A second generation synthesis of the cruentaren A core structure based on oxetane and oxirane opening reactions

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Dedicated to Prof. Johann Mulzer on the occasion of his 65th birthday

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Abstract

A second generation synthesis of the core structure of the macrolactone cruentaren A, a potent F-ATPase inhibitor, involves the highly functionalized benzoic acid **36** and reaction of an aryl lithium intermediate with the terminal epoxide **30**. A methyl benzyl ether in the aryl bromide served as a surrogate for a carboxyl function. Epoxide **30** originated from the aldol product **24**. The alkyne of **30** was introduced via opening of an oxetane ring.

Keywords: Cruentaren A, oxetane opening, aldol, protecting group

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Introduction

The discovery of cytotoxic natural products from various sources revealed a number of Achilles' heels of cancer cells.[1] Many of these targets include important functional proteins, like membrance-bound proteins that are engaged in signal transduction (kinases) or the control and use of ion gradients.[2] With regard to the latter, ATPases are important examples.[3] This group of enzymes enables fundamental cellular events such as the synthesis of ATP or transport processes that consume ATP.[4] The vacuolar ATPase (V-ATPase), for example, is wide-spread in eukaryotic cells. It functions as a molecular motor and results in the transport of protons against a proton gradient. Some important inhibitors of V-ATPases include bafilomycin A_1, the archazolides, and the benzolactone enamides.[5] The macrolide cruentaren A[6] (**1**) (Figure 1) on the other hand, turned out to be an inhibitor of mitochondrial F-ATPase[7] (F-ATPase = F-type adenosine triphosphatase). These proteins are located in the inner membrane of mitrochondria. Their function is the production of ATP driven by a proton gradient across the membrane. In a cellular assay with the L929 cell line, cruentaren A showed potent cytotoxicity with an IC_{50} value of 1.2 ng mL^{-1}. Noteworthy structural features of cruentaren A include a 12-membered macrolactone with a *Z*-double bond. Furthermore, the side chain extending from C15 contains a stereotetrad and an (*Z*)-allyl amide.

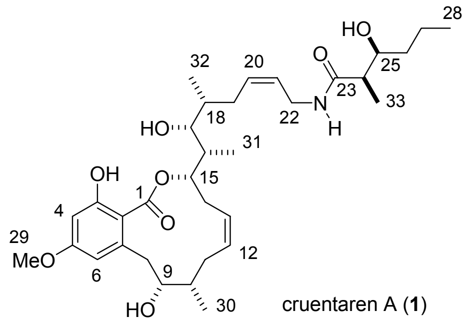
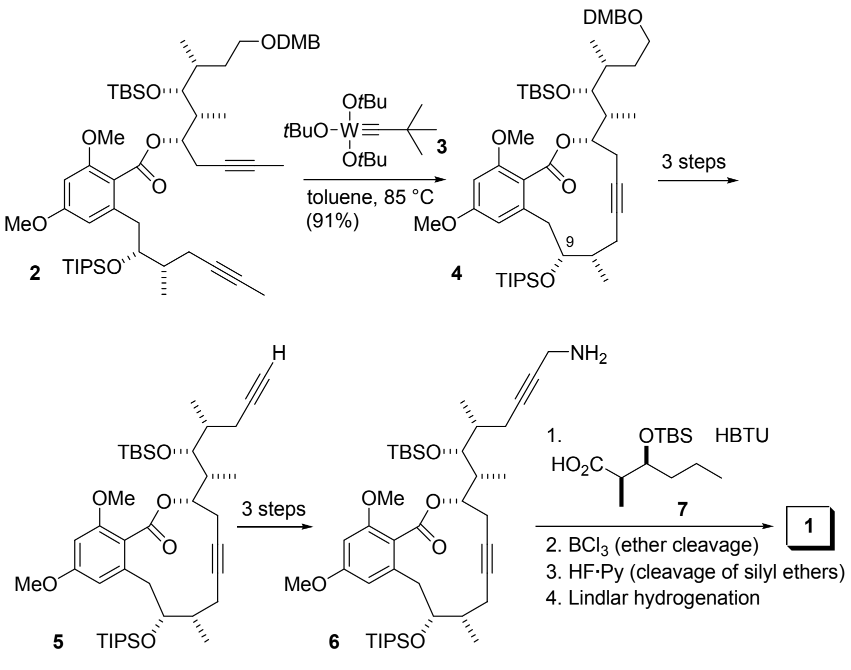


Figure 1. Structure of cruentaren A (**1**).

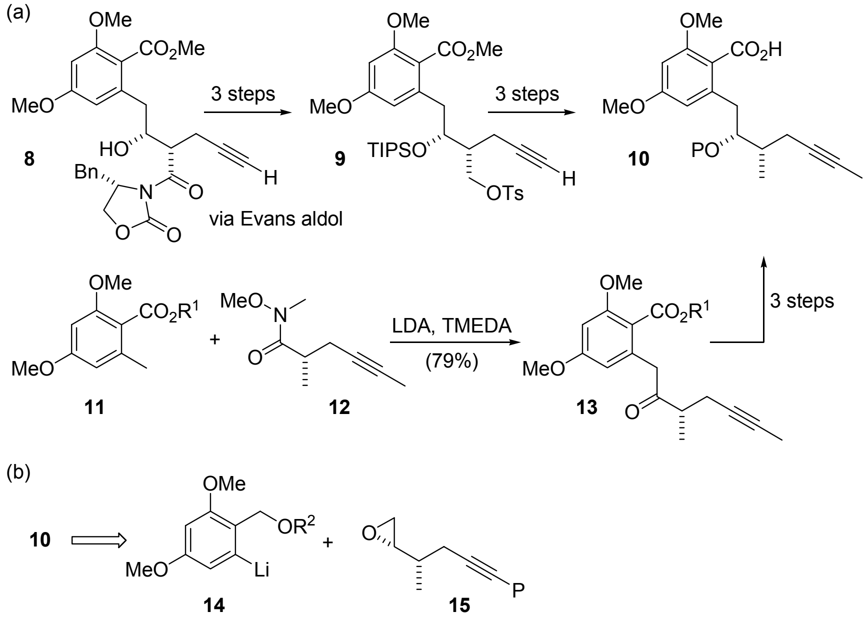
So far two total synthesis of cruentaren A have been reported, one by our group,[8] and the second one by Fürstner et al.[9] In both syntheses the 12-membered macrolactone ring was closed by ring-closing alkyne metathesis (RCAM).[10,11] The triple bond in the macrolactone was kept until the final stages of the synthesis in order to prevent an unwanted translactonization to the six-membered lactone. The final step was a Lindlar hydrogenation that reduced the macrolactone and the side chain triple bond.[8b]



Scheme 1. Key steps in our previous synthesis of cruentaren A (**1**).

The route developed was then used to prepare a number of cruentaren A analogues.[12] In particular, it was found that modifications in the amide part **7** (truncation, removal of the 25-OH group) cause a significant drop in activity. However, other derivatives are required to illuminate the role of the relative and absolute stereochemistry in the hexanoic acid. We therefore looked into a potentially shorter synthesis of the cruentaren A core structure. We initially focused on the functionalized 6-alkynyl-benzoic acid **10** and keeping with the proven RCAM reaction. The two stereocenters in this section of the molecule have been previously established via an Evans aldol reaction[8a] [Scheme 2 (a)]. In order to prepare a similar compound, the Fürstner group relied on the acylation of a lithiated *o*-toluic acid derivative.[9] This was followed by a CBS reduction of the resulting ketone **13**. Another option that can be considered is the use of a metallated aryl species **14** in the opening of an epoxide, such as **15** [Scheme 2 (b)].

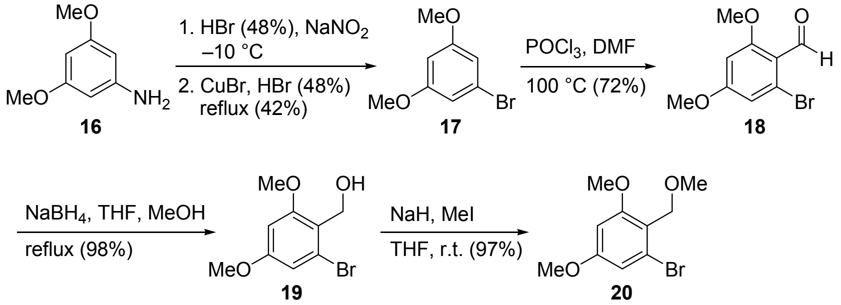
In this paper we report the realization of this strategy. We considered using a suitable protected derivative of (2-bromo-4,6-dimethoxyphenyl)-methanol. Since the aryl ring is highly election rich, deprotection under oxidative conditions should be facile. While the use of a derivative of 2,4-dimethoxybenzoic acid seemed to be more logical, directed metalation and reaction with an epoxide would certainly lead to the unwanted δ-lactone.[13,14]



Scheme 2. (a) Previous routes to the benzoic acid **10**. (b) Plan for the synthesis of the functionalized benzoic acid **10** using an arylmetal derivate. P = silyl protecting group, R^1 = $CH_2CH_2SiMe_3$, R^2 = alkyl.

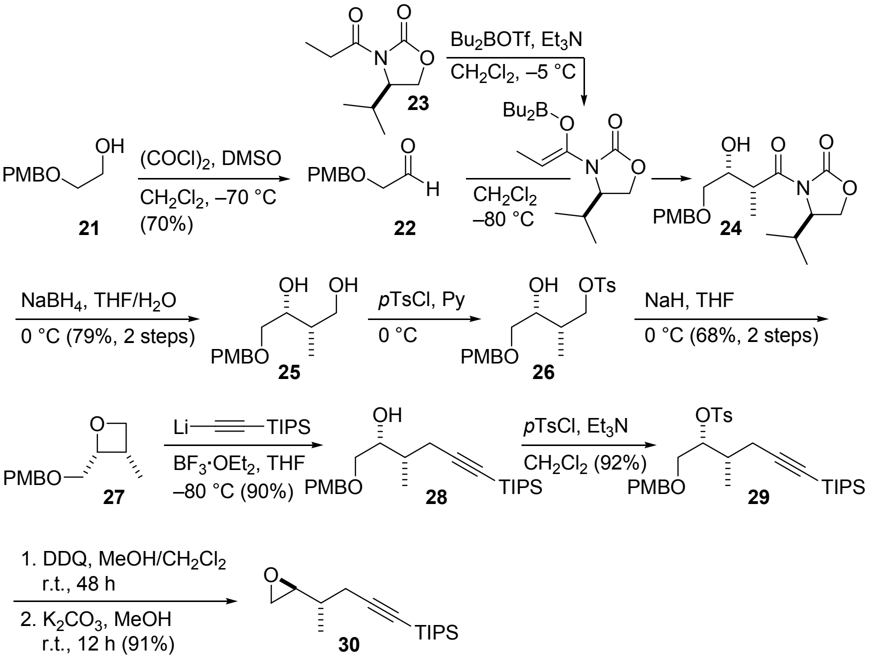
Results and Discussion

The synthesis of benzyl methyl ether **20** started from 3,5-dimethoxyaniline[15] (**16**) (Scheme 3). Diazotation followed by a Sandmeyer reaction with CuBr gave aryl bromide **17**.[16] Vilsmeier formylation provided benzaldehyde **18** in reasonable yield.[17] Sodium borohydride reduction[18] gave benzyl alcohol **19** which was converted to the corresponding methyl ether **20** under standard conditions (NaH, THF, MeI).



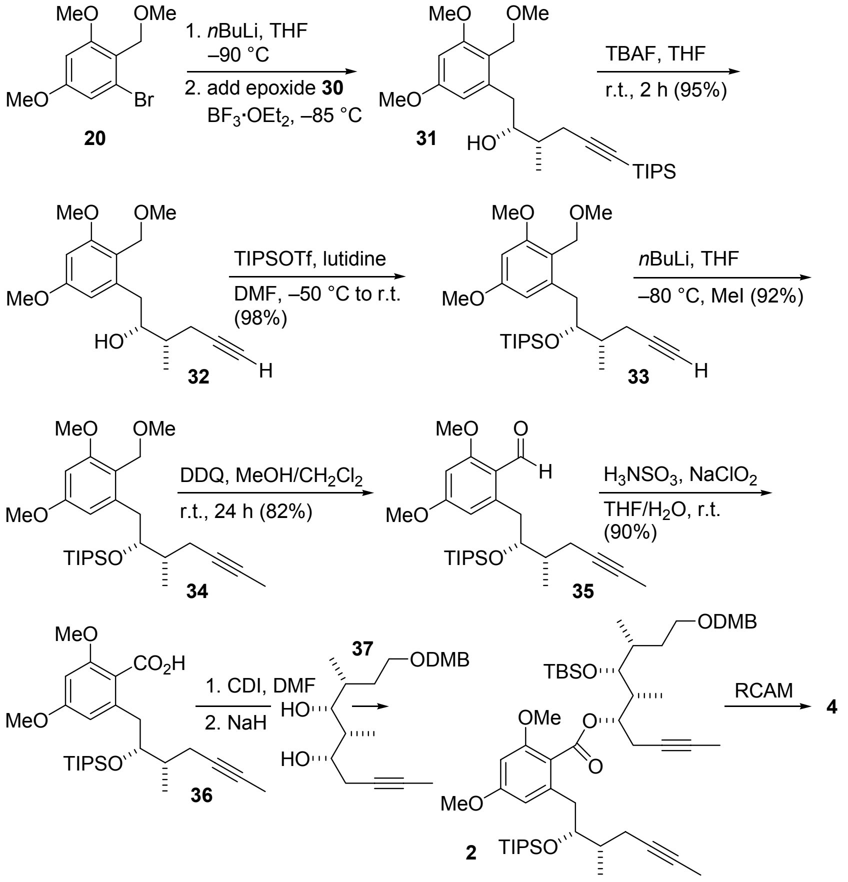
Scheme 3. Synthesis of aryl bromide **20** from dimethoxyaniline **16**.

The two stereocenters in the epoxide building block were established *via* an Evans aldol reaction.[19] Thus, (4-methoxybenzyloxy)acetaldehyde (**22**), prepared from the corresponding alcohol[20] **21** via Swern oxidation,[21,22] was subjected to an aldol reaction[23] using the boron enolate of propionyloxazolidinone **23** (Scheme 4). Since the aldol product **24** tends to decompose upon chromatography on silica gel, the auxiliary was immediately removed under reductive conditions to give the monoprotected triol **25** in good yield. In the following, substitution of the primary alcohol function of **25** by acetylide was required. The primary alcohol function was converted to the corresponding tosylate **26**. The crude tosylate was added to a suspension of NaH in THF to give oxetane **27** in 68% yield from diol **25**.[24] Opening of the oxetane could be achieved by reaction with a mixture of lithium triisopropylsilylacetylide and boron trifluoride etherate in THF. The monoprotected diol unit of **28** could now be transformed into the required epoxide. Accordingly, the hydroxyl function of **28** was converted to tosylate **29** using *p*TsCl/Et_3N in CH_2Cl_2. Oxidative cleavage of the PMB ether with DDQ in MeOH/CH_2Cl_2 led to the corresponding alcohol. Treatment of the crude hydroxy-toluenesulfonate with K_2CO_3 in methanol gave the desired epoxide **30**.



Scheme 4. Preparation of the epoxide building block **30**.

With the two building blocks **20** and **30** in hand, their combination could be studied (Scheme 5). We found it to be crucial to perform the halogen-metal exchange reaction on aryl bromide **20** at temperatures below –85 °C. Thus, metalation of **20** with *n*-butyllithium (1 equiv) was immediately followed by the addition of epoxide **30** (0.84 equiv) in the presence of a slight excess of boron trifluoride etherate. Under these conditions, an excellent yield of the alkylation product **31** could be obtained. The acetylenic TIPS group was cleaved before the alcohol function was protected with TIPS triflate. Now the terminal alkyne **33** could be deprotonated with *n*-butyllithium and alkylated with MeI. This led to 1,5-dimethoxy-(2-methoxymethyl)-3(5-heptynyl) benzene **34**. Since **34** has a resemblance to a dimethoxybenzyl methyl ether, ether cleavage should be possible.[25] Indeed, treatment of methyl benzyl ether **34** with DDQ in a MeOH/CH$_2$Cl$_2$ mixture induced formation of benzaldehyde **35**.[26] A final oxidation using sulfamic acid and sodium chlorite led to the known benzoic acid **36**. This method had proven useful for the side-chain oxidation of electron-rich aromatics.[27] As we had described previously,[8a] acid **36** was converted to the ester **2** via the corresponding carbonyl imidazolide and the alcoholate of diol **37**. In this esterification reaction it is crucial to use a rather concentrated solution of the acid and the reagents. A final ring-closing alkyne metathesis (RCAM) reaction on ester **2** using the Schrock tungsten catalyst **3** gave macrolactone **4**.



Scheme 5. Combination of the aryl bromide **20** with the epoxide **30** and conversion of **31** to the macrolactone **4**.

Conclusions

In summary, a novel route to the cruentaren A macrolactone has been developed. A key step involves the nucleophilic opening of epoxide **30** with the lithio derivative of aryl bromide **20**. The aryl bromide is available in three steps from the known bromide **17**. Epoxide **30** could be efficiently obtained from the aldol reaction between (4-methoxybenzyloxy)acetalde (**22**) and propionyloxazlidinone **23**. *Via* oxetane **27** the alkyne was introduced before the diol function was converted to the epoxide. In the final stages the electron-rich nature of the aryl ring was exploited in the facile cleavage of a benzyl methyl ether. This novel route to acid **36** requires 15 steps from known compounds. The developed strategy offers potential for the synthesis of related benzolactones.

Experimental Section

1-Bromo-3,5-dimethoxybenzene (17). Dimethoxyaniline (15.0 g, 98.0 mmol) was added slowly to vigorously stirred concentrated HBr (48%, 52.5 mL). The resulting suspension was heated to 65 °C for 30 min (white crystals are forming) and then cooled to –10 °C. Now, a solution of $NaNO_2$ (11.15 g, 161.6 mmol) in water (30 mL) was added with a pipette directly under the surface of the suspension (inner temperature should not rise over 0 °C). In a separate flask, a solution of CuBr (7.87 g, 54.84 mmol) in HBr (48%, 15 mL) was heated to its boiling point. After complete addition of $NaNO_2$, the diazonium salt solution was stirred at –10 to 0 °C until strong gas evaluation had ceased and then poured slowly into the hot CuBr solution (it is necessary to pour the diazonium salt solution directly into the CuBr solution without contact to the hot vessel and slowly to maintain the temperature). After complete addition of the diazonium solution, the reaction mixture was stirred for 2 min. Water (about five times the volume of the reaction mixture) was added at r.t. and the product was isolated by steam distillation. The destillate was extracted several times with diethylether. The combined organic layers were washed with 1 M NaOH solution, saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. The bromide **17** (8.93 g, 42%) was obtained as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.76 (s, 6H), 6.37 (t, *J* = 2.2 Hz, 1H, aryl H), 6.65 (d, *J* = 2.3 Hz, 2H, aryl H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.5 (OMe), 99.8 (aryl C), 109.8 (aryl C), 122.9 (aryl C), 161.2 (aryl C).

2-Bromo-4,6-dimethoxybenzaldehyde (18). $POCl_3$ (8.6 mL, 93.7 mmol) was added to dry DMF (20 mL) at r.t. The mixture was heated to 100 °C for 30 to 45 min., and then cooled to r.t. again. At this point a solution of aryl bromide **17** (8.12 g, 37.5 mmol) in dry DMF (10 mL) was added dropwise followed by stirring the mixture at 100 °C for 4 h. The mixture was poured on ice, stirred for 1 h, and then extracted thrice with CH_2Cl_2. The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 4:1) or by crystallisation from petroleum ether/ethyl acetate. The aldehyde **18** (6.6 g, 72%) was obtained as a colorless solid. TLC (petroleum ether/ethyl acetate, 4/1): R_f = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 3H, OMe), 3.88 (s, 3H, OMe), 6.42 (d, *J* = 2.0 Hz, 1H, aryl H), 6.77 (d, *J* = 2.0 Hz, 1H, aryl H), 10.3 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.9 (OMe), 56.1 (OMe), 98.2 (aryl C), 111.5 (aryl C), 116.9 (aryl C), 127.4 (aryl C), 163.6 (aryl C), 164.4 (aryl C), 189.2 (CHO).

(2-Bromo-4,6-dimethoxyphenyl)methanol (19). A suspension of aldehyde **18** (5.3 g, 21.6 mmol) and powdered $NaBH_4$ (2.5 g, 65 mmol) in dry THF (40 mL) was heated to reflux and carefully treated dropwise with dry methanol (23 mL) over a period of 30 min. After complete addition, the solution was evaporated, the residue taken up in diethylether, treated with water, and the mixture extracted thrice with diethyl ether. The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (short column, petroleum ether/ethyl acetate, 4:1). The alcohol **19** (5.24 g, 98%) was obtained as a colorless solid. TLC (petroleum ether/ethyl acetate, 4:1): $R_f = 0.19$; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (t, J = 6.7, 1H, OH), 3.78 (s, 3H, OMe), 3.83 (s, 3H, OMe), 4.79 (d, J = 6.6 Hz, 2H, CH_2Ar), 6.41 (d, J = 2.0 Hz, 1H, aryl H), 6.69 (d, J = 2.2 Hz, 1H, aryl H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.6 (OMe), 55.9 (OMe), 59.9 (CH_2Ar), 98.3 (aryl C), 108.9 (aryl C), 121.4 (aryl C), 125.5 (aryl C), 159.4 (aryl C), 160.5 (aryl C).

1-Bromo-3,5-dimethoxy-2-(methoxymethyl)benzene (20). To a solution of alcohol **19** (3.2 g, 13 mmol) in dry THF (60 mL) was slowly added a suspension of sodium hydride in mineral oil (0.63 g, 60% in oil, 15.7 mmol) followed by stirring of the mixture for 2 min. Thereafter, methyl iodide (1.6 mL, 26 mmol) was added and stirring continued for 12 h at r.t. The mixture was carefully treated with saturated NH_4Cl solution and extracted with diethyl ether. The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (short column, petroleum ether/ethyl acetate, 9:1) to give methyl ether **20** (3.28 g, 97%) as a colorless oil. TLC (petroleum ether/ethyl acetate, 9:1): $R_f = 0.24$. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.38 (s, 3H, CH_2OCH_3), 3.78 (s, 3H, OMe), 3.80 (s, 3H, OMe), 4.57 (s, 2H, CH_2Ar), 6.4 (d, J = 2.3 Hz, 1H, aryl H), 6.72 (d, J = 2.3 Hz, 1H, aryl H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.5 (OMe), 56.0 (OMe), 58.0 (OMe), 67.7 (CH_2Ar), 98.2, 109.0, 118.7, 127.3, 159.9, 160.7 (aryl C).

(4-Methoxybenzyloxy)acetaldehyde (22). A solution of oxalyl chloride (13.5 mL, 0.16 mol) in dry CH_2Cl_2 (330 mL) was cooled to –80 °C and treated dropwise (the inner temperature should not rise above –70 °C) with dry DMSO (22.7 mL, 0.32 mol) within 15 min. The solution was stirred for 5 min before a solution of alcohol[20] **21** (16.2 g, 88.9 mmol) in dry CH_2Cl_2 (43 mL) was added dropwise. The reaction mixture was stirred for 30 to 45 min at –80 °C. Thereafter, triethylamine (68.2 mL, 0.490 mol) was added at this temperature. The mixture was warmed slowly to –30 °C and stirred for an additional h. For work-up, petroleum ether (900 mL) was added and the mixture was washed twice with HCl (0.5 M) and twice with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 3:2) providing aldehyde **22** (11.2 g, 70%) as a colorless oil. TLC (petroleum ether/ethyl acetate, 3:2): $R_f = 0.31$; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3H, OMe), 4.06 (s, 2H, CH_2CHO), 4.55 (s, 2H, CH_2Ar), 6.89 (d, J = 8.7 Hz, 2H, aryl H), 7.28 (d, J = 8.4 Hz, 2H, aryl H), 9.69 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.1 (OMe), 73.2 (CH_2Ar), 74.9 (CH_2CHO), 113.8 (aryl CH), 128.8 (aryl C), 129.6 (aryl CH), 159.5 (aryl C), 200.5 (CHO).

(4*R*)-3-{(2*R*,3*R*)-3-Hydroxy-4-[(4-methoxybenzyl) oxy]-2-methylbutanoyl}-4-isopropyl-1,3-oxazolidin-2-one (24). To a cooled (ice salt bath) solution of propionyl oxazolidinone **23** (4.0 g, 21.6 mmol) in dry CH_2Cl_2 was added dropwise a solution of $n$$Bu_2BOTf$ (1 M in CH_2Cl_2, 26 mL, 26 mmol) followed by dry triethylamine (3.9 mL, 28 mmol). The reaction mixture was stirred for 5 min at this temperature then cooled to –80 °C and now treated dropwise with a solution of aldehyde **22** (5.2 g, 28.8 mmol) in dry CH_2Cl_2 (30 mL). The resulting solution was stirred at this temperature for 10 min and then over night (12 h) at 5 °C. The solution was cooled to –10 °C (ice salt bath) and treated with a pH 7 phosphate buffer solution (26 mL) and methanol (78 mL), followed by addition of a 2/1 solution of methanol and H_2O_2 (78 mL) (the inner temperature should not rise above +3°C). This mixture was then stirred for 1 h at 0 °C. The volatile compounds were evaporated and the residue was extracted with diethyl ether. The combined organic layers were washed with saturated $NaHCO_3$ solution, NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude aldol product **24** was used without further purification for the next step, since it is decomposing on a silica gel column. TLC (petroleum ether/ethyl acetate, 3:2): $R_f = 0.38$. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.85$ (d, $J = 6.8$ Hz, 3H, $CH(CH_3)_2$), 0.88 (d, $J = 7.1$ Hz, 3H, $CH(CH_3)_2$), 1.25 (d, $J = 7.1$ Hz, 3H, $CHCH_3$), 2.24-2.38 (m, 1H, $CHMe_2$), 2.90 (bs, 1H, OH), 3.48 (d, $J = 5.6$ Hz, 2H, CH_2OBn), 3.79 (s, 3H, OMe), 3.88-3.96 (m, 1H, $CHCH_3$), 4.08-4.15 (m, 1H, CHOH), 4.16 (d, $J = 5.8$ Hz, 2 H, OCH_2CH), 4.31-4.40 (m, 1H, $CHCHMe_2$), 4.45 (s, 2H, CH_2Ar), 6.86 (d, $J = 8.3$ Hz, 2 H, aryl H), 7.23 (d, $J = 8.6$ Hz, 2H, aryl H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.3$ ($CHCH_3$), 14.7 ($CH(CH_3)_2$), 17.9 ($CH(CH_3)_2$), 28.3 ($CH(CH_3)_2$), 40.1 (CHMe), 55.3 (OMe), 58.3 ($CHCH(CH_3)_2$), 63.3 (OCH_2CHN), 70.6 (CH_2OPMB), 71.1 (CH_2Ar), 73.0 (CHOH), 113.8 (aryl CH), 129.5 (aryl CH), 129.9 (aryl C), 153.5 (O(C=O)N), 159.3 (aryl C), 176.5 (C=O).

(2*S*,3*R*)-4-[(4-Methoxybenzyl)oxy]-2-methylbutan-1,3-diol (25). To a solution of aldol product **24** (7.9 g, 21.6 mmol) in THF (590 mL) was added a solution of $NaBH_4$ (4.1 g, 108 mmol) in water (150 mL) at 0 °C and the resulting mixture was stirred for 7 h and allowed to warm to r.t. It was then cooled again to 0 °C, treated with saturated NH_4Cl solution (250 mL) and stirred at r.t. for one additional h. The mixture was extracted with diethyl ether, the combined organic layers were washed with saturated $NaHCO_3$ and NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to give diol **25** (4.1 g, 79%, 2 steps) as colorless oil. TLC (petroleum ether/ethyl acetate, 1:1): R_f (auxiliary) = 0.28, R_f (diol **25**) = 0.19; $[\alpha]^{20}_D = -3.26$ ($c = 2.022$, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.92$ (d, $J = 7.1$ Hz, 3H, $CHCH_3$), 1.81-1.93 (m, 1H, $CHCH_3$), 2.21-2.50 (m, 2H, OH), 3.49 (d, $J = 6.1$ Hz, 2H, CH_2OPMB), 3.60-3.71 (m, 2H, CH_2OH), 3.80 (s, 3H, OMe), 3.94-4.02 (m, 1H, CHOH), 4.43-4.52 (m, 2H, CH_2Ar), 6.88 (d, $J = 8.6$ Hz, 2H, aryl H), 7.25 (d, $J = 8.3$ Hz, 2H, aryl H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.2$ (CH_3), 37.4 (CHMe), 55.3 (OMe), 66.3 (CH_2OH), 72.0 (CH_2OPMB), 72.8 (CH_2Ar), 73.1 (CHOH), 113.9, 129.4, 129.8, 159.4 (aryl C); HRMS (ESI): $[M+Na]^+$ calcd for $C_{13}H_{20}O_4Na$ 263.1253802, found 263.12531.

(2*S*,3*R*)-2-[(4-Methoxybenzyloxy)methyl]-3-methyloxetane (27). Tosyl chloride (8.5 g, 44.4 mmol) was added in three portions within 15 min to a solution of diol **25** (8.9 g, 36.9 mmol) in dry pyridine (170 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 40 h. It was poured into a vigorously stirred mixture of 10% HCl (245 mL) and diethyl ether (245 mL) at 0 °C. The phases were separated and the organic layer was washed with ice cooled 10% HCl. The combined water layers were washed three times with diethyl ether. The organic layers were again washed once with cooled 10% HCl, then with 0.2 M $CuSO_4$ solution and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to one third of the volume.[24] This solution was again washed with cooled 10% HCl (three times), with 0.2 M $CuSO_4$ solution (two times) and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude tosylate **26** was used without further purification. TLC (petroleum ether/ethyl acetate, 1:1): R_f = 0.59.

A solution of the crude tosylate **26** in dry THF (30 mL) was added dropwise to a suspension of NaH (60% in mineral oil, 3.0 g, 73.7 mmol) in THF (60 mL) and the resulting reaction mixture was stirred for 2 h at r.t. At 0 °C first methanol (13 mL) was slowly added followed by water (60 mL). The reaction was diluted with diethyl ether (60 mL), the phases were separated and the water layer was extracted three times with diethyl ether. The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/diethyl ether, 5:1) to give oxetane **27** (5.6 g, 68%) as a slightly yellow oil. TLC (petroleum ether/ethyl acetate, 5:1): R_f = 0.23; $[\alpha]^{20}_D$ = +12.2 (*c* = 1.05, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 7.1 Hz, 3H, $CHCH_3$), 3.09-3.20 (m, 1H, $CHCH_3$), 3.69 (d, *J* = 5.9 Hz, 2H, CH_2OPMB), 3.80 (s, 3H, OMe), 4.18 (dd, *J* = 6.0, 6.0 Hz, 1H, CH_2OCH), 4.46 (d, *J* = 11.7 Hz, 1H, CH_2Ar), 4.52 (d, *J* = 11.4 Hz, 1H, CH_2Ar), 4.75 (dd, *J* = 7.9, 5.9 Hz, 1H, CH_2OCH), 4.91-4.96 (m, 1H, $CHCH_2OPMB$), 6.87 (d, *J* = 8.7 Hz, 2H, aryl H), 7.26 (d, *J* = 8.1 Hz, 2H, aryl H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3 (CH_3), 31.2 (*C*HMe), 55.3 (OMe), 69.9 (CH_2OBn), 73.1 (CH_2Ar), 76.7 (CH_2OCH), 82.9 ($CHCH_2OPMB$), 113.7, 129.4, 130.2, 159.2 (aryl C); HRMS (ESI): $[M+Na]^+$ calcd for $C_{13}H_{18}O_3Na$ 245.11482, found 245.11478.

(2*R*,3*S*)-1-(4-Methoxybenzyloxy)-3-methyl-6-(triisopropylsilyl)hex-5-yn-2-ol (28). A solution of trisopropylacetylene (2.5 g, 13.5 mmol) in dry THF (21 mL) was cooled to –80 °C, before *n*BuLi (2.5 M in hexane, 5.4 mL, 13.5 mmol) was added dropwise and the resulting mixture was stirred for 1 h at –80 °C. After addition of boron trifluoro etherate (2.6 mL, 21 mmol) stirring was continued for 1 h. At this point, oxetane **27** (2.5 g, 11.3 mmol) in dry THF (7 mL) was added and stirring was maintained for 1.5 h at –80 °C. The reaction was quenched by the addition of saturated NH_4Cl solution, and the mixture extracted thrice with diethyl ether. The combined organic layers were washed with saturated $NaHCO_3$ and NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 9:1) to give alkyne **28** (3.1 g, 68%, 90% brsm) as a colorless oil. TLC (petroleum ether/ethyl acetate, 9:1): R_f = 0.25; $[\alpha]^{20}_D$ = –16.2 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00-1.07 (m, 24H, TIPS, $CHCH_3$), 1.76-1.87 (m, 1H, *CH*Me), 2.23 (dd, *J* = 16.9, 6.8 Hz, 1H, $CH_2C{\equiv}C$), 2.34 (dd, *J* = 16.9, 5.6 Hz, 1H, $CH_2C{\equiv}C$), 3.41-3.54 (m, 2H, CH_2OPMB), 3.80 (s, 3H, OMe), 3.81-3.88 (m, 1H, *CH*OH), 4.47 (bs, 2H, CH_2Ar), 6.87 (d, *J* = 8.6 Hz, 2H, aryl H), 7.24 (d, *J* = 7.6 Hz, 2H, aryl H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.3 (CH_{TIPS}), 14.6 (CH_3), 18.6 (CH_{3TIPS}), 24.0 ($CH_2C{\equiv}C$), 35.3 (*C*HMe), 55.3 (OMe), 72.2 (CH_2Ar), 72.9 (CHOH), 73.0 (CH_2OPMB), 81.9 (C≡*C*TIPS), 107.1 (*C*≡CTIPS), 113.8, 129.3, 130.1, 159.3 (aryl C); HRMS (ESI): $[M+Na]^+$ calcd for $C_{24}H_{40}O_3SiNa$ 427.26389, found 427.26398.

(1*R*,2*S*)-1-[(4-Methoxybenzyloxy)methyl]-2-methyl-5-(triisopropylsilyl)pent-4-ynyl-4-methylbenzylsulfonate (29). To a solution of alcohol **28** (3.85 g, 9.51 mmol) in dry CH_2Cl_2 (16 mL) was added triethylamine (3.6 mL, 25.7 mmol), DMAP (0.16 g, 1.33 mmol) and tosyl chloride (2.54 g, 13.3 mmol). The reaction mixture was stirred for 48 h (a white percipitate appears), treated with 1 N HCl (15 mL) and extracted thrice with diethyl ether. The combined organic layers were washed with saturated $NaHCO_3$ and NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography **(petroleum ether/ethyl acetate = 12/1, length ca. 20 cm)** resulting in tosylate **29** (4.9 g, 92%) as a colorless oil. TLC (petroleum ether/ethyl acetate, 9:1); R_f = 0.33; $[\alpha]^{20}_D$ = +8.2 (*c* = 1.01, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$) 1.01-1.09 (m, 21H, TIPS), 2.12-2.27 (m, 1H, C*H*Me), 2.21 (d, *J* = 5.8 Hz, 2H, $CH_2C{\equiv}C$), 2.41 (s, 3H, $C_6H_4CH_3$), 3.56 (dd, *J* = 4.6, 1.5 Hz, 2H, CH_2OPMB), 3.80 (s, 3H, OMe), 4.31 (d, *J* = 11.2 Hz, 1H, CH_2Ar), 4.36 (d, *J* = 11.6 Hz, 1H, CH_2Ar), 4.67-4.74 (m, 1H, CHOTos), 6.84 (d, *J* = 8.6 Hz, 2H, aryl H), 7.14 (d, *J* = 7.6 Hz, 2H, aryl H), 7.25 (d, *J* = 7.6 Hz, 2H, tosyl H), 7.76 (d, *J* = 8.3 Hz, 2H, tosyl H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.3 (*C*H_{TIPS}), 14.6 (CH*C*H_3), 18.6 (*C*H_{3TIPS}), 21.6 (C_6H_4*C*H_3), 23.5 (*C*$H_2C{\equiv}C$), 33.9 (*C*HMe), 55.3 (OMe), 68.6 (CH_2OPMB) 72.8 (CH_2Ar), 82.4 (C≡*C*TIPS), 84.2 (CHOTos), 105.8 (*C*≡CTIPS), 113.7 (aryl C), 127.9 (tosyl C), 129.2 (aryl C), 129.6 (tosyl C), 129.8 (aryl C), 134.3 (tosyl C), 144.4 (tosyl C), 159.2 (aryl C); HRMS (ESI): $[M+Na]^+$ calcd for $C_{31}H_{46}O_5SSiNa$ 581.27274, found 581.27294.

(2*S*)-2-[(1*S*)-1-Methyl-4-triisopropylsilyl-3-butynyl]oxirane (30). To a solution of tosylate **29** (4.88 g, 8.74 mmol) in dry MeOH/CH_2Cl_2 (1:1, 300 mL) was added DDQ (4.0 g, 17.5 mmol) and the mixture stirred for 48 h at r.t. Then roughly half of the solvent mixture was evaporated (400 mbar, 40 °C), the residue was diluted with dry methanol (150 mL), dry K_2CO_3 (7.2 g, 52.4 mmol) was added and the mixture stirred overnight (12 h). Thereafter, the mixture was diluted with diethyl ether and treated with water. The aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/diethyl ether, 35:1) yielding epoxide **30** (2.1 g, 91%) as a slightly yellow oil. TLC (petroleum ether/ethyl acetate, 20:1): R_f = 0.51; $[\alpha]^{20}_D$ = –6.36 (*c* = 1.09, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03-1.08 (m, 24H, TIPS, CHC*H*$_3$), 1.51-1.61 (m, 1H, C*H*Me), 2.37 (dd, *J* = 16.8, 6.6 Hz, 1H, $CH_2C{\equiv}C$), 2.45 (dd, *J* = 16.8, 4.8 Hz, 1H, $CH_2C{\equiv}C$), 2.56 (dd, *J* = 5.0, 2.7 Hz, 1H, C*H*$_2$OCH), 2.76 (dd, *J* = 4.8, 4.1 Hz, 1H, C*H*$_2$OCH), 2.89 (ddd, *J* = 7.1, 4.1, 2.8 Hz, 1H, C*H*OCH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.3 (CH_{TIPS}), 14.9 (CH*C*H_3), 18.6 (*C*H_{3TIPS}), 24.3 (*C*$H_2C{\equiv}C$), 35.6 (*C*H_2OCH), 46.3 (*C*HMe), 55.4 (*C*HOCH_2), 82.0 (C≡*C*TIPS), 106.0 (*C*≡CTIPS); HRMS (ESI): $[M+Na]^+$ calcd for $C_{16}H_{30}OSiNa$ 289.19581, found 289.19589.

(2*R*,3*S*)-1-[3,5-Dimethoxy-2-(methoxymethyl)-phenyl]-3-methyl-6-(triisopropylsilyloxy)hex-5-yn-2-ol (31). At –85 to –90 °C *n*BuLi (2.7 M in hexane, 3.43 mL, 9.27 mmol) was added dropwise to a solution of aryl bromide **20** (2.42 g, 9.27 mmol) in dry THF (56 mL). The resulting mixture was stirred for 1 min before a solution of epoxide **30** (2.06 g, 7.73 mmol) in dry THF (25 mL) was added dropwise, followed by boron trifluoro etherate (1.1 mL, 10 mmol). Stirring was continued for one more h at –85 °C, then the reaction was quenched with saturated NH_4Cl solution. The mixture was extracted thrice with diethyl ether. The combined organic layers were washed with saturated $NaHCO_3$ and NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (gradient elution, petroleum ether/ethyl acetate, 9:1 to 7:1). The aryl derivative **31** (3.2 g, 92%) was obtained as a slightly yellow oil. TLC (petroleum ether/ethyl acetate, 9:1): R_f = 0.14; $[\alpha]^{20}_D$ = 15.4 (*c* = 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.98-1.08 (m, 21H, TIPS), 1.15 (d, *J* = 6.8 Hz, 3H, $CHC\mathit{H}_3$), 1.83-1.92 (m, 1H, C*H*Me), 2.33 (dd, *J* = 16.9, 7.8 Hz, 1H, $CH_2C\equiv C$), 2.53 (dd, *J* = 16.9, 5.1 Hz, 1H, $CH_2C\equiv C$), 2.67 (dd, *J* = 13.6, 10.4 Hz, 1H, $ArC\mathit{H}_2CH$), 2.88 (dd, *J* = 13.8, 2.4 Hz, 1H, $ArC\mathit{H}_2CH$), 3.39 (s, 3H, $CH_2OC\mathit{H}_3$), 3.50 (d, *J* = 4.6 Hz, 1H, OH), 3.61-3.69 (m, 1H, C*H*OH), 3.78 (s, 3H, ArOMe), 3.79 (s, 3H, ArOMe), 4.32 (d, *J* = 10.6 Hz, 1H, $ArC\mathit{H}_2OMe$), 4.67 (d, *J* = 10.4 Hz, 1H, $ArC\mathit{H}_2OMe$), 6.34 (d, *J* = 2.3 Hz, 1H, aryl H), 6.36 (d, *J* = 2.0 Hz, 1H, aryl H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.3 (CH_{TIPS}), 15.7 ($CH\mathit{C}H_3$), 18.6 (CH_{3TIPS}), 23.2 ($\mathit{C}H_2C\equiv C$), 37.4 ($Ar\mathit{C}H_2CH$), 39.6 (*C*HMe), 55.2 (ArOMe), 55.7 (ArOMe), 57.8 ($CH_2O\mathit{C}H_3$), 64.4 ($Ar\mathit{C}H_2OMe$), 75.5 (CHOH), 81.2 ($C\equiv\mathit{C}TIPS$), 96.7 (aryl *C*H), 106.1 (aryl *C*H), 108.0 ($\mathit{C}\equiv CTIPS$), 117,4 (aryl C), 142.4 (aryl C), 159.2 (aryl C), 160.6 (aryl C); HRMS (ESI): $[M+Na]^+$ calcd for $C_{26}H_{44}O_4SiNa$ 471.29011, found 471.28997.

(2*R*,3*S*)-1-[3,5-Dimethoxy-2-(methoxymethyl)-phenyl]-3-methylhex-5-yn-2-ol (32). Tetrabutylamonium fluoride (3.65 g, 11.6 mmol) was added to a solution of TIPS protected alkyne **31** (3.47 g, 7.73 mmol) in THF (36 mL) and stirred for 2 h. The mixture was treated with saturated $NaHCO_3$ solution and extracted three times with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1) to give alkyne **32** (2.15 g, 95%) as a colorless, amorphous solid. TLC (petroleum ether/ethyl acetate, 5:1): R_f = 0.21; $[\alpha]^{20}_D$ = 36.2 (*c* = 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 6.6 Hz, 3H, $CHC\mathit{H}_3$), 1.86 (ddd, *J* = 19.5, 13.2, 6.7 Hz, 1H, C*H*Me), 1.97 (t, *J* = 2.7, 2.7 Hz, 1H, $C\equiv CH$), 2.28 (ddd, *J* = 16.8, 7.8, 2.7 Hz, 1H, $CH_2C\equiv C$), 2.46 (ddd, *J* = 16.8, 5.1, 2.5 Hz, 1H, $CH_2C\equiv C$), 2.65 (dd, *J* = 13.6, 10.1 Hz, 1H, $ArC\mathit{H}_2CH$), 2.88 (dd, *J* = 13.6, 2.4 Hz, 1H, $ArC\mathit{H}_2CH$), 3.39 (s, 3H, $CH_2OC\mathit{H}_3$), 3.54 (d, *J* = 4.6 Hz, 1H, OH), 3.60-3.68 (m, 1H, CHOH), 3.80 (bs, 6H, ArOMe), 4.33 (d, *J* = 10.7 Hz, 1H, $ArC\mathit{H}_2OMe$), 4.66 (d, *J* = 10.4 Hz, 1H, $ArC\mathit{H}_2OMe$), 6.34 (d, *J* = 2.3 Hz, 1H, aryl H), 6.38 (d, *J* = 2.3 Hz, 1H, aryl H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8 ($CH\mathit{C}H_3$), 21.8 ($\mathit{C}H_2C\equiv C$), 37.5 ($Ar\mathit{C}H_2CH$), 39.0 (*C*HMe), 55.3 (ArOMe), 55.7 (ArOMe), 57.8 ($CH_2O\mathit{C}H_3$), 64.4 ($Ar\mathit{C}H_2OMe$), 69.2 ($C\equiv\mathit{C}H$), 75.3 (*C*HOH), 83.5 ($\mathit{C}\equiv CH$), 96.6 (aryl CH), 106.3 (aryl CH), 117.4 (aryl C), 142.3 (aryl C), 159.2 (aryl C), 160.6 (aryl C); HRMS (ESI): $[M+Na]^+$ calcd for $C_{17}H_{24}O_4Na$ 315.15668, found 315.15660.

1-[(2*R*,3*S*)-2-(Triisopropylsilyl)oxy-3-methyl-5-hexynyl]-3,5-dimethoxy-2-(methoxymethyl)benzene (33). At –50 °C lutidine (2.5 mL, 21.3 mmol) and triisopropylsilyltriflate (3.82 mL, 14.2 mmol) were added to a solution of alcohol **32** (2.08 g, 7.1 mmol) in dry DMF (130 mL). The reaction mixture was stirred for 12 h and allowed to warm to r.t. It was then treated with 1 N HCl (65 mL) and extracted three times with diethyl ether. The organic layers were washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (aluminium oxide, petroleum ether/DE, 5:1). The silyl ether **33** (3.1 g, 98%) was obtained as a colorless oil. TLC (petroleum ether/ethyl acetate, 15:1): R_f = 0.3; $[\alpha]^{20}_D$ = 30.0 (*c* = 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.93-1.00 (m, 21H, TIPS), 1.06 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 1.91-1.99 (m, 1H, C*H*Me), 1.97 (t, *J* = 2.7, 2.7 Hz, 1H, C≡CH), 2.18 (ddd, *J* = 16.9, 7.8, 2.7, 1H, $CH_2C≡C$), 2.31 (ddd, *J* = 17.0, 6.9, 2.7, 1H, $CH_2C≡C$), 2.77 (d, *J* = 6.8 Hz, 2H, PhC*H*$_2$CH), 3.35 (s, 3H, CH_2OC*H*$_3$), 3.79 (s, 3H, ArOMe), 3.79 (s, 3H, ArOMe), 4.25 (ddd, *J* = 6.7, 6.7, 2.8 Hz, 1H, CHOTIPS), 4.46 (d, *J* = 10.6 Hz, 1H, $ArCH_2OMe$), 4.50 (d, *J* = 10.6 Hz, 1H, $ArCH_2OMe$), 6.32 (d, *J* = 2.5 Hz, 1H, aryl H), 6.40 (d, *J* = 2.5 Hz, 1H, aryl H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9 (CH_{TIPS}), 14.9 (CH*C*H$_3$), 18.0 (CH_{3TIPS}), 18.1 (CH_{3TIPS}), 21.5 (*C*H$_2$C≡C), 35.8 (Ar*C*H$_2$CH), 38.0 (CHMe), 55.2 (ArOMe), 55.8 (ArOMe), 57.9 (CH_2OCH_3), 64.9 (Ar*C*H$_2$OMe), 69.2 (C≡*C*H), 76.1 (CHOTIPS), 83.7 (*C*≡CH), 96.7 (aryl CH), 107.3 (aryl CH), 118.0 (aryl C), 141.9 (aryl C), 159.6 (aryl C), 160.0 (aryl C); HRMS (ESI): $[M+Na]^+$ calcd for $C_{26}H_{44}O_4SiNa$ 471.29011, found 471.29020.

1-[(2*R*,3*S*)-2-(Triisopropylsilyl)oxy-3-methyl-5-heptynyl]-3,5-dimethoxy-2-(methoxymethyl) benzene (34). At –80 °C *n*BuLi (2.7 M in hexane, 3.42 mL, 9.23 mmol) was added dropwise to a solution of alkyne **33** (3.2 g, 7.1 mmol) in dry THF (105 mL), stirred for 45 minutes, and treated with MeI (10.65 mmol, 0.67 ml). Stirring was continued for 1 h (during this time the solution was allowed to warm to r.t.). The reaction mixture was then treated with saturated NH_4Cl solution and extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 15:1) to give the heptyne derivative **34** (3.0 g, 92%) as a colorless oil. TLC (petroleum ether/ethyl acetate, 15:1): R_f = 0.35; $[\alpha]^{20}_D$ = 36.2 (*c* = 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88-0.99 (m, 21H, TIPS), 1.02 (d, *J* = 6.8, 3H, CHC*H*$_3$), 1.77 (t, *J* = 2.5, 2.5 Hz, 3H, $C≡CCH_3$), 1.88-1.97 (m, 1H, CHMe), 2.10-2.23 (m, 2H, $CH_2C≡C$), 2.69 (dd, *J* = 13.6, 8.6 Hz, 1H, ArC*H*$_2$CH), 2.78 (dd, *J* = 13.7, 4.3 Hz, 1H, ArC*H*$_2$CH), 3.36 (s, 3H, CH_2OC*H*$_3$), 3.78 (s, 3H, ArOMe), 3.78 (s, 3H, ArOMe), 4.25-4.29 (m, 1H, CHOTIPS), 4.48 (d, *J* = 10.6 Hz, 1H, $ArCH_2OMe$), 4.51 (d, *J* = 10.6 Hz, 1H, $ArCH_2OMe$), 6.31 (d, *J* = 2.3 Hz, 1H, aryl H), 6.40 (d, *J* = 2.5 Hz, 1H, aryl H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.45 (C≡C*C*H$_3$), 12.9 (CH_{TIPS}), 14.9 (CH*C*H$_3$), 18.0 (CH_{3TIPS}), 18.1 (CH_{3TIPS}), 22.3 (*C*H$_2$C≡C), 35.2 (Ar*C*H$_2$CH), 38.8 (CHMe), 55.1 (ArOMe), 55.8 (ArOMe), 57.8 (CH_2OCH_3), 64.8 (Ar*C*H$_2$OMe), 76.1 (CHOTIPS), 76.6 (C≡*C*Me), 78.2 (*C*≡CMe), 96.7 (aryl CH), 107.4 (aryl CH), 118.0 (aryl C), 142.3 (aryl C), 159.5 (aryl C), 160.0 (aryl C); HRMS (ESI): $[M+Na]^+$ calcd for $C_{27}H_{46}O_4SiNa$ 485.30576, found 485.30582.

2,4-Dimethoxy-6-{(2*R*,3*S*)-3-methyl-2-[(triisopropylsilyl)oxy]hept-5-ynyl}benzaldehyde (35). DDQ (2.1 g, 9.0 mmol) was added at r.t. to a solution of methyl ether **34** (1.9 g 4.1 mmol) in dry MeOH/CH_2Cl_2 (1/1, 140 mL). The solution was stirred for 24 h, concentrated, and then diethyl ether and water were added. The phases were separated and the organic layer was extracted three times with diethyl ether. The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 15:1) to provide aldehyde **35** (1.5 g, 82%) as a colorless oil. TLC (petroleum ether/ethyl acetate, 15:1): R_f = 0.31;

$[\alpha]^{20}_{D}$ = 59.2 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87-0.99 (m, 21H, TIPS), 1.03 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 1.76 (bs, 3H, C≡CCH_3), 1.82-1.91 (m, 1H, CHMe), 2.07-2.14 (m, 1H, CH_2C≡C), 2.37-2.43 (m, 1H, CH_2C≡C), 2.80 (dd, *J* = 12.6, 8.6 Hz, 1H, ArC*H*$_2$CH), 3.26 (dd, *J* = 12.6, 3.8 Hz, 1H, ArC*H*$_2$CH), 3.84 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.16 (ddd, *J* = 8.2, 3.4, 3.3 Hz, 1H, CHOTIPS), 6.32 (d, *J* = 2.0 Hz, 1H, aryl H), 6.40 (d, *J* = 1.8 Hz, 1H, aryl H), 10.44 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.52 (C≡C*C*H$_3$), 12.9 (CH_{TIPS}), 14.3 (CH*C*H$_3$), 18.0 (CH_{3TIPS}), 18.1 (CH_{3TIPS}), 22.2 (*C*H$_2$C≡C), 37.2 (Ar*C*H$_2$CH), 39.5 (*C*HMe), 55.3 (ArOMe), 55.9 (ArOMe), 75.6 (CHOTIPS), 76.0 (C≡*C*Me), 78.8 (*C*≡CMe), 96.6 (aryl CH), 110.2 (aryl CH), 117.5 (aryl C), 146.1 (aryl C), 164.0 (aryl C), 165.2 (aryl C), 190.2 (CHO); HRMS (ESI): $[M+Na]^+$ calcd for $C_{26}H_{42}O_4SiNa$ 469.27446, found 469.27455.

2,4-Dimethoxy-6-{(2R,3S)-3-methyl-2-[(triisopropylsilyl)oxy]hept-5-ynyl}benzoic acid (36). A solution of aldehyde **35** (1.45 g, 3.25 mmol) in THF/water (2:1, 22 mL), was treated with sulfamic acid (0.39 g, 4.1 mmol) and methoxypropene (1.55 mL, 16.2 mmol, to prevent chlorination of the aryl ring) and stirred for 5 min. Now, a solution of sodium chlorite (0.35 g, 3.9 mmol) in water (2.7 mL) was added dropwise (the solution immediately turned from golden yellow to slightly yellow in this exothermic reaction). The reaction mixture was stirred for 15 min, and then extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 4:1) provided benzoic acid **36** (1.35 g, 90%) as a colorless solid. TLC (petroleum ether/ethyl acetate, 4:1): R_f = 0.27; $[\alpha]^{20}_{D}$ = 111.9 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87-0.95 (m, 21H, TIPS), 1.03 (d, *J* = 5.8 Hz, 3H, CHC*H*$_3$), 1.80 (t, *J* = 2.0, 2.0 Hz, 3H, C≡CC*H*$_3$), 2.05-2.15 (m, 2H, CHMe, CH_2C≡C), 2.18-2.27 (m, 1H, CH_2C≡C), 2.78 (dd, *J* = 13.6, 3.5 Hz, 1H, ArC*H*$_2$CH), 2.85 (dd, *J* = 13.7, 10.4 Hz, 1H, ArC*H*$_2$CH), 3.81 (s, 3H, OMe), 3.84 (s, 3H, OMe), 4.40-4.46 (m, 1H, CHOTIPS), 6.36 (d, *J* = 2.0 Hz, 1H, aryl H), 6.37 (d, *J* = 2.0 Hz, 1H, aryl H), 11.0 (bs, 1H, CO_2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.4 (C≡C*C*H$_3$), 12.7 (CH_{TIPS}), 13.4 (CH*C*H$_3$), 17.6 (CH_{3TIPS}), 17.9 (CH_{3TIPS}), 23.3 (*C*H$_2$C≡C), 34.4 (Ar*C*H$_2$CH), 38.6 (*C*HMe), 55.3 (OMe), 56.2 (OMe), 77.0 (C≡*C*Me), 77.2 (CHOTIPS), 77.2 (*C*≡CMe), 97.5 (aryl CH), 106.9 (aryl CH), 117.0 (aryl C), 140.6 (C-arom.), 159.4 (aryl C), 162.0 (aryl C), 166.4 (CO_2H); HRMS (ESI): $[M+Na]^+$ calcd for $C_{26}H_{42}O_5SiNa$ 485.26937, found 485.26946.

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