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Stereocontrolled formation of highly substituted *cis*-decalins via INOC annulation. An access to the branimycin core

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Abstract—Quinic acid was used as a chiral scaffold for elaborating the highly substituted *cis*-decalin core system of branimycin via an Eschenmoser–Ireland rearrangement-INOC annulation sequence.

1. Introduction

Branimycin, an unusual member of the nargenicin antibiotic family,[1] was isolated from *Streptomyces* and structurally characterised by the Laatsch group.[2] Preliminary biological tests have shown that branimycin is highly active against *Streptomyces viridochromogenes*. The structure of branimycin has been reliably elucidated by multidimensional ^{1}H and ^{13}C NMR experiments. The interesting biological activity, combined with the complex highly oxygenated *cis*-fused decaline core, the 1,4-oxygen bridge and the macrolide ring present is of considerable challenge for total synthesis.

The retrosynthetic concept is shown in Figure 1. As a key disconnection the 1,2-addition of vinyllithium subunit **B**[3] to bicyclic ketone **A**[4,5] was envisaged. This highly convergent approach necessitates efficient synthesis of both **A** and **B**.

2. Results and discussion

Encouraged by recent model studies,[4] we concentrated on the fully substituted core compound **A**. Our retrosynthetic plan based on using an intramolecular nitrile oxide olefin cyclisations (INOC reaction),[6] a useful method for the construction of *cis*-decalin system, in intermediate **A2**, which after Claisen rearrangement following reductive cleavage of the N–O bond could give β-hydroxy compound **A1**. Accordingly, intermediate **A2** was identified as a key synthetic target. Antithetic disconnection leads to nitrile oxide **A3** an expected product from *cis*-unsaturated aldehyde **A4**. In turn, aldehyde **A4** would be assembled in stereoselective fashion from known ketone **2**, readily available from (−)-quinic acid.[7]

For a successful synthesis two key obstacles had to be overcome. Firstly, it had turned out that ketone **2** is resistant towards direct alkylation via its lithium enolate,[7] so the introduction of the methylene-methoxy side chain was a critical point in our synthesis. Secondly, it was not clear whether we could convert aldehyde **A4** to the corresponding oxime without isomerisation of the *cis* double bond.

We started with the conversion of ketone **2** into the silyl-enol ether **3**[7] (Scheme 1). The high reactivity of **3** towards suitable electrophiles (NBS, *m*-CPBA)[7] prompted us to try introduction of the methylene-methoxy group under Mukaiyama conditions.[8] After intensive investigation we found, that compound **3** reacts with dimethoxy-ethane in the presence of 5 mol % TMSOTf[9] to give **4** as a single diastereomer in 55% yield (73% after recycling of the starting material). The relative stereochemistry of **4** was assigned on the basis of the small ^{3}J coupling constant of 3.9 Hz between H-5 (known axial orientation due to the bis-ketal protecting group) and H-6 and was secured by NOE experiments. Attempts to improve the yield by longer reaction times resulted in epimerisation of **4**. Reduction of **4** gave alcohol **1** stereoselectively, which was esterified with $BnOCH_2COOH$ under Mitsunobu conditions to give the protected glycolate ester **5** in 93% yield. In the next step chelation-controlled glycolate enolate Claisen rearrangement[10] led to acid **6** as a single isomer in 91% yield. (The stereochemistry of **6** was confirmed by transformation of the corresponding Bn protected acid to lactone **6a** and NOE experiments). Formation of the methyl ester followed by DIBAH reduction afforded aldehyde **7**, which was subjected to Still–Gennari olefination. The resulting (*Z*)-α,β-enoate was reduced to the alcohol and reoxidised to aldehyde **8** in 76% yield.

Keywords: Branimycin; Natural products; Total synthesis; INOC reaction.
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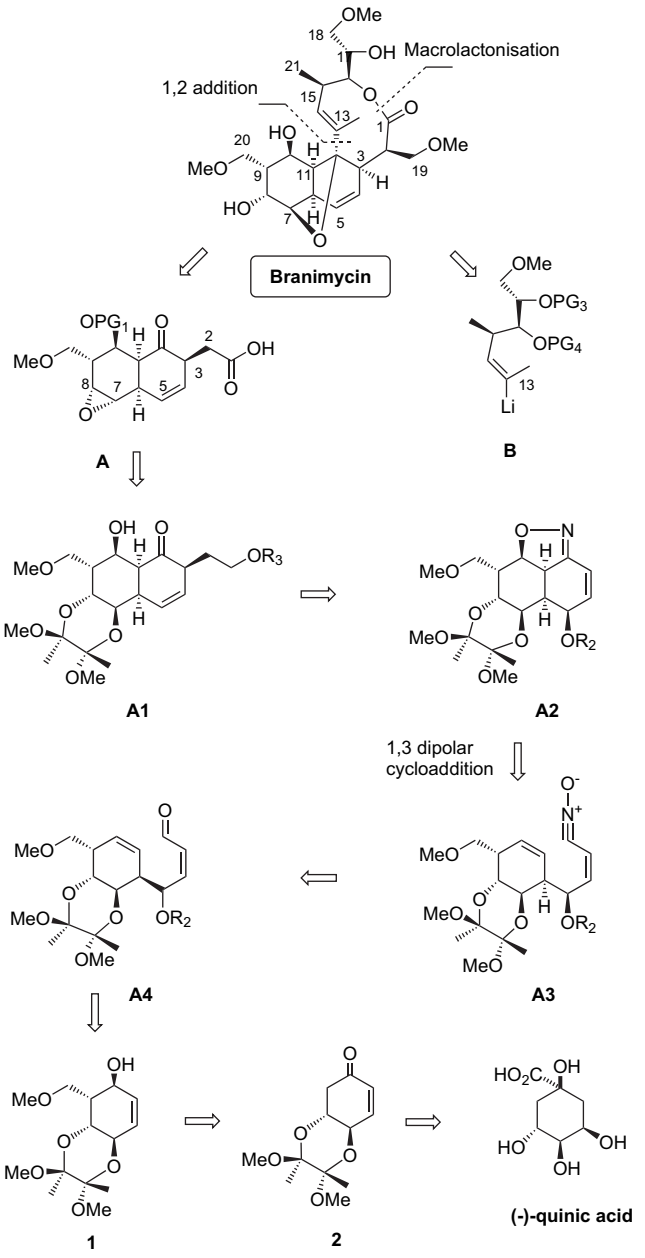
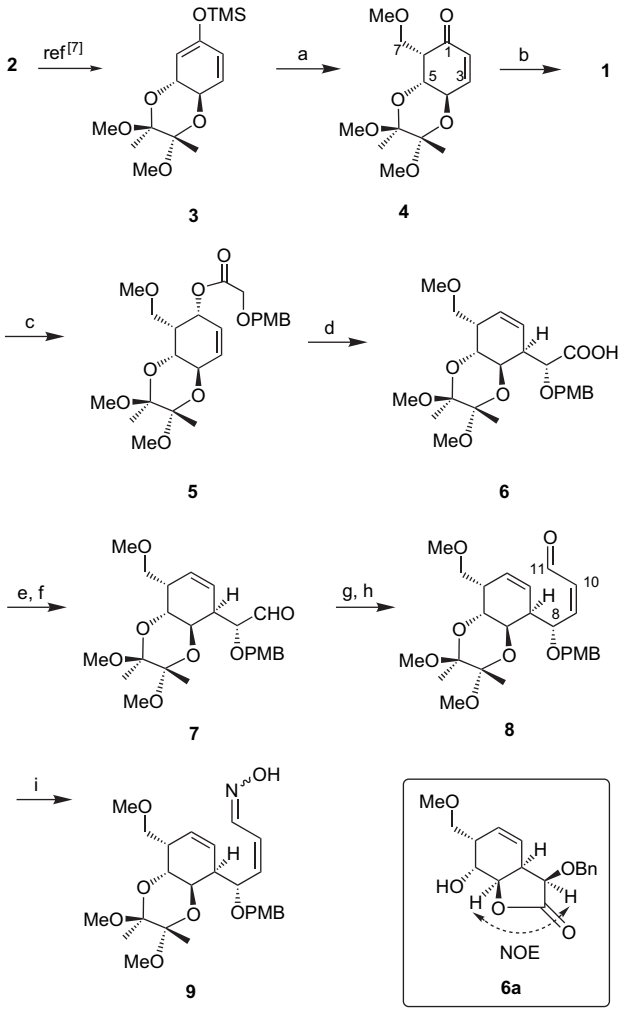


Figure 1.



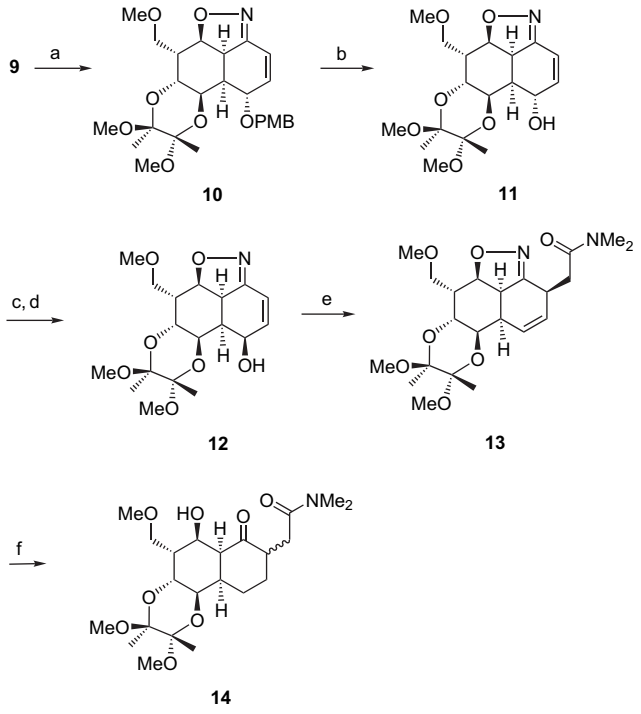
Scheme 1. (a) $CH_2(OMe)_2$, TMSOTf, 2,6-di-*tert*-butyl-pyridine, 55%; (b) $NaBH_4/CeCl_3$, quant; (c) PPh_3, DEAD, $PMBOCH_2COOH$, THF/CH_2Cl_2, 0 °C, 24 h, 93%; (d) LiHMDS/TMSCl, THF, −78 to 0 °C, 91%; (e) $TMSCHN_2$, Tol/MeOH; (f) DIBAH, CH_2Cl_2, −78 °C, 3.5 h, 80%; (g) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, Crown-6, THF, −78 °C, 88%; (h) i. DIBAH, ii. DMP/$NaHCO_3$, 86% and (i) $NH_2OH\cdot HCl$, 2,6-di-*tert*-butyl-pyridine, MS 4 Å, 60%.

The next problem was the conversion of **8** to the oxime without isomerisation of the double bond. After testing a variety of conditions we found that hydroxylamine hydrochloride in the presence of molecular sieves (4 Å) and 3 equiv of polymer-supported 2,6-di-*tert*-butyl-pyridine converted **8** into a separable mixture of 60% *cis*-α,β-unsaturated oxime **9** and 5% of the *trans*-isomer. Aldehyde recovered unchanged was 20%.

The stage was now set for the construction of bicyclic system **A2** (Scheme 2). The INOC reaction was initiated by heating oxime **9** with 1.1 equiv NCS and a catalytic amount of pyridine.[11] The resulting nitrile oxide immediately formed isoxazoline **10** in 92% yield. The configuration of **10** was secured by NOE experiments. Removal of the PMB group furnished alcohol **11**, which was oxidised to the ketone and reduced with $NaBH_4$ to give alcohol **12**. For the completion of the **A1** skeleton, alcohol **12** was subjected to a Claisen–Eschenmoser rearrangement to give amide **13** in 82% yield.

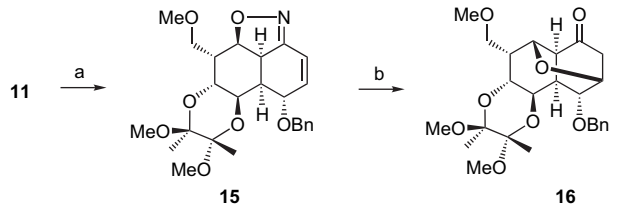
With intermediate **13** in hand, the reductive cleavage of the isoxazoline ring to the corresponding β-hydroxy compound was attempted. Unfortunately, exposure of **13** to hydrogen in the presence of Raney-Ni and boronic acid[12] resulted in hydrogenation of the double bond and epimerisation at C-3 to furnish compound **14** as an inseparable diastereomeric mixture. This highly undesirable result was interpreted via an imine–enamine tautomerisation[13] followed by reduction (Scheme 3).

Several conditions were investigated to suppress the formation of the enamine such as variation of the catalysts (Pd/C,[14] $Rh/CaCO_3$, Lindlar catalyst[15] and SmI_2[16]) and Lewis and Brønsted acids ($AlCl_3$,[12] $BF_3\cdot Et_2O$, 1 N HCl), however without success.

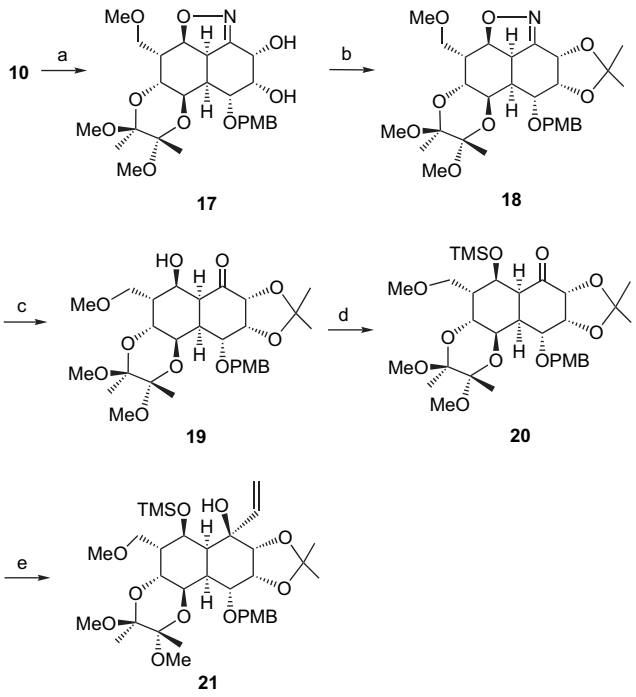


Scheme 2. (a) NCS, pyridine, $CHCl_3$, 60 °C, 92%; (b) DDQ, CH_2Cl_2, 77%; (c) DMP, 89%; (d) $NaBH_4$, $CeCl_3$, 96%; (e) $Me_2NCH(OMe)_2$, MS 4 Å, xylene, 155 °C, 82% and (f) H_2, Raney-Ni, H_3BO_3.

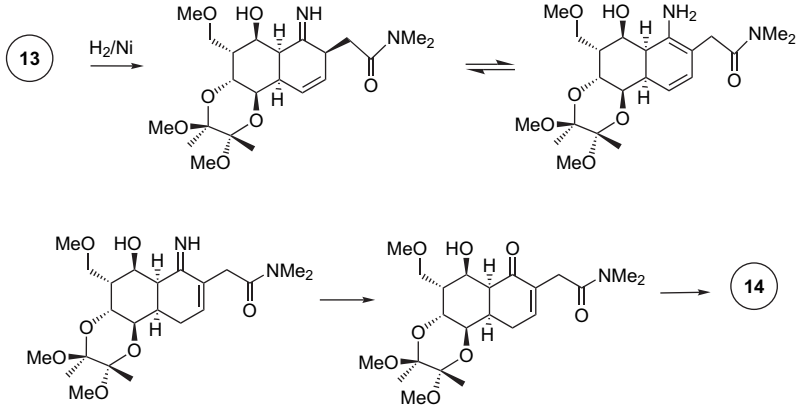
At this point, we decided to step back and to perform the Claisen–Eschenmoser rearrangement after the cleavage of N–O bond of isoxazoline ring. Accordingly, alcohol **11** was benzylated and the resulting benzyl ether **15**[17] was treated with $Mo(CO)_6$ in refluxing acetonitrile.[18] Unfortunately, the formation of the desired α,β-enone was immediately followed by an intramolecular Michael addition to afford the cyclic ether **16** in an 82% yield (Scheme 4).



Scheme 4. (a) BnBr, NaH, THF/DMF, 87% and (b) $Mo(CO)_6$, $MeCN/H_2O$, reflux, 82%.



Scheme 5. (a) 2 equiv OsO_4, pyridine, −25 °C, 86%; (b) $Me_2C(OMe)_2$, PTS, 48 h, 97%; (c) H_2, Raney-Ni, H_3BO_3, 0.5 h, 90%; (d) TMSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 56% and (e) vinylmagnesium bromide, THF, −78 °C, 72%.



Scheme 3. Presumptive formation of **14**.

To suppress the formation of **16**, the double bond in **10** was converted into diol[19] **17** stereoselectively, which was protected as acetonide **18**. Now, the cleavage of the isoxazoline proceeded smoothly to give β-hydroxy ketone **19** in 92% yield. Protection as TMS ether **20** and addition of vinylmagnesium bromide furnished adduct **21** (72%) with high stereoselectivity (Scheme 5).

In conclusion, we have shown that quinic acid may be used as a chiral scaffold for elaborating the highly substituted

cis-decalin core system of branimycin via an Eschenmoser–Ireland rearrangement-INOC annulation sequence. All reactions proceed with high stereo- and regiocontrol in reasonable yields. Work towards the completion of the synthesis is well underway in our labs.

3. Experimental section

3.1. General

Reactions were conducted in flame-dried or oven-dried glassware under an atmosphere of dry argon. All solvents used in reactions were purified before use. Diethyl ether and 1,2-dimethoxyethane were distilled from $LiAlH_4$. Tetrahydrofuran was distilled from molten potassium metal. Dichloromethane (DCM) and pyridine were distilled from CaH_2. Toluene was distilled over molten sodium metal. Commercially available reagents were used without further purification unless otherwise specified. Flash column chromatography was performed with Merck silica gel 60 (230–400 mesh). Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} plates. Compounds were visualised with UV light, and/or ceric ammonium molybdate. Melting points (mp) were measured on a Kofler apparatus and are uncorrected. Infrared spectra were recorded with films on single-crystal silica plates using a Perkin–Elmer FT 1600 spectrometer and are reported in wave numbers (cm^{-1}) with broad signals denoted by (br). NMR spectra were recorded at 300 K on Avance spectrometers (Bruker Biospin GmbH, Rheinstetten, Germany), i.e., DPX 250, DRX 400 WB, or DRX 600. Residual $CHCl_3$ signal was used as an internal reference for ^1H (δ=7.26 ppm), for ^{13}C the $CDCl_3$ carbon was adjusted to 77.00 ppm. ^{13}C NMR spectra were measured *J*-modulated and proton decoupled. The assignment was accomplished by standard 2D NMR techniques (the numbering is according to Scheme 1 or starting from compound **10** to branimycin). The analysis of the coupling constants (*J*, in hertz) was supported by the software SpinWorks (provided by Kirk Marat, University of Manitoba, Canada). Mass spectra (MS) were recorded on a Finnigan (MAT 8230, 9008) machine.

3.1.1. Compound 4. To a solution of **3** (13.0 g, 41.3 mmol) in DCM (80 mL) 2,6-di-*tert*-butyl-pyridine (0.94 mL, 4.2 mmol) and dimethoxymethane (6.3 g, 82.9 mmol) were added and the reaction mixture was cooled to 0 °C. TMSOTf (0.756 mL, 4.2 mmol) was added dropwise, the reaction was stirred for 2 h at 0 °C and quenched with a saturated $NaHCO_3$ solution. The phases were separated and extracted with DCM (3×70 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by HPLC to yield **4** (6.5 g, 55%) as the desired product and 5.2 g of starting material. ^1H NMR (400.13 MHz, $CDCl_3$): δ=6.81 (1H, H(3), dd, *J*=10.1, 1.8), 5.99 (1H, H(2), ddd, *J*=10.2, 2.6, 0.7), 4.88 (1H, H(4), ddd, *J*=9.4, 2.6, 1.7), 4.16 (1H, H(5), dd, *J*=9.4, 6.4), 3.87 (1H, H(7), dd, *J*=9.2, 3.9), 3.76 (1H, H(7), dd, *J*=9.2, 3.9), 3.29 (3H, CH_3O(4), s), 3.28 (3H, CH_3O(7), s), 3.23 (3H, CH_3O(5), s), 2.71 (1H, H(6), dddd, *J*=6.4, 3.9, 3.9, 0.7), 1.34 (3H, CH_3, s), 1.32 (3H, CH_3, s); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=198.79 (s), 148.53 (d), 129.85 (d), 100.66 (s), 99.92 (s), 69.32 (d), 69.09 (t), 66.07 (d), 59.16 (q), 50.23 (d), 47.98 (q), 47.94 (q), 17.76 (q), 17.59 (q); IR (Si, film) ν_{max}=3346, 2950, 2833, 1683, 1619, 1455, 1110, 1012, 931, 901, 611, 571; MS (EI, 70 eV, 40 °C): *m*/*z*=255, 218, 197, 176, 154, 138, 123, 101, 73, 55; HRMS (EI, 70 eV, 60 °C) calcd for $C_{13}H_{19}O_5$ (M^+−MeOH): 255.1232, found: 255.1236.

3.1.2. Compound 1. A solution of ketone **4** (3 g, 10.5 mmol) in MeOH (50 mL) was cooled to 0 °C, $CeCl_3$ (0.47 g, 1.3 mmol) was added and the solution was stirred for 15 min. $NaBH_4$ (0.47 g, 12.5 mmol) was added in three portions and after 15 min the reaction was quenched with NH_4Cl. The solvent was removed under reduced pressure and the residue was hydrolysed with H_2O (20 mL) and EtOAc (100 mL). The two phases were separated and the aqueous phase was extracted with EtOAc (2×25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give **1** (3.1 g, 100%) as a colourless oil. ^1H NMR (400.13 MHz, $CDCl_3$): δ=5.71 (1H, H(2), dddd, *J*=10.3, 2.5, 2.3, 1.2), 5.54 (1H, H(3), ddd, *J*=10.2, 2.3, 1.8), 4.57 (1H, H(1), m, *J*=5.6, 5.2, 2.9, 2.3, 2.3), 4.12 (1H, H(4), m, *J*=9.0, 2.9, 2.5, 1.8, 0.5), 3.84 (1H, OH, d, *J*=5.2), 3.78 (1H, H(5), dd, *J*=9.0, 2.8), 3.77 (1H, H(7), dd, *J*=9.3, 3.9), 3.63 (1H, H(7), dd, *J*=9.3, 9.1), 3.35 (3H, CH_3O(7), s), 3.23 (3H, CH_3O(4), s), 3.21 (3H, CH_3O(5), s), 2.57 (1H, H(6), m, *J*=9.1, 5.6, 3.9, 2.8, 1.3, 0.5), 1.28 (3H, CH_3, s), 1.27 (3H, CH_3, s); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=132.63 (d), 125.01 (d), 100.33 (s), 100.27 (s), 70.45 (d), 68.93 (t), 68.45 (d), 65.73 (d), 58.93 (q), 47.81 (q), 47.76 (q), 42.08 (d), 17.81 (q), 17.66 (q); IR (Si, film) ν_{max}=3476, 2992, 2949, 2900, 2833, 1456, 1376, 1130, 1042, 933; MS (EI, 70 eV, 60 °C): *m*/*z*=257, 225, 156, 140, 101, 78, 55. HRMS (EI, 70 eV, 60 °C) calcd for $C_{13}H_{21}O_5$ (M^+−MeOH): 257.1389, found: 257.1384.

3.1.3. Compound 5. A solution of the alcohol **1** (2.6 g, 9.0 mmol) in THF (70 mL) and DCM (70 mL) was cooled to 0 °C. Ph_3P (8.2 g, 31.3 mmol) and 5 min later *p*-methoxybenzyloxy acetic acid (2.8 g, 14.3 mmol) were added. After additional 5 min, DEAD (7.2 mL, 45 mmol) was added dropwise and the reaction mixture was stirred for 30 min at 0 °C. Then the solution was stored in the refrigerator at +4 °C for 24 h. The reaction mixture was diluted with toluene (80 mL) and concentrated under reduced pressure. The crude product was purified by column chromatography to yield **5** (3.9 g, 93%). ^1H NMR (400.13 MHz, $CDCl_3$): δ=7.28 (2H, H(ar), d, *J*=8.6), 6.87 (2H, H(ar), d, *J*=8.6), 5.86–5.78 (2H, H(2,3), m), 5.50 (1H, H(1), m), 4.55 (2H, OCH_2(ar), s), 4.16 (1H, H(4), m), 4.03 (1H, H(7), dd, *J*=9.7, 4.7), 4.02 (1H, C(O)CH_2, d, *J*=16.5), 4.00 (1H, C(O)CH_2, d, *J*=16.5), 3.80 (3H, CH_3O(ar), s), 3.74 (1H, H(5), dd, *J*=9.4, 3.4), 3.34 (3H, CH_3O(7), s), 3.29 (1H, H(7), dd, *J*=9.7, 9.5), 3.24 (3H, CH_3O, s), 3.21 (3H, CH_3O, s), 2.28 (1H, H(6), m), 1.31 (3H, CH_3, s), 1.28 (3H, CH_3, s); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=169.68 (s), 159.45 (s), 131.83 (d), 129.68 (2×d), 129.18 (s), 124.75 (d), 113.85 (2×d), 100.46 (s), 100.30 (s), 72.87 (t), 70.10 (d), 67.97 (t), 66.80 (t), 66.39 (d), 65.31 (d), 58.94 (q), 55.24 (q), 47.84 (q), 47.77 (q), 42.29 (d), 17.79 (q), 17.73 (q); HRMS (EI, 70 eV, 60 °C) calcd for $C_{24}H_{34}O_9$ (M^+): 466.2203, found: 466.2196.

3.1.4. Compound 6. To a solution of **5** (0.92 g, 1.97 mmol) in THF (47 mL) was added at −78 °C TMSCl (1.18 mL and 3 drops of triethylamine). After 5 min LiHMDS (6.8 mL of 1 M solution in toluene) was added and stirring was continued for 30 min at −78 °C and 2 h at room temperature. The reaction was quenched with water and the pH was adjusted to 3 (HCl concd). The phases were separated and extracted with EtOAc (3×50 mL), and the organic phases were combined and washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was filtered through silica gel to give **6** (0.84 g, 91%). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=~8.3 (CO_2H, very br), 7.23 (2H, H(ar), d, J=8.8), 6.87 (2H, H(ar), d, J=8.8), 5.97 (1H, H(1), ddd, J=10.0, 5.2, 1.7), 5.64 (1H, H(2), ddd, J=10.0, 4.6, 1.2), 4.55 (1H, OCH_2(ar), d, J=10.6), 4.52 (1H, OCH_2(ar), d, J=10.6), 4.48 (1H, H(5), dd, J=11.3, 6.8), 4.10 (1H, H(4), dd, J=11.3, 7.3), 4.04 (1H, H(8), d, J=2.1), 3.80 (3H, CH_3O(ar), s), 3.74 (1H, H(7), dd, J=8.9, 4.1), 3.38 (1H, H(7), dd, J=8.9, 8.4), 3.35 (3H, CH_3O(7), s), 3.18 (1H, H(3), m), 3.18 (3H, CH_3O, s), 2.96 (3H, CH_3O, s), 2.62 (1H, H(6), m), 1.21 (3H, CH_3, s), 1.20 (3H, CH_3, s); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=172.58 (s), 159.74 (s), 131.41 (d), 129.78 (2×d), 128.69 (s), 125.94 (d), 113.93 (2×d), 99.35 (s), 99.29 (s), 78.75 (d), 74.43 (t), 72.29 (t), 65.68 (d), 65.39 (d), 59.04 (q), 55.30 (q), 48.00 (q), 47.39 (q), 42.19 (d), 39.25 (d), 17.54 (q), 17.09 (q).

3.1.5. Compound 6a. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=7.42–7.29 (5H, H(ar), m), 5.79 (1H, H(2), dddd, J=10.4, 2.9, 2.9, 1.0), 5.72 (1H, H(1), dddd, J=10.4, 1.7, 1.7, 1.6), 4.97 (1H, OCH_2(ar), d, J=12.2), 4.80 (1H, OCH_2(ar), d, J=12.2), 4.53 (1H, H(4), ddd, J=4.8, 4.8, 1.0), 4.39 (1H, H(5), ddd, J=4.8, 4.3, 1.6), 4.33 (1H, H(8), d, J=7.8), 3.77 (1H, H(7), dd, J=9.5, 3.4), 3.73 (1H, H(7), dd, J=9.5, 4.7), 3.54 (1H, OH, br s), 3.39 (3H, CH_3O, s), 3.28 (1H, H(3), m, J=7.8, 4.8, 3.0, 2.9, 1.6), 2.56 (1H, H(6), m, J=4.7, 4.3, 3.4, 3.0, 2.9, 1.7); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=174.13 (s), 136.80 (s), 128.59 (2×d), 128.19 (d), 128.02 (2×d), 127.65 (d), 122.16 (d), 75.08 (d), 74.98 (d), 74.56 (t), 72.67 (t), 67.51 (d), 59.41 (q), 36.64 (d), 35.36 (d).

3.1.6. Compound 7. A mixture of **6** (0.66 g, 1.4 mmol) in toluene/methanol, 5:1 (10 mL) and trimethylsilyldiazomethane (1 mL, 2 M solution) was stirred at room temperature until the starting material was consumed. The solvent was removed under reduced pressure and the methyl ester (0.67 g, 99%) was used without further purification. ^{1}H NMR (600.13 MHz, $CDCl_3$): δ=7.30 (2H, H(ar), d, J=8.8), 6.84 (2H, H(ar), d, J=8.8), 5.85 (1H, H(1), ddd, J=10.0, 5.0, 1.5), 5.54 (1H, H(2), ddd, J=10.0, 4.9, 1.0), 4.68 (1H, OCH_2(ar), d, J=11.2), 4.39 (1H, OCH_2(ar), d, J=11.2), 4.31 (1H, H(5), dd, J=11.2, 6.9), 4.11 (1H, H(8), d, J=3.0), 4.06 (1H, (H4), dd, J=11.2, 7.1), 3.80 (3H, CH_3O(ar), s), 3.74 (1H, H(7), dd, J=8.9, 4.2), 3.70 (3H, CO_2CH_3, s), 3.37 (1H, H(7), dd, J=8.9, 8.9), 3.34 (3H, CH_3O(7), s), 3.19 (3H, CH_3O, s), 3.15 (3H, CH_3O, s), 3.09 (1H, H(3), m), 2.58 (1H, H(6), m), 1.23 (3H, CH_3, s), 1.22 (3H, CH_3, s); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=172.53 (s), 159.06 (s), 130.48 (d), 130.45 (s), 129.27 (2×d), 125.63 (d), 113.50 (2×d), 99.09 (s), 98.97 (s), 77.78 (d), 72.68 (t), 72.59 (t), 65.75 (d), 65.50 (d), 59.01 (q), 55.27 (q), 51.34 (q), 47.68 (q), 47.57 (q), 43.01 (d), 39.28 (d), 17.76 (q), 17.57 (q); IR (Si, film) ν_{max}=2948, 1751, 1613, 1586, 1514, 1463, 1374, 1174, 1220, 1174, 1038, 884 cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity): 465 (M^+-CH_3OH, 0.3), 347 (0.6), 312 (1.5), 282 (1.5), 121 (100); HRMS (EI, 70 eV, 60 °C) calcd for $C_{24}H_{33}O_9$ (M^+-CH_3): 465.2125, found: 465.2133.

DIBAH (1.4 mL, 1.5 M solution) was added dropwise to a solution of the ester (0.66 g, 1.4 mmol) in DCM (16 mL) at −78 °C. After 3.5 h at −78 °C the reaction was quenched with methanol (1 mL) and a saturated solution of aqueous sodium-potassium tartarate (50 mL) was added. The mixture was stirred overnight at room temperature. The phases were separated and the aqueous phase was extracted with DCM (3×30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography to give aldehyde **7** (0.50 g, 80%) and unreacted ester (0.12 g, 18%). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=9.72 (1H, H(9), d, J=1.2), 7.29 (2H, H(ar), d, J=8.8), 6.86 (2H, H(ar), d, J=8.8), 5.92 (1H, H(1), ddd, J=10.0, 5.2, 1.8), 5.58 (1H, H(2), ddd, J=10.0, 4.6, 1.2), 4.59 (1H, OCH_2(ar), d, J=11.5), 4.53 (1H, OCH_2(ar), d, J=11.5), 4.48 (1H, H(5), dd, J=11.2, 6.9), 4.03 (1H, H(4), dd, J=11.2, 7.4), 3.80 (3H, CH_3O(ar), s), 3.78 (1H, H(8), dd, J=2.5, 1.2), 3.74 (1H, H(7), dd, J=9.0, 4.2), 3.37 (1H, H(7), dd, J=8.9, 8.8), 3.43 (3H, CH_3O(7), s), 3.14 (3H, CH_3O, s), 3.12 (3H, CH_3O, s), 3.06 (1H, H(3), m), 2.61 (1H, H(6), m), 1.23 (6H, 2×CH_3, s); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=204.36 (d), 159.22 (s), 130.90 (d), 130.06 (s), 129.01 (2×d), 125.91 (d), 113.67 (2×d), 99.53 (s), 99.14 (s), 84.15 (d), 73.30 (t), 72.51 (t), 65.82 (d), 65.67 (d), 59.03 (q), 55.28 (q), 47.84 (q), 47.53 (q), 44.88 (d), 39.22 (d), 17.73 (q), 17.66 (q); IR (Si, film) ν_{max}=2926, 2833, 1730, 1613, 1586, 1515, 1463, 1375, 1195, 1137, 1082, 963, 886 cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity): 418 (M^+-CH_3OH, 1), 309 (0.5), 282 (1.5), 121 (100); HRMS (EI, 70 eV, 60 °C) calcd for $C_{23}H_{30}O_7$ (M^+-CH_3OH): 418.1991, found: 418.1998.

3.1.7. Compound 8. A solution of *O*,*O*′-bis-(2,2,2-trifluoroethyl)-(methyoxy-carbonylmethyl)-phosphonate (0.21 mL, 0.98 mmol), 18-crown-6-ether (1.55 g, 5.9 mmol) and KHMDS (2 mL, 0.5 M solution) in THF (11 mL) was stirred at −78 °C for 75 min. The reaction mixture was cooled to −90 °C and a solution of **7** (2.18 g, 4.84 mmol) in THF (10 mL) was added dropwise. After 3 h at −90 °C and 3 h at −80 °C the reaction was quenched with saturated NH_4Cl solution and warmed to room temperature. The phases were separated and the aqueous phase was extracted with diethyl ether (3×30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel to obtain the (*Z*)-enoate (2.15 g, 88%). ^{1}H NMR (600.13 MHz, $CDCl_3$): δ=7.26 (2H, H(ar), d, J=8.6), 6.84 (2H, H(ar), d, J=8.6), 6.26 (1H, H(9), dd, J=11.7, 9.8), 5.89 (1H, H(10), dd, J=11.7, 1.0), 5.88 (1H, H(1), ddd, J=10.1, 5.0, 1.4), 5.79 (1H, H(2), ddd, J=10.1, 4.7, 1.0), 5.54 (1H, H(8), ddd, J=9.8, 3.7, 1.0), 4.45 (1H, OCH_2(ar), d, J=11.3), 4.44 (1H, OCH_2(ar), d, J=11.3), 4.13 (1H, H(5), dd, J=11.5, 6.7), 4.02 (1H, H(4), dd, J=11.5, 7.2), 3.79 (3H, CH_3O(ar), s), 3.74 (1H, H(7), dd, J=8.9, 4.2), 3.71 (3H, CO_2CH_3, s), 3.36 (1H, H(7), dd, J=8.9, 8.9), 3.34, (3H, CH_3O(7), s), 3.21 (3H, CH_3O(4), s), 3.12 (3H, CH_3O(5), s), 2.99 (1H,

H(3), m), 2.58 (1H, H(6), m), 1.213 (3H, CH_3, s), 1.12 (3H, CH_3, s); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=166.09 (s), 158.89 (s), 148.14 (d), 131.42 (s), 129.75 (d), 128.97 (2×d), 125.76 (d), 120.81 (d), 113.55 (2×d), 98.94 (s), 98.84 (s), 73.36 (d), 72.76 (t), 70.67 (t), 65.54 (d), 65.50 (d), 59.01 (q), 55.26 (q), 51.00 (q), 47.74 (q), 47.23 (q), 44.64 (d), 39.52 (d), 17.64 (q), 17.63 (q); IR (Si, film) ν_{max}=2948, 1731, 1613, 1514, 1434, 1374, 1174, 1123, 1039, 823 cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity): 474 (M^+-CH_3OH, 0.4), 443 (0.2), 360 (0.5), 338 (5), 121 (100); HRMS (EI, 70 eV, 60 °C) calcd for $C_{26}H_{34}O_8$ (M^+-CH_3OH): 474.2254, found: 474.2261.

A solution of the (*Z*)-enoate (1.36 g, 2.69 mmol) in DCM (30 mL) was cooled to −78 °C and DIBAH (6.2 mL of 1 M solution) was added dropwise. After 5 h the reaction was quenched with methanol, diluted with saturated aqueous potassium-sodium tartarate solution and stirred overnight at room temperature. The phases were separated and the aqueous phase was extracted with DCM (3×30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give the alcohol (1.29 g, quant). The crude product was used without further purification. ^1H NMR (250 MHz, $CDCl_3$): δ=7.22 (2H, d, *J*=8.6), 6.85 (2H, d, *J*=8.6), 5.92 (1H, dd, *J*=10.5, 4.4), 5.89 (1H, dd, *J*=10.8, 3.8), 5.86 (1H, *J*=10.5, 3.4), 5.43 (1H, dd, *J*=10.8, 1.1), 4.67 (1H, dd, *J*=10.6, 4.0), 4.42 (1H, t, *J*=11.4), 4.40 (1H, d, *J*=11.4), 4.21 (1H, d, *J*=11.4), 4.14 (1H, dd, *J*=11.6, 7.6), 4.06 (1H, dd, *J*=11.6, 6.7), 3.86 (1H, m), 3.79 (3H, s), 3.71 (1H, dd, *J*=8.9, 4.1), 3.44 (1H, dd, *J*=11.0, 2.1), 3.37 (1H, t, *J*=8.7), 3.34 (3H, s), 3.22 (3H, s), 3.20 (3H, s), 2.51 (1H, m), 1.27 (3H, s), 1.25 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=159.38, 133.88, 131.36, 130.12, 129.60, 129.34, 125.82, 114.07, 100.11, 99.37, 73.01, 72.16, 69.55, 66.06, 59.41, 58.74, 55.66, 48.10, 47.86, 43.93, 39.84, 30.08, 18.23, 17.81; IR (Si, film) ν_{max}=3475, 2933, 2834, 1612, 1248, 1123, 1036, 845 cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity): 446 (M^+-CH_3OH, 0.3), 415 (0.25), 360 (0.2), 121 (100); HRMS (EI, 70 eV, 60 °C) calcd for $C_{25}H_{34}O_7$ (M^+-CH_3OH): 446.2305, found: 446.2294.

To a slurry of Dess–Martin periodinane (2.2 g) and $NaHCO_3$ (1.75 g) in DCM (30 mL) a solution of the alcohol (1.926 g, 4.03 mmol) in DCM (67 mL) was added dropwise at room temperature and the mixture was stirred until the starting material was consumed (TLC). The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel to give **8** (1.88 g, 99%). ^1H NMR (400.13 MHz, $CDCl_3$): δ=10.01 (1H, H(11), d, *J*=8.2), 7.22 (2H, H(ar), d, *J*=8.8), 6.87 (2H, H(ar), d, *J*=8.8), 6.46 (1H, H(9), dd, *J*=11.3, 10.4), 6.04 (1H, H(10), ddd, *J*=11.3, 8.2, 0.8), 5.93 (1H, H(1), ddd, *J*=10.2, 5.1, 1.4), 5.87 (1H, H(2), ddd, *J*=10.2, 4.2, 1.0), 5.22 (1H, H(8), dd, *J*=10.4, 3.6), 4.49 (1H, OCH_2(ar), d, *J*=11.3), 4.35 (1H, OCH_2(ar), d, 11.3), 4.13 (1H, H(5), dd, *J*=11.6, 7.5), 3.96 (1H, H(4), dd, *J*=11.6, 6.7), 3.80 (3H, CH_3O(ar), s), 3.71 (1H, H(7), dd, *J*=9.0, 4.1), 3.37 (1H, H(7), dd, *J*=9.0, 8.4), 3.34 (3H, CH_3O(7), s), 3.22 (3H, CH_3O, s), 3.11 (1H, H(3), m), 3.01 (3H, CH_3O, s), 2.55 (1H, H(6), m), 1.22 (3H, CH_3, s), 1.20 (3H, CH_3, s); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=192.18 (s), 159.26 (s), 149.16 (d), 131.95 (d), 130.43 (d), 130.06 (s), 129.18 (2×d), 124.53 (d), 113.83 (2×d), 99.17 (s), 98.95 (s), 72.39 (t), 72.17 (d), 70.39 (t), 65.45 (d), 65.29 (d), 59.01 (q), 55.28 (q), 47.85 (q), 46.88 (q), 44.64 (d), 44.14 (d), 39.56 (d), 17.80, (q), 17.50 (q); IR (Si, film) ν_{max}=2946, 1738, 1680, 1613, 1514, 1373, 885, 822 cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity): 476 (M^+, 0.5), 445 (1), 338 (3), 207 (10), 121 (100), 101 (25); HRMS (EI, 70 eV, 60 °C) calcd for $C_{25}H_{33}O_7$ (M^+-OMe): 445.2226, found: 445.2235.

3.1.8. Compound 9. A mixture of **8** (1.88 g, 3.96 mmol), hydroxylamine hydrochloride (1 g, 15.8 mmol) and 2,6-di-*tert*-butyl-pyridine polymer supported (10.9 g, 19.8 mmol) in THF (200 mL) was stirred at 40 °C for 24 h. After cooling, the mixture was diluted with toluene and filtered through a Celite pad. The solvent was removed under reduced pressure and the residue was purified by column chromatography to obtain **9** (1.22 g, 61%), the *trans*-oxime (0.11 g, 5%) and unreacted **8** (0.36 g, 20%). **9**: ^1H NMR (400.13 MHz, $CDCl_3$): δ=8.15 (1H, H(11), dd, *J*=10.4, 0.9), ~8.1 (1H, OH, br s), 7.23 (2H, H(ar), d, *J*=8.8), 6.87 (2H, H(ar), d, *J*=8.8), 6.26 (1H, H(10), ddd, *J*=11.2, 10.5, 0.8), 5.89 (1H, H(2), dd, *J*=10.4, 4.8), 5.85 (1H, H(1), dd, *J*=10.4, 3.8), 5.75 (1H, H(9), ddd, *J*=11.2, 10.3, 0.9), 4.76 (1H, H(8), dd, *J*=10.3, 3.5), 4.40 (1H, OCH_2(ar), d, *J*=11.2), 4.27 (1H, OCH_2(ar), d, *J*=11.2), 4.07 (1H, H(4), dd, *J*=11.5, 6.8), 4.02 (1H, H(5), dd, *J*=11.5, 6.2), 3.80 (3H, CH_3O(ar), s), 3.72 (1H, H(7), dd, *J*=8.9, 4.1), 3.36 (1H, H(7), dd, *J*=8.9, 8.9), 3.34 (3H, CH_3O(7), s), 3.23 (3H, CH_3O, s), 3.04 (1H, H(3), m), 3.04 (3H, CH_3O, s), 2.55 (1H, H(6), m), 1.29 (3H, CH_3, s), 1.20 (3H, CH_3, s); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=159.05 (s), 149.06 (d), 136.85 (d), 130.65 (s), 129.74 (d), 129.13 (2×d), 125.27 (d), 125.15 (d), 113.72 (2×d), 99.26 (s), 98.73 (s), 73.12 (d), 72.67 (t), 69.86 (t), 65.38 (d), 65.14 (d), 58.98 (q), 55.26 (q), 47.77 (q), 47.66 (q), 44.23 (d), 39.46 (d), 17.66 (q), 17.63 (q); IR (Si, film) ν_{max}=3345, 2947, 1613, 1514, 1463, 1376, 1122, 1040, 797, 733 cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity): 460 (M^+-CH_3O, 3), 385 (2), 323 (10), 121 (100); HRMS (EI, 70 eV, 60 °C) calcd for $C_{25}H_{34}O_7N$ (M^+-CH_3O): 460.2335, found: 460.2327.

3.1.9. Compound 10. A solution of **9** (0.61 g, 1.24 mmol), NCS (0.168 g, 1.26 mmol) and pyridine (72 μL) in chloroform (20 mL) was heated for 10 min at 40 °C and for 1 h at 60 °C. After removing the solvent under reduced pressure water (50 mL) was added and the mixture was extracted with DCM (3×50 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography to give **10** (0.56 g, 92%). ^1H NMR (400.13 MHz, $CDCl_3$): (branimycin numbering) δ=7.26 (2H, H(ar), d, *J*=8.6), 6.87 (2H, H(ar), d, *J*=8.6), 6.60 (1H, H(3), d, *J*=10.0), 6.40 (1H, H(4), dd, *J*=10.0, 5.3), 4.97 (1H, H(10), d, *J*=10.6), 4.56 (1H, OCH_2(ar), d, *J*=11.2), 4.52 (1H, OCH_2(ar), d, *J*=11.2), 4.42 (1H, H(5), dd, *J*=5.3, 1.6), 4.03 (1H, H(7), dd, *J*=10.8, 10.6), 3.89 (1H, H(8), dd, *J*=10.6, 4.5), 3.80 (3H, CH_3O(ar), s), 3.74 (1H, H(11), dd, *J*=10.6, 6.7), 3.53 (1H, H(20), dd, *J*=9.5, 3.9), 3.42 (1H, H(20), dd, *J*=9.5, 6.7), 3.33 (3H, CH_3O(20), s), 3.14 (3H, CH_3O(7), s), 3.09 (3H, CH_3O(8), s), 2.96 (1H, H(6), ddd, *J*=10.8, 6.7, 1.6), 2.14 (1H, H(9), m), 1.17 (3H, CH_3, s), 1.12 (3H, CH_3, s); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=159.38 (s), 156.67 (s), 135.55 (d), 130.33 (s), 129.38 (2×d), 119.56 (d), 113.88 (2×d),

100.33 (s), 99.90 (s), 80.28 (d), 70.95 (t), 69.12 (d), 68.69 (t), 65.99 (d), 65.21 (d), 58.91 (q), 55.29 (q), 47.56 (q), 47.52 (q), 44.10 (d), 42.48 (d), 35.16 (d), 17.66 (q), 17.63 (q); IR (Si, film) ν_{max}=2946, 2055, 1891, 1613, 1585, 1514, 1455, 1376, 1249, 1106, 881 cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity): 489 (M^+, 2.5), 458 (1.5), 358 (1.5), 336 (2.5), 294 (2), 121 (100); HRMS (EI, 70 eV, 60 °C) calcd for $C_{26}H_{35}O_8$ (M^+): 489.2363, found: 489.2358.

3.1.10. Compound 11. A mixture of **10** (0.190 g, 0.39 mmol) and DDQ (0.180 g, 0.78 mmol) in DCM/phosphate buffer pH=7 (20 mL, 1:1) was sonificated in an ultrasound bath for 2 h, diluted with saturated aqueous $NaHCO_3$ and extracted with diethyl ether (3×30 mL). The organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography to give **11** (0.110 g, 77%). ^1H NMR (400.13 MHz, $CDCl_3$): (branimycin numbering) δ=6.58 (1H, H(3), d, *J*=10.0), 6.40 (1H, H(4), dd, *J*=10.0, 4.9), 4.99 (1H, H(10), dd, *J*=10.7, 1.5), 4.72, (1H, H(5), m), 4.12 (1H, H(7), dd, *J*=10.6, 10.4), 3.89 (1H, H(8), dd, *J*=10.6, 5.3), 3.73 (1H, H(11), dd, *J*=10.7, 7.5), 3.56 (1H, H(20), dd, *J*=9.5, 4.2), 3.48 (1H, H(20), dd, *J*=9.5, 6.1), 3.34 (3H, CH_3O(20), s), 3.20 (3H, CH_3O, s), 3.11 (3H, CH_3O, s), 2.89 (1H, H(6), ddd, *J*=10.4, 7.5, 2.7), 2.15 (1H, H(9), m), 1.78 (1H, OH, d, *J*=5.2), 1.20 (3H, CH_3, s), 1.16, (3H, CH_3, s); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=155.12 (s), 137.39 (d), 119.05 (d), 100.21 (s), 99.83 (s), 80.20 (d), 68.80 (t), 65.81 (d), 65.43 (d), 63.51 (d), 58.90 (q), 47.72 (q), 47.64 (q), 43.83 (d), 42.06 (d), 37.86 (d), 17.86 (q), 17.64 (q); IR (Si, film) ν_{max}=3460, 2930, 1420, 1115, 1064, 945, 847 cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity): 369 (M^+, 14), 338 (25), 280 (15), 263 (28), 238 (43), 221 (65), 176 (100), 160 (62), 130 (71), 101 (100); HRMS (EI, 70 eV, 60 °C) calcd for $C_{18}H_{27}O_7N$ (M^+): 369.1788, found: 369.1797.

3.1.11. Compound 12. To a slurry of Dess–Martin periodinane (0.046 g) and $NaHCO_3$ (0.05 g) in DCM (1 mL) a solution of **11** (0.05 g, 0.136 mmol) in DCM (1.8 mL) was added dropwise at room temperature and the mixture was stirred until the starting material was consumed (TLC). The reaction mixture was purified by filtration through silica gel to give the ketone (0.048 g, 97%). ^1H NMR (400.13 MHz, $CDCl_3$): (branimycin numbering) δ=7.35 (1H, H(3), d, *J*=10.1), 6.28 (1H, H(4), dd, *J*=10.1, 0.3), 5.11 (1H, H(10), d, *J*=10.9), 4.22 (1H, H(7), dd, *J*=11.1, 10.3), 4.06 (1H, H(8), dd, *J*=10.3, 4.6), 3.82 (1H, H(11), dd, *J*=10.9, 7.7), 3.55 (1H, H(20), dd, *J*=9.6, 4.6), 3.51 (1H, H(20), dd, *J*=9.6, 4.1), 3.46 (1H, H(6), dd, *J*=11.1, 7.7), 3.33 (3H, CH_3O(20), s), 3.15 (3H, CH_3O, s), 3.13 (3H, CH_3O, s), 2.21 (1H, H(9), ddd, *J*=4.6, 4.6, 4.1), 1.20 (3H, CH_3, s), 1.11 (3H, CH_3, s); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=195.47 (s), 154.18 (s), 133.69 (d), 131.51 (d), 100.44 (s), 100.69 (s), 82.32 (d), 68.60 (t), 66.20 (d), 65.35 (d), 59.02 (q), 47.79 (q), 47.66 (q), 45.36 (d), 44.94 (d), 43.64 (d), 17.57 (q), 17.56 (q); IR (Si, film) ν_{max}=2930, 1717, 1420, 1115, 1064, 947 cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity): 367 (M^+, 25), 336 (12), 280 (27), 236 (33), 219 (31), 174 (100), 158 (29), 129 (33), 101 (82); HRMS (EI, 70 eV, 60 °C) calcd for $C_{18}H_{25}O_7N$ (M^+): 367.1631, found: 369.1638.

A mixture of the ketone (0.48 g, 1.30 mmol), $CeCl_3\cdot 7H_2O$ (0.06 g) and $NaBH_4$ (0.06 g) was stirred in MeOH (19 mL) at 0 °C for 30 min. The reaction was diluted with saturated aqueous NH_4Cl (10 mL), EtOAc (10 mL) and saturated aqueous NaCl (5 drops). The phases were separated and extracted with EtOAc (3×10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by flash chromatography to give alcohol **12** (0.48 g, 99%), white crystals, mp=134.0–134.2 °C (from hexane). ^1H NMR (400.13 MHz, $CDCl_3$): (branimycin numbering) δ=6.39 (1H, H(3), dd, *J*=10.2, 2.6), 6.33, (1H, H(4), ddd, *J*=10.2, 1.8, 0.8), 4.95 (1H, H(10), d, *J*=10.2), 4.67 (1H, H(5), m), 4.29 (1H, H(7), dd, *J*=10.5, 10.3), 4.28 (1H, OH, d, *J*=11.8), 4.18 (1H, H(8), dd, *J*=10.5, 4.7), 3.51 (1H, H(11), dd, *J*=10.2, 6.0), 3.505 (1H, H(20), dd, *J*=9.5, 4.2), 3.48 (1H, H(20), dd, *J*=9.5, 5.2), 3.33 (3H, CH_3O(20), s), 3.23 (3H, CH_3O(7), s), 3.20 (1H, H(6), m), 3.13 (3H, CH_3O(8), s), 2.13 (1H, H(9), ddd, *J*=5.2, 4.7, 4.2), 1.24 (3H, CH_3, s), 1.21 (3H, CH_3, s); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=155.82 (s), 144.01 (d), 115.76 (d), 101.08 (s), 100.19 (s), 80.05 (d), 70.76 (d), 68.71 (t), 68.13 (d), 66.67 (d), 58.94 (q), 48.21 (q), 47.71 (q), 46.97 (d), 44.04 (d), 36.04 (d), 17.81 (q), 17.70 (q); IR (Si, film) ν_{max}=3460, 2930, 1415, 1114, 1064, 947, 847 cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity): 369 (M^+, 10), 338 (12), 280 (16), 238 (17), 221 (100), 176 (87), 160 (45), 130 (41), 101 (80); HRMS (EI, 70 eV, 60 °C) calcd for $C_{18}H_{27}O_7N$ (M^+): 369.1788, found: 369.1781.

3.1.12. Eschenmoser rearrangement to 13. A mixture of **12** (0.28 g, 0.75 mmol) MS (0.1 g, 4 Å) and $Me_2NH(OMe)_2$ (1 g, 9 mmol) in toluene was heated for 1 h at 110 °C under argon in a sealed tube. The mixture was cooled to room temperature and an additional portion of $Me_2NH(OMe)_2$ (0.2 g) was added and the mixture was heated for 5 h at 155 °C under argon. During the additional 5 h of heating a further two portions of reagent (0.2 g) were added. The mixture was filtered through Celite and the residue was washed with EtOAc (15×2 mL). The solvent was removed under reduced pressure. The crude product was purified by flash chromatography to give **13** (0.27 g, 82%), as white crystals, mp 122.1–122.9 °C (from hexane). ^1H NMR (600.13 MHz, $CDCl_3$): (branimycin numbering) δ=5.92 (1H, H(5), ddd, *J*=10.1, 4.1, 2.9), 5.80 (1H, H(4), ddd, *J*=10.1, 2.3, 2.3), 4.86 (1H, H(10), dd, *J*=11.3, 3.5), 4.01 (1H, H(7), dd, *J*=11.0, 9.1), 3.76 (1H, H(3), m), 3.755 (1H, H(8), dd, *J*=11.0, 6.2), 3.64 (1H, H(11), ddd, *J*=11.5, 10.3, 1.6), 3.61 (1H, H(20), dd, *J*=9.4, 5.1), 3.54 (1H, H(20), dd, *J*=9.4, 5.2), 3.33 (3H, CH_3O(20), s), 3.22 (3H, CH_3O(7), s), 3.19 (1H, H(6), m), 3.16 (3H, CH_3O(8), s), 3.05 (1H, H(2), dd, *J*=16.2, 5.4), 3.03 (3H, CH_3N, s), 2.98 (3H, CH_3N, s), 2.47 (1H, H(2), dd, *J*=16.2, 8.4), 2.19 (1H, H(9), dddd, *J*=6.2, 5.2, 5.1, 3.5), 1.23 (3H, CH_3, s), 1.22 (3H, CH_3, s); ^{13}C NMR (chemical shifts from 2D HSQC spectrum, no quarternary carbons) (150.90 MHz, $CDCl_3$): δ=129.4 (d), 126.4 (d), 80.1 (d), 69.5 (t), 66.4 (d), 65.3 (d), 59.1 (q), 48.1 (q), 48.0 (q), 46.6 (d), 42.8 (d), 37.7 (q), 35.9 (q), 35.6 (t), 35.6 (d), 32.8 (d), 18.1 (2×q); IR (Si, film) ν_{max}=2946, 1735, 1650, 1459, 1112, 885, 849 cm^{-1}; HRMS (EI, 70 eV, 60 °C) calcd for $C_{22}H_{34}O_7N_2$ (M^+): 438.2366, found: 438.2370.

3.1.13. Compound 15. To a slurry of NaH (0.016 g, 60%, 0.41 mmol) in THF/DMF, 1:1 (8 mL) was added at 0 °C a solution of **11** (0.1 g, 0.27 mmol) in THF (1.5 mL) and the mixture was stirred for 1 h. Then BnBr (0.06 mL, 2 equiv)

was added and the mixture was stirred for 16 h at room temperature. The reaction was quenched with saturated $NaHCO_3$ solution. The mixture was diluted with toluene (10 mL) and H_2O (5 mL), the organic layer was separated and the aqueous phase was extracted with toluene (2×5 mL). The combined organic layers were washed with brine and the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel to give **15** (0.11 g, 87%). ^{1}H NMR (400.13 MHz, $CDCl_3$): (branimycin numbering) δ=7.40–7.27 (5H, H(ar), m), 6.62 (1H, H(3), d, J=10.0), 6.42 (1H, H(4), dd, J=10.0, 5.2), 4.98 (1H, H(10), d, J=10.7), 4.64 (1H, OCH_2(ar), d, J=11.6), 4.59 (1H, OCH_2(ar), d, J=11.6), 4.43 (1H, H(5), dd, J=5.2, 1.7), 4.04 (1H, H(7), dd, J=10.7, 10.4), 3.89 (1H, H(8), dd, J=10.4, 4.7), 3.76 (1H, H(11), dd, J=10.7, 6.7), 3.53 (1H, H(20), dd, J=9.5, 3.9), 3.43 (1H, H(20), dd, J=9.5, 6.7), 3.33 (3H, CH_3O(20), s), 3.13 (3H, CH_3O(7), s), 3.09 (3H, CH_3O(8), s), 2.99 (1H, H(6), ddd, J=10.7, 6.7, 1.7), 2.14 (1H, H(9), m), 1.18 (3H, CH_3, s), 1.12 (3H, CH_3, s); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=155.64 (s), 138.24 (s), 135.34 (d), 128.47 (2×d), 127.84 (d), 127.76 (2×d), 119.73 (d), 100.33 (s), 99.90 (s), 80.30 (d), 71.26 (t), 69.41 (d), 68.70 (t), 65.98 (d), 65.19 (d), 58.92 (q), 47.57 (q), 47.52 (q), 44.11 (d), 42.48 (d), 35.19 (d), 17.65 (q), 17.63 (q).

3.1.14. Compound 16. A mixture of **15** (0.050 g, 0.1 mmol) and $Mo(CO)_6$ (0.014 g, 0.11 mmol) in CH_3CN (5 mL, 5 drops H_2O) was refluxed for 2 h. The reaction was cooled to room temperature and the solvent removed in vacuo. The residue was filtered through silica gel to give **16** (0.042 g, 82%). ^{1}H NMR (600.13 MHz, $CDCl_3$): (branimycin numbering) δ=7.41–7.27 (5H, H(ar), m), 4.63 (1H, OCH_2(ar), d, J=12.1), 4.47 (1H, OCH_2(ar), d, J=12.1), 4.34 (1H, H(10), m), 4.25 (1H, H(4), ddd, J=6.3, 3.5, 1.8), 4.19 (1H, H(8), dd, J=10.6, 6.6), 4.18 (1H, H(5), d, J=6.3), 3.75 (1H, H(7), dd, J=10.6, 4.6), 3.62 (1H, H(20), dd, J=10.0, 4.1), 3.33 (1H, H(20), dd, J=10.4, 10.0), 3.28 (3H, CH_3O(20), s), 3.24 (3H, CH_3O(7), s), 3.23 (3H, CH_3O(8), s), 2.78 (1H, H(3), dd, J=19.2, 1.9), 2.65 (1H, H(11), dd, J=3.2, 1.2), 2.53 (1H, H(3), ddd, J=19.2, 3.5, 1.1), 2.41 (1H, H(9), dddd, J=10.4, 6.6, 4.1, 3.2), 2.32 (1H, H(6), m), 1.33 (3H, CH_3, s), 1.28 (3H, CH_3, s); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ=210.39 (s), 138.20 (s), 128.28 (2×d), 127.99 (2×d), 127.60 (d), 100.19 (s), 100.07 (s), 71.48 (d), 70.78 (d), 69.83 (d), 69.79 (t), 67.73 (t), 66.37 (d), 65.12 (d), 59.04 (q), 47.95 (q), 47.83 (q), 46.34 (d), 42.28 (d), 42.17 (d), 39.46 (t), 17.87 (q), 17.74 (q); IR (Si, film) ν_{max}=2923, 2853, 1737, 1651, 1455, 1376, 1198, 1118, 885 cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity): 462 (M^+, 0.8), 447 (2.5), 431 (6), 314 (15), 223 (10), 156 (18), 91 (100); HRMS (EI, 70 eV, 60 °C) calcd for $C_{25}H_{34}O_8$ (M^+): 462.2254, found: 462.2244.

3.1.15. Compound 17. A solution of OsO_4 (0.04 g) in pyridine (0.8 mL) was added dropwise at −25 °C to a solution of **10** (0.04 g, 0.082 mmol) in pyridine (1 mL). After stirring for 1 h at −25 °C and 1 h at room temperature THF (4 mL), Florisil® (3.2 g) and $Na_2S_2O_5$ (1.28 g) were added. After 24 h the residue was diluted with EtOAc (10 mL), filtered through silica gel, and the solvent was removed under reduced pressure to give **17** (0.037 g, 86%), white crystals, mp=119.3–120.1 °C (from hexane). ^{1}H NMR (400.13 MHz, $CDCl_3$): (branimycin numbering) δ=7.25 (2H, H(ar), d, J=8.7), 6.89 (2H, H(ar), d, J=8.7), 4.96 (1H, H(10), dd, J=12.0, 1.0), 4.65 (1H, H(3), dd, J=11.0, 4.0), 4.60 (2H, CH_2O(ar), s), 4.26 (1H, H(5), dd, J=3.0, 2.7), 4.12 (1H, H(4), ddd, J=10.2, 4.0, 2.7), 4.02 (1H, H(7), dd, J=11.3, 10.8), 3.83 (1H, OH(3), d, J=11.0), 3.81 (3H, CH_3O(ar), s), 3.74 (1H, H(11), dd, J=12.0, 8.4), 3.67 (1H, H(8), dd, J=10.8, 4.3), 3.49 (1H, H(20), dd, J=9.7, 4.3), 3.46 (1H, H(20), dd, J=9.7, 5.1), 3.31 (3H, CH_3O(20), s), 3.16 (3H, CH_3O(7), s), 3.11 (3H, CH_3O(8), s), 2.91 (1H, H(6), ddd, J=11.3, 8.4, 3.0), 2.91 (1H, OH(4), d, J=10.2), 2.11 (1H, H(9), dddd, J=5.1, 4.3, 4.3, 1.0), 1.20 (3H, CH_3, s), 1.195 (3H, CH_3, s); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=159.77 (s), 158.30 (s), 129.75 (2×d), 128.99 (s), 114.11 (2×d), 100.25 (s), 99.73 (s), 80.38 (d), 80.05 (d), 73.79 (t), 70.12 (d), 68.61 (t), 67.43 (d), 65.62 (d), 64.76 (d), 58.91 (q), 55.29 (q), 47.68 (q), 47.66 (q), 43.76 (d), 39.83 (d), 34.57 (d), 17.67 (q), 17.55 (q); IR (Si, film) ν_{max}=3456, 2946, 1612, 1514, 1377, 1251, 1115, 1075, 847 cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity): 491 (M^+-CH_3OH, 4), 375 (3), 239 (3), 121 (100); HRMS (EI, 70 eV, 60 °C) calcd for $C_{25}H_{33}NO_9$ (M^+-CH_3OH): 491.2155, found: 491.2164.

3.1.16. Compound 18. A solution of **17** (0.177 g, 0.338 mmol), 2,2-dimethoxypropane (26 mL) and a catalytic amount of PPTS was stirred in DMF (5 mL) at room temperature for 48 h until the staring material was consumed. After the addition of pyridine (0.2 mL) water (30 mL) was added the mixture was extracted with EtOAc (3×50 mL). After drying ($MgSO_4$), the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel to give **18** (0.185 g, 97%), white crystals, mp=87.0–87.7 °C (from hexane). ^{1}H NMR (400.13 MHz, $CDCl_3$): (branimycin numbering) δ=7.31 (2H, H(ar), d, J=8.7), 6.85 (2H, H(ar), d, J=8.7), 4.83 (1H, H(3), d, J=7.2), 4.71 (1H, H(10), dd, J=11.4, 3.9), 4.67 (1H, OCH_2(ar), d, J=11.5), 4.56 (1H, OCH_2(ar), d, J=11.5), 4.51 (1H, H(4), dd, J=7.2, 2.5), 4.10 (1H, H(7), dd, J=11.0, 8.6), 3.90 (1H, H(8), dd, J=11.0, 5.5), 3.797 (3H, CH_3O(ar), s), 3.795 (1H, H(11), dd, J=11.4, 10.7), 3.64 (1H, H(5), dd, J=10.4, 2.5), 3.32 (3H, CH_3O(20), s), 3.24 (3H, CH_3O(8), s), 3.18 (3H, CH_3O(7), s), 2.96 (1H, H(6), ddd. J=10.7, 10.4, 8.6), 2.28 (1H, H(9), dddd, J=5.5, 5.2, 4.8, 3.9), 1.54 and 1.34 (2×3H, $C(CH_3)_2$, s), 1.27 (6H, 2×CH_3, s); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=159.13 (s), 156.56 (s), 130.88 (s), 129.30 (2×d), 113.66 (2×d), 110.50 (s), 100.10 (s), 99.55 (s), 81.23 (d), 75.96 (d), 74.25 (d), 71.68 (t), 68.69 (t), 68.66 (d), 65.72 (d), 65.01 (d), 58.74 (q), 55.27 (q), 47.78 (q), 47.76 (q), 42.61 (d), 40.53 (d), 35.95 (d), 26.62 (q), 24.39 (q), 17.87 (q), 17.69 (q); IR (Si, film) ν_{max}=2936, 1612, 1514, 1459, 1375, 1211, 1124, 896 cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity): 531 (M^+-CH_3OH, 2.5), 311 (12), 244 (7), 163 (8), 134 (30), 121 (100); HRMS (EI, 70 eV, 60 °C) calcd for $C_{28}H_{37}NO_9$ (M^+-CH_3OH): 531.2468, found: 531.2456.

3.1.17. Compound 19. Raney-nickel (0.02 g, 50% in water), boronic acid (0.050 g) and **18** (0.05 g, 0.0888 mmol) were stirred in MeOH/H_2O, 10:1 (4.4 mL) at room temperature under hydrogen atmosphere for 4 h. The reaction mixture was filtered through a Celite path and the filtrate was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated in vacuo to provide **19** (0.045 g, 90%) after

chromatography. ^{1}H NMR (400.13 MHz, $CDCl_3$): (branimycin numbering) δ=7.36 (2H, H(ar), d, J=8.6), 6.88 (2H, H(ar), d, J=8.6), 4.86 (1H, OCH_2(ar), d, J=12.6), 4.75 (1H, OCH_2(ar), d, J=12.6), 4.65 (1H, H(5), dd, J=11.5, 3.6), 4.44 (1H, H(8), dd, J=11.5, 5.9), 4.242 (1H, H(3), d, J=4.8), 4.239 (1H, H(10), m), 4.13 (1H, H(4), dd, J=4.8, 3.6), 3.81 (3H, CH_3O(ar), s), 3.766 (1H, H(20), dd, J=9.6, 3.3), 3.762 (1H, H(7), dd, J=11.5, 5.0), 3.36 (3H, CH_3O(8), s), 3.32 (3H, CH_3O(20), s), 3.26 (1H, H(20), dd, J=10.0, 9.6), 3.21 (3H, CH_3O(7), s), 2.94 (1H, H(6), ddd, J=11.5, 5.7, 5.0), 2.79 (1H, H(11), m), 2.25 (1H, H(9), m), 1.73 (1H, OH, dd, J=3.8, 1.8), 1.38 and 1.33 (2×3H, $C(CH_3)_2$, s), 1.31 (3H, CH_3, s), 1.30 (3H, CH_3, s); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=209.86 (s), 159.10 (s), 131.82 (s), 129.62 (2×d), 113.61 (2×d), 109.36 (s), 99.41 (s), 99.19 (s), 79.02 (d), 78.56 (d), 73.28 (t), 72.49 (d), 70.44 (d), 68.58 (t), 67.07 (d), 63.47 (d), 59.04 (q), 55.25 (q), 50.96 (d), 47.98 (q), 47.91 (q), 37.80 (d), 27.25 (q), 25.79 (q), 17.73 (q), 17.66 (q); IR (Si, film) ν_{max}=3606, 2924, 1727, 1681, 1651, 1557, 1455, 1373, 1123, 807 cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity): 534 (M^+-CH_3OH, 5), 516 (3), 282 (2), 205 (2.5), 138 (7), 121 (100); HRMS (EI, 70 eV, 60 °C) calcd for $C_{28}H_{38}O_{10}$ (M^+-CH_3OH): 534.2465, found: 534.2457.

3.1.18. Compound 20. To a solution of **19** (0.05 g, 0.9 mmol) in DCM (5 mL), 2,6-lutidine (0.31 mL, 2.6 mmol) was added, and the mixture was cooled to −78 °C. TMSOTf (0.32 mL, 1.41 mmol) was added dropwise over 15 min and the reaction mixture was stirred for additional 30 min at −78 °C. Then it was warmed to room temperature and after 1.5 h quenched with saturated $NaHCO_3$ solution. The mixture was diluted with toluene (10 mL) and H_2O (5 mL), the organic layer was separated and the aqueous phase was extracted with toluene (2×5 mL). The combined organic layers were washed with brine and the solvent was removed under reduced pressure to give the residue that was purified by flash chromatography on silica gel to give **20** (0.03 g, 56%). ^{1}H NMR (250.13 MHz, $CDCl_3$): (branimycin numbering) δ=7.36 (2H, H(ar), d, J=8.5), 6.88 (2H, H(ar), d, J=8.5), 4.79 (2H, OCH_2(ar), s), 4.68 (1H, H(5), dd, J=11.5, 3.2), 4.40 (1H, H(8), dd, J=11.6, 5.8), 4.21 (1H, H(10), dd, J=4.4, 4.4), 3.91 (2H, H(3,4), m), 3.81 (3H, CH_3O(ar), s), 3.75 (1H, H(7), dd, J=11.6, 5.3), 3.73 (1H, H(20), dd, J=10.0, 3.3), 3.36 (3H, CH_3O(20), s), 3.30 (3H, CH_3O(8), s), 3.23 (1H, H(20), dd, J=10.0, 9.4), 3.21 (3H, CH_3O(7), s), 2.92 (1H, H(6), ddd, 10.7, 5.3, 5.3), 2.77 (1H, H(11), dd, J=5.1, 2.9), 2.28 (1H, H(9), m), 1.36 (6H, $C(CH_3)_2$, s), 1.30 (6H, 2×CH_3, s), 0.05 (9H, $Si(CH_3)_3$, s); IR (Si, film) ν_{max}=2924, 1727, 1681, 1651, 1557, 1455, 1373, 1123, 807 cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity): 534 (M^+-CH_3OH, 5), 516 (3), 282 (2), 205 (2.5), 138 (7), 121 (100): HRMS (EI, 70 eV, 60 °C) calcd for $C_{32}H_{50}O_{11}Si$ (M^+): 638.3122, found: 638.3118.

3.1.19. Compound 21. To a solution of **20** (0.05 g, 0.8 mmol) in THF (5 mL) was added a solution of vinylmagnesium bromide (0.09 mL, 1.7 M in THF) at −78 °C. The mixture was stirred for 1 h and quenched with saturated NH_4Cl solution. The mixture was diluted with toluene (10 mL) and H_2O (5 mL), the organic layer was separated and the aqueous phase was extracted with toluene (2×5 mL). The combined organic layers were washed with brine and the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel to give **21** (0.047 g, 72%). ^{1}H NMR (600.13 MHz, $CDCl_3$): (branimycin numbering) δ=7.39 (2H, H(ar), d, J=8.5), 6.86 (2H, H(ar), d, J=8.5), 5.79 (1H, H(13), dd, J=17.2, 10.7), 5.40 (1H, H(14), dd, J=17.2, 1.4), 5.22 (1H, H(14), dd, J=10.7, 1.4), 4.76 (1H, OCH_2(ar), d, J=12.7), 4.74 (1H, OCH_2(ar), d, J=12.7), 4.41 (1H, H(5), dd, J=11.7, 5.7), 4.29 (1H, H(8), dd, J=11.3, 6.0), 4.17 (1H, H(10), dd, J=2.3, 1.9), 4.02 (1H, H(3), d, J=6.5), 3.88 (1H, H(4), dd, J=6.5, 4.7), 3.80 (3H, CH_3O(ar), s), 3.76 (1H, H(7), dd, J=11.3, 5.3), 3.73 (1H, H(20), dd, J=9.9, 3.6), 3.35 (3H, CH_3O(8), s), 3.28 (3H, CH_3O(20), s), 3.21 (3H, CH_3O(7), s), 3.20 (1H, H(20), dd, J=10.2, 9.9), 2.91 (1H, H(6), ddd, 11.7, 5.3, 4.4), 2.74 (1H, OH, s), 2.24 (1H, H(9), m), 2.02 (1H, H(11), dd, J=4.4, 2.3), 1.56 and 1.28 (2×3H, $C(CH_3)_2$, s), 1.30 (3H, CH_3, s), 1.29 (3H, CH_3, s), 0.05 (9H, $Si(CH_3)_3$, s); ^{13}C NMR (chemical shifts from 2D HSQC and HMBC spectra) (150.90 MHz, $CDCl_3$): δ=159.0 (s), 141.7 (d), 132.0 (s), 129.5 (2×d), 114.8 (t), 113.3 (2×d), 108.3 (s), 99.1 (s), 98.9 (s), 81.0 (s), 77.2 (d), 74.9 (d), 72.5 (t), 71.8 (d), 70.2 (d), 69.2 (t), 68.2 (d), 64.2 (d), 59.0 (q), 55.3 (q), 48.2 (d), 48.0 (q), 47.8 (q), 46.1 (d), 34.8 (d), 26.5 (q), 24.5 (q), 17.8 (2×q), 0.05 (3×q); HRMS (EI, 70 eV, 60 °C) calcd for $C_{34}H_{54}O_{11}Si$ (M^+): 666.3435, found: 666.33423.

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