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A Synthesis of Cyanolide **1** by Intramolecular oxa-Michael Addition.

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Abstract: A synthesis of cyanolide, a diolide natural product, has been achieved using a diastereoselective Barbier reaction, early-stage glycosylation and intramolecular oxa-Michael addition to form the THP ring.

Key words: Michael addition, Barbier reaction, cyclization, glycosylation, natural products.

The synthesis of several tetrahydropyran natural products using intramolecular oxa-Michael addition is now well established.¹ The Michael acceptor may be installed by either a cross metathesis reaction or by the more conventional Horner-Wadsworth-Emmons or Wittig reactions. Several reports are from this laboratory.² While the oxa-Michael addition appears to proceed smoothly when an allylic substituent is present, this significantly slows, but does not prohibit, the cross metathesis. Recently, the isolation and structure of cyanolide **1**, a symmetrical diolide with activity against *Biomphalaria glabrata*, the vector of schistosomiasis, has been reported.³ Following the cross metathesis and intramolecular oxa-Michael addition strategy (Scheme 1), this molecule would have two allylic substituents and would be ideal to challenge this strategy at this extreme, with the option of ozonolysis-Horner-Wadsworth-Emmons in reserve if metathesis failed.

Scheme 1 Cyanolide and its retrosynthesis

Cyanolide **1** has been the subject of several syntheses,⁴ including a short and elegant contribution by Krische *et al.*^{4h} While She employed a Liotta-Semmelhack palladium catalysed cyclocarbonylation

for the formation of the THP,^{4c} Rychnovsky used a remarkable Sakurai dimerisation^{4e} and Jennings employed oxonium ion chemistry.^{4f} Hong,^{4a} Reddy,^{4b} Pabbaraja^{4d} and Krische^{4h} each employed oxa-Michael additions, the latter two in the opposite direction to that intended by us.

To begin the synthesis (Scheme 2), 1,2-epoxybutane was resolved using Jacobsen's catalyst.⁵ Ring opening of the (*R*)-enantiomer **2** of the epoxide with lithium acetylide gave the homopropargylic alcohol **3** (79%).⁶ Lindlar reduction then gave the homoallylic alcohol **4** (80%).⁷ This procedure proved higher yielding and more scaleable than straightforward epoxide opening with a vinyl Grignard reagent. Cross metathesis of alkene **4** with methyl acrylate proceeded efficiently (70% yield) at a quite modest catalyst loading (≤ 1 mole%). The resulting hydroxy ester **5** was subjected to Evans' conditions⁸ to give the 1,3-dioxane **6** as a single isomer (68%), as in the Jennings synthesis.^{4f} This compound proved labile and it was found to be more efficient to directly reduce the crude mixture with lithium aluminum hydride to the alcohol **7**, which could be purified. IBX oxidation then gave the labile aldehyde **8** in 70% yield. This two step conversion of ester **6** to the aldehyde **8** proved to be superior, in our hands, to direct reduction with DIBAL. We intended to introduce the reverse-prenyl moiety by a Barbier reaction with prenyl bromide. There is little precedent for the stereochemical outcome of such additions to β -substituted aldehydes.⁹ In the case of indium mediated reactions, the vast majority of studies involve α -substitution. Aldehyde **8** was immediately subjected to Barbier addition using prenyl bromide. Three metals were employed, Sn(II), In(0) and Zn(0) (Table 1). In each case, the same diastereoisomer **9** was found to be the major product. The Mukaiyama conditions¹⁰ (entry 2) using tin(II) gave modest diastereoselectivity and the lowest yield. The use of indium¹¹ in DMF gave a higher yield, but a similar diastereoselectivity at room temperature (entry 3). Both the yield and the diastereoselectivity could be improved by employing lower temperatures (entries 4 and 5). Addition of lanthanum triflate¹² also provided some enhancement of the reaction, as did the addition of other (cheaper) Lewis acids (entries 7 to 10). The use of zinc under Luche conditions¹³ gave the optimum result (entry 1) with the formation of a mixture of two diastereoisomers in a better than 4:1 ratio, and in 87% yield. This is in contrast to the

results of She^{4c} who obtained a 1:1 ratio for a substrate with a free alcohol group under similar conditions. The minor isomer of **9** proved to be crystalline and X-ray crystallography¹⁴ showed that it possessed the all *syn* oxygenation pattern, indicating

that the major isomer possessed the desired *anti-syn* pattern. This is consistent with the addition of an *in situ* generated prenyl nucleophile to the aldehyde group of the substrate in the form of chelate complex **10**.

Table 1 Barbier Reactions

Entry	Reagent(s)	Solvent	Time/h	Temp/°C	Yield ^a /%	<i>anti:syn</i>
1	Zn	aq. NH ₄ Cl, THF (5:1)	18	0	87	80 : 20
2	SnCl ₂ , NaI,	DMF, H ₂ O (8:1)	42	r.t	55 ^b	69 : 31
3	In	DMF, AcOH (2:1)	18	r.t.	75	67 : 33
4	In	DMF, AcOH (2:1)	18	-10	89	68 : 32
5	In	DMF, AcOH (2:1)	18	-40	90	74 : 26
6	In	aq. NH ₄ Cl, THF (5:1)	18	-40	90	78 : 22
7	In, La(OTf) ₃	aq. NH ₄ Cl, THF	18	r.t	93	77 : 23
8	In, La(OTf) ₃	aq. NH ₄ Cl,)))	3	r.t	85 ^b	80 : 20
9	In, ZnCl ₂	aq. NH ₄ Cl, THF	18	r.t	91	75 : 25
10	In, CeCl ₃	aq. NH ₄ Cl, THF	18	r.t	92	76 : 24

a: combined yield of *anti* and *syn* isomers; b: incomplete reaction

At this point, we wished to protect the free alcohol group of Barbier adduct **9**. Rather than use a standard protecting group, we decided to take the opportunity of installing the trimethyl xylose moiety (Table 2). Most other syntheses leave this operation to a late or even final stage. Interestingly, under the conditions often employed, the reaction of the alcohol **9** with thioglycoside **11**, activated by methyl triflate and buffered with a bulky pyridine,^{4a} we observed a very slow reaction (120 hours) in diethyl ether giving a 45% yield of the desired β -glycoside **12**, but as a single diastereoisomer (entry 1), while use of a greater

excess of reagents for an even longer time, raised the yield but eroded the diastereoselectivity (entry 2). Use of other solvents gave much lower yields (entries 3 to 6). This stands in contrast to the reports of glycosylation after THP formation in which the reaction is more facile, but the stereoselectivity is much lower. It appears that the greater bulk of the acyclic system slows the reaction but enhances the selectivity. Use of *N*-iodosuccinimide (NIS) and triflic acid (entries 6 and 7) or NIS and TMS triflate¹⁵ (entries 8 -10) or the benzenesulfinyl morpholine (BSM)-triflic anhydride combination¹⁶ (entries 11 and 12) as the activating agents did not give results that were an overall improvement.

Table 2

Entry	Reagent ^a	Solvent	Time/h	Temp/°C	Yield ^b / %	$\alpha:\beta$
1	MeOTf	Et ₂ O	120	r.t.	45	β only
2	MeOTf	Et ₂ O	144	r.t.	61	20:80
3	MeOTf	THF	o.n.	r.t.	0 (dec)	-
4	MeOTf	CH ₃ CN	96	r.t.	28	
5	MeOTf	CH ₂ Cl ₂	48	r.t.	55	50:50
6	NIS, TfOH	CH ₂ Cl ₂	20	-15 - r.t.	60	67 : 33
7	NIS, TfOH	CH ₃ CN	20	-15 - r.t.	20 ^c	72 : 28
8	NIS, TMSOTf	CH ₂ Cl ₂ , CH ₃ CN 1:3	o.n.	-55	50 ^c	31 : 69
9	NIS, TMSOTf	CH ₂ Cl ₂ , CH ₃ CN, EtCN 1:1:2	o.n.	-80	30	99 β
10	NIS, TMSOTf (x2)	CH ₂ Cl ₂ , CH ₃ CN, EtCN 1:1:2	o.n.	-80	50 ^c	30 : 70
11	BSM, Tf ₂ O	CH ₂ Cl ₂	0.5	-75 - r.t.	50	74 : 26

a: all reactions were run in the presence of activated 4Å molecular sieves and DTBMP, except entry 9 (4Å MS only); b: yield of isolated β -anomer; c: incomplete reaction.

Attempts to carry out the cross metathesis¹⁷ of alkene **12** with MVK (as a model Michael acceptor) using the Grubbs II catalyst, the Hoveyda-Grubbs II catalyst, and the Stewart-Grubbs catalyst,¹⁸ developed for hindered alkenes, were all fruitless, giving none of the

the THP ring was obtained as a single, 2,6-*cis* diastereoisomer. The synthesis was then completed by cleavage of the α -hydroxy ketone moiety to carboxylic acid **17** with sodium periodate on silica gel,²⁰ followed by macrodimerisation in 60% yield by the method of Shiina using 2-methyl-6-nitrobenzoic anhydride (MNBA).^{21,4h} The sample of cyanolide A **1** obtained was spectroscopically and chiroptically identical to those reported ($[\alpha]_{\text{D}}^{21} = -51.3$ (c 0.15, CHCl₃); Lit.^{3,4h} $[\alpha]_{\text{D}}^{21} = -59$ (c 0.6, CHCl₃), -41.92 (c 0.33, CHCl₃)).

This synthesis of cyanolide A illustrates both that the oxa-Michael addition can be employed even in highly hindered systems, and also demonstrates that, given an appropriate protecting group, Barbier additions to β -substituted aldehydes can proceed with synthetically useful diastereoselectivity.

from activated magnesium under nitrogen. All other solvents and reagents were used as received. Flash chromatography was carried out on silica gel, 230-400 Mesh.

¹H NMR spectra were recorded at 300, 400 or 500 MHz in CDCl₃ solutions. ¹³C NMR spectra were recorded at the corresponding frequency on the same

instruments at 75, 100 or 125 MHz. Chemical shifts are recorded in ppm and coupling constants are recorded in Hz. Optical rotations are given with units of $10^{-1}\text{degcm}^2\text{g}^{-1}$. Rotations were measured at a wavelength of 589 nm. Melting points are uncorrected.

(R)-hex-5-yn-3-ol (3). A solution of (*R*)-(+)-1,2-epoxybutane **2** (8.35 g, 115 mmol) in anhydrous DMSO (5 ml) was added dropwise to a suspension of lithium acetylide ethylene diamine complex (16 g, 174 mmol) in anhydrous DMSO (50 ml) at 5°C under nitrogen. The mixture was stirred at 5°C for 45 minutes then at room temperature overnight. The mixture was poured into ice water (150 ml) and stirred until effervescence ceased. The mixture was neutralised with 20% HCl and the solution was extracted with Et₂O (3 x 60 ml). The combined organic layers were washed with dilute NaHCO₃ (1 x 30 ml) and brine (50 ml), dried over MgSO₄, and concentrated. The residue was purified by short-path distillation (155°C, 1 atm) to give (*R*)-hex-5-yn-3-ol **3** as a colorless oil (8.96 g, 91.3 mmol, 79%).

$[\alpha]_{\text{D}}^{23} = -5.0$ (*c* 1.04, CHCl₃) {Lit.⁶ (*S*)-enantiomer $[\alpha]_{\text{D}}^{20} = +5.4$ (*c* 1.16, CHCl₃)}.

¹H NMR (396 MHz, CDCl₃) δ 3.67-3.72 (m, 1H), 2.44 (ddd, *J* = 16.7, 4.7, 2.6 Hz, 1H), 2.32 (ddd, *J* = 16.7, 6.8, 2.7 Hz, 1H), 2.05 (dd, *J* = 3.5, 1.7 Hz, 1H), 1.85 (s, 1H), 1.73 – 1.48 (m, 2H), 0.97 (t, *J* = 7.5 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 81.0, 71.3, 70.8, 29.2, 27.0, 10.0.

(R)-hex-5-en-3-ol (4). A solution of (*R*)-hex-5-yn-3-ol **3** (1.5 g, 15.3 mmol) in Et₂O (30 ml) containing Lindlar's catalyst (0.15 g) was stirred under H₂ at room temperature for 2 hours. The mixture was flushed with nitrogen, filtered through a pad of celite and the solvent was evaporated carefully by distillation to give (*R*)-hex-5-en-3-ol **4** as a colorless oil (1.226 g, 80%) which was without further purification.

$[\alpha]_{\text{D}}^{23} = +4.1$ (*c* 1.01, CHCl₃) {Lit.²² $[\alpha]_{\text{D}}^{23} = +5.3$ (*c* 10.76, C₆H₆)}.

¹H NMR (400 MHz, CDCl₃) δ 5.90 – 5.73 (m, 1H), 5.19 – 5.08 (m, 2H), 3.57 (dt, *J* = 8.1, 5.8 Hz, 1H), 2.36 – 2.26 (m, 1H), 2.18 – 2.08 (m, 1H), 1.55 – 1.43 (m, 2H), 1.02 – 0.89 (m, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 135.1, 118.2, 72.2, 41.6, 29.7, 10.1;

(R,E)-methyl 5-hydroxyhept-2-enoate (5). A solution of Grubbs II catalyst (143 mg, 0.168 mmol) in CH₂Cl₂ (5 ml) was added in 4 portions over 4 hours to a solution of (*R*)-hex-5-en-3-ol **4** (2.40 g, 24.0 mmol) and methyl acrylate (6.20 g, 47.6 mmol) in CH₂Cl₂ (20 ml) under N₂. The mixture was heated at reflux overnight, then concentrated *in vacuo*. The residue was distilled (75 °C, 0.5 torr) and purified by flash chromatography on silica gel (5-20% EtOAc/

Hexane) to give (*R,E*)-methyl 5-hydroxyhept-2-enoate **5** as a colorless oil (2.65 g, 70%).

$[\alpha]_{\text{D}}^{22} = -11.5$ (*c* 1.03, CHCl₃); *R_f* = 0.24 (1: 3 EtOAc/Hexane).

$\nu_{\text{max}}/\text{cm}^{-1}$: 3428, 1730, 1715, 1659, 1651

¹H NMR (396 MHz, CDCl₃) δ 6.99 (dt, *J* = 15.0, 7.4 Hz, 1H), 5.90 (dd, *J* = 15.5, 0.7 Hz, 1H), 3.76 – 3.65 (m, 1H), 3.73 (s, 3H), 2.46 – 2.28 (m, 2H), 1.68 – 1.41 (m, 3H), 0.96 (dd, *J* = 7.7, 7.2 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 166.8, 145.6, 123.5, 72.0, 51.6, 39.8, 30.1, 10.0.

MS: (ESI) 181.1 [M+Na]⁺.

HRMS: (EI) Calcd. For C₈H₁₅O₃ [M+H]⁺: 159.1021, Found: 159.1029;

Methyl 2-((4*R*,6*R*)-6-ethyl-2-phenyl-1,3-dioxan-4-yl)acetate (6). Freshly distilled benzaldehyde (2.36 g, 2.3 ml, 22.2 mmol) followed by potassium *t*-butoxide solution (1M in THF, 4 ml, 4 mmol) were added to a solution (*R,E*)-methyl 5-hydroxyhept-2-enoate **5** (3.2 g, 20.2 mmol) in THF (30 ml) at 0°C under N₂. The addition of benzaldehyde (2.36 g, 2.3 ml, 22.2 mmol) and potassium *t*-butoxide solution (4 ml, 4 mmol) was repeated twice at 15 minutes intervals at 0°C. The mixture was quenched with excess pH 7 phosphate buffer (100 ml) and extracted with Et₂O (3 x 30 ml). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (1-5% EtOAc/Hexane) to give dioxolane **6** as a colorless oil (3.6 g, 68%).

$[\alpha]_{\text{D}}^{22} = +2.7$ (*c* 1.03, CHCl₃); *R_f* = 0.66 (1:3 EtOAc/Hexane).

$\nu_{\text{max}}/\text{cm}^{-1}$: 2963, 1738, 1437, 1348, 1217, 1171, 1138, 1099, 1028

¹H NMR (400 MHz, CDCl₃) δ 7.50 (m, 2H), 7.35 (m, 3H), 5.56 (s, 1H), 4.31 (dtd, *J* = 11.3, 6.7, 2.4 Hz, 1H), 3.75 (m, 1H), 3.71 (s, 3H), 2.75 (dd, *J* = 15.7, 7.0 Hz, 1H), 2.53 (dd, *J* = 15.7, 6.2 Hz, 1H), 1.76-1.74 (m, 1H), 1.72 – 1.54 (m, 2H), 1.41 (dt, *J* = 12.9, 11.2 Hz, 1H), 1.00 (dd, *J* = 9.5, 5.5 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 171.2, 138.6, 128.6, 128.1, 126.1, 100.6, 77.9, 73.2, 51.7, 40.8, 36.1, 28.8, 9.5;

MS: (ESI) 287.2 [M+Na]⁺.

HRMS: (EI) Calcd. For C₁₅H₂₁O₄ [M+H]⁺: 265.1440, Found: 265.1440.

2-((2*R*,4*S*,6*R*)-6-ethyl-2-phenyl-1,3-dioxan-4-yl)ethanol (7). Lithium aluminum hydride (0.392 g, 10.3 mmol) was added portionwise to a solution of methyl 2-((4*R*, 6*R*)-6-ethyl-2-phenyl-1,3-dioxan-4-yl)acetate **6** (1.82 g, 6.89 mmol) in Et₂O (30 ml) cooled in an ice water bath under N₂. The mixture was stirred for 2 h at room temperature, then quenched cautiously with water in an ice bath until no further effervescence was observed and a white precipitate had formed. The mixture was filtered through a pad of

celite, dried over MgSO_4 , and concentrated *in vacuo* to give alcohol **7** as a colorless solid which was used without further purification (1.62 g, quantitative).

Mp: 69 – 72 °C; $[\alpha]_{\text{D}}^{22} = -8.9$ (*c* 0.55, CHCl_3).

$\nu_{\text{max}}/\text{cm}^{-1}$: 3393, 2951, 2723, 1641, 1346, 1153, 1053, 1020.

^1H NMR (400 MHz, CDCl_3) δ 7.49 (dd, *J* = 3.9, 1.8 Hz, 2H), 7.39 – 7.31 (m, 3H), 5.55 (s, 1H), 4.12 – 4.06 (m, 1H), 3.88 – 3.82 (m, 2H), 3.79 – 3.72 (m, 1H), 2.15 (t, *J* = 5.2 Hz, 1H), 2.00 – 1.77 (m, 2H), 1.77 – 1.43 (m, 5H), 1.00 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 138.9, 128.9, 128.4, 126.2, 100.9, 78.3, 76.3, 60.7, 38.3, 36.6, 29.0, 9.7.

MS: (ESI) 259.2 $[\text{M}+\text{Na}]^+$.

HRMS: (EI) Calcd. For $\text{C}_{14}\text{H}_{21}\text{O}_3$ $[\text{M}+\text{H}]^+$: 237.1491, Found: 237.1505.

2-((4*R*,6*R*)-6-ethyl-2-phenyl-1,3-dioxan-4-yl)acetaldehyde (8**).** 2-((2*R*,4*S*,6*R*)-6-ethyl-2-phenyl-1,3-dioxan-4-yl)ethanol **7** (0.953 g, 4.03 mmol) was added to a solution of 2-iodoxybenzoic acid (IBX) (1.69 g, 6.05 mmol) in DMSO (40 ml). The mixture was stirred overnight at room temperature. Water (40 ml) and Et_2O (40 ml) were added and the mixture was filtered through a pad of celite. The organic layers were separated and the aqueous layer was extracted with Et_2O (3 x 30 ml). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (15% EtOAc /Hexane) to give aldehyde **8** as a colorless viscous oil (0.83 g, 88%).

$[\alpha]_{\text{D}}^{22} = +2.3$ (*c* 0.58, CHCl_3) {Lit.¹⁵ $[\alpha]_{\text{D}}^{23} = +1.2$ (*c* 0.049, $\text{C}_2\text{H}_2\text{Cl}_2$)}; $R_f = 0.33$ (1:3 EtOAc /Hexane).

$\nu_{\text{max}}/\text{cm}^{-1}$: 3034, 2964, 2874, 2729, 1727, 1452, 1400, 1344, 1158, 1136, 1107, 1063, 1026.

^1H NMR (400 MHz, CDCl_3) δ 9.86 (t, *J* = 1.8 Hz, 1H), 7.49 (dd, *J* = 7.7, 1.5 Hz, 2H), 7.39 – 7.29 (m, 3H), 5.58 (s, 1H), 4.47 – 4.37 (m, 1H), 3.83 – 3.75 (m, 1H), 2.82 (ddd, *J* = 16.8, 7.3, 2.1 Hz, 1H), 2.62 (ddd, *J* = 16.8, 5.2, 1.6 Hz, 1H), 1.77 – 1.68 (m, 2H), 1.64 – 1.53 (m, 1H), 1.52 – 1.40 (m, 1H), 1.00 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 200.5, 138.5, 128.8, 128.3, 126.1, 100.8, 78.1, 72.0, 49.6, 36.3, 28.8, 9.5.

MS: (ESI) 257.2 $[\text{M}+\text{Na}]^+$.

HRMS: (ESI) Calcd. For $\text{C}_{14}\text{H}_{19}\text{O}_3$ $[\text{M}+\text{H}]^+$: 235.1334, Found: 235.1330.

Barbier adduct (9**).** Aldehyde **8** (1.0 g, 4.31 mmol, 1 equiv) and prenyl bromide²³ (1.4 g, 9.45 mmol) was dissolved in a mixture of saturated aqueous NH_4Cl and THF (5:1, 30 ml). The mixture was cooled in an ice bath. Activated zinc powder (0.62 g, 9.45 mmol) was added portionwise over 15 minutes. The mixture was stirred for one hour in the ice bath and at room temperature overnight. Et_2O (15 ml) was added and the mixture was filtered through a pad of celite. The

layers were separated and the aqueous layer was extracted with Et_2O (3 x 15 ml). The combined organic layers were dried over MgSO_4 , and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (10% EtOAc /Hexane) to give the major isomer *anti*-**9** (0.692 g, 69%) as a colorless viscous oil and the minor isomer *syn*-**9** (0.171 g, 17%) as a colorless crystalline solid.

Major isomer: $[\alpha]_{\text{D}}^{22} = -32.0$ (*c* 0.49, CHCl_3); $R_f = 0.53$ (1:3 EtOAc /Hexane).

$\nu_{\text{max}}/\text{cm}^{-1}$: 3499, 2963, 1738, 1638, 1454, 1344, 1138, 1101, 1067, 1028, 1015.

^1H NMR (400 MHz, CDCl_3) δ 7.50 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.39 – 7.29 (m, 3H), 5.85 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.53 (s, 1H), 5.07 (ddd, *J* = 16.8, 12.0, 1.4 Hz, 2H), 4.12 (ddt, *J* = 10.9, 8.0, 2.9 Hz, 1H), 3.81 – 3.67 (m, 2H), 2.09 (d, *J* = 3.9 Hz, 1H), 1.82 – 1.64 (m, 2H), 1.62 – 1.45 (m, 4H), 1.03 (d, *J* = 4.2 Hz, 6H), 0.99 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 145.5, 139.1, 128.7, 128.3, 126.2, 113.4, 100.8, 78.4, 74.6, 73.9, 41.4, 37.5, 36.6, 29.0, 23.1, 22.3, 9.7.

MS: (ESI) 327.3 $[\text{M}+\text{Na}]^+$.

HRMS: (ESI) Calcd. For $\text{C}_{14}\text{H}_{19}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 327.1936, Found: 327.1932.

Minor isomer: Mp: 45–48 °C; $[\alpha]_{\text{D}}^{21} = +3.2$ (*c* 0.48, CHCl_3); $R_f = 0.57$ (1:3 EtOAc /Hexane).

$\nu_{\text{max}}/\text{cm}^{-1}$: 3516, 2961, 2872, 1638, 1454, 1410, 1346, 1215, 1099, 1016.

^1H NMR (396 MHz, CDCl_3) δ 7.47 (dd, *J* = 7.6, 1.9 Hz, 2H), 7.36 – 7.29 (m, 3H), 5.86 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.56 (s, 1H), 5.03 (ddd, *J* = 10.8, 6.1, 1.4 Hz, 2H), 4.14 – 4.03 (m, 1H), 3.81 – 3.70 (m, 1H), 3.63 – 3.56 (m, 1H), 3.17 (d, *J* = 1.8 Hz, 1H), 1.77 – 1.38 (m, 6H), 1.03 (d, *J* = 1.2 Hz, 6H), 0.98 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 145.6, 138.4, 128.8, 128.4, 126.1, 112.58, 100.9, 78.3, 78.2, 78.0, 41.3, 37.6, 36.7, 28.8, 23.2, 22.2, 9.5.

MS: (ESI) 327.3 $[\text{M}+\text{Na}]^+$.

HRMS: (ESI) Calcd. For $\text{C}_{14}\text{H}_{19}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 327.1936, Found: 327.1932.

Thioglycoside (11**).** Sodium hydride (7.96 g of a 60% w/w suspension in mineral oil, 200 mmol) was added slowly, portionwise to a solution of *p*-tolyl 1-thio- β -D-xylopyranoside²⁴ in anhydrous DMSO (60 ml) under N_2 and cooled in an ice water bath. Additional anhydrous DMSO (20 ml) was added to the slurry and MeI (9.5 ml, 152 mmol) in anhydrous DMSO (10 ml) was added slowly to the reaction mixture over a period of an hour. The mixture was stirred for another hour in an ice water bath and then allowed to warm to rt overnight. The reaction was quenched with methanol (1 ml) and stirred for a further 20 minutes. The mixture was diluted with EtOAc (50 ml) and water (100 ml). The aqueous layer was extracted with

EtOAc (2 x 40 ml) and the combined organic layers were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (10% -15% EtOAc/Hexane) to give thioglycoside **11** as a colorless low melting solid (5.6 g, 73%).

$[\alpha]_{\text{D}}^{21} = -8.5$ (*c* 5.4, CHCl_3); $R_f = 0.45$ (1:3 EtOAc/Hexane).

$\nu_{\text{max}}/\text{cm}^{-1}$: 2976, 2932, 2901, 2832, 1633, 1597, 1492, 1445, 1180, 1159, 1130, 1098.

^1H NMR (396 MHz, CDCl_3) δ 7.44 – 7.40 (m, 2H), 7.13 – 7.09 (m, 2H), 4.50 (d, $J = 8.9$ Hz, 1H), 4.10 (dd, $J = 11.3$, 4.6 Hz, 1H), 4.03 – 3.95 (m, 1H), 3.62 (s, $J = 1.5$ Hz, 3H), 3.60 (s, $J = 3.9$ Hz, 3H), 3.46 (s, $J = 1.5$ Hz, 3H), 3.23 – 3.11 (m, 2H), 3.03 (dd, $J = 8.8$, 8.1 Hz, 1H), 2.33 (s, $J = 2.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 137.8, 132.7, 132.2, 129.8, 129.8, 88.2, 86.6, 82.0, 79.2, 66.5, 60.7, 58.7, 21.2.

MS : (ESI) 321.16 $[\text{M}+\text{Na}]^+$.

HRMS: (ESI) Calcd. For $\text{C}_{15}\text{H}_{22}\text{O}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 321.1137, Found: 321.1134.

Glycoside (12). A solution of alcohol *anti*-**9** (0.457 g, 1.50 mmol), thioglycoside **11** (1.12 g, 3.75 mmol), and 2,6-di-*t*-butyl-4-methylpyridine (0.923 g, 4.5 mmol) in Et_2O (35 ml) containing 4Å MS (~80 mg) under N_2 was stirred at room temperature for 15 minutes. MeOTf (0.863 g, 0.6 ml, 5.25 mmol) was added and the mixture was stirred for 5 days at room temperature. The reaction was quenched with saturated aqueous NaHCO_3 , diluted with Et_2O (20 ml) and filtered through a pad of celite. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 20 ml). The combined organic layers were dried over MgSO_4 , and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (5-10% EtOAc/Hexane) to give glycoside **12** as a colorless viscous oil (0.442 g, 61%).

β anomer: $[\alpha]_{\text{D}}^{21} = -69.3$ (*c* 0.26, CHCl_3); $R_f = 0.50$ (1:3 EtOAc/Hexane).

$\nu_{\text{max}}/\text{cm}^{-1}$: 3489, 2964, 2245, 1740, 1638, 1454, 1406, 1346, 1215, 1161, 1136, 1103.

^1H NMR (396 MHz, CDCl_3) δ 7.54 – 7.47 (m, 2H), 7.39 – 7.29 (m, 3H), 5.92 (dd, $J = 17.9$, 10.4 Hz, 1H), 5.47 (s, 1H), 5.04 – 4.96 (m, 2H), 4.30 (d, $J = 7.7$ Hz, 1H), 4.20 (t, $J = 10.9$ Hz, 1H), 3.85 (dd, $J = 11.5$, 5.2 Hz, 1H), 3.80 – 3.70 (m, 2H), 3.63 (s, 3H), 3.62 (s, 3H), 3.44 (s, 3H), 3.28 – 3.18 (m, 1H), 3.13 – 2.92 (m, 3H), 1.79 – 1.63 (m, 2H), 1.60 – 1.42 (m, 3H), 1.38 – 1.26 (dd, $J = 23.8$, 11.2 Hz, 1H), 1.09 (s, 3H), 1.08 (s, 3H), 0.99 (t, $J = 7.5$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 145.5, 139.7, 128.4, 128.2, 126.1, 112.2, 105.0, 100.2, 86.2, 84.6, 82.9, 79.9, 78.4, 72.9, 63.5, 61.0, 59.0, 42.2, 38.2, 37.30, 29.1, 24.7, 22.3, 9.7.

MS: (ESI) 501.5 $[\text{M}+\text{Na}]^+$.

HRMS: (ESI) Calcd. For $\text{C}_{27}\text{H}_{42}\text{O}_7\text{Na}$ $[\text{M}+\text{Na}]^+$: 501.2828, Found: 501.2827.

α anomer: $[\alpha]_{\text{D}}^{20} = +27.6$ (*c* 0.42, CHCl_3); $R_f = 0.45$ (1:3 EtOAc/Hexane).

^1H NMR (400 MHz, CDCl_3) δ 7.50 (d, $J = 6.8$ Hz, 2H), 7.41 – 7.30 (m, 3H), 5.98 – 5.87 (m, 1H), 5.51 (s, 1H), 5.04 – 4.94 (m, 3H), 4.31 (t, $J = 10.7$ Hz, 1H), 3.77 – 3.67 (m, 2H), 3.63 (s, 3H), 3.66 – 3.60 (m, 2H), 3.53 (s, 3H), 3.48 (s, 3H), 3.49 – 3.41 (m, 1H), 3.23 (dt, $J = 15.9$, 8.1 Hz, 1H), 3.13 (dd, $J = 9.6$, 3.7 Hz, 1H), 1.88 – 1.79 (m, 1H), 1.74 – 1.50 (m, 3H), 1.40 – 1.29 (m, 2H), 1.07 (s, 3H), 1.05 (s, 3H), 0.99 (t, $J = 7.5$ Hz, 3H).

MS: (ESI) 501.5 $[\text{M}+\text{Na}]^+$.

HRMS: (ESI) Calcd. For $\text{C}_{27}\text{H}_{42}\text{O}_7\text{Na}$ $[\text{M}+\text{Na}]^+$: 501.2828, Found: 501.2837.

Aldehyde (13). Ozone in oxygen was passed through a solution of glycoside **12** (0.27 g, 0.57 mmol) CH_2Cl_2 (20 ml) at -78°C until the solution became blue. Ozone was passed through the solution for another 10 minutes. The excess ozone was flushed out with O_2 for 15 minutes. A solution of PPh_3 (0.44 g, 1.7 mmol) in CH_2Cl_2 (5 ml) was added at -78°C . The mixture was allowed to warm to room temperature and it was stirred overnight. The mixture was concentrated *in vacuo* and purified by flash chromatography on silica gel (20% EtOAc/Hexane) to give the aldehyde as a colorless crystalline solid (0.22 g, 80%).

Mp: 93 – 95 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{20} = -122.0$ (*c* 0.73, CHCl_3); $R_f = 0.24$ (1:3 EtOAc/Hexane).

$\nu_{\text{max}}/\text{cm}^{-1}$: 2962, 2934, 2833, 1726, 1458, 1404, 1344, 1215, 1161, 1101, 1078

^1H NMR (396 MHz, CDCl_3) δ 9.63 (s, 1H), 7.49 (d, $J = 7.4$ Hz, 2H), 7.39 – 7.31 (m, 3H), 5.47 (s, 1H), 4.26 (d, $J = 7.8$ Hz, 1H), 4.24 – 4.19 (m, 1H), 4.15 (dd, $J = 9.0$, 2.0 Hz, 1H), 3.89 (dd, $J = 11.5$, 5.3 Hz, 1H), 3.81 – 3.72 (m, 1H), 3.61 (s, 3H), 3.55 (s, 3H), 3.45 (s, 3H), 3.26 – 3.18 (m, 1H), 3.13 – 2.99 (m, 2H), 2.91 (dd, $J = 8.9$, 7.8 Hz, 1H), 1.73 – 1.51 (m, 5H), 1.43 – 1.30 (m, 1H), 1.15 (s, 3H), 1.08 (s, 3H), 0.99 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 205.6, 139.4, 128.6, 128.3, 126.2, 126.1, 105.0, 100.3, 86.1, 84.2, 80.6, 79.7, 78.3, 72.5, 63.5, 61.0, 59.0, 51.3, 38.0, 37.1, 29.0, 19.1, 17.9, 9.7.

MS: (ESI) 504.2 $[\text{M}+\text{Na}]^+$.

HRMS: (ESI) Calcd. For $\text{C}_{26}\text{H}_{40}\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$: 503.2621, Found: 501.2614.

Phosphonate (14). *n*-BuLi (8.25 ml of a 1.6 M solution in hexanes, 13.2 mmol) was added dropwise to a solution of methyl diethylphosphonate (2.15 g, 14.1 mmol) in anhydrous THF (30 mL) at -78°C . The mixture was stirred for 15 minutes. A solution of methyl glycolate TBS ether²⁵ (1.93 g, 9.43 mmol) in THF (5 mL) was added to the mixture, which stirred for one hour at -78°C and at r.t. for 2 hours. The

mixture was quenched with water and extracted with EtOAc (2 x 20 ml). The combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (50%-85% EtOAc/Hexane with 0.05% MeOH) to give phosphonate **14** as a colorless oil (2.14 g, 70%).

R_f = 0.05 (1:3 EtOAc/Hexane).

$\nu_{\text{max}}/\text{cm}^{-1}$: 2981, 2955, 2857, 2359, 1734, 1630, 1472, 1393, 1152, 1024.

^1H NMR (396 MHz, CDCl_3) δ 4.29 (s, 2H), 4.18 – 4.09 (m, 4H), 3.16 (d, J = 22.6 Hz, 2H), 1.33 (td, J = 7.1, 0.5 Hz, 6H), 0.91 (s, J = 0.8 Hz, 9H), 0.10 – 0.08 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ 201.8 (d, J = 6.7 Hz), 69.7, 62.7 (d, J = 7.0 Hz), 37.5 (d, J = 128.8 Hz), 25.9, 18.5, 16.5 (d, J = 6.7 Hz), -5.3.

MS : (ESI) 325.08 $[\text{M}+\text{H}]^+$.

HRMS: (ESI) Calcd. For $\text{C}_{13}\text{H}_{29}\text{O}_5\text{PSiNa}$ $[\text{M}+\text{Na}]^+$: 3347.1420, Found: 347.1389.

Alkene (15). A solution of phosphonate **14** (0.22 g, 0.66 mmol) in anhydrous THF (2 ml) and added slowly to a stirred suspension of NaH (0.026 g (60% w/w), 0.66 mmol) in anhydrous THF (2 ml) under N_2 . The mixture was stirred at room temperature for 10 minutes. A solution of aldehyde **13** (0.080 g, 0.17 mmol) in anhydrous THF (2 ml) was added to the solution and it was heated at reflux for 24 h. The mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 x 15 ml). The combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (20% EtOAc/Hexane) to give the alkene **15** as a colorless oil (0.066 g, 60%).

$[\alpha]_{\text{D}}^{22}$ = -90.6 (c 0.47, CHCl_3); R_f = 0.32 (1:3 EtOAc/Hexane).

$\nu_{\text{max}}/\text{cm}^{-1}$: 2957, 2931, 2857, 2247, 1715, 1694, 1622, 1454, 1344, 1257, 1161, 1103, 1076.

^1H NMR (396 MHz, CDCl_3) δ 7.49 (d, J = 6.9 Hz, 2H), 7.42 – 7.23 (m, 3H), 7.06 (d, J = 16.3 Hz, 1H), 6.36 (d, J = 16.3 Hz, 1H), 5.46 (s, 1H), 4.33 (s, 2H), 4.25 (d, J = 7.6 Hz, 1H), 4.19 (t, J = 10.7 Hz, 1H), 3.86 (dd, J = 11.5, 5.3 Hz, 1H), 3.81 (d, J = 9.4 Hz, 1H), 3.78–3.71 (m, 1H), 3.62 (s, 6H), 3.44 (s, 3H), 3.35 – 3.15 (m, 1H), 3.13 – 2.89 (m, 3H), 1.75 – 1.62 (m, 2H), 1.60 – 1.41 (m, 3H), 1.40 – 1.29 (m, 1H), 1.16 (s, 3H), 1.12 (s, 3H), 0.99 (t, J = 7.4 Hz, 3H), 0.92 (s, 9H), 0.09 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ 198.8, 153.8, 139.5, 128.4, 128.2, 126.0, 123.2, 104.8, 100.2, 86.1, 84.4, 82.4, 79.7, 78.2, 72.5, 68.6, 63.5, 61.0, 60.9, 58.9, 42.5, 38.2, 37.1, 29.0, 25.9, 23.6, 23.0, 18.4, 9.7, -5.3.

MS: (ESI) 673.6 $[\text{M}+\text{Na}]^+$.

HRMS: (ESI) Calcd. For $\text{C}_{35}\text{H}_{58}\text{O}_9\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 673.3748, Found: 673.3725.

Tetrahydropyran (16). A solution of **15** (0.12 g, 0.18 mmol) and CSA (0.017 g, 72 μmol) in MeOH (3 ml) was stirred overnight at room temperature. The mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (80% EtOAc/Hexane) to give tetrahydropyran **16** as a colorless viscous oil (0.052 g, 65%).

$[\alpha]_{\text{D}}^{21}$ = -47.7 (c 0.22, CHCl_3); R_f = 0.18 (7:3 EtOAc/Hexane).

$\nu_{\text{max}}/\text{cm}^{-1}$: 3584, 3418, 2965, 2936, 2878, 1726, 1715, 1622, 1470, 1454, 1391, 1163, 1093.

^1H NMR (396 MHz, CD_2Cl_2) δ 4.32 – 4.13 (m, 3H), 3.91 (dd, J = 11.6, 5.2 Hz, 1H), 3.68 – 3.53 (m, 3H), 3.56 (s, 3H), 3.56 (s, 3H), 3.42 (s, 3H), 3.32 (dd, J = 11.6, 4.8 Hz, 1H), 3.19 (ddd, J = 9.8, 8.6, 5.2 Hz, 1H), 3.05 (td, J = 10.1, 2.0 Hz, 2H), 2.90 (dd, J = 8.9, 7.6 Hz, 1H), 2.74 – 2.49 (m, 3H), 2.44 (dd, J = 15.8, 2.3 Hz, 1H), 1.87 (ddd, J = 13.0, 4.7, 2.3 Hz, 1H), 1.60 – 1.43 (m, 3H), 1.43 – 1.29 (m, 2H), 0.96 (s, 3H), 0.90 (s, 3H), 0.87 (t, J = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, CD_2Cl_2) δ 208.9, 105.9, 85.5, 84.5, 84.0, 79.9, 79.5, 77.1, 72.6, 69.0, 63.2, 60.7, 60.4, 58.5, 42.1, 38.7, 38.4, 36.8, 30.2, 21.9, 13.3, 9.6.

MS: (ESI) 471.5 $[\text{M}+\text{Na}]^+$.

HRMS: (ESI) Calcd. For $\text{C}_{22}\text{H}_{40}\text{O}_9\text{Na}$ $[\text{M}+\text{Na}]^+$: 471.2570, Found: 471.2575.

Carboxylic acid (17). NaIO_4 on silica (0.070 g, 0.20 mmol) was added to a solution of tetrahydropyran **16** (0.015 g, 35 μmol) in CH_2Cl_2 (2 ml). The mixture was stirred for 45 minutes at room temperature, filtered through a pad of celite, washing thoroughly with CHCl_3 (3 x 10 ml) followed by EtOAc (3 x 10 ml). The filtrate was concentrated *in vacuo* to give the carboxylic acid **17** as a colorless crystalline solid (0.014 g, 93%).

Mp 170 $^\circ\text{C}$ (dec.); $[\alpha]_{\text{D}}^{21}$ = -36.7 (c 0.30, CHCl_3) {Lit.^{4h} $[\alpha]_{\text{D}}^{23}$ = +50.34 (c 0.99, C_6H_6)}; R_f = 0.18 (7:3 EtOAc/Hexane).

$\nu_{\text{max}}/\text{cm}^{-1}$: 3584, 3472, 2965, 2936, 2880, 1726, 1464, 1396, 1163, 1093.

^1H NMR (396 MHz, CDCl_3) δ 4.24 (d, J = 7.6 Hz, 1H), 3.94 (dd, J = 11.5, 5.1 Hz, 1H), 3.81 – 3.73 (m, 1H), 3.71 – 3.63 (m, 1H), 3.62 (s, 3H), 3.61 (s, 3H), 3.54 (dd, J = 10.4, 1.4 Hz, 1H), 3.47 (s, 3H), 3.30 (dd, J = 11.4, 4.9 Hz, 1H), 3.23 (ddd, J = 9.8, 8.6, 5.1 Hz, 1H), 3.13 – 3.04 (m, 2H), 2.97 (dd, J = 9.0, 7.7 Hz, 1H), 2.51 – 2.33 (m, 3H), 1.91 – 1.84 (m, 1H), 1.66 – 1.38 (m, 5H), 0.99 (s, 3H), 0.90 (s, 3H), 0.87 (t, J = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 174.8, 106.2, 85.7, 84.9, 84.1, 81.2, 79.5, 77.9, 74.1, 63.4, 61.1, 61.0, 59.0, 40.9, 38.8, 37.1, 35.1, 29.8, 22.3, 13.6, 9.6.

MS: (ESI) 457.5 $[\text{M}+\text{Na}]^+$.

HRMS: (ESI) Calcd. For $\text{C}_{22}\text{H}_{40}\text{O}_9\text{Na}$ $[\text{M}+\text{Na}]^+$: 457.2414, Found: 457.2425.

Cyanolide A (1). A solution of carboxylic acid **17** (0.042 g, 96.7 μ mol) in toluene (15 ml) was added over 5 hours via syringe pump to a solution of DMAP (0.236 g, 1.93 mmol) and MNBA (0.100 g, 290 μ mol) in anhydrous toluene (45 ml) at 90°C. The mixture was stirred overnight at 90°C, then concentrated *in vacuo* and purified by flash chromatography on silica gel (60% EtOAc/Hexane) to give cyanolide A **1** as a colorless oil (0.025 g, 60%).

$[\alpha]_D^{21} = -51.3$ (c 0.15, CHCl₃); $R_f = 0.16$ (2:3 EtOAc/Hexane).

$\nu_{\max}/\text{cm}^{-1}$: 2967, 2934, 1738, 1096.

¹H NMR (396 MHz, CDCl₃) δ 4.90 (dd, $J = 14.1$, 6.7 Hz, 2H), 4.24 (d, $J = 7.6$ Hz, 2H), 3.97 (dd, $J = 11.6$, 5.1 Hz, 2H), 3.61 (s, 6H), 3.60 (s, 6H), 3.46 (s, 6H), 3.51 – 3.41 (m, 4H), 3.30 (dd, $J = 11.5$, 4.8 Hz, 2H), 3.27 – 3.19 (m, 2H), 3.13 – 3.04 (m, 4H), 2.99 – 2.92 (m, 2H), 2.38 (dd, $J = 16.2$, 1.3 Hz, 2H), 2.32 – 2.17 (m, 2H), 2.00 – 1.93 (m, 2H), 1.82 (dt, $J = 16.3$, 8.4 Hz, 2H), 1.70 – 1.23 (m, 8H), 0.95 (s, 6H), 0.87 (s, 6H), 0.85 (t, $J = 7.6$ Hz, 6H).

¹³C NMR (100 MHz, CDCl₃) δ 171.9, 106.2, 85.9, 85.6, 84.3, 80.6, 79.6, 75.5, 74.1, 63.5, 61.2, 61.1, 59.0, 40.8, 38.9, 37.2, 35.3, 28.5, 22.3, 13.8, 9.7.

MS: (ESI) 855.6 [M+Na]⁺.

HRMS: (ESI) Calcd. For C₄₂H₇₂O₁₆Na [M+Na]⁺: 855.4718, Found: 855.4703.

Supporting Information for this article is available online at <http://www.thieme-connect.de/ejournals/toc/synthesis>.

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