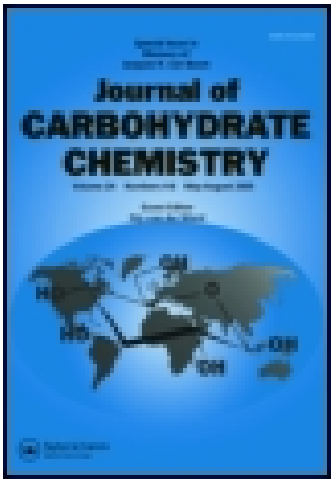

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STUDIES ON THE SYNTHESIS OF THE *C*-GLYCOSIDIC PART OF NOGALAMYCIN, PART 3

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ABSTRACT

The addition of the metalated 1,4-dimethoxybenzenes **17a-c** to the methyl ketone **14** was investigated in connection with the construction of the *C*-glycosidic part of nogalamycin. In most reactions, a selectivity towards the undesired (*S*)-isomer **16a** was observed. However, the reaction of the lithiated aromate **17c** with **14** at low temperatures in THF favored the formation of the desired (*R*)-alcohol **15a** (**15a**:**16a** = 4.8:1) in accordance with the chelate model **A**. The selectivity was considerably enhanced in the addition of the more hindered lithiated naphthalene **18** yielding the (*R*)-isomer **15b** exclusively. Reduction of **15b** afforded the dimethylamino compound **19b**, a direct precursor of the CDEF-ring system of nogalamycin.

INTRODUCTION

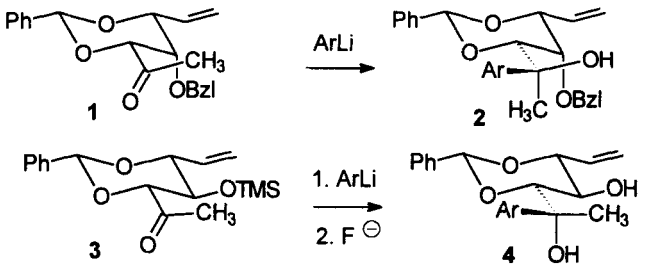
In parts 1 and 2 of this series, the formation of the *C*-glycosidic bond of the DEF-ring system of nogalamycin was tested on substrates lacking the dimethylamino group at C-5.[1,2] We found that the methyl ketone **1** with an axial benzyloxy substituent at C-5 gave mainly the (*S*)-configured tertiary alcohol **2** by an *Si*-side attack of the aryl

nucleophile.[1] A better result was obtained with the isomeric methyl ketone **3** with an equatorial trimethylsiloxy substituent yielding the desired (*R*)-configured alcohol **4** (3:1 in favor of **4**) by addition of the aryllithium in THF (Scheme 1).[2]

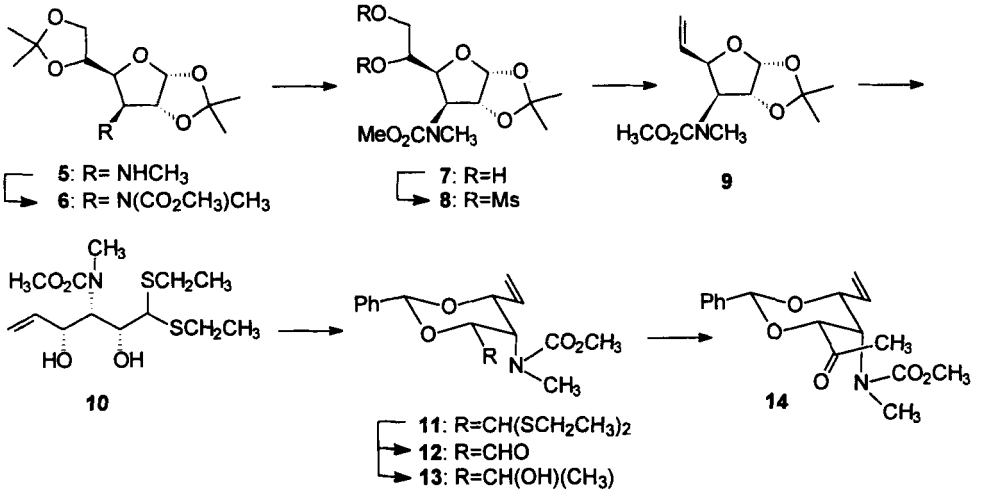
In this investigation we examined the direction of the addition of metalated aryls to the methyl ketone **14** which carries the axial dimethylamino substituent at C-3 required for the synthesis of the fully functionalized CDEF-ring system of nogalamycin.

RESULTS AND DISCUSSIONS

The methyl amine **5**, prepared from D-glucose according to a procedure of Meyer zu Reckendorf et al., was the starting material for the required methyl ketone **14**.[3] Protection of the methylamine **5** with methyl chloroformate yielded the carbamic acid methyl ester **6** (Scheme 2).[4] The carbamic acid ester can easily be reduced with lithium alanate at a later stage to afford the dimethylamino substituent of the CDEF-ring system of nogalamycin.[4] It is worth noting that all of the cyclic carbamates (e.g. **11–16**) showed two rotameric conformers in the NMR spectra. The next steps required the introduction of the C-5,6 double bond and the same reaction sequence was used that was previously applied to prepare the corresponding benzyl ether.[1] The 5,6-acetal of **6** was cleaved selectively with diluted acid to yield the diol **7**, mesylation then gave the dimesylate **8** followed by reductive elimination with sodium iodide to yield the olefin **9** following the procedure of Jones et al.[5] The sugar had to be transformed into an open chain derivative for the anticipated extension of the carbon chain at C-1. This was achieved by conversion of **9** into the dithioacetal **10** using ethanethiol and anhydrous zinc chloride.[6] The secondary hydroxy groups of the dithioacetal **10** were then protected as cyclic benzylidene acetal **11**. It is worth noting that this procedure did not require a discrimination between primary and secondary hydroxy groups. Also, the reduction and reoxidation steps of the aldehyde function as described in the preceding papers[1,2] was not necessary. The dithioacetal **11** was subsequently cleaved by treatment with iodine under basic conditions[7] to yield the aldehyde **12** which was reacted with MeMgBr to yield the mixture of isomeric secondary alcohols **13**. Oxidation of the alcohols **13** using pyridinium



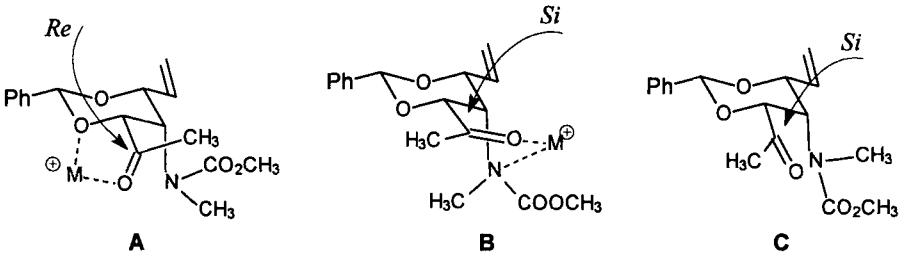
Scheme 1



Scheme 2

chromate/acetic acid anhydride (PDC/Ac_2O)[8] gave the methyl ketone **14** which was the starting material to study the formation of the *C*-glycosidic bond.

The formation of the *C*-glycosidic bond can proceed via chelation (cyclic Cram model)[9,10] or non-chelation control (Felkin-Anh model).[11,12] There are two possibilities of chelate formation for the methyl ketone **14**. The α-chelate **A** can be formed by chelation of the lithium cation with one oxygen of the benzylidene acetal (O-3) and the β-chelate **B** by chelation of the metal cation with the nitrogen of the dimethylamino group (Scheme 3). In the α-chelate **A** the attack from the *Re*-side is expected to be favored

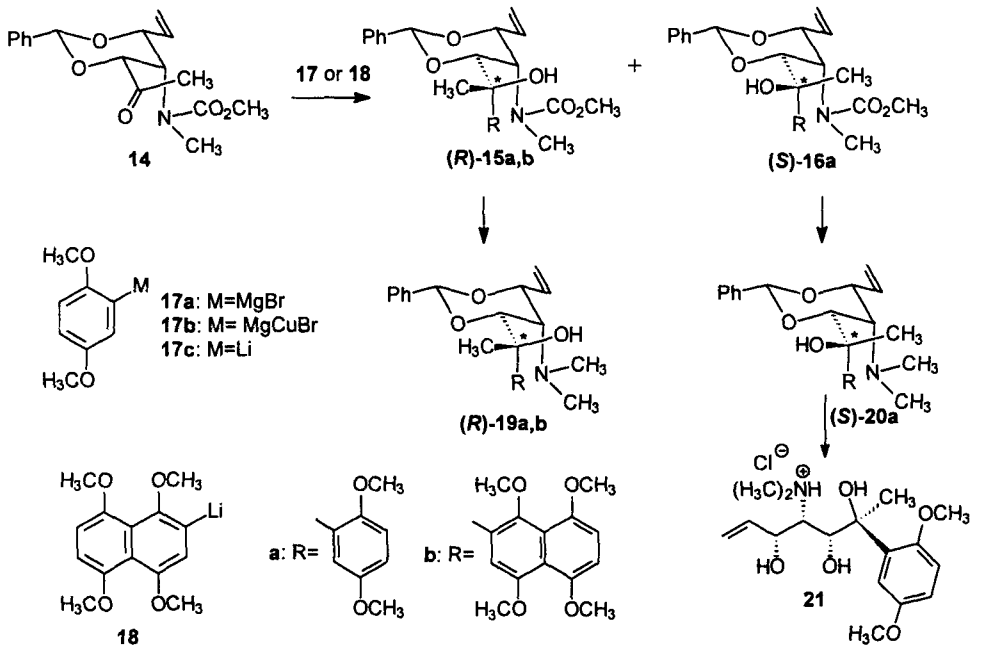


Scheme 3

because the axial carbamic acid ester group hinders the approach from the *Si*-side. By contrast, in the β-chelate **B** the incoming nucleophile is least hindered from the *Si*-side of the carbonyl group. Inspection of the Felkin-Anh model **C** suggests that the nucleophilic attack on the non-chelated methyl ketone **14** probably occurs preferably from the *Si*-side.

The results of the various experiments performed to find the optimum reaction conditions to yield the desired (*R*)-alcohol **15a** are shown in Table 1. Interestingly, despite the different stereochemistry at C-5,[2] a close resemblance to the oxygen analogue **3** can be stated. The addition of the magnesium and magnesium cuprate reagents **17a** and **17b** yielded mainly the undesired (*S*)-alcohol **16a** (entries 1–3). No solvent influence was observed in these cases (THF versus diethyl ether). By contrast, the reaction of the ketone **14** with the aryl lithium compound **17c** showed a strong solvent dependence of the product ratio (entries 4–12). In diethyl ether, the addition reactions showed a selectivity ranging from 5.2–7.1:1 in favor of the (*S*)-isomer **16a** depending on the reaction temperature (entry 4–6). Gratifyingly, the reaction in THF at very low temperature resulted in the predominate formation of the desired (*R*)-alcohol **15a** (**15a:16a** = 4.8:1, entry 9). The reaction of **14** under non-chelating conditions (dimethoxy-THF or addition of TMEDA) again afforded the (*S*)-alcohol **16a** as major product (entries 11 and 12) in agreement with the Felkin-Anh model **C**.

As mentioned earlier, the carbamates **11–16** showed the presence of two rotameric conformers in the NMR spectra complicating the assignment. The adducts **15a** and **16a** were therefore converted by reduction with lithium aluminum hydride into the dimethylamines **19a** and **20a** for structural characterization and determination of their



Scheme 4

Table1. Reaction of the metalaryls **17** and methyl nucleophiles with the ketones **14** and **23**

Entry	Temp.	Educt	Reagent	Solvent	**15a:16a**	Yield **16a**
1	0°C	**14**	**17a**	Et_2O	1:2.1	54 %
2	–78°C	**14**	**17a**	THF	1:3.7	61 %
3	0°C	**14**	**17b**	Et_2O	2.1:1	52 %
4	–20°C	**14**	**17c**	Et_2O	1:5.2	64 %
5	–30°C	**14**	**17c**	Et_2O	1:7.1	68 %
6	–50°C	**14**	**17c**	Et_2O	1:5.6	64 %
7	–60°C	**14**	**17c**	THF	1.9:1	28 %
8	–95°C	**14**	**17c**	THF	4.8:1	14 %
9	0°C	**14**	**17c**	THF/Et_2O	1:6.9	70 %
10	–70°C	**14**	**17c**	$(MeO)_2C_4H_6O$	1:8.5	66 %
11	–80°C	**14**	**17c**	THF/TMEDA	1:1.9	33 %
12	–70°C	**23**	MeMgBr	Et_2O	1:2.2[a]	62 %[a]
13	–70°C	**23**	MeMgBr	THF	1:1[a]	73 %[a]
14	–90°C	**23**	MeLi	Et_2O	1.4:1[a]	71 %[a]
15	–90°C	**23**	MeLi	THF	1:1.7[a]	64 %[a]

a. Ratio and combined yields of **15a** and **16a** were determined by GC.

stereochemistry. As expected, the NMR spectra of the dimethylamines **19a** and **20a** did not show the doubled signals observed for the corresponding carbamate precursors **11-16**. However, an unambiguous assignment of the configuration of the adducts **15a** and **16a** by NMR spectroscopy alone was not possible in spite of the simplified NMR spectra. Therefore, we tried to obtain a suitable crystalline derivative for X-ray analysis. To this end the benzylidene acetal of **20a** was cleaved with methanolic HCl to yield the ammonium salt **21**. This salt gave crystals which could be used for X-ray analysis. Figure 1 shows the ORTEP plot of the ammonium salt **21** proving the absolute (*S*)-configuration of the tertiary alcohol **16a** and by deduction that of the related (*R*)-isomer **15a**.

Syntheses of the naphthalene substituted alcohol (15b)

Encouraged by the results of the addition of lithiodimethoxybenzene (**17c**) to ketone **14** (Table 1, entry 8), we decided to construct an advanced precursor of the nogalamycin CDEF-ring system by addition of **18** to the methyl ketone **14** (Scheme 4). This reaction yielded only one diastereomer **15b** underlining the increased facial selectivity of the very bulky tetramethoxy naphthalene nucleophile. The stereochemistry of **15b** was again determined by conversion of the carbamate **15b** into the dimethylamine **19b** by LAH reduction. Although the corresponding ammonium salt prepared for X-ray analysis proved to be unstable, the comparison of the NMR spectra of **19b** with those of the related compounds **19a** and **20a** allowed an unambiguous assignment. The complete compatibility of the relevant signals of **19b** with those of **19a** proved that the desired (*R*)-isomer **15b** was exclusively formed in the addition reaction.

Inversion of the addition sequence

Finally, we want to report the result of experiments in which the addition sequence of the organometallic reagents was inverted, similarly as described in the preceding communication.[2] The undesired (*S*)-isomer **16a** was formed in good selectivity under chelate control (model **B**, entries 4, 9 and 10). A high selectivity can also be expected in the reaction of arylketone **23** with MeMgBr in favor of the (*R*)-alcohol **15a** provided a chelate related to **B** is controlling the stereochemistry of the addition. The arylketone **23** was obtained by treatment of the aldehyde **12** with lithiodimethoxybenzene

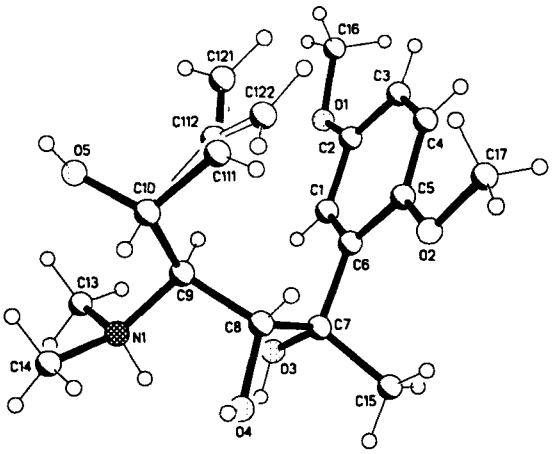


Figure 1. The molecular structure of the cation of **21**. Split positions see text.

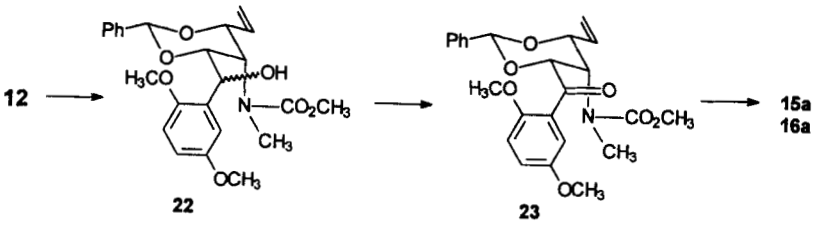
(**17c**) followed by oxidation of the resulting mixture of isomeric alcohols **22** with PDC (Scheme 5). However, the reaction of the aryl ketone **23** with the methyl nucleophiles MeMgBr and MeLi showed only a low selectivity towards the desired (*R*)-isomer **15a** (entries 12–15, Table 1). The reason for these results might be a different orientation of the acetyl group in **23** as compared to **14**. In addition, the facial selectivity of the methyl nucleophile is expected to be lower than that of the bulky aryl nucleophiles **17** and **18**.

In summary, the problem of stereoselective construction of the *C*-glycosidic bond was solved in a general way by addition of the lithiated naphthalene **18** to the methyl ketone **14** yielding the advanced CDEF-ring precursor **15b** of nogalamycin.

EXPERIMENTAL

For general procedures and instrumentation see reference 13. All reactions were performed under a dry nitrogen atmosphere.

3-Deoxy-3-(*N*-methoxycarbonyl-*N*-methylamino)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (6). A suspension of dry powdered K_2CO_3 (2.56 g, 18.3 mmol) in anhydrous acetone (40 mL) was treated with methylamine **5**[3] (1.00 g, 3.66 mmol) and methyl chloroformate (0.71 mL, 9.15 mL). After refluxing for 3 h, the solution was cooled to rt, filtered and concentrated. Column chromatography on silica gel of the



Scheme 5

residue (petroleum ether/diethyl ether 80/20) yielded **6** (1.10 g, 85 %) as colorless needles: mp 103 °C. $[\alpha]_D^{20}$ 4.5 (*c* 2.3, $CHCl_3$); IR (CH_2Cl_2) 2997 cm^{-1}, 2937, 2893, 1701 (C=O), 1375; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 6 H, CH_3), 1.37 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 2.91 (s, 3 H, NCH_3), 3.68 (s, 3 H, OCH_3), 3.97–4.17 (m, 5 H, 3-H, 4-H, 5-H, 6-H, 6'-H), 4.70–5.00 (br. s, 1 H, 2-H). 5.90–6.10 (br. s, 1 H, 1-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.32, 25.89, 26.62, 26.77 (q, CH_3), 52.73 (q, OCH_3), 66.00 (d, C-3), 67.61 (t, C-6), 73.11 (d, C-2), 81.46 (d, C-5), 84.75 (d, C-4), 106.00 (s, $C(CH_3)_2$), 109.33 (d, C-1), 101.00 (s, $C(CH_3)_2$), 156.69 (s, CO).

Anal. Calcd for $C_{15}H_{25}NO_7$: C, 54.35; H, 7.61; N, 4.23. Found: C, 54.19; H, 7.58; N, 4.25.

3–Deoxy–3–(*N*–methoxycarbonyl–*N*–methylamino)–1,2–*O*–isopropylidene–α–D–glucofuranose (7). A solution of **6** (0.76 g, 2.39 mmol) in methanol (26 mL), acetic acid (18 mL) and water (25 mL) was heated at 55 °C for 14 h. After concentration, the residue was dissolved in CH_2Cl_2, the organic phase was washed with saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated to dryness to yield **7** (0.48 g, 70 %) as an oil. $[\alpha]_D^{20}$ 65 (*c* 1.1, $CHCl_3$); IR (CH_2Cl_2) 3439 cm^{-1} (OH), 2937 (C-H), 1670 (C=O), 1491, 1395, 1194, 1086, 1005; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 2.81 (s, 3 H, NCH_3), 3.67 (s, 3 H, OCH_3), 3.57–3.77 (m, 4 H, 3-H, 4-H, 5-H, 6'-H), 4.07–4.11 (dd, $J_{6,6'}$ = 9.2 Hz, $J_{5,6}$ = 4.1 Hz, 1 H, 6-H), 4.50 (br. s, 1 H, OH), 4.73 (br. s, 1 H, 2-H), 5.86 (d, $J_{1,2}$ = 3.6 Hz, 1 H, 1-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.73, 26.22 (q, CH_3), 33.08 (q, NCH_3), 53.25 (q, OCH_3), 63.00 (d, C-3), 64.18 (t, C-6), 69.11 (d, C-2), 80.47 (d, C-5), 82.84 (d, C-4), 104.98 (d, C-1), 111.15 (s, $C(CH_3)_2$), 158.32 (s, CO).

Anal. Calcd for $C_{12}H_{21}NO_7$: C, 49.46; H, 7.27; N, 4.81. Found: C, 49.34; H, 7.35; N, 5.06.

3–Deoxy–3–(*N*–methoxycarbonyl-*N*-methylamino)-5,6-di-*O*-methanesulfonyl-1,2-*O*-isopropylidene-α-D-glucofuranose (8). A solution of **7** (0.35 g, 1.20 mmol) in dry CH_2Cl_2 (15 mL) was treated with Et_3N (425 μL, 3.05 mmol). After cooling to 0 °C and addition of mesyl chloride (195 μL, 2.50 mmol), the solution was allowed to warm to rt and diluted with CH_2Cl_2. The reaction mixture was then washed successively with an aqueous solution of $NaHSO_4$ (10 %), a saturated aqueous solution of $NaHCO_3$ and brine. The combined organic phases were dried (Na_2SO_4), filtered and concentrated to yield **8** (0.53 g, 98 %) as an oil. $[\alpha]_D^{20}$ 24.1 (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 2.78 (s, 3 H, SO_2CH_3), 2.99 (s, 3 H, NCH_3), 3.05 (s, 3 H, SO_2CH_3), 3.60 (s, 3 H, OCH_3), 4.32–4.37 (dd, $J_{6,6'}$ = 11.9 Hz, $J_{5,6}$ = 4.5 Hz, 2 H, 6-H, 6'-H), 4.54–4.78 (m, 4 H, 2-H, 3-H, 4-H, 5-H), 5.88 (d, $J_{1,2}$ = 3.5 Hz, 1 H, 1-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.79, 26.44 (q, CH_3), 31.44 (q, NCH_3), 37.38, 38.64 (q, SO_2CH_3), 53.05 (q, OCH_3), 60.18 (d, C-3), 66.88 (d, C-2), 68.25 (t, C-6), 76.57 (d, C-5), 83.94 (d, C-4), 104.89 (d, C-1), 111.63 (s, $C(CH_3)_2$), 157.02 (s, CO).

Anal. Calcd for $C_{14}H_{25}NO_{11}S_2$: C, 37.58; H, 5.84; N, 3.13. Found: C, 37.88; H; 5.42; N, 3.27.

3-(*N*-Methoxycarbonyl-*N*-methylamino)-1,2-*O*-isopropylidene-3,5,6-trideoxy-α-D-*xylo*-hex-5-enofuranose (9). A suspension of **8** (0.53 g, 1.19 mmol) and NaI (0.89 g, 5.93 mmol) in dry butanone (12 mL) was heated at 70 °C for 15 h. The reaction mixture was then treated with $Na_2S_2O_3$ (1.0 g) and water (4 mL). After stirring for 15 min, the organic phase was extracted with CH_2Cl_2. The combined organic phases were washed with water, dried (Na_2SO_4), filtered and concentrated. Column chromatography on silica gel (ethyl acetate) of the crude product yielded **9** (0.29 g, 97 %) as an oil. $[\alpha]_D^{20}$ 26 (*c* 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 2.70 (s, 3 H, NCH_3), 3.58 (s, 3 H, OCH_3), 4.65 (d, $J_{1,2}$ = 3.8 Hz, 1 H, 2-H), 4.53–4.70 (m, 2 H, 3-H, 4-H), 5.14 (dd, $J_{5,6}$ = 10.8 Hz, 1 H, 6-H (H_{cis})), 5.32 (dd, $J_{5,6'}$ = 17.6 Hz, 1 H, 6-H (H_{trans})), 5.65 (m, 1 H, 5-H), 5.88 (d, $J_{1,2}$ = 3.7 Hz, 1 H, 1-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.62, 26.25 (q, CH_3), 32.06 (q, NCH_3), 52.52 (q, OCH_3), 63.80 (d, C-3), 80.43 (d, C-2), 83.82 (d, C-4), 104.43 (d, C-1), 110.65 (s, $C(CH_3)_2$), 117.75 (t, C-6), 131.37 (d, C-5), 156.10 (s, CO).

Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.00; H, 7.45;N, 5.45. Found: C, 55.88; H, 7.40; N, 5.58.

[(1*S*)–(2,2-Bis-ethylsulfanyl-(1*R*)-hydroxyethyl)-(2*R*)-hydroxybut-3-enyl]-methylcarbamic Acid Methyl Ester (10). A solution of **9** (0.55 g, 2.13 mmol) in dry

CH_2Cl_2 (5 mL) was treated with anhydrous $ZnCl_2$ (2.00 g) and EtSH (0.33 mL, 4.30 mmol) and stirred at rt for 12 h. The reaction mixture was washed with water and the combined organic phases were dried (Na_2SO_4), filtered and concentrated. Column chromatography on silica gel of the crude product yielded **10** (0.68 g, 98 %) as an oil. $[\alpha]_D^{20}$ –7.1 (*c* 1.2, CH_2Cl_2); IR (CH_2Cl_2) 3614 cm^{-1}, 2968, 1674, 1491; ^1H NMR (200 MHz, $CDCl_3$) δ 1.20–1.43 (m, 6 H, 2 x CH_3), 2.60–2.79 (m, 4 H, 2 x CH_2), 3.03 (s, 3 H, NCH_3), 3.50 (br. s, 1 H, 2'-H), 3.70 (s, 3 H, OCH_3), 4.07–4.53 (m, 3 H, 1-H, 1'-H, 2-H), 5.20 (br. d, $J_{3,4}$ = 10.4 Hz, 1 H, 4-H_{cis}), 5.40 (br. d, $J_{3,4}$ = 17.1 Hz, 1 H, 4-H_{trans}), 5.88 (ddd, $J_{3,4}$ = 17.0 Hz, $J_{3,4}$ = 10.4 Hz, $J_{3,2}$ = 4.9 Hz, 1 H, 3-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.97 (q, 2 x CH_3), 26.15 (t, 2 x CH_2), 53.13 (q, OCH_3), 53.85, 54.94 (d, C-1, C-2'), 71.43, 71.86 (d, C-1', C-2), 115.08 (t, C-4), 138.08 (d, C-3), 159.26 (s, CO), (NCH_3-signal is missing); MS (80 eV); *m/z* (%) 324 (3) [M^+ + 1], 306 (1) [324 – H_2O], 262 (1) [324 – EtSH], 200 (100) [262 - EtSH], 162 (16), 135 (25).

Anal. Calcd for $C_{13}H_{25}NO_4S_2$: C, 48.27; H, 7.79; N, 4.33. Found: C, 48.14; H, 7.96; N, 4.54.

[(4*R*)-(Bis-ethylsulfanylmethyl)-(2*R*)-phenyl-(6*R*)-vinyl-[1,3]dioxane-(5*S*)-yl]-methylcarbamic Acid Methyl Ester (11). A solution of **10** (0.26 g, 0.80 mmol), benzaldehyde dimethylacetal (0.12 mL, 0.80 mmol) and *p*-TsOH (cat) in dry CH_2Cl_2 (5 mL) was stirred at rt for 14 h. The reaction mixture was then washed with a saturated aqueous solution of $NaHCO_3$ and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated to yield **11** (0.31 g, 94 %) as an oil. $[\alpha]_D^{20}$ 3.5 (*c* 1.1, CH_2Cl_2); IR (CH_2Cl_2) 2963 cm^{-1}, 2930, 2872, 1701, 1456; ^1H NMR (300 MHz, $CDCl_3$) rotameric mixture A, B; δ 1.38 (m, 12 H, 2 x $CH_3)_{A,B}$, 2.88 (m, 8 H, 2 x $CH_2)_{A,B}$, 3.32 (s, 3 H, $NCH_3)_A$, 3.37 (s, 3 H, $NCH_3)_B$, 3.86 (s, 3 H, $OCH_3)_A$, 3.87 (s, 3 H, $OCH_3)_B$, 4.07 (d, $J_{1',4}$ = 10.2 Hz, 1 H, 1'-H)$_B$, 4.11 (d, $J_{1',4}$ = 9.4 Hz, 1 H, 1'-H)$_A$, 4.24 (dd, $J_{4,1'}$ = 10.2 Hz, $J_{4,5}$ = 2.5 Hz, 1 H, 4-H)$_B$, 4.35 (dd, $J_{4,1'}$ = 9.3 Hz, $J_{4,5}$ = 2.9 Hz, 1 H, 4-H)$_A$, 4.77 (br. s, 2 H, 5-H, 6-H)$_B$, 4.83 (br. s, 1 H, 6-H)$_A$, 4.94 (t, $J_{5,6}$ = 3.0, $J_{5,4}$ = 3.0 Hz, 1 H, 5-H)$_A$, 5.39, 5.43 (m, 2 H, CH=CH_2 (H_{cis}))$_{A,B}$, 5.64, 5.70 (m, 2 H, CH=CH_2 (H_{trans}))$_{A,B}$, 5.88 (s, 1 H, 2-H)$_B$, 5.91 (s, 1 H, 2-H)$_A$, 6.04 (m, 2 H, C*H*=$CH_2)_{A,B}$, 7.54 (m, 6 H, $H_{Ar})_{A,B}$, 7.70 (m, 4 H, $H_{Ar})_{A,B}$; ^{13}C NMR (75 MHz, $CDCl_3$) rotameric mixture A, B; δ 14.15 (q, $CH_3)_A$, 14.16 (q, $CH_3)_B$, 14.22(q, $CH_3)_A$, 14.30 (q, $CH_3)_B$, 24.13 (t, $CH_2)_A$, 24.37 (t, $CH_2)_B$, 25.56 (t, $CH_2)_A$, 25.95 (t, $CH_2)_B$, 33.33 (q, $NCH_3)_A$, 33.63 (q, $NCH_3)_B$, 51.27 (C-1', C-5)$_{A,B}$, 52.61 (q, $OCH_3)_B$,

52.70 (q, $OCH_3)_A$, 80.11 (d, C-6)$_A$, 80.21 (d, C-6)$_B$, 81.97 (d, C-4)$_B$, 82.34 (d, C-4)$_A$, 101.20 (d, C-2)$_A$, 101.31 (d, C-2)$_B$, 116.14 (t, CH=$CH_2)_A$, 116.79 (t, CH=$CH_2)_B$, 125,89 (d, $C_{Ar})_{A,B}$, 128.05 (d, $C_{Ar})_A$, 128.08 (d, $C_{Ar})_B$, 128.66 (d, $C_{Ar})_A$, 128.73 (d, $C_{Ar})_B$, 133.17 (d, *C*H=$CH_2)_B$, 133.50 (d, *C*H=$CH_2)_A$, 137.55 (s, $C_{Ar})_B$, 137.69 (s, $C_{Ar})_A$, 157.64 (s, CO)$_B$, 157.99(s, CO)$_A$; MS (80 eV), *m/z* (%) 350 (3) [M^+ – SCH_2CH_3], 306 (4) [M^+ – C_6H_5CO], 248 (48), 244 (21), 188 (100), 170 (15), 131 (20), 105 (8), 82 (10).

Anal. Calcd $C_{20}H_{29}NO_4S_2$: 58.37; H, 7.10; N, 3.04. Found: C, 58.17; H, 7.31; N, 3.17.

{(4*R*)–Formyl–(2*R*)–phenyl–(6*R*)–vinyl-[1,3]dioxane-(5*S*)-yl}-methylcarbamic Acid Methyl Ester (12). A solution of **11** (107 mg, 0.26 mmol) in a mixture of acetone/water (3 mL, 7.5:1) was treated at 0 °C with $NaHCO_3$ (92 mg, 1.06 mmol) and I_2 (140 mg, 0.56 mmol). After stirring at rt for 6 h (TLC), the suspension was stirred with an aqueous solution of $Na_2S_2O_3$ and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried ($MgSO_4$), filtered and concentrated to yield **12** (76 mg, 96 %) as an oil. $[\alpha]_D^{20}$ 46.7 (*c* 0.8, CH_2Cl_2); IR (CH_2Cl_2) 3372 cm^{-1}, 2999, 2957, 1742, 1694, 1385; ^1H NMR (300 MHz, $CDCl_3$) rotameric mixture A, B; δ 3.11 (s, 3 H, $NCH_3)_A$, 3.16 (s, 3 H, $NCH_3)_B$, 3.69 (s, 3 H, $OCH_3)_A$, 3.71 (s, 3 H, $OCH_3)_B$, 3.65–3.94 (m, 6 H, 4-H, 5-H, 6-H)$_{A,B}$, 5.30 (m, 2 H, CH=C*H*$_2$ (H_{cis}))$_{A,B}$, 5.51 (m, 2 H, CH=C*H*$_2$ (H_{trans}))$_{A,B}$, 5.79 (s, 2 H, 2-H)$_{A,B}$, 5.87 (m, 2 H, C*H*=$CH_2)_{A,B}$, 7.44 (m, 6 H, $H_{Ar})_{A,B}$, 7.58 (m, 4 H, $H_{Ar})_{A,B}$, 9.66 (s, 1 H, CHO)$_A$, 9.68 (s, 1 H, CHO)$_B$; ^{13}C NMR (75 MHz, $CDCl_3$) rotameric mixture A, B; δ 33.02 (q, $NCH_3)_A$, 33.54 (q, $NCH_3)_B$, 49.69 (d, C-5)$_A$, 50.18 (d, C-5)$_B$, 52.88 (q, $OCH_3)_B$, 52.99 (q, $OCH_3)_A$, 79.54 (d, C-6)$_A$, 79.77 (d, C-6)$_B$, 82.68 (d, C-4)$_B$, 83.15 (d, C-4)$_A$, 100.92 (d, C-2)$_A$, 101.00 (d, C-2)$_B$, 117.21 (t, CH=*C*$H_2)_A$, 117.68 (t, CH=*C*$H_2)_B$, 126.14 (d, $C_{Ar})_{A,B}$, 128.27 (d, $C_{Ar})_A$, 128.32 (d, $C_{Ar})_B$, 129.24 (d, $C_{Ar})_A$, 129.32 (d, $C_{Ar})_B$, 132.36 (d, *C*H=$CH_2)_B$, 132.58 (d, *C*H=$CH_2)_A$, 136.87 (s, $C_{Ar})_{A,B}$, 157.89 (s, CO)$_{A,B}$, 196.47 (d, CHO)$_A$, 197.67 (d, CHO)$_B$; MS (80 eV), *m/z* (%) rotamer A: 304 (2) [M^+ – H], 200 (100) [M^+ – C_6H_5CO], 142 (13), 115 (30), 84 (5), 56 (12); rotamer B: 304 (3) [M^+ – H], 200 (62) [M^+ – C_6H_5CO], 142 (21), 115 (100), 105 (11), 100 (12), 84 (9), 82 (10), 56 (17).

Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.86; H, 6.35; N, 4.40.

{(4*R*)-[(1*S*- and 1*R*)-Hydroxyethyl]-(2*R*)-phenyl-(6*R*)-vinyl-[1,3]dioxane-(5*S*)-yl}-methylcarbamic Acid Methyl Ester (13). A solution of MeMgBr (17 mL, 3 M, 50.0

mmol) in diethyl ether (30 mL) was treated at 0 °C with a solution of **12** (3.0 g, 9.8 mmol) in dry ethyl ether (10 mL). After stirring at rt for 6 h, the mixture was hydrolyzed with cold water and saturated aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether and the combined organic phases were dried ($MgSO_4$), filtered and concentrated. Column chromatography on silica gel (petroleum ether/diethyl ether 50/50) of the crude product yielded the alcohol **13** (2.90 g, 93 %) as an oil which was oxidized to the ketone **14** without separation of the isomers.

Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.53; H, 7.21; N, 4.36. Found: C, 63.41; H, 7.38; N, 4.26.

{(4*R*)-Acetyl-(2*R*)-phenyl-(6*R*)-vinyl-[1,3]dioxane-(5*S*)-yl}methylcarbamic Acid Methyl Ester (14). A suspension of PDC (163 mg, 0.43 mmol) in dry CH_2Cl_2 (3 mL) was treated successively with acetic acid anhydride (0.24 mL, 2.40 mmol) and a solution of **13** (240 mg, 0.72 mmol) in dry CH_2Cl_2 (2 mL). After stirring at rt over night, the reaction mixture was transferred to the top of a short column of silica gel in ethyl acetate with a layer of ethyl acetate above the gel to precipitate chromium compounds. The eluate was concentrated and the pyridine was removed by azeotropic destillation with toluene. Column chromatography on silica gel (CH_2Cl_2/MeOH 97/3) of the crude product yielded **14** (210 mg, 91 %) as an oil. $[\alpha]_D^{20}$ 46.77 (*c* 0.8, CH_2Cl_2); IR (CH_2Cl_2) 3055 cm^{-1}, 2987, 2304, 1720, 1695, 1313; ^1H NMR (200 MHz, $CDCl_3$) rotameric mixture A, B; δ 2.27 (s, 3 H, $CH_3)_A$, 2.28 (s, 3 H, $CH_3)_B$, 3.12 (s, 3 H, $NCH_3)_A$, 3.18 (s, 3 H, $NCH_3)_B$, 3.69 (s, 3 H, $OCH_3)_A$, 3.72 (s, 3 H, $OCH_3)_B$, 4.63–4.78, 4.92–4.95 (m, 6 H, 4-H, 5-H, 6-H)$_{A,B}$, 5.26–5.32 (m, 2 H, CH=CH_2 (H_{cis}))$_{A,B}$, 5.45–5.57 (m, 2 H, CH=CH_2 (H_{trans}))$_{A,B}$, 5.77 (s, 2 H, 2-H)$_{A,B}$, 5.81–5.96 (m, 2 H, C*H*=$CH_2)_{A,B}$, 7.39–7.47, 7.53–7.60 (m, 10 H, H_{Ar}); ^{13}C NMR (50 MHz, $CDCl_3$) rotameric mixture A, B; δ 26.81 (q, $CH_3)_{A,B}$, 33.45 (q, $NCH_3)_A$, 33.97 (q, $NCH_3)_B$, 50.98 (q, $OCH_3)_A$, 51.35 (q, $OCH_3)_B$, 53.50 (d, C-5)$_{A,B}$, 80.49 (d, C-6)$_A$, 80.65 (d, C-6)$_B$, 84.31 (d, C-4)$_A$, 84.40 (d, C-4)$_B$, 101.42 (d, C-2)$_A$, 101.53 (d, C-2)$_B$, 117.53 (t, CH=*C*$H_2)_A$, 117.96 (t, CH=*C*$H_2)_B$, 126.74, 128.81, 129.66 (d, $C_{Ar})_{A,B}$, 133.41 (d, *C*H=$CH_2)_B$, 133.54 (d, *C*H=$CH_2)_A$, 137.80 (s, $C_{Ar})_{A,B}$, 157.68 (s, CO)$_B$, 158.55 (s, CO)$_A$, 204.01 (s, CO)$_A$, 205.53 (s, CO)$_B$; MS (80 eV), *m/z* (%) 318 (3) [M^+ – H], 214 (100) [318 – C_6H_5CO], 142 (22), 114 (31), 105 (19) [C_6H_5CO], 85 (7).

Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.73; H, 6.50; N, 4.24.

(*R*-) and (*S*)-{(4*R*)-[(2,5-Dimethoxyphenyl)-hydroxymethyl]-(2*R*)-phenyl-(6*R*)-vinyl-[1,3]dioxane-(5*S*)-yl}-methylcarbamic Acid Methyl Ester (22). A solution of 2-

bromo-1,4-dimethoxybenzene (0.24 mL, 1.6 mmol) in dry THF (5 mL) was treated at –60 °C with *n*-BuLi (1.00 mL, 1.6 M in *n*-hexane, 1.6 mmol). The reaction mixture was allowed to warm to –10 °C within 45 min and was then treated at –60 °C with a solution of **12** (240 mg, 1.3 mmol) in dry THF (2 mL). After warming up to rt, a saturated aqueous solution of NH_4Cl was added and the aqueous phase was extracted with diethyl ether (20 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated. Column chromatography on silica gel (CH_2Cl_2/MeOH 98/2) of the residue yielded the mixture of isomers **22** (235 mg, 41 %) as an oil in addition to the starting material **12** (75 mg, 31 %). The alcohols **22** were oxidized to the ketone **23** without separation.

{(4*R*)–(2,5–Dimethoxybenzoyl)–(2*R*)–phenyl–(6*R*)-vinyl-[1,3]dioxane-(5*S*)-yl}-methylcarbamic Acid Methyl Ester (23). A suspension of PDC (83 mg, 0.22 mmol) in dry CH_2Cl_2 (2 mL) was treated successively with acetic acid anhydride (0.11 mL, 1.20 mmol) and a solution of **22** (100 mg, 0.22 mmol) in dry CH_2Cl_2 (1 mL). After stirring at rt for 3 h, the reaction mixture was transferred to the top of a short column of silica gel in ethyl acetate with a layer of ethyl acetate above the gel to precipitate chromium compounds. The eluate was concentrated and the pyridine was removed by repeated azeotropic distillations with toluene. Column chromatography on silica gel (CH_2Cl_2/MeOH 98/2) of the crude product yielded **23** (76 mg, 78 %) as an oil. $[\alpha]_D^{20}$ 51.7 (*c* 0.2, CH_2Cl_2); IR (CH_2Cl_2) 3626 cm^{-1}, 2945, 2362, 1697, 1604, 1496; ^1H NMR (300 MHz, $CDCl_3$) rotameric mixture A, B; δ 3.03, 3.08 (s, 6 H, $NCH_3)_{A,B}$, 3.08, 3.37 (s, 6 H, $OCH_3)_{A,B}$, 3.68, 3.69 (s, 6 H, $OCH_3,)_{A,B}$, 3.83, 3.84 (s, 6 H, $OCH_3)_{A,B}$, 4.55 (t, J = 3.3 Hz, 1 H, 5-H)$_A$, 4.66 (m, 1 H, 6-H)$_A$, 4.72 (m, 1 H, 6-H)$_B$, 4.81 (t, J = 3.4 Hz, 1 H, 5-H)$_B$, 5.14 (m, 2 H, CH=CH_2 (H_{cis}))$_{A,B}$, 5.43 (m, 2 H, CH=CH_2 (H_{trans}))$_{A,B}$, 5.60–5.75 (m, 4 H, 4-H, C*H*=$CH_2)_{A,B}$, 5.76, 5.78 (s, 2 H, 2-H)$_{A,B}$, 6.85 (d, J = 8.9 Hz, 2 H, 3"-H)$_{A,B}$, 6.94–7.01 (m, 4 H, 4"-H, 6"-H)$_{A,B}$, 7.28–7.53 (m, 10 H, $H_{Ar})_{A,B}$; ^{13}C NMR (75 MHz, $CDCl_3$) rotameric mixture A, B; δ 32.69 (q, $NCH_3)_A$, 33.05 (q, $NCH_3)_B$, 50.15 (d, C-5)$_A$, 50.46 (d, C-5)$_B$, 52.20 (q, $OCH_3)_B$, 52.50 (q, $OCH_3)_A$, 55.54 (q, $OCH_3)_B$, 55.67 (q, $OCH_3)_A$, 56.10 (q, $OCH_3)_A$,, 56.33 (q, $OCH_3)_B$, 79.94 (d, C-6)$_{A,B}$, 83.97 (d, C-4)$_{A,B}$, 100.98 (d, C-2)$_A$, 101.10 (d, C-2)$_B$, 112.77 (d, C-3")$_B$, 112.84 (d, C-3")$_A$, 113.49, 113.88, 120.16, 120.55 (d, C-4", C-6")$_{A,B}$, 116.62 (t, CH=*C*$H_2)_A$, 117.29 (t, CH=*C*$H_2)_B$, 126.35, 128.17, 128.94 (d, $C_{Ar})_A$, 126.38, 128.20, 129.02 (d, $C_{Ar})_B$, 132.94 (d, *C*H=$CH_2)_B$, 133.19 (d, *C*H=$CH_2)_A$, 137.35 (s, $C_{Ar})_B$, 137.52 (s, $C_{Ar})_A$, 151.76, 152.17, 153.56, 153.79 (s, C-2",

C-5")$_{A,B}$, 156.48 (s, CO)$_B$, 157.34 (s, CO)$_A$, 195.40 (s, CO)$_B$, 195.66 (s, CO)$_A$; MS (80 eV) *m/z* (%) 441 (0.4) [M^+], 279 (15), 190 (13), 170 (15), 165 (100), 144 (32), 141 (15), 114 (17), 111 (10), 105 (18) [C_6H_5CO], 97 (18), 85 (19), 83 (20), 77 (19), 71 (31), 70 (11), 69 (21), 59 (10), 57 (50), 56 (10), 55 (26), 43 (33), 42 (13), 41 (21).

Anal. Calcd for $C_{24}H_{27}NO_7$, 441.1799. Found: 441.1788 (HRMS).

Reaction of metalated 2,5-dimethoxybenzenes 17a-c with the methyl ketone 14.

Method I. A suspension of 2-bromo-1,4-dimethoxybenzene (0.23 mL, 1.50 mmol) and magnesium turnings (48 mg, 2.00 mmol) in dry THF (2 mL) or dry diethyl ether (2 mL) was treated with 1,2-dibromoethane (20 µL) and refluxed for 1 h. A solution of the methyl ketone **14** (70 mg, 0.21 mmol) in dry THF (2 mL) or dry diethyl ether (2 mL) was then added at –78 °C and the mixture was allowed to warm to rt within 3 h. The reaction was quenched by addition of saturated aqueous solution of ammonium chloride (5 mL), the organic phase was separated and the aqueous phase extracted with diethyl ether (30 mL). The combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated to afford a mixture of the diastereoisomers **15a** and **16a**. The ratio was determined by gas chromatography and the major product **16a** was isolated by column chromatography on silica gel. For reaction temperatures, the ratio and the yields see Table 1, entries 1 and 2.

Method II. The Grignard reagent **17a** was prepared as described above by reaction of 2-bromo-1,4-dimethoxybenzene (0.45 mL, 3.00 mmol) and Mg (87 mg, 3.60 mmol). The suspension was then treated at 0 °C with CuBr-DMS (60 mg, 3.00 mmol) and stirred for 45 min. The mixture was treated with a solution of **14** (50 mg, 0.15 mmol) in dry diethyl ether (1 mL), stirred for 3 h at 0 °C and worked up as described above. For reaction temperatures, the ratio and yields see Table 1, entry 3.

Method III. A solution of **17c** was prepared by reaction of 2-bromo-1,4-dimethoxybenzene (0.19 mL, 1.30 mmol) in dry diethyl ether or THF (9 mL) and a solution of *n*-BuLi (0.81 mL, 1.6 M in *n*-hexane, 1.30 mmol) at –60 °C and warming up to –10 °C within 45 min. The reagent was reacted with ketone **14** (250 mg, 0.78 mmol) at the temperatures and conditions given in Table 1 (entries 4–10). Workup was performed as described above. For ratio and yields see Table 1, entries 4–10. Entry 10: Reaction in 2,5-dimethoxytetrahydrofuran (10 mL). Entry 11: Addition of TMEDA (0.22 mL, 1.5 mmol).

Reaction of MeMgBr or MeLi with the arylketone 23.

Method I. A solution of the arylketone **23** (10 mg, 0.03 mmol) in dry diethyl ether (2 mL) (entry 12) or dry THF (2 mL) (entry 13) was treated dropwise at –70 °C with a solution of MeMgBr (0.05 mL, 3 M in diethyl ether, 0.15 mmol). The mixture was allowed to warm to rt within 2 h. Workup was performed as described above. The ratio of **15a**:**16a** and the combined yields were determined by gas chromatography (Table 1, entries 11 and 12).

Method II. In related experiments, the arylketone **23** (10 mg, 0.03 mmol) in dry diethyl ether (2 mL) or in dry THF (2 mL) was treated at –90 °C with MeLi (0.1 mL, 1.6 M in diethyl ether, 0.16 mmol). Workup was performed as described above. The ratio of **15a**:**16a** and the combined yields were determined by gas chromatography (Table 1, entries 13 and 14).

[(1*R*)-(2,5-Dimethoxyphenyl)]-1-{(5*S*)-dimethylamino-(2*R*)-phenyl-(6*R*)-vinyl-[1,3]dioxane-(4*R*)-yl}-ethanol (19a). A mixture of **15a** and **14** (60 mg) and LAH (16 mg, 0.44 mmol) in dry diethyl ether (1.5 mL) was refluxed for 8 h. After quenching of the reaction by addition of methanol (1 mL), the solution was concentrated. The residue was rinsed with ethyl acetate and the organic phase was concentrated to dryness. Column chromatography on silica gel (petroleum ether/diethyl ether 50/50) yielded **19a** (33 mg) as a colorless oil. $[\alpha]_D^{20}$ –27.5 (*c* 0.3, CH_2Cl_2); IR (CH_2Cl_2) 2939 cm^{-1}, 2358, 1712, 1493; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65 (s, 3 H, CH_3), 2.68 (br. s, 3 H, NCH_3), 2.79 (br. s, 3 H, NCH_3), 3.14 (t, 1 H, J = 2.4 Hz, 5'-H), 3.79 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 4.63 (m, 2 H, 4'-H, 6'-H), 5.31 (m, 1 H, CH=CH_2 (H_{cis})), 5.58 (dt, 1 H, J_{trans} = 17.3 Hz, J = 1.7 Hz, CH=CH_2 (H_{trans})), 5.58 (s, 1 H, 2'-H), 6.22 (ddd, 1 H, J_{trans} = 17.3 Hz, J_{cis} = 10.8 Hz, J = 5.0 Hz, C*H*=CH_2), 6.74 (dd, 1 H, J_{ortho} = 8.7 Hz, J_{meta} = 2.9 Hz, 4"-H), 6.79 (d, 1 H, J_{ortho} = 8.7 Hz, 3"-H), 7.26 (m, 5 H, H_{Ar}), 7.49 (d, 1 H, J_{meta} = 2.9 Hz, 6"-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.76 (q, CH_3), 41.50 (q, NCH_3), 47.36 (q, NCH_3), 55.60 (q, OCH_3), 55.67 (q, OCH_3), 59.85 (d, C-5'), 75 81 (s, C-1'), 80.62, 82.28 (d, C-4', C-6'), 100.95 (d, C-2'), 111.64, 112.65 (d, C-3", C-4"), 113.38 (d, C-6"), 115.93 (t, CH=*C*H_2), 125.64, 127.72, 128.06 (d, C_{Ar}), 135.15 (s, C-1"), 136.09 (d, *C*H=CH_2), 138.26 (s, C_{Ar}), 149.57, 153.56 (s, C-2", C-5"); MS (80 eV), *m/z* (%) 414 (58) [M^+], 396 (5) [$M^+ - H_2O$], 308 (2) [$M^+ - C_6H_5CHO$], 290 (5) [308 – H_2O], 251 (10), 236 (100), 220 (17), 208 (8), 181 (29), 165 (28), 148 (17), 105 (22) [$C_6H_5CO^+$], 82 (41).

Anal. Calcd for $C_{24}H_{32}NO_5$: C, 69.70; H, 7.56; N, 3.39. Found: C, 69.37; H, 7.23; N, 3.23.

[(1*S*)-(2,5-Dimethoxyphenyl)]-1-{(5*S*)-dimethylamino-(2*R*)-phenyl-(6*R*)-vinyl-[1,3]dioxane-(4*R*)-yl)}-ethanol (20a). A mixture of **16a** (140 mg, 0.30 mmol) and LAH (40 mg, 1.13 mmol) in dry diethyl ether (2 mL) was refluxed for 8 h. After quenching of the reaction by addition of methanol (1 mL) the solution was concentrated to dryness. The residue was redissolved in ethyl acetate and the organic phase was concentrated. Column chromatography on silica gel (petroleum ether/diethyl ether 50/50) yielded **20a** (95 mg, 76 %) as colorless oil. $[\alpha]_D^{20}$ –5.4 (*c* 0.6, CH_2Cl_2); IR (CH_2Cl_2) 3685 cm^{-1}, 2939, 2834, 2358, 1712, 1606; ^1H NMR (300 MHz, $CDCl_3$) δ 1.64 (s, 3 H, CH_3), 2.30 (br. s, 3 H, NCH_3), 2.32 (t, J = 2.3 Hz, 1 H, 5-H), 2.80 (br. s, 3 H, NCH_3), 3.81 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.44 (m, 1 H, 6'-H), 4.58 (d, J = 2.2 Hz, 1 H, 4'-H), 5.19 (dt, J_{cis} = 10.8 Hz, J = 18 Hz, 1 H, CH=CH_2 (H_{cis})), 5.47 (dt, J_{trans} = 17.2 Hz, J = 1.8 Hz, 1 H, CH=CH_2 (H_{trans})), 5.81 (s, 1 H, 2'-H), 6.02 (ddd, J_{trans} = 17.2 Hz, J_{cis} = 10.8 Hz, J = 4.8 Hz, 1 H, *CH*=CH_2), 6.80 (dd, J_{ortho} = 8.8 Hz, J_{meta} = 2.9 Hz, 1 H, 4"-H), 6.86 (d, J_{ortho} = 8.8 Hz, 1 H, 3"-H), 7.40 (m, 3 H, H_{Ar}), 7.48 (d, J_{meta} = 2.9 Hz, 6"-H), 7.66 (m, 2 H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.23 (q, CH_3), 41.54 (q, NCH_3), 47.19 (q, NCH_3), 55.59 (q, OCH_3), 55.75 (q, OCH_3), 59.82 (d, C-5'), 75.81 (s, C-1'), 80.67 (d, C-4'), 82.22 (d, C-6'), 101.74 (d, C-2'), 112.42, 112.87 (d, C-3", C-4"), 113.51 (d, C-6"), 115.84 (t, *CH*=*CH*$_2$), 126.23, 127.94, 128.45 (d, C_{Ar}), 135.77 (d, *CH*=CH_2), 136.05 (s, C-1"), 138.40 (s, C_{Ar}), 149.72, 153.72 (s, C-2", C-5"); MS (80 eV), *m/z* (%) 413 (11) [M^+ – H], 395 (1) [413 – H_2O], 307 (1) [413 – C_6H_4CHO], 250 (4), 235 (100), 207 (6), 180 (22), 164 (27), 150 (8), 105 (12), [$C_6H_5CO^+$], 82 (22), 58 (25).

Anal. Calcd for $C_{24}H_{32}NO_5$: (414.2), C, 69.70; H, 7.56; N, 3.39. Found: C, 69.46; H, 7.35; N, 3.74.

(2*S*)-(2,5-Dimethoxyphenyl)-(4*S*)-dimethylammoniumhept-6-ene-(3*R*,5*R*)-triol chloride (21). A solution of **20a** (15 mg, 0.036 mmol) in dry methanol (1 mL) was treated with methanolic HCl (3 drops, 2.7 N) and stirred over night at ambient temperature. After concentration, the residue was crystallized from CH_2Cl_2/Et_2O to yield **21** (12 mg, 91 %) as colorless crystalls. $[\alpha]_D^{20}$ –56.89 (*c* 0.3 in MeOH); ^1H NMR (200 MHz, CD_3OD) δ 1.65 (s, 3 H, 1-H), 2.69 (d, J = 10.4 Hz, 1 H, 4-H), 2.87 (s, 3 H, NCH_3), 3.21 (s, 3 H, NCH_3), 3.79 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 4.53–4.62 (m, 2 H, 3-H, 5-H), 5.28–5.47 (m, 3 H, 6-H, 2 x 7-H), 6.92 (dd, J_{ortho} = 8.9 Hz, J_{meta} = 2.9 Hz, 1 H, 4'-H), 6.98 (d, J_{ortho} = 8.9 Hz, 1 H, 3'-H), 7.38 (d, J_{meta} = 2.9 Hz, 1 H, 6'-H); ^{13}C NMR (75 MHz, CD_3OD) δ 24.4 (q, C-1), 40.7 (q, NCH_3), 47.7 (q, NCH_3), 56.1 (q, OCH_3), 56.3 (q,

OCH_3), 69.9 (d, C-3), 71.7, 71.8 (d, C-4, C-5), 79.6 (s, C-2), 113.4, 113.9 (d, C-3', C-4'), 114.3 (d, C-6'), 120.3 (t, C-7), 134.4 (s, C-1'), 137.9 (d, C-6), 150.5, 155.3 (s, C-2', C-5'); MS (80 eV), *m/z* (%) 268 (8) [$M^+ - C_3H_5O - HCl$], 182 (11), 181 (100) [$C_{10}H_{13}O_3$], 114 (21), 88 (56) [$C_4H_{10}NO$], 44 (13), 43 (34), 28 (18).

Anal. Calcd for $C_{14}H_{22}NO_4$, 268.1550. Found: 268.1549 (HRMS).

Crystal Structure Determination of 21:[14] $[C_{17}H_{28}NO_5][Cl]$, M_r = 361.8, monoclinic, space group P 2_1, a = 7.584(2), b = 8.844(2), c = 14.722(3) Å, β = 96.80(3)°, V = 980.5(3) $Å^3$, Z = 2, D_r = 1.226 g/cm^3, F(000) = 388, T = 296(1) K. Siemens R3m diffractometer, graphite monochromator, λ(MoKα) = 0.71073 Å, μ = 0.22 mm^{-1}, colorless crystal, size 0.10 x 0.38 x 0.63 mm, ω scan, 2500 intensities collected $4 < 2\theta < 55°$, $-9 < h < 9$, $0 < k < 11$, $0 < l < 19$, 3 standards every 400 reflections showed only random deviations, Lp correction, 2413 unique intensities (R_{int} = 0.021), 1576 with $F > 4\sigma(F)$. Structure solved by direct methods,[15] full-matrix least-squares refinement based on F^2 and 245 parameters,[16] all but H atoms refined anisotropically, H atoms refined with riding model on idealized positions, ethene group C11-C12 was treated by a split model with half occupation each, refinement converged at R1(F) = 0.048, wR2(F^2, all data) = 0.119, S = 1.020, $\max(\Delta/\sigma) < 0.001$, min/max height in final ΔF map −0.15/0.19 e/$Å^3$. Figure 1 shows the molecular structure of the cation.

{(4*R*)–[(1*R*)–Hydroxy–1–(1,4,5,8–tetramethoxynaphthalene–2-yl)-ethyl]-(2*R*)-phenyl-(6*R*)-vinyl-[1,3]dioxane-(5*S*)-yl}methylcarbamic Acid Methyl Ester (15b). A solution of 1,4,5,8-tetramethoxynaphthalene (1.0 g, 4.03 mmol) in dry THF (100 mL) was treated at 0 °C with *n*-BuLi (2.5 mL, 1.6 M in *n*-hexane, 4.03 mmol) and stirred at this temperature for 45 min. A solution of **14** (0.8 g, 2.5 mmol) in dry THF (6 mL) was then added and the mixture was allowed to warm to rt within 2 h. After quenching with saturated NH_4Cl, the aqueous phase was extracted with diethyl ether. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was treated with diethyl ether (3 x 10 mL) and the poorly soluble tetramethoxynaphthalene (0.49 mg) was separated by filtration. The eluate was concentrated and purified by column chromatography on silica gel (CH_2Cl_2/MeOH 99/1) to yield further tetramethoxynaphthalene (150 mg), starting ketone **14** (0.21 mg, 26 %) and **15b** (0.61 mg, 43 %) as an oil. Traces of the isomer corresponding to **16a** could not be detected in any of the fractions.

(1*R*)-{(5*S*)-(Dimethylamino-(2*R*)-phenyl-(6*R*)-vinyl-[1,3]dioxane-(4*R*)-yl)}-1-(1,4,5,8-tetramethoxynaphthalene-2-yl)]-ethanol (19b). A mixture of **15b** (65 mg,

0.115 mmol) and LAH (34 mg, 0.916 mmol) in dry diethyl ether (2 mL) was refluxed for 8 h. After quenching with methanol (1 mL), the mixture was concentrated. The residue was redissolved in ethyl acetate and the organic phase was concentrated to dryness. Column chromatography on silica gel yielded **19b** (45 mg, 75 %) as an oil. $[\alpha]_D^{20}$ –38.99 (*c* 1.1, CH_2Cl_2); IR (CH_2Cl_2) 3001 cm^{-1}, 2933, 2839, 1695, 1601, 1466; ^1H NMR (300 MHz, $CDCl_3$) δ 1.82 (s, 3 H, CH_3), 2.71 (br. s, 3 H, NCH_3), 2.84 (br. s, 3 H, NCH_3), 3.19 (m, 1 H, 5'-H), 3.69, 3.88, 3.91, 3.99 (s, 12 H, 4 x OCH_3), 4.56 (m, 1 H, 4'-H), 4.67 (m, 1 H, 6'-H), 5.30 (dt, J = 10.8 Hz, 1 H, CH=CH_2 (H_{cis})), 5.58 (dt, J = 17.2 Hz, 1 H, CH=CH_2 (H_{trans})), 5.63 (s, 1 H, 2'-H), 6.23 (ddd, J = 17.2 Hz, J = 10.8 Hz, J = 5.0 Hz, 1 H, C*H*=CH_2), 6.76, 6.80 (d, J_{ortho} = 8.6 Hz, 2 H, 6"-H, 7"-H), 7.20–7.39 (m, 5 H, H_{Ar}), 7.60 (s, 1 H, 3"-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.07 (q, CH_3), 41.62, 47.47 (q, NCH_3), 56.92, 57.21, 57.38 (q, 4 x OCH_3), 59.95 (d, C-5'), 76.06 (d, C-1'), 81.89, 82.13 (d, C-4', C-6'), 100.61 (d, C-2'), 106.75, 107.80, 108.62 (d, C-3", C-6", C-7"), 116.04 (t, CH=*C*H_2), 125.64, 127.69, 128.09 (d, C_{Ar}), 135.49 (s, C-2"), 136.02 (t, *C*H=CH_2), 138.13 (s, C_{Ar}), 145.68, 149.72, 151.47, 151.91 (s, C-1", C-4", C-5", C-8"); MS (80 eV), *m/z* (%) 523 (3) [M^+], 522 (3) [M^+ – H], 521 (7) [M^+ – 2H], 346 (25), 298 (10), 292 (18), 291 (100), 290 (18), 276 (42) [$M^+ - C_{14}H_{15}O_4$], 275 (15), 114 (12), 112 (10), 105 (13) [C_6H_5CO], 86 (14), 82 (15), 58 (13), 43 (14), 42 (11).

Anal. Calcd for $C_{30}H_{35}NO_7$, 521.2415. Found: 521.2414 (HRMS).

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