Ring-Closing Alkyne Metathesis in the Synthesis of Alkyne-Linked Glycoamino Acids

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Abstract: Synthesis of alkyne-linked glycoamino acids via ring-closing alkyne metathesis is investigated. Two different strategies are described to attach alkynylamino acids to an alkynyl sugar, either via a linker at O-4 or at O-9 of the alkynyl sugar. Ring-closing alkyne metathesis of the O-4 linked diynes failed to proceed, but alkyne-linked glycoamino acids of different chain length were effectively synthesized via attachment at O-9.

Key words: alkynes, glycopeptides, ring-closing alkyne metathesis, ring closure

Rarely a novel synthetic transformation attained wide application in synthetic organic chemistry as rapidly as the olefin-metathesis reaction for the synthesis of unsaturated carbo- and heterocycles. In particular, the preparation of the first efficient metathesis catalyst by Schrock,[1] and the efforts of Grubbs, who developed air-stable catalysts with much broader functional group compatibility,[2] led to an explosion in number of applications of olefin metathesis in the mid 1990s.

A conceptually similar transformation is alkyne metathesis, first reported by Pennella et al. in the late 1960s[3] and applied in the synthesis of organic macrocycles by Fürstner et al.[4] The inherent advantages of alkyne over alkene metathesis reside in the fact that RCAM is particularly useful for large (>12-membered) rings without high dilution and cannot lead to *E*,*Z*-mixtures. More than that, under the proper conditions the resulting triple bond can be stereoselectively reduced to a desired *E*- or *Z*-olefin. However, due to the lack of a stable and generally applicable catalyst, alkyne metathesis lags far behind olefin metathesis in popularity. Often, temperatures as high as 400 °C are required when heterogeneous silica-bound tungsten oxides are applied. Mortreux and co-workers later developed[5] a soluble $Mo(CO)_6$ catalyst able to perform at lower temperatures (160 °C), but only internal acetylenes undergo metathesis, while terminal acetylenes lead exclusively to polymerization.[6] Fürstner et al. developed several molybdenum catalysts of the general type [Mo{N(*t*-Bu)(Ar)}$_3$],[7] but a major drawback of these complexes is incompatibility with oxygen, nitrogen, moisture, acidic protons, and secondary amides. The most widely applicable catalyst [(*t*-BuO)$_3$WCCMe$_3$] (**13**) was developed by Schrock et al.,[8] a catalyst that operates under fairly mild conditions, sometimes ambient temperature, and effects up to several hundred catalytic turnovers per minute.

In the past decade, ring-closing alkyne metathesis (RCAM) has been regularly applied in the total synthesis of natural products.[9] In a collaborative effort, we have also shown that RCAM can be successfully applied in the synthesis of diaminosuberic acid derivatives, with an all-carbon chain mimicking the natural cystine bridge.[10] Along the same line, we showed[11] that conformationally restricted β-turn peptide mimetics can be obtained by performing RCAM on a dialkyne-containing linear peptide, an approach later adapted by Liskamp et al.[12] in the synthesis of a mimic of the lantibiotic nisin Z.

The examples above demonstrate the versatility of RCAM for the synthesis of cycloalkynes or *Z*-configured alkenes. Based on these observations, we became interested in the synthesis of alkyne-linked glycoamino acids via RCAM of alkynyl glucoside **3** and 2-butynyl glycine **4** (Scheme 1). The resulting alkyne-linked glycoamino acids **1** were projected as chemically and metabolically stable all-carbon glycopeptide isosteres. Moreover, the alkyne-linked glycoamino acids can be stereoselectively reduced, giving selective access to *E*- or *Z*-configured alkene-linked derivatives from a common precursor. Similar *C*-glycoamino acids have earlier been prepared via olefin metathesis by Westermann et al.[13] However, with longer chains, mixtures of *E*- and *Z*-cycloalkenes were formed upon ring closure.

Two retrosynthetic disconnections were devised for the assembly of alkyne-linked glycoamino acid **1** by RCAM of a 2-propynyl sugar **3** with L-2-butynyl glycine **4** (Scheme 1). In one case, the amino acid is connected at the former anomeric center of the carbohydrate (C-4 of glycosylacetylene **2a**), in the other case at the former 6-position (C-9 of **2b**).

First, the route of RCAM of diynes linked via C-4 was investigated. To this end, the known lactone **5**[14] was converted into propynyl glucoside **6** (Scheme 2) by subjection to nucleophilic addition of the in situ generated Li-acetylide from 1-bromopropene and two equivalents *n*-BuLi.[15]

It is known that RCAM is suitable for the formation of cycloalkynes of ring size 12 or larger.[16] Therefore, a spacer between the alkynyl sugar and 2-butynyl glycine was pro-

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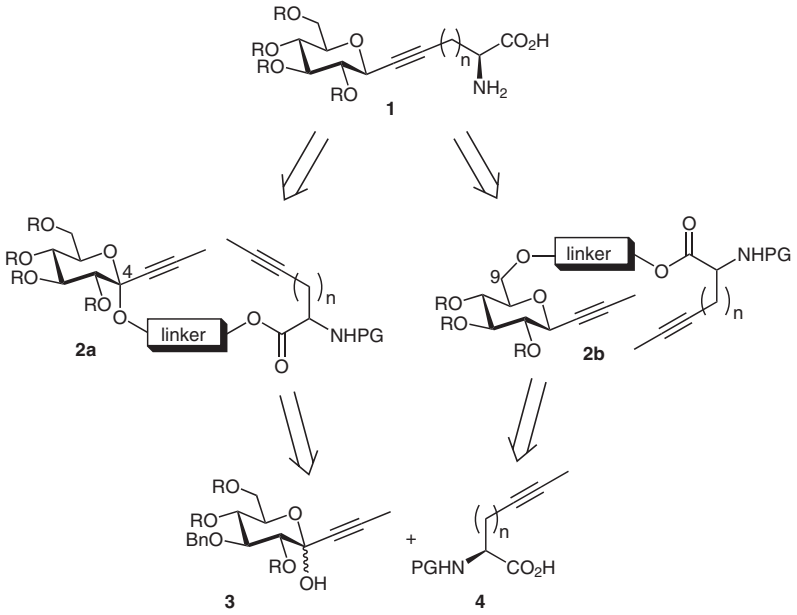
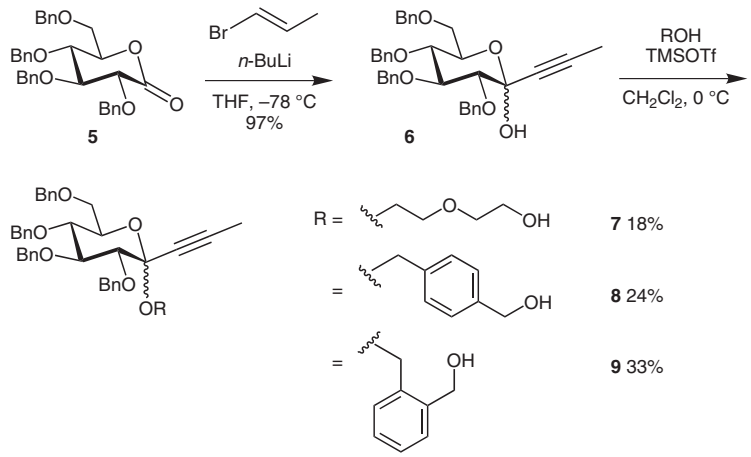
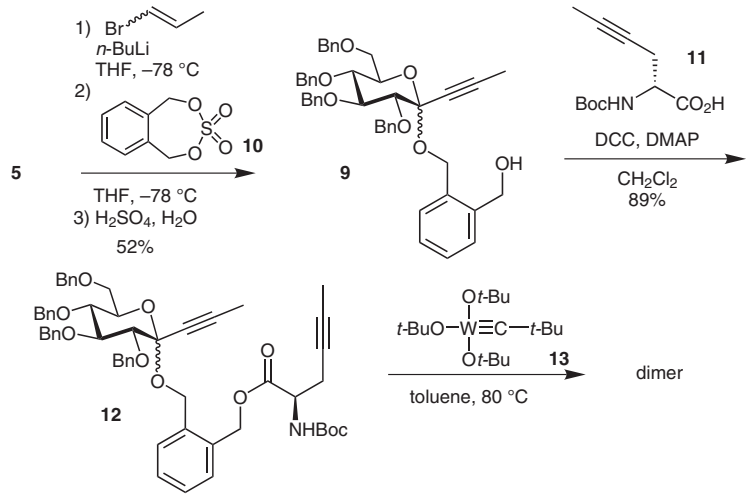


Scheme 1 Retrosynthesis



Scheme 2 Synthesis of anomeric coupled linkers



Scheme 3 Coupling of amino acid to anomeric linker and RCAM

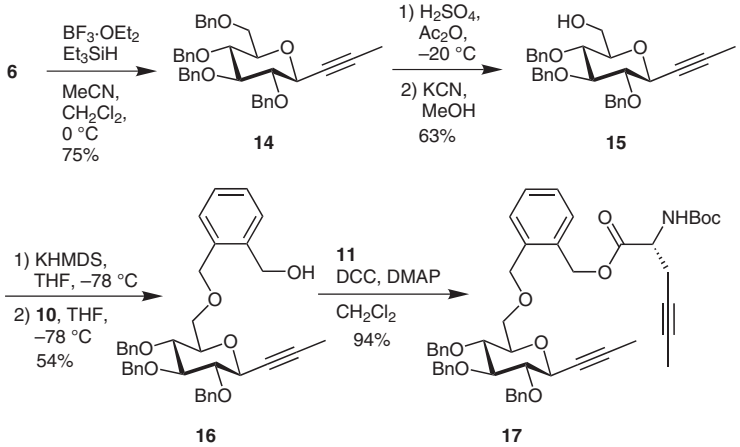
jected, connected at the newly generated acetal at C-4 (former C-1 of gluconolactone). Three different diols were investigated as linkers. Firstly, hemiacetal **6** was condensed with diethyleneglycol under the action of a Lewis acid (TMSOTf) in the presence of a drying agent ($MgSO_4$).[17] However, despite the fact that a large excess of diethyleneglycol was added (5 equiv), compound **7** could not be obtained in a yield exceeding 18%, especially due to incomplete conversion and the formation of dimers. The five-fold excess of diethyleneglycol is apparently not sufficient to prevent double glycosylation with carbohydrate **6**. A similar result was obtained by addition of 1,4-benzenedimethanol instead of diethyleneglycol (**8**, 24%), whereas a slight increase in yield was observed for *ortho*-benzenedimethanol to afford the desired glycoside **9** in 33% yield.

An alternative mode of introduction of a linker, not involving dehydrative condensation with excess diol, entails nucleophilic attack of **6** at a suitable electrophile. A suitable approach appeared the application of cyclic sulfate technology, with the inherent advantage that only single addition is possible and a free alcohol is liberated for esterification with the amino acid. Thus, 1,2-benzenedimethanol was converted into cyclic sulfate **10**[18] as described by O'Brien et al.[19] It was reasoned that conversion of **6** into a good nucleophile could be effected by deprotonation with a strong base. However, a more direct approach was followed, involving addition of cyclic sulfate **10** to the alkoxide formed in situ by acetylide addition to lactone **5** (Scheme 3). Subsequent hydrolysis of O-sulfate with sulfuric acid and water proceeded in a one-pot procedure leading to the desired alcohol **9** in 52% overall yield from lactone **5**. Compound **9** was isolated as an α,β-mixture in a ratio of 3:4.

Next, Boc-protected 2-butynyl glycine **11**[20] was coupled to the free hydroxyl of **9** under the action of DCC and DMAP, leading to diyne **12**. Compound **12** is suitably geared for ring-closing alkyne metathesis and was dissolved in toluene and degassed before addition of the tungsten-based catalyst **13**. After heating the reaction mixture to 80 °C for 30 minutes, TLC analysis showed the disappearance of starting material and the formation of a less lipophilic product. Unfortunately, analysis of the formed product after workup and silica gel purification showed that only cross-metathesis had occurred, giving rise to dimer formation.[21] Since the ring size of the desired product (12-ring) is sufficiently large to enable formation of a cycloalkyne (as indicated by Fürstner's rule),[16] an alternative explanation for the lack of ring closure may be found in steric hindrance of the tertiary anomeric center in vicinity to the sugar alkyne.

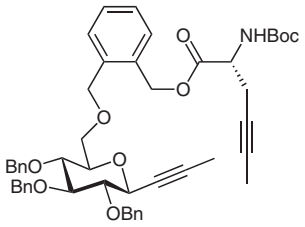
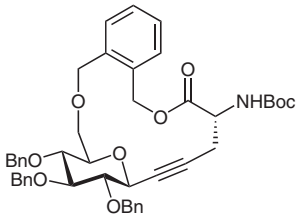
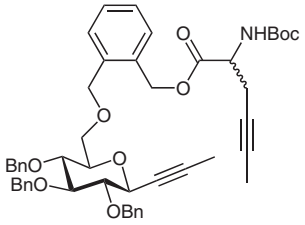
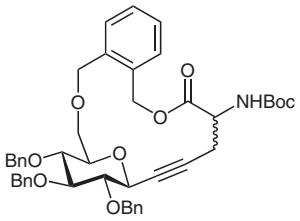
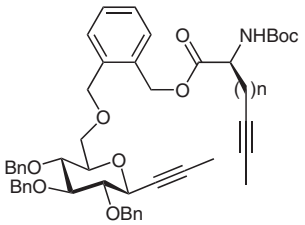
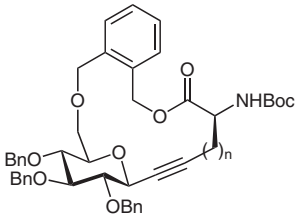
Since RCAM of a diyne linked via the anomeric center was not successful, another strategy was considered to attach 2-butynyl glycine to one of the alcohols of the carbohydrate. An additional advantage of such a strategy is that a late-stage deoxygenation of the anomeric carbon (C-4) is avoided. The O-9 position (former O-6) was considered most amenable for selective deprotection. Thus, the C-4 hemiacetal of **6** was first deoxygenated under the action of $BF_3{\cdot}OEt_2$ and Et_3SiH yielding stereoselectively the β-configured alkynyl glucoside **14** (Scheme 4).[22] Selective removal of the benzyl group at O-9 by acetolysis (H_2SO_4, Ac_2O), followed by removal of the resulting acetyl gave the desired glucosyl acetylene **15** with a free primary hydroxyl.[23] Introduction of the linker was performed under similar conditions as above, involving deprotonation of the alcohol by KHMDS in THF, and subsequent addition of cyclic sulfate **10**, leading to chain-extended compound **16**.[24] Diimide-mediated esterification of **16** with Boc-protected 2-butynyl glycine proceeded uneventfully, affording the RCAM precursor **17** in good yield.[25]

Diyne **17** was now subjected to RCAM as described earlier. Thus, thorough drying and degassing was executed to avoid premature decomposition of the sensitive catalyst. Much to our satisfaction, prolonged treatment of **17** with the tungsten-based RCAM catalyst **13** led to the cyclized alkyne **18** in 80% yield (entry 1, Table 1).[26] The structure of cycloalkyne **18** was corroborated by NMR and mass spectral analysis.[26] We were interested if the rate of RCAM depends on the α-configuration of the amino acid. Therefore, racemic 2-butynyl glycine (±)-**11** was attached to the carbohydrate derivative **16** and subjected to ring



Scheme 4 Synthesis of glucoamino acid **16**

Table 1 Synthesis of RCAM Precursors and RCAM Products

Esterification[a]	Yield (%)	RCAM[b]	Yield (%)
 **17**	94	 **18**	80
 **19**	92	 **20**	80
 **21**: n = 2 **23**: n = 3	(92) (84)	 **22**: n = 2 **24**: n = 3	(62) (29)

[a] Conditions: DCC, DMAP, CH_2Cl_2.
[b] Conditions: **13**, toluene, 80 °C.

closure. No difference in reaction rate between the two epimers could be observed, leading to a 1:1 mixture of diastereomeric cycloalkynes **20**. Some L-diastereomeric glycoamino acids were also prepared by applying L-3-pentynyl glycine and L-4-hexynyl glycine[20] to the synthetic sequence of esterification–RCAM (entries 3 and 4, respectively). In both cases, the desired cycloalkynes were successfully formed, although extension of the amino acid side chain led to reduced yields, i.e. giving the corresponding cyclic acetylenes from 3-pentynyl glycine and 4-hexynyl glycine in yields of 62% and 29%, respectively.

In conclusion, acetylene-linked glycoamino acids were successfully prepared by application of ring-closing alkyne metathesis. To this end, alkynyl sugars and alkynyl-amino acids were coupled via a benzenedimethanol linker, derived from cyclic sulfate **10**. Attachment points for the amino acid were either the newly formed anomeric center at C-4 or the primary hydroxyl at C-9. Performing RCAM on the anomerically linked dialkyne led exclusively to dimerization and failed to yield cycloalkyne product, presumably due to steric hindrance. Linkage via O-9, however, before subjection to RCAM proceeded smoothly for 2-butynyl glycine of different configuration and chain lengths, leading to the desired glucoamino acids with ring sizes varying between 15 and 17. Further processing of the ring-closed alkynyl glycoamino acids **18**, **22**, and **24** as versatile isosteres of glycoamino acids is currently under way.

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(23) To a solution of **14**[22] (1.3 g 2.4 mmol) in Ac_2O (45 mL), H_2SO_4 (5% in Ac_2O, 10 mL) was added dropwise at –20 °C. The reaction was stirred for 10 min. The reaction was quenched with aq NaOAc, diluted with EtOAc, and washed with sat. $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash chromatography (EtOAc–heptane, 1:5) and yielded the acetolyzed product (1.0 g, 81%) as a white solid. To a solution of the acetolyzed product (1.0 g, 1.9 mmol) in MeOH (40 mL) was added KCN (15 mg, 0.23 mmol). The reaction was stirred for 24 h. The mixture was neutralized with basic Amberlyst, filtrated, and evaporated. The mixture was redissolved in EtOAc and washed with NH_4Cl, dried ($MgSO_4$), and evaporated. Purification by flash chromatography (EtOAc–heptane, 1:2) yielded **15** as a white solid (0.75 g, 1.6 mmol, 82%). R_f = 0.30 (EtOAc–heptane, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.24 (m, 15 H), 4.99 (d, *J* = 10.6 Hz, 1 H), 4.92 (d, *J* = 11.1 Hz, 1 H), 4.87–4.80 (m, 3 H), 4.65 (d, *J* = 10.9 Hz, 1 H), 4.05 (dd, *J* = 1.6, 9.5 Hz, 1 H), 3.87 (dd, *J* = 2.3, 12.0 Hz, 1 H), 3.70–3.50 (m, 4 H), 3.35–3.31 (m, 1 H), 2.05 (br s, 1 H), 1.88 (d, *J* = 1.2 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.6, 138.2, 138.0, 128.6, 128.5, 128.3, 128.1, 128.0, 128.0, 127.9, 127.8, 86.0, 83.0, 82.8, 79.4, 77.6, 76.5, 75.8, 75.6, 75.3, 70.1, 62.1, 3.9. $[\alpha]_D^{20}$ –8.25 (*c* 0.63, $CHCl_3$). IR (neat): ν = 3373, 3036, 2902, 2859, 2245. HRMS (CI): *m/z* calcd for $C_{30}H_{33}O_5$ [M + H]: 473.2328; found: 473.2331.
(24) Compound **15** (0.76 g, 1.6 mmol) was dissolved in anhyd THF (50 mL) and cooled to –78 °C. Then, KHMDS (0.5 M in toluene, 4.8 mL, 2.4 mmol) was added and stirred for 30 min at –78 °C. Cyclic sulfate **10** (0.64 g, 3.2 mmol)[19,27] was added. The temperature was raised overnight to r.t. After stirring for 20 h, the reaction mixture was poured into aq sat. NH_4Cl and extracted with EtOAc (2 × 100 mL). The sulfate was concentrated and redissolved in THF (100 mL). Afterwards, H_2SO_4 (0.40 mL) and H_2O (0.15 mL) were added and the reaction was stirred for 4 d. Half of the THF was evaporated and the reaction mixture was diluted with EtOAc (200 mL) and washed with H_2O (3 × 100 mL), brine, dried ($MgSO_4$), and evaporated. Purification by flash chromatography (EtOAc–heptane, 1:2) afforded compound **16** (0.51 g, 54%) as a white solid. R_f = 0.20 (EtOAc–heptane, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.20 (m, 19 H), 4.98 (d, *J* = 10.6 Hz, 1 H), 4.90 (d, *J* = 11.1 Hz, 1 H), 4.84–4.76 (m, 3 H), 4.66 (d, *J* = 5.3 Hz, 2 H), 4.61 (d, *J* = 11.5 Hz, 2 H), 4.53 (d, *J* = 11.1 Hz, 1 H), 3.99 (dd, *J* = 2.0, 9.2 Hz, 1 H), 3.72 (dd, *J* = 2.0, 10.6 Hz, 1 H), 3.63–3.50 (m, 4 H), 3.43–3.40 (m, 1 H), 3.10 (br t, *J* = 6.1 Hz, 1 H), 1.88 (d, *J* = 2.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.6, 138.4, 138.0, 138.0, 135.7, 130.2, 129.8, 128.9, 128.4, 128.3, 128.2, 127.9, 127.8, 127.8, 127.7, 127.6, 86.1, 83.0, 82.7, 78.4, 77.8, 76.2, 75.8, 75.5, 75.2, 72.8, 70.3, 69.0, 63.7, 4.2. $[\alpha]_D^{20}$ +6.4 (*c* 1.0, $CHCl_3$). IR (film): ν = 3480, 3062, 3027, 2905, 2868, 2250. HRMS (CI): *m/z* calcd for $C_{38}H_{41}O_6$ [M + H]: 593.2903; found: 593.2875.
(25) A solution of 2-butynyl glycine **11** (18 mg, 79 μmol) and alcohol **16** (34 mg, 56 μmol) in CH_2Cl_2 (1 mL) was stirred at 0 °C. Then, DMAP (0.7 mg, 6 mol) and DCC (15 mg, 73 μmol) in CH_2Cl_2 (1 mL) were added and the reaction was stirred overnight at r.t. The reaction mixture was filtered and the residue was washed with CH_2Cl_2. The organic layer was evaporated. Flash chromatography afforded dialkyne **17** (42 mg, 94%) as a white solid. R_f = 0.43 (EtOAc–heptane, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.12 (m, 19 H), 5.34–5.25 (m, 3 H), 5.00 (d, *J* = 10.6 Hz, 1 H), 4.91 (d, *J* = 11.0 Hz, 1 H), 4.82–4.79 (m, 3 H), 4.64 (d, *J* = 12.4 Hz, 2 H), 4.50 (d, *J* = 10.8 Hz, 1 H), 4.45–4.42 (m, 1 H), 4.00 (dd, *J* = 1.7, 9.2 Hz, 1 H), 3.73 (d, *J* = 10.8 Hz, 1 H), 3.67 (dd, *J* = 4.5, 10.8 Hz, 1 H), 3.63–3.53 (m, 3 H), 3.43 (dd, *J* = 2.9, 9.2 Hz, 1 H), 2.72–2.56 (m, 2 H), 1.88 (d, *J* = 1.8 Hz, 3 H), 1.67 (t, *J* = 2.2 Hz, 3 H), 1.44 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 154.9, 138.4, 138.1, 137.9, 136.4, 133.7, 129.3, 129.0, 128.3, 128.3, 128.1, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 86.1, 82.7, 82.7, 80.1, 79.4, 78.9, 78.0, 76.6, 75.8, 75.5, 75.2, 73.2, 71.1, 70.2, 69.3, 64.9, 52.6, 28.6, 23.4, 4.2, 3.9. $[\alpha]_D^{20}$ +6.6 (*c* 0.8, $CHCl_3$). IR (film): ν = 3723, 3425, 3058, 3028, 2967, 2911, 2855, 2250, 1740, 1722. ESI-HRMS: *m/z* calcd for $C_{49}H_{55}NNaO_9$ [M + Na]: 824.3775; found: 824.3774.
(26) Dialkyne **17** (108 mg, 0.135 mmol) was coevaporated with toluene (2 × 10 mL) and subsequently (*t*-BuO)$_3$W≡C*t*-Bu (**13**, 22 mg, 47 μmol) was added. This was dissolved in toluene (2 mL) and stirred for 30 min at 80 °C. The reaction was concentrated and purified by flash chromatography (EtOAc–heptane, 1:4) to yield cyclized product **18** (81 mg, 80%) as a white solid. R_f = 0.43 (EtOAc–heptane, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 19 H), 5.34–5.23 (m, 3 H), 4.94–4.77 (m, 6 H), 4.71 (d, *J* = 11.7 Hz, 1 H), 4.62–4.58 (m, 2 H), 3.92 (d, *J* = 9.6 Hz, 2 H), 3.61–3.43 (m, 5 H), 2.96 (d, *J* = 16.4 Hz, 1 H), 2.56 (ddd, *J* = 2.1, 5.5, 16.6 Hz, 1 H), 1.39 (s, 9 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.1, 155.2, 138.5, 138.1, 138.0, 138.0, 137.5, 132.8, 130.2, 128.9, 128.6, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 85.9, 82.2, 81.9, 81.4, 80.4, 79.5, 78.3, 75.9, 75.3, 75.3, 71.8, 69.7, 69.3, 65.2, 53.5, 28.4, 23.9. $[\alpha]_D^{20}$ –30.0 (*c* 0.26, $CHCl_3$). IR (film): ν = 3321, 3062, 3032, 2967, 2907, 2868, 2258, 1701. ESI-HRMS: *m/z* calcd for $C_{45}H_{49}NNaO_9$ [M + Na]: 770.3305; found: 770.3366.
(27) Leone, A.; Consiglio, G. *Helv. Chim. Acta* **2005**, *88*, 210.