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Synthesis of a C1–C12 Fragment of Gulmirecin B

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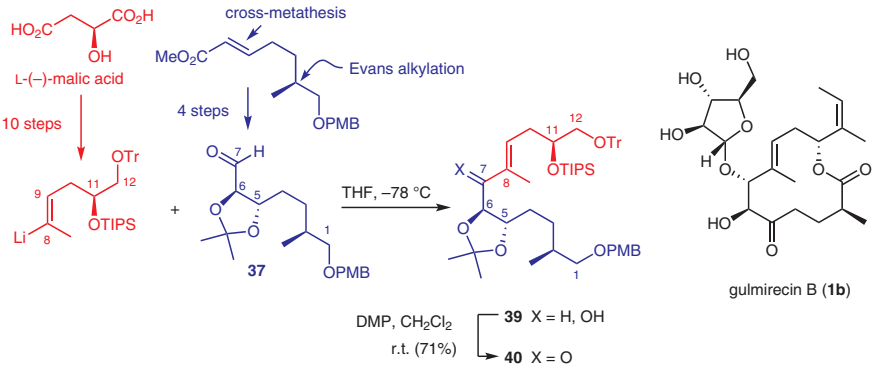

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Abstract The synthesis of a C1–C14 fragment of the macrolide antibiotic gulmirecin B through formation of the C7–C8 bond by addition of a vinyllithium intermediate to a C1–C7 aldehyde was investigated. This crucial coupling was successful with a vinyllithium reagent corresponding to a C8–C12 fragment. The C8–C12 vinyl bromide was prepared from L-malic acid. The C1–C7 aldehyde building block was synthesized from hex-5-enoic acid by using an Evans alkylation, a cross-metathesis, and an asymmetric dihydroxylation as key steps.

Key words gulmirecin B, disciformycin, hydrozirconation, asymmetric dihydroxylation, cross-metathesis, Evans alkylation

In 2014, the groups of Nett[1] and Müller[2] independently described the isolation, structure elucidation, and biosynthesis of similar 12-membered glycosylated macrolides (Figure 1). These polyketides, which were named gulmirecins A and B (**1a** and **1b**, respectively) by the Nett group, and disciformycins A and B (**2a** and **2b**, respectively) by the Müller group, displayed promising activities against gram-positive bacteria. Both groups isolated these natural products from *Pyxidicoccus fallax* strains, which are predatory bacteria of the Myxococcaceae type. All the macrolides share a D-arabinose residue at the 7-OH group. Differences can be identified in the region C2–C4. Due to their novel structures and biological activity, these macrolides represent valuable targets for total synthesis. In particular, the selective glycosylation poses a certain challenge. In addition, the creation of the stereocenters and the construction of the two trisubstituted double bonds have to be addressed.

The first synthesis of the disciformycins was published by the Fürstner group in 2018.[3] They used a ring-closing alkyne metathesis (rcam) on ester **3** to forge the macrolactone ring of **4** (formation of the C8–C9 bond; Scheme 1).

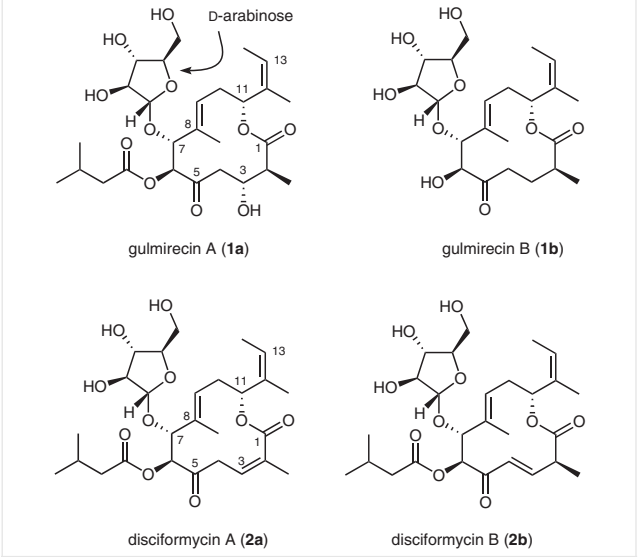
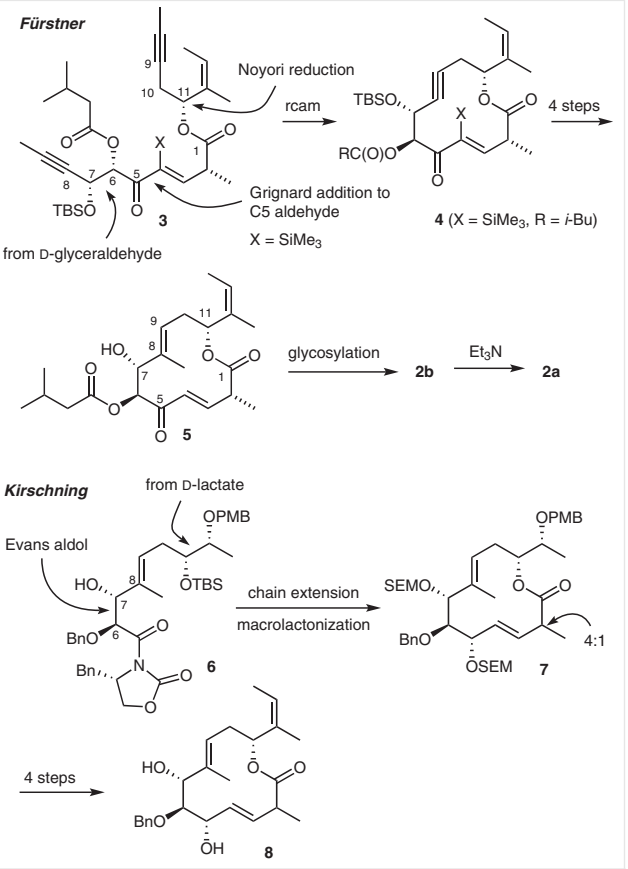


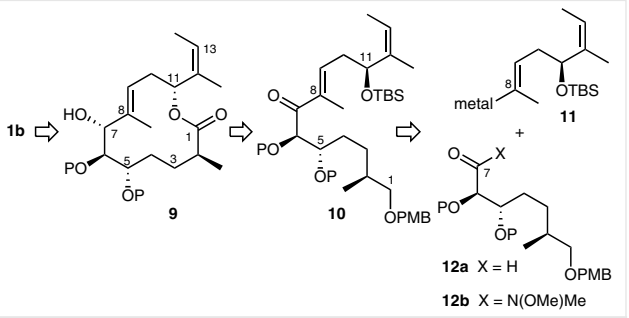
Figure 1 Structures of the macrolides gulmirecin A and B and disciformycin A and B

The 4-trimethylsilyl group was expected to keep the C3–C4 double bond in place. A subsequent *trans*-selective hydrostannylation permitted the introduction of the methyl group at C8.

Recent publications by Kirschning and co-workers describe a synthesis of the aglycon of disciformycin B (**2b**).[4] A key feature of their synthesis is an Evans aldol reaction of a glycolate derivative to form the C6–C7 bond of compound **6**. The required C7–C12 aldehyde was constructed from D-lactate. Chain extension reactions on **6** delivered a seco acid that was converted into the macrolactone **7**. The C12–C13 double bond was installed at the end of the macrolactone by a Wittig reaction to give compound **8**.



Scheme 1 Key intermediates in the synthesis of disciformycins by the Fürstner group and of the disciformycin aglycon by the Kirschning group



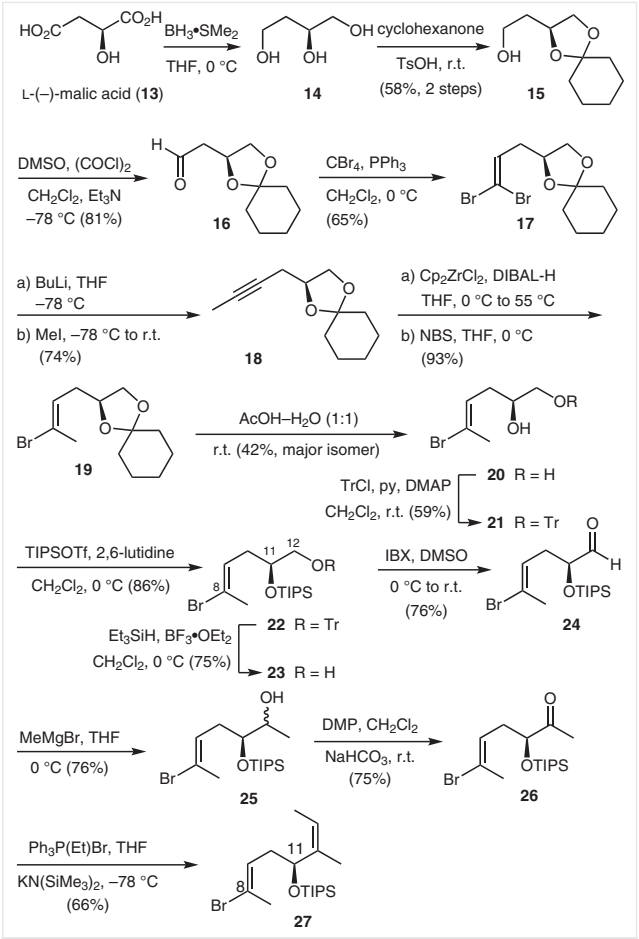
Scheme 2 Retrosynthetic considerations for the synthesis of an acyclic aglycon of gulmirecin B (**1b**)

For the disconnection of the acyclic C1–C14 precursor, the region around C5–C8 seems the most suitable (Scheme 2). A key issue, however, is the differentiation of the three oxygen functionalities at C5–C7. In an initial study, we envisioned the formation of the C7–C8 bond through attack of a vinylmetal intermediate **11** at aldehyde **12a**. Depending on the stereoselectivity of this reaction, the resulting C7 secondary alcohol might be used for attachment of the sugar. Alternatively, we considered an oxidation/reduction sequence to create a single configuration at C7. The enone **10** might also be available from addition of a vinylmetal species to Weinreb amide **12b**. Alternatively, a Horner–Wadsworth–Emmons reaction might be used to form enone **10** (C8–C9 bond) but this would require different building blocks.

We began our synthesis of the C8–C14 fragment **27** from L-(–)-malic acid (**13**) (Scheme 3), because the L-compound is cheaper than its enantiomer. This required a Mitsunobu macrolactonization of the seco acid. Reduction of the carboxylic acid groups furnished the butanetriol **14**, which was converted into the dioxolane **15** by reaction with cyclohexanone.[5] Oxidation of alcohol **15** under Swern conditions furnished aldehyde **16** in high yield.[6] For the next three steps, we adapted a known sequence published for a related compound.[7] Thus, aldehyde **16** was converted into the 1,1-dibromoalkene **17** by using CBr_4 and Ph_3P. Treatment of **17** with BuLi in THF generated the corresponding terminal acetylide, which was alkylated with MeI to give the internal alkyne **18** in 74% yield. A subsequent hydrozirconation followed by quenching of the vinylzirconocene intermediate with *N*-bromosuccinimide (NBS) gave the vinyl bromide **19**. Here, the Schwartz reagent, zirconocene hydrochloride, was generated in situ from Cp_2ZrCl_2 and DIBAL-H.[8] The hydrozirconation produced a mixture of regioisomers (~4:1) that was carried on the next step. Hydrolysis of the acetal with aqueous acetic acid allowed us to isolate the pure vinyl bromide **20** with a terminal vicinal diol moiety. Differentiation of the two hydroxy groups was possible by tritylation of the primary alcohol to give the ether **21**, followed by silylation of the secondary hydroxy group by using TIPSOTf with 2,6-lutidine as the base. This led to the completely protected vinyl bromide **22**. This compound presented itself for coupling with an aldehyde.

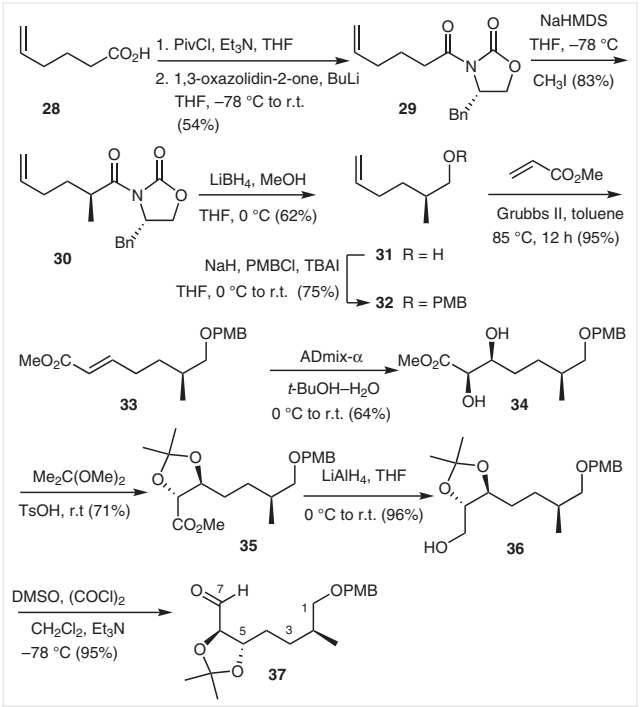
To introduce the C12–C13 double bond, the trityl ether of **22** was selectively cleaved under reductive conditions by using Et_3SiH and $BF_3{\cdot}OEt_2$.[9] Oxidation of the resulting alcohol **23** with 2-iodoxybenzoic acid (IBX) in DMSO furnished aldehyde **24** in 76% yield. Chain extension of **24** with methylmagnesium bromide led to alcohol **25** as a mixture of diastereomers. Alcohol **25** was converted into the ketone **26** by treatment with the Dess–Martin periodinane reagent in CH_2Cl_2. A final Wittig reaction of ketone **26** with the phosphonium salt derived from ethyl bromide, with potassium hexamethyldisilazide [$KN(SiMe_3)_2$][10] as base, in THF provided the C8–C14 fragment **27** as a single diastereomer. The configuration of the double bond was inferred from the strong cross peaks in its NOESY spectrum between 11-H/14-H and 10-H/14-H (gulmirecin numbering).

For the synthesis of a C1–C7 fragment with a protected 5,6-diol subunit, one might start with L-tartrate. However, we opted instead for an asymmetric dihydroxylation approach. Thus, hex-5-enoic acid[11] (**28**) was conjugated with the Evans auxiliary, derived from L-phenylalanine through a



Scheme 3 Synthesis of the vinyl bromides **22** (C8–12 fragment) and **27** (C8–C14 fragment)

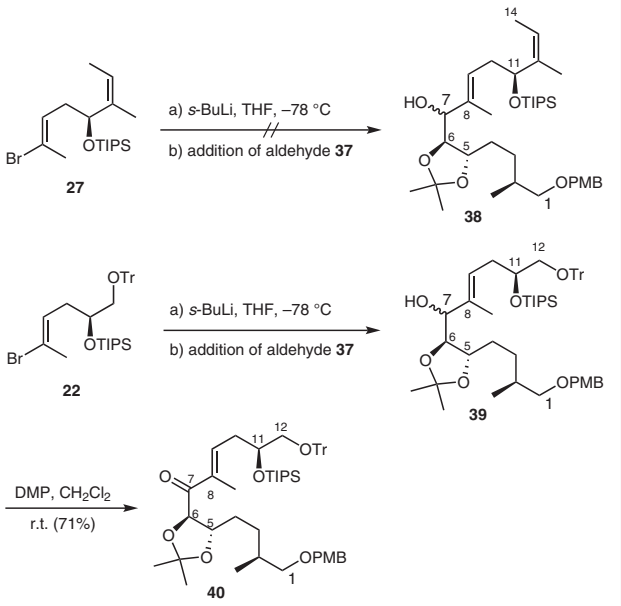
mixed anhydride, to give the oxazolidinone derivative[12] **29** (Scheme 4). Alkylation of the sodium enolate of hexenoic acid derivative **29** with methyl iodide provided the corresponding 2-methylhex-5-enoic acid derivative **30**.[12a,b] Reductive removal of the chiral auxiliary by treatment with lithium borohydride in methanol led to alkenol **31**.[12a,b,13] The hydroxy group of **31** was subsequently protected as a *p*-methoxybenzyl ether[14] **32** by treatment with NaH and *p*-methoxybenzyl chloride. Chain extension of the alkene terminus was accomplished by a cross-metathesis reaction[15] with methyl acrylate in the presence of the Grubbs II catalyst in hot toluene to give enoate **33** in 95% yield. Sharpless asymmetric dihydroxylation[16] of enoate **33** with ADmix-α in *tert*-BuOH–H_2O gave the dihydroxy ester **34** in reasonable yield; the fact that we observed only one set of signals in the ^{13}C NMR spectrum of **34** indicated a high diastereoselectivity in this reaction. Treatment of diol **34** with dimethoxypropane in the presence of a catalytic amount of TsOH delivered the 1,3-dioxolane **35**. A final redox sequence consisting of reduction of the ester group with $LiAlH_4$ to give alcohol **36** and Swern oxidation of **36** gave aldehyde **37**, corresponding to the C1–C7 fragment of gulmirecin B.



Scheme 4 Synthesis of the C1–C7 fragment **37** of gulmirecin B

With fragments **22**, **27**, and **37** in hand, we investigated the formation of the C7–C8 bond (Scheme 5). To our disappointment, halogen–metal exchange on vinyl bromide **27** (~0.025M in THF) by using *t*-BuLi (2.2 equiv) in THF at –78 °C, followed by addition of aldehyde **37**, did not give the desired alcohol **38**. Instead, substantial amounts of the debrominated derivative of **27** were isolated. Other conditions [*s*-BuLi (1.5 equiv), THF, –78 °C; *i*-PrMgCl·LiCl (1.25 equiv), THF, –78 °C; $CrCl_2$ (5 equiv), $NiCl_2$ (1 equiv), DMF/THF (1:1), r.t.] proved no better. In contrast, the addition of the vinyllithium derivative of **22**, generated in the same way from *s*-BuLi, proceeded smoothly with aldehyde **37** to give alcohol **39** as a mixture of C7 diastereomers.[17] At this moment, we cannot explain these differences. Oxidation of alcohol **39** with the Dess–Martin reagent provided enone **40**, which corresponds to a C1–C12 fragment of gulmirecin B. An internal redox isomerization of the dihydroxy ketone subunit should set the correct functionality at C5–C7. Installation of the C12–C13 double bond would have to be done after coupling the two key fragments if this strategy was to be used. Possibly, other coupling strategies might be preferable.[18]

In summary, we have developed routes to key building blocks for the synthesis of the macrolide antibiotic gulmirecin B. The plan in this study was to find out whether formation of the C7–C8 bond through attack of a vinylmetal intermediate on a C1–C7 fragment with an aldehyde or carbox-



Scheme 5 Attempts to couple vinyl bromides **27** and **22** with aldehyde **37**. Only the vinyllithium derivative of bromide **22** reacted with aldehyde **37**.

ylic acid function to construct an acyclic precursor of gulmirecin B would be possible. A C1–C7 aldehyde **37** was prepared through an Evans alkylation to set the C2 stereogenic center and an ADH reaction on the derived enoate **33** to generate the dihydroxy carbonyl unit at the C5–C7 terminus. The vinyl bromides **22** (C8–C12 fragment) and **27** (C8–C14 fragment) were prepared by routine steps from malic acid. Initial investigations showed that neither the vinyllithium derivative of **27** nor that of **22** added to the Weinreb amide of **35**. Whereas the vinyllithium derivative of **27** did not add to aldehyde **37**, the vinyllithium species of the C8–C12 fragment **22** did react with aldehyde **37**.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611559.

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(17) **C1–C12 fragment 39**
Vinyl bromide **22** (0.15 g, 0.25 mmol) was dried by dissolving it in a 1:1 mixture of benzene and toluene (3 mL), followed by evaporation of the solvents using a Rotavapor and placing the residue under a high vacuum for 1 h. THF (1.5 mL) was then added under argon and the flask was cooled to –78 °C. A 1.4 M solution of *s*-BuLi in cyclohexane (0.21 mL, 0.30 mmol) was added dropwise and the mixture was stirred for 30 min at –78 °C before a solution of aldehyde **37** (0.14 g, 0.43 mmol) in THF (1.5 mL) was added dropwise. After completion of the addition, the mixture was stirred at –78 °C for 2 h and then at r.t. for 1 h. Finally, the mixture was treated with sat. aq NH_4Cl solution (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 8 mL). The combined organic layers were washed with sat. aq NaCl (5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude allylic alcohol **39** (yield: 86 mg; dr = 10:4) was used in the next reaction without chromatographic purification. HRMS (ESI-TOF):

m/z [M + Na]$^+$ calcd for $C_{53}H_{74}NaO_7Si$: 873.5094; found: 873.5094.

Enone 40

DMP (70 mg, 0.16 mmol) and $NaHCO_3$ (20 mg, 0.24 mmol) were added to a solution of alcohol **39** (70 mg, 0.08 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The cooling bath was then removed and the mixture was stirred for 2 h at r.t. The mixture was diluted with sat. aq $NaHCO_3$ (5 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with sat. aq NaCl (8 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography [silica gel, PE–EtOAc (85:15)] to give a colorless oil; yield: 50 mg (71%); R_f = 0.48 (PE–EtOAc, 9:1); $[\alpha]_D^{19}$ –6.85 (*c* = 0.52, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.7 Hz, 3 H, 2-CH_3), 0.94–0.96 {m, 21 H, Si[CH(CH_3)$_2$]$_3$}, 1.25–1.30 (m, 1 H, 3-H), 1.30 [s, 3 H, C(CH_3)$_2$], 1.37–1.44 [m, 4 H, C(CH_3)$_2$, 3-H], 1.50–1.53 (m, 1 H, 4-H), 1.56–1.60 (m, 1 H, 4-H), 1.68–1.73 (m, 1 H, 2-H), 1.80 (s, 3 H, 8-CH_3), 2.70–2.73 (m, 2 H, 10-H), 2.97 (t, *J* = 8.3 Hz, 1 H, 12-H), 3.10–3.20 (m, 2 H, 12-H, 1-H), 3.26 (dd, *J* = 9.0, 5.8 Hz, 1 H, 1-H), 3.77 (s, 3 H, OCH_3), 4.10–4.18 (m, 1 H, 11-H), 4.22–4.26 (m, 1 H, 5-H), 4.34 (d, *J* = 7.4 Hz, 1 H, 6-H), 4.48 (d, *J* = 1.8 Hz, 2 H, CH_2Ar), 6.86 (d, *J* = 8.6 Hz, 2 H, ArH), 6.97 (t, *J* = 6.4 Hz, 1 H, 9-H), 7.17–7.27 (m, 12 H, ArH), 7.38–7.41 (m, 5 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8 (8-CH_3), 12.3 {Si[*C*H(CH_3)$_2$]$_3$}, 16.9 (2-CH_3), 18.0 {Si[CH(*C*H_3)$_2$]$_3$}, 26.2 [C(*C*H_3)$_2$], 27.2 [C(*C*H_3)$_2$], 29.7 (C-3), 30.6 (C-4), 33.4 (C-2), 34.8 (C-1), 55.2 (OCH_3), 66.3 (C-12), 70.3 (C-11), 72.6 (CH_2Ar), 75.5 (C-1), 78.0 (C-5 or C-6), 80.3 (C-6 or C-5), 86.6 (CPh_3), 109.8 [*C*(CH_3)$_2$], 113.7, 127.0, 127.7, 128.6, 129.0, 130.8 (6 × Ar), 137.7 (C-8), 142.5 (C-9), 143.9 (Ar C), 159.0 (Ar C), 197.5 (C-7). HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{53}H_{72}NaO_7Si$: 871.4929; found: 871.4929.

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