn), 6.34 (1 H, dd, *J* 1.4 and 5.8, *H-9*), 6.42 (1 H, d, *J* 5.8, *H-10*) and 7.24–7.34 (5 H, m, C*H* Ph); δ_C ($CDCl_3$) −5.4, −5.1 (2 × Si–*C*H_3), 12.6 (*C*H_3C-3), 18.0 (*C*(CH_3)$_3$), 25.6 (C(*C*H_3)$_3$), 29.8 (*C-7*), 43.7 (*C-6*), 48.8 (*C*H_2Ph), 55.2 (*C-3*), 71.3 (*C-2*), 77.8 (*C-8*), 91.8 (*C-1*), 127.5, 128.1, 128.6 (*C*H Ph), 136.0 (*C-10*), 136.2 (*C-9*), 137.3 (C_q Ph) and 170.8 (*C-5*); HRMS (ESI) *m/z* 400.2200 (M + H^+ requires 400.2307).

(1*S*,2*S*,3*S*,6*R*,8*S*)-4-Benzyl-2-*O*-(*tert*-butyldimethylsilyl)-3-ethyl-11-oxa-4-aza-tricyclo[6.2.1.0^{1,6}]undec-9-en-5-one (17)

Colourless oil (42%). *v* (cm^{-1}) 1647, 1471, 1462, 1457, 1434, 1258, 1260, 1123, 1082, 1039, 998, 875, 836, 779, 706, 699 and 618; δ_H ($CDCl_3$) −0.26, 0.07 (2 × 3 H, 2 × s, 2 × Si–CH_3), 0.81 (9 H, s, C(CH_3)$_3$), 0.94 (3 H, t, *J* 7.5, CH_3), 1.67–1.79 (1 H, m, CH_2), 1.97 (1 H, dd, *J* 9.2 and 11.9, *H-7β*), 1.92–2.04 (1 H, m, CH_2), 2.08 (1 H, dt, *J* 4.4 and 11.9, *H-7α*), 2.58 (1 H, dd, *J* 4.1 and 9.2, *H-6*), 3.17 (1 H, ddd, *J* 1.5, 3.2 and 11.2, *H-3*), 3.83 (1 H, d, *J* 15.0, C*H* Bn), 4.31 (1 H, d, *J* 1.4, *H-2*), 4.99 (1 H, dd, *J* 1.6 and 4.6, *H-8*), 5.54 (1 H, d, *J* 15.0, C*H* Bn), 6.38 (1 H, dd, *J* 1.5 and 5.8, *H-9*), 6.35 (1 H, d, *J* 5.8, *H-10*), 7.22–7.34 (5 H, m, C*H* Ph); δ_C ($CDCl_3$) −5.2, −4.4 (2 × Si–*C*H_3), 11.7 (*C*H_3), 17.7 (*C*(CH_3)$_3$), 22.5 (*C*H_2), 25.6 (C(*C*H_3)$_3$), 32.3 (*C-7*), 40.1 (*C-6*), 47.2 (*C*H_2Ph), 64.7, 64.8 (*C-2*, *C-3*), 79.0 (*C-8*), 88.4 (*C-1*), 127.1, 128.3, 128.5 (*C*H Ph), 135.9 (*C-10*), 136.3 (*C-9*), 137.2 (C_q Ph) and 171.1 (*C-5*); HRMS (ESI) *m/z* 414.2535 (M + H^+ requires 414.2464).

(1*S*,2*S*,3*S*,6*S*,8*S*)-4-Benzyl-2-*O*-(*tert*-butyldimethylsilyl)-3-ethyl-11-oxa-4-aza-tricyclo[6.2.1.0^{1,6}]undec-9-en-5-one (18)

Colourless oil (20%). *v* (cm^{-1}) 1647, 1471, 1462, 1457, 1434, 1258, 1260, 1123, 1082, 1039, 998, 875, 836, 779, 706, 699 and 618; ^{1}H NMR δ_H ($CDCl_3$) −0.03, 0.04 (2 × 3 H, 2 × s, 2 × Si–CH_3), 0.76 (9 H, s, C(CH_3)$_3$), 0.99 (3 H, t, *J* 7.4, CH_3), 1.75 (1 H, dd, *J* 4.2 and 11.2, *H-7β*), 1.78–1.89 (2 H, m, CH_2), 2.17 (1 H, ddd, *J* 4.6, 9.1 and 11.6, *H-7α*), 2.56 (1 H, dd, *J* 4.2 and 9.1, *H-6*), 3.32 (1 H, dt, *J* 3.6 and 7.8, *H-3*), 3.73 (1 H, d, *J* 14.6, C*H* Bn), 4.28 (1 H, dd *J* 0.8 and 3.6, *H-2*), 4.98 (1 H, dd, *J* 1.6

† CCDC reference numbers 214952. See http://www.rsc.org/suppdata/ob/b3/b307275d/ for crystallographic data in .cif or other electronic format.

and 4.6, *H-8*), 5.30 (1 H, d, *J* 14.5, C*H* Bn), 5.84 (1 H, d, *J* 5.8, *H-10*), 6.49 (1 H, ddd, *J* 1.6, 4.1 and 5.8, *H-9*) and 7.22–7.34 (5 H, m, C*H* Ph); δ_C ($CDCl_3$) −5.3, −4.2 (2 × Si–*C*H_3), 9.0 (*C*H_3), 17.8 (*C*$(CH_3)_3$), 24.7 (*C*H_2), 25.5 (C(*C*$H_3)_3$), 29.2 (*C-7*), 41.9 (*C-6*), 47.1 (*C*H_2Ph), 66.1 (*C-3*), 72.1 (*C-2*), 80.0 (*C-8*), 89.6 (*C-1*), 127.5, 128.7 (*C*H Ph), 130.8 (*C-10*), 137.0 (C_q Ph), 139.4 (*C-9*) and 170.6 (*C-5*); HRMS (ESI) *m*/*z* 414.2535 (M + H^+ requires 414.2464).

(1*R*,2*S*,3*S*,6*S*,8*R*)-4-Benzyl-2-*O*-(*tert*-butyldimethylsilyl)-3-ethyl-11-oxa-4-aza-tricyclo[6.2.1.0^{1,6}]undec-9-en-5-one (19)

Colourless oil (0.18 g, 22%). $[\alpha]_D^{20}$ = 1.0 (*c* = 1, $CHCl_3$); *ν* (cm^{-1}) 1638, 1464, 1453, 1420, 1248, 1126, 1094, 835, 775 and 699; δ_H ($CDCl_3$) 0.07, 0.08 (2 × 3 H, 2 × s, 2 × Si–C*H*$_3$), 0.81 (9 H, s, C(C*H*$_3)_3$), 0.83 (3 H, t, *J* 7.3, C*H*$_3$), 1.72–1.78 (2 H, m, C*H*$_2$), 1.94 (1 H, dd, *J* 8.9 and 12.0, *H-7α*), 2.26 (1 H, dd, *J* 4.2 and 12.0, *H-7β*), 2.43 (1 H, dd, *J* 3.7 and 8.9, *H-6*), 3.53 (1 H, dq, *J* 4.1 and 7.5, *H-3*), 4.03 (1 H, d, *J* 15.5, C*H* Bn), 4.39 (1 H, d, *J* 7.5, *H-2*), 5.06 (1 H, dd, *J* 1.6 and 4.4, *H-8*), 5.43 (1 H, d, *J* 15.5, C*H* Bn), 6.16 (1 H, d, *J* 5.7, *H-10*), 6.40 (1 H, dd, *J* 1.6 and 5.7, *H-9*) and 7.17–7.29 (5 H, m, C*H* Ph); δ_C ($CDCl_3$) −4.5, −3.8 (2 × Si–*C*H_3), 7.3 (*C*H_3), 18.3 (*C*$(CH_3)_3$), 20.3 (*C*H_2), 25.8 (C(*C*$H_3)_3$), 33.7 (*C-7*), 43.1 (*C-6*), 46.8 (*C*H_2Ph), 59.5 (*C-3*), 66.9 (*C-2*), 77.8 (*C-8*), 88.3 (*C-1*), 126.8, 127.1, 128.3 (*C*H Ph), 135.3 (*C-10*), 136.6 (C_q Ph), 137.2 (*C-9*) and 172.5 (*C-5*); HRMS (ESI) *m*/*z* 462.2519 (M + H^+ requires 414.2464).

(1*S*,2*S*,3*R*,6*R*,8*S*)-4-Benzyl-2-*O*-(*tert*-butyldimethylsyl)-3-ethyl-11-oxa-4-aza-tricyclo[6.2.1.0^{1,6}]undec-9-en-5-one (20)

Colourless oil (60 mg, 7%). $[\alpha]_D^{20}$ = 54.2 (*c* = 1, $CHCl_3$); *ν* (cm^{-1}) 1647, 1471, 1462, 1457, 1434, 1258, 1260, 1123, 1082, 1039, 98, 875, 836, 779, 706, 699 and 618; δ_H ($CDCl_3$) −0.29, −0.20 (2 × 3 H, 2 × s, 2 × Si–C*H*$_3$), 0.76 (9 H, s, C(C*H*$_3)_3$), 0.88 (3 H, t, *J* 7.5, C*H*$_3$), 1.56–1.62 (1 H, m, C*H*$_2$), 1.63 (1 H, dd, *J* 8.1 and 11.3, *H-7β*), 1.96–2.08 (1 H, m, C*H*$_2$), 2.50 (1 H, dd, *J* 4.2 and 8.1, *H-6*), 2.55 (1 H, dd, *J* 4.4 and 11.3, *H-7α*), 3.17 (1 H, dq, *J* 4.6 and 5.7, *H-3*), 3.71 (1 H, d, *J* 14.4, C*H* Bn), 3.83 (1 H, d, *J* 5.7, *H-2*), 4.95 (1 H, dd, *J* 1.6 and 4.4, *H-8*), 5.62 (1 H, d, *J* 14.4, C*H* Bn), 6.31 (1 H, ddd, *J* 0.5, 1.6 and 5.8, *H-9*), 6.39 (1 H, d, *J* 5.8, *H-10*) and 7.25–7.34 (5 H, m, C*H* Ph). δ_C ($CDCl_3$) −5.7, −5.3 (2 × Si–*C*H_3), 11.9 (*C*H_3), 17.9 (*C*$(CH_3)_3$), 21.1 (*C*H_2), 25.5 (C(*C*$H_3)_3$), 29.5 (*C-7*), 44.2 (*C-6*), 50.7 (*C*H_2Ph), 61.3 (*C-3*), 72.0 (*C-2*), 77.9 (*C-8*), 92.4 (*C-1*), 127.6, 128.5, 128.6 (*C*H Ph), 136.1 (*C-9*, *C-10*), 137.1 (C_q Ph) and 171.1 (*C-5*); HRMS (ESI) *m*/*z* 414.2540 (M + H^+ requires 414.2464).

(1*S*,2*S*,3*S*,6*S*,8*S*)-4-Benzyl-2-*O*-(*tert*-butyldimethylsilyl)-3-phenyl-11-oxa-4-aza-tricyclo[6.2.1.0^{1,6}]undec-9-en-5-one (21)

Colourless oil (0.39 g, 42%). $[\alpha]_D^{20}$ = −76.6 (*c* = 1, $CHCl_3$); *ν* (cm^{-1}) 1665, 1416, 1249, 1218, 1160, 1124, 1073, 1017, 971, 867, 835, 778 and 696; δ_H ($CDCl_3$) −0.36, −0.19 (2 × 3 H, 2 × s, 2 × Si–C*H*$_3$), 0.71 (9 H, s, C(C*H*$_3)_3$), 1.85 (1 H, dd, *J* 4.4 and 11.6, *H-7β*), 2.31 (1 H, ddd, *J* 4.4, 9.2 and 11.6, *H-7α*), 2.82 (1 H, dd, *J* 4.4 and 9.2, *H-6*), 3.23 (1 H, d, *J* 14.5, C*H* Bn), 4.15 (1 H, d, *J* 6.2, *H-3*), 4.43 (1 H, dd, *J* 0.9 and 6.2, *H-2*), 5.03 (1 H, dd, *J* 1.5 and 4.6, *H-8*), 5.39 (1 H, d, *J* 14.5, C*H* Bn), 5.97 (1 H, d, *J* 5.8, *H-10*), 6.62 (1 H, dt, *J* 1.5 and 5.8, *H-9*), 7.07–7.10 (2 H, m, C*H* Ph) and 7.25–7.43 (8 H, m, C*H* Ph); δ_C ($CDCl_3$) −5.5, −4.7 (2 × Si–*C*H_3), 17.9 (*C*$(CH_3)_3$), 25.6 (C(*C*$H_3)_3$), 29.7 (*C-7*), 43.2 (*C-6*), 46.6 (*C*H_2Ph), 68.8 (*C-3*), 77.0 (*C-2*), 80.1 (*C-8*), 88.3 (*C-1*), 127.5, 127.7, 128.2, 128.5, 128.8, 128.9 (*C*H Ph), 129.9 (*C-10*), 136.7, 139.9 (C_q Ph), 140.3 (*C-9*) and 170.7 (*C-5*); HRMS (ESI) *m*/*z* 462.2498 (M + H^+ requires 462.2364).

(1*S*,2*S*,3*S*,6*R*,8*S*)-4-Benzyl-2-*O*-(*tert*-butyldimethylsilyl)-3-phenyl-11-oxa-4-aza-tricyclo[6.2.1.0^{1,6}]undec-9-en-5-one (22)

Colourless oil (70 mg, 8%). $[\alpha]_D^{20}$ = −108.4 (*c* = 1, $CHCl_3$); *ν* (cm^{-1}) 1639, 1463, 1448, 1432, 1257, 1091, 1061, 868, 833, 776, 746, 697 and 595; δ_H ($CDCl_3$) −0.13, 0.10 (2 × 3 H, 2 × s, 2 × Si–C*H*$_3$), 0.82 (9 H, s, C(C*H*$_3)_3$), 2.03 (1 H, dd, *J* 9.2 and 11.9, *H-7β*), 2.20 (1 H, dd, *J* 4.4 and 11.9, *H-7α*), 2.68 (1 H, dd, *J* 4.1, *J* 9.2, *H-6*), 3.39 (1 H, d, *J* = 14.7, C*H* Bn), 4.41 (1 H, d, *J* 1.6, *H-2*), 4.60 (1 H, br s, *H-3*), 4.89 (1 H, dd, *J* 1.4 and 4.6, *H-8*), 5.76 (1 H, d, *J* 14.7, C*H* Bn), 6.27 (1 H, d, *J* 5.7, *H-10*), 6.30 (1 H, dd, *J* 1.5 and 5.8, *H-9*) and 7.15–7.35 (10 H, m, C*H* Ph); δ_C ($CDCl_3$) −5.2, −4.3 (2 × Si–*C*H_3), 17.7 (*C*$(CH_3)_3$), 25.6 (C(*C*$H_3)_3$), 32.5 (*C-7*), 40.4 (*C-6*), 47.5 (*C*H_2Ph), 66.8 (*C-3*), 69.9 (*C-2*), 78.9 (*C-8*), 88.3 (*C-1*), 127.3, 127.5, 127.7, 128.1, 128.5, 128.6 (*C*H Ph), 135.4 (*C-10*), 136.4 (*C-9*), 136.8, 137.0 (C_q Ph) and 172.2 (*C-5*); HRMS (ESI) *m*/*z* 462.2501 (M + H^+ requires 462.2364).

(1*S*,2*S*,3*R*,6*R*,8*S*)-4-Benzyl-2-*O*-(*tert*-butyldimethylsilyl)-3-phenyl-11-oxa-4-aza-tricyclo[6.2.1.0^{1,6}]undec-9-en-5-one (23)

Colourless oil (0.10 g, 11%). $[\alpha]_D^{20}$ = 23.6 (*c* = 1, $CHCl_3$); *ν* (cm^{-1}) 1663, 1452, 1423, 1251, 1212, 1125, 1035, 836, 778, 699 and 610; δ_H ($CDCl_3$) −0.40, −0.09 (2 × 3 H, 2 × s, 2 × Si–C*H*$_3$), 0.84 (9 H, s, C(C*H*$_3)_3$), 1.65 (1 H, dd, *J* 9.6 and 12.9, *H-7β*), 2.37–2.43 (2 H, m, *H*-6, H-7*α*), 3.67 (1 H, d, *J* 14.6, C*H* Bn), 4.20 (1 H, d, *J* 4.9, *H-2*), 4.58 (1 H, d, *J* = 4.9, *H-3*), 4.94 (1 H, dd, *J* 1.6 and 4.1, *H-8*), 5.76 (1 H, d, *J* 14.6, C*H* Bn), 6.06 (1 H, d, *J* 5.8, *H-10*), 6.21 (1 H, ddd, *J* 0.4, 1.6 and 5.8, *H-9*) and 7.18–7.51 (10 H, m, C*H* Ph); δ_C ($CDCl_3$) −4.8 (2 × Si–*C*H_3), 18.0 (*C*$(CH_3)_3$), 25.7 (C(*C*$H_3)_3$), 30.5 (*C-7*), 43.0 (*C-6*), 49.0 (*C*H_2Ph), 61.3 (*C-3*), 73.0 (*C-2*), 77.9 (*C-8*), 91.0 (*C-1*), 127.6, 127.7, 127.9, 128.3, 128.4, 128.6, (*C*H Ph), 135.4 (*C-10*), 136.0, 136.8 (C_q Ph), 136.4 (*C-9*) and 172.2 (*C-5*); HRMS (ESI) *m*/*z* 462.2384 (M + H^+ requires 462.2364).

(1*S*,2*S*,3*R*,6*R*,8*S*)-4-Benzyl-2-*O*-(*tert*-butyldimethylsilyl)-3-nitrile-11-oxa-4-aza-tricyclo[6.2.1.0^{1,6}]undec-9-en-5-one (24)

Colourless oil (0.71 g, 87%). $[\alpha]_D^{20}$ = 54.3 (*c* = 0.7, $CHCl_3$); *ν* (cm^{-1}) 1675, 1417, 1253, 1200, 1131, 1044, 999, 948, 878, 838, 753, 702, 668 and 617; δ_H ($CDCl_3$) −0.18, 0.11 (2 × 3 H, 2 × s, 2 × Si–C*H*$_3$), 0.81 (9 H, s, C(C*H*$_3)_3$), 1.72 (1 H, dd, *J* 8.5 and 11.9, *H-7β*), 2.56 (1 H, dd, *J* 4.2 and 11.9, *H-7α*), 2.79 (1 H, dd, *J* 4.0 and 8.5, *H-6*), 3.94 (1 H, d, *J* 5.7, *H-2*), 4.01 (1 H, d, *J* 14.8, C*H* Bn), 4.10 (1 H, d, *J* 5.7, *H-3*), 5.02 (1 H, dd, *J* 1.6 and 4.5, *H-8*), 5.38 (1 H, d, *J* 14.8, C*H* Bn), 6.40 (1 H, dd, *J* 1.3 and 5.8, *H-9*), 6.54 (1 H, d, *J* 5.8, *H-10*) and 7.25–7.39 (5 H, m, C*H* Ph); δ_C ($CDCl_3$) −5.7, −5.2 (2 × Si–*C*H_3), 17.8 (*C*$(CH_3)_3$), 25.4 (C(*C*$H_3)_3$), 29.7 (*C-7*), 44.1 (*C-6*), 49.1 (*C*H_2Ph), 51.3 (*C-3*), 70.3 (*C-2*), 78.5 (*C-8*), 91.1 (*C-1*), 115.7 (*C*N), 128.4, 129.1 (*C*H Ph), 134.7 (*C-10*), 135.0 (C_q Ph), 136.7 (*C-9*) and 170.4 (*C-5*); HRMS (ESI) *m*/*z* 433.1976 (M + Na^+ requires 433.1923).

(1*S*,2*S*)-2-*N*-Acryloyl-1-(2′-furyl)-1-*O*-(*tert*-butyldimethylsilyl)propane (25)

To a solution of 20 mmol of **3** in 40 mL of dry diethyl ether was added dropwise 22 mmol of Grignard reagent in a total volume of 24 mL of diethyl ether. The mixture was refluxed for one hour, cooled to −20 °C and 20 mL of MeOH was added. After further cooling to −70 °C, 40 mmol of $NaBH_4$ (1.52 g, 2 eq.) was added and the mixture was allowed to warm to rt overnight. Diethyl ether and water were added. The water layer was extracted three times with diethyl ether and the combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. The crude product (brown–yellow oil, 5.75 g) was dissolved in 80 mL of dichloromethane and a solution of 24 mmol of Na_2CO_3 (2.74 g) in 40 mL of water was added. After dropwise addition of freshly distilled acryloylchloride (22 mmol, 1.99 g), the mixture was stirred overnight and the layers were separated. The water layer was washed once with CH_2Cl_2. The combined organic layers were washed with a 10% Na_2CO_3 solution and brine, dried with $MgSO_4$ and the solvent was evaporated. Purification by column chromatography (pet. ether (40–60)–EtOAc

85 : 15) yielded **25** as a yellowish oil (4.9 g, 80% from **3**). δ_H ($CDCl_3$) −0.12, −0.01 (2 × 3 H, 2 × s, 2 × Si–C*H*$_3$), 0.88 (9 H, s, C(C*H*$_3$)$_3$), 1.06 (3 H, d, *J* 7.0, *H-3*), 4.26–4.44 (1 H, m, *H-2*), 4.83 (1H, d, *J* 3.7, *H-1*), 5.61 (1H, dd, *J* 1.8 and 10.0, C*H*=CH_2), 5.86 (1H, d, *J* 8.0, N*H*), 6.06 (1H, dd, *J* 10.0 and 17.0, CH=C*H*$_2$), 6.20 (1H, dd, *J* 0.7 and 2.9, *H-3′*), 6.24 (1H, dd, *J* 1.8 and 17.0, CH=C*H*$_2$), 6.29 (1H, dd, 1.8 and 2.9, *H-4′*) and 7.33 (1H, dd, *J* 0.7 and 1.8, *H-5′*); δ_C ($CDCl_3$) −5.7, −5.6 (2 × Si–*C*H$_3$), 14.2 (*C*H$_3$), 17.6 (*C*(CH$_3$)$_3$), 25.2 (C(*C*H$_3$)$_3$), 49.1 (*C-2*), 70.1 (*C-1*), 106.5, 109.5 (*C-3′*, *C-4′*), 125.1 (*C*H$_2$=CH), 131.0 (*C*H=CH$_2$), 141.0 (*C-5′*), 154.4 (*C-2′*) and 166.4 (*C*ON).

(1*S*,2*S*,3*S*,6*R*,8*S*)-4-Acetyl-2-*O*-(*tert*-butyldimethylsilyl)-3-methyl-11-oxa-4-aza-tricyclo[6.2.1.0^{1,6}]undec-9-en-5-one (26)

Compound **25** (2 mmol) was dissolved in 10 mL of acetic anhydride and the resulting solution was refluxed overnight. Excess acetic anhydride was evaporated under reduced pressure to give a brown oil. Purification by column chromatography (pet. ether (40–60)–EtOAc 85 : 15) yielded **26** as a white solid (0.33 g, 47%). Mp. 72 °C; δ_H ($CDCl_3$) 0.10, 0.13 (2 × 3 H, 2 × s, 2 × Si–C*H*$_3$), 0.84 (9 H, s, C(C*H*$_3$)$_3$), 1.24 (3 H, d, *J* 7.2, C*H*$_3$C-3), 1.89 (1H, dd, *J* 9.1 and 12.0, *H-7β*), 2.14 (1H, dd, *J* 4.4 and 12.0, *H-7α*), 2.41 (3 H, s, C*H*$_3$CO), 2.65 (1H, dd, *J* 4.1 and 9.1, *H-6*), 4.27 (1H, d, *J* 5.6, *H-2*), 4.63 (1H, dq, *J* 2.2 and 7.2, *H-3*), 4.99 (1H, dd, *J* 1.5 and 4.6, *H-8*), 6.36 (1H, d, *J* 5.8, *H-10*) and 6.38 (1H, dd, *J* 1.5 and 5.8, *H-9*); δ_C ($CDCl_3$) −5.2, −5.0 (2 × Si–*C*H$_3$), 17.4 (*C*H$_3$C-3), 17.5 (*C*(CH$_3$)$_3$), 25.3 (C(*C*H$_3$)$_3$), 26.5 (*C*H$_3$CO), 31.5 (*C-7*), 43.4 (*C-6*), 56.0 (*C-3*), 68.1 (*C-2*), 78.8 (*C-8*), 88.7 (*C-1*), 135.7 (*C-10*), 136.6 (*C-9*) and 173.1, 175.2 (*C-5*, CH$_3$*C*O); MS (ESI) *m*/*z* 374.1 (M + Na$^+$ requires 374.1).

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