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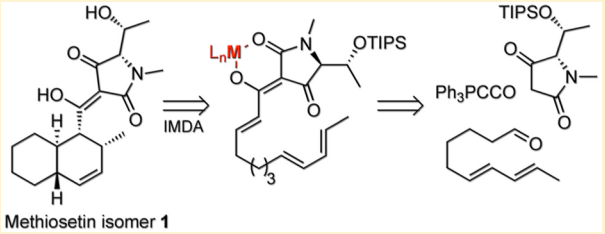
Synthesis of an Isomer of the Decalinoyltetramic Acid Methiosetin by a Stereocontrolled IMDA Reaction of a Metal-Chelated 3-Trienoyltetramate

Markus Winterer,[†] Karl Kempf,[†] and Rainer Schobert*

Organic Chemistry Laboratory, University Bayreuth, 95440 Bayreuth, Germany

Supporting Information

ABSTRACT: An isomer of the 3-decalinoyltetramic acid methiosetin was synthesized for the first time. The decalin moiety was established by a late-stage intramolecular Diels–Alder cyclization catalyzed by Me_2AlCl or $La(OTf)_3$. Its high diastereoselectivity arose from stereoinduction by a well-defined metal *O*,*O*-chelate complex of the 3-acyltetramic acid moiety. The nature of the metal and the bulkiness of the residues at the tetramic acid chelator are decisive for the stereochemical outcome.



INTRODUCTION

(+)-Methiosetin **1** is a 3-decalinoyltetramic acid[1−3] with antibacterial activity against *Staphylococcus aureus* and *Haemophilus influenzae* that was isolated in 2011 by Singh et al.[4] from a sooty mold *Capnodium* sp. This group also assigned the relative configuration of the decalin moiety on grounds of NMR studies and proposed the structure shown in Figure 1,

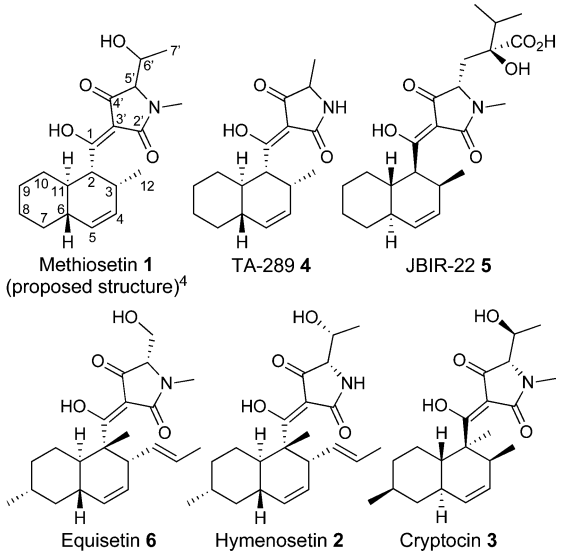


Figure 1. Natural 3-decalinoyltetramic acids.

which leaves the absolute configurations at C-5′ and C-6′ of the tetramic acid core unassigned. So far, there are examples known of decalinoyltetramic acids derived from either L-threonine, such as hymenositin **2**, or L-*allo*-threonine, such as cryptocin **3** (Figure 1). Decalinoyltetramic acids lacking a methyl group at C-2 are scarce. They may feature absolute configurations of the decalin like the one proposed for methiosetin (e.g., TA-289 **4**) recently isolated by Atkinson et al. from an unidentified *Fusarium* sp. fungus[5] or the inverted configuration like JBIR-22 **5**.

The majority of synthetic 3-decalinoyltetramic acids were prepared by assembling the *trans*-decalin by an intramolecular Diels–Alder (IMDA) reaction using auxiliaries or chiral catalysts for stereocontrol. The tetramate ring was established either prior to or following this IMDA cyclization. For instance, Gao et al.[6] prepared cryptocin **3** and derivatives of equisetin **6** and fusarisetin A by generating the tetramic acid according to Ley et al.[7,8] via aminolysis of a *β*-keto thioester, linked to the full-fledged decalin, with the respective amino ester, followed by a basic Dieckmann condensation of the resulting *N*-*β*-ketoamino ester. Similarly, Opatz et al. synthesized hymenosetin **2** by first establishing an enantiopure decalin aldehyde by IMDA reaction of a trienal derived from (+)-citronellal, followed by attachement of an *N*-*β*-ketoacylthreoninate and its Lacey-Dieckmann condensation.[9] In contrast, Westwood and Healy prepared highly enantioenriched diastereomers of JBIR-22 **5** by first attaching a trienoyl residue to a tetramic acid via a Horner–Wadsworth–Emmons olefination and then initiating the IMDA of this residue with an external magnesium bisoxazoline complex as a catalyst.[10] A third conceivable approach to 3-decalinoyltetramic acids is the attachment of a decalinoic acid to the respective preformed tetramic acid by means of condensation agents such as DCC/DMAP (Yoshi[11]–Yoda[12] acylation) or BF_3 etherate (Jones acylation).[13] However, neutral condensation agents usually lead to the formation of 4-*O*-decalinoyltetramic acids, which are difficult to rearrange to the 3-decalinoyltetramates, and BF_3 etherate may lead to racemization at C-2 or C-5′.

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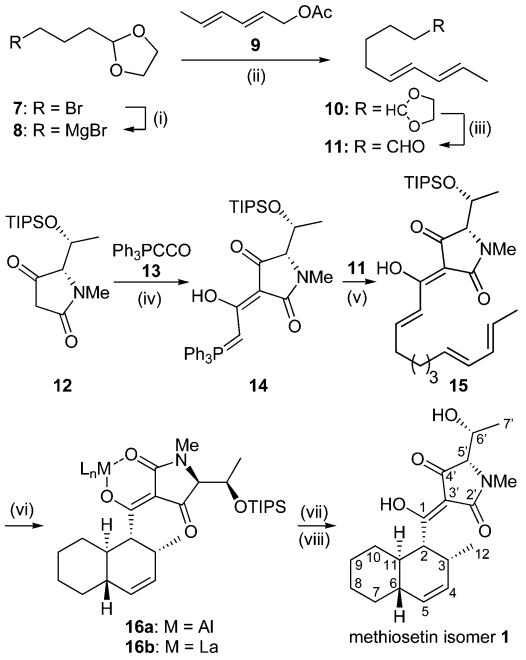
Herein, we describe a conceptionally new approach to 3-decalinoyltetramic acids which utilizes the attachment of an unsaturated aldehyde to a tetramic acid bearing a 3-acyl ylide[14] via a Wittig reaction, followed by an IMDA cyclization of the unsaturated side chain, which is stereocontrolled not by an external catalyst, as in the strategy of Westwood and Healy, but by a metal chelate complex of the 3-acyltetramic acid itself.

RESULTS AND DISCUSSION

Synthesis of a Proposed Stereoisomer of Methiosetin.

We intended to attach a 3-trienoyl residue to an enantiopure tetramic acid and then establish the decalin system via an IMDA reaction stereocontrolled by the tetramate moiety. To this end, TIPS-protected L-threonine-derived tetramic acid **12** was prepared as previously reported[15,16] and acylated with the cumulated phosphorus ylide Ph_3PCCO **13**[14,17] to give the stabilized ylide **14** in quantitative yield (Scheme 1). This was

Scheme 1. Synthesis of Methiosetin Isomer 1 via a Late-Stage IMDA Reaction[a]



[a]Reagents and conditions: (i) Mg, THF, −40 °C, 1.5 h; (ii) 0.25 equiv of $CuBr(Me_2S)$, −40 °C (3 h) → rt, 12 h, 78%; (iii) AcOH/THF/H_2O, 90 °C, 1.5 h, 97%; (iv) THF, reflux, 5 h, 99%; (v) CH_2Cl_2, KO*t*Bu, then **11**, rt, 12 h, 81%; (vi) for **16a**: 2 equiv of Me_2AlCl, CH_2Cl_2, rt, 3 days; for **16b**: 1 equiv of $La(OTf)_3$, CH_2Cl_2, rt, 2 days; (vii) for **16a**: $BF_3 \times Et_2O$, CH_2Cl_2, rt, 12 h; for **16b**: HF/pyridine, THF, rt, 24 h; (viii) for **16**a: MeOH, reflux, 2 h (29% over 3 steps); for **16b**: Et_3SiH, 30 min (59% over 3 steps).

deprotonated with KO*t*Bu to afford an anionic ylide species that underwent an *E*-selective olefination when treated with decadienal **11** to give the immediate IMDA precursor **15** in 81% yield. The aldehyde **11** was synthesized in analogy to a method by Paintner et al.[18] starting with a copper-mediated coupling reaction between the Grignard derivative **8** of commercially available 2-(3-bromopropyl)-1,3-dioxolane **7** and (*E*2,*E*4)-hexadienyl acetate **9**. By replacing Paintner's Li_2CuCl_4 with $CuBr(Me_2S)$, we increased the yield of product dioxolane **10** by 10% to 78%. Its deprotection gave deca-6,8-dienal **11** in near quantitative yield. An attempt to cyclize the IMDA precursor **15** in the presence of BF_3 etherate led to decomposition products. However, the use of 2 equiv of Me_2AlCl as a catalyst gave, after demetalation and deprotection, one predominant methiosetin stereoisomer **1** in 29% yield with separable trace amounts of a second one. With $La(OTf)_3$ as the catalysts, the same product was obtained even in 59% yield. A conceivable explanation for this stereoinduction is offered by the fact that 3-acyltetramic acids form chelate complexes with a broad range of metals[19] by engaging the exocyclic enol OH group at C-1 and either the 4′-keto or the amide 2′-carbonyl group of the heterocycle, depending on the metal. Both types of chelate complexes are distinguishable by analyzing the 1700−1500 cm^{-1} carbonyl region of their IR spectra.[20,21] The IR spectra of the complexes **16**, recorded immediately after the IMDA reaction, showed bands at 1694 and 1599 cm^{-1}, typical of metal coordination by the amide carbonyl (cf. the Supporting Information, Figure S1). It is reasonable that the IMDA precursor **15** showed the same sort of metal coordination. The predominance of one product stereoisomer may then be rationalized by the conformationally rigidifying effect of the bulky TIPS group near the two stereocenters C-5′ and C-6′. Indirect proof for this rationale is provided by the fact that TA-289 **4**, bearing a less bulky methyl residue at C-5′, was not accessible diastereoselectively by this method, which afforded only an inseparable 1:1.85 mixture of two major *endo*-diastereoisomers. For the removal of the metal in the presumed product complex **16a**, the crude product was treated first with BF_3 etherate to substitute the metal for BF_2 and then with hot methanol to liberate the 3-acyltetramic acid **1**. Gratifyingly, the treatment with BF_3 etherate led to a swift cleavage of the TIPS protecting group but not to an undesired subsequent elimination of water. The crude lanthanum complex **16b** was deprotected and demetalated with HF in pyridine and Et_3SiH to give the same methiosetin isomer **1** in 59% yield.

For the stereochemical assignment of the decalin moiety of our synthetic methiosetin isomer **1**, we cleaved it oxidatively at the formal double bond between C-1 and C-3′ under conditions described by Opatz et al.[9] for hymenosetin (Scheme 2, top row). The resulting decalinoic acid **17** showed a specific optical rotation of $[\alpha]_D^{24}$ −157.2 (*c* 0.50, CH_2Cl_2). For the identification of its absolute configuration, we prepared it independently according to a protocol by Paintner[18] (Scheme 2).

Aldehyde **11** was olefinated with enantiopure amide ylide **18**, readily accessible by reaction of 4-benzyloxazolidin-2-one with cumulated ylide **13** according to Boeckman et al.,[22] to give an IMDA precursor **19** in 57% yield. The latter was cyclized in the presence of 2 equiv of Me_2AlCl at −30 °C to give the decalin derivative **20** with high *endo*-diastereoselectivity (*endo*/*exo* ≥ 50:1) and in 99% yield. The absolute configuration of compound **20** had been elucidated by Paintner et al.[18] via single-crystal X-ray diffraction analysis of its dibromo adduct (CCDC199999). For the cleavage of the Evans auxiliary, the IMDA product **20** was first converted quantitatively to the thioester **21** with a mixture of propanethiol and *n*-BuLi according to a general protocol by Damon et al.[23] Since Paintner had reported a partial epimerization upon basic hydrolysis of this thioester, we now developed an epimerization-free hydrolysis by means of silver nitrate in aqueous dioxane, in analogy to a protocol by Gerlach et al.,[24] which left the acid **17** as a pure enantiomer in 93% yield. It showed a specific optical rotation of $[\alpha]_D^{20}$ −159.2 (*c* 0.97, CH_2Cl_2) and was identical to the product obtained from oxidative cleavage of

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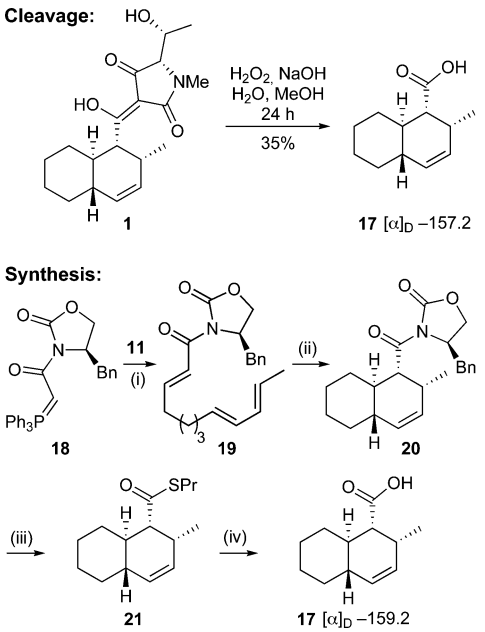
Scheme 2. Oxidative Cleavage of Methiosetin Isomer 1 and Synthesis of Decalinoic Acid 17[a]



[a]Reagents and conditions: (i) toluene, 80 °C, 16 h, 57%; (ii) 2 equiv of Me_2AlCl, CH_2Cl_2, −30 °C, 12 h, 99%; (iii) propanethiol, *n*-BuLi, THF, 0 °C, 10 min, 99%; (iv) $AgNO_3$, dioxane/H_2O (4:1), reflux, 2 h, 93%.

synthetic methiosetin isomer **1** also with respect to NMR and MS analytics. As to the configuration of the tetramic acid moiety of our synthetic methiosetin isomer **1**, we assume it to be (5′*S*,6′*R*) because we can exclude an *allo*-threonine configuration from the ^{1}H NMR coupling constants, which are identical to those of the "L-threonine residue" of hymenosetin,[9] and because C-6′ is not prone to racemization or inversion under the conditions of the IMDA reaction. Taken together, our synthetic methiosetin isomer **1** features the structure shown in Schemes 1 and 2.

However, the stereochemistry of the natural isolate remained unclear. While the synthetic methiosetin isomer **1** showed a specific optical rotation of $[\alpha]_D^{24}$ −63 (*c* 1.0, MeOH), the isolated natural product had $[\alpha]_D^{23}$ +12.4 (*c* 1.0, MeOH). The ^{1}H NMR shifts and coupling constants of both were in perfect agreement when measured in methanol-d_4 yet differed somewhat when recorded in $CDCl_3$. The ^{13}C NMR shifts were also a close match and differed by more than 0.2 ppm only for carbon atoms 11, 4′, and 5′ (cf. the Supporting Information, Tables S1 and S2). In conclusion, the natural isolate probably featured a decalin moiety which is the enantiomer of our synthetic methiosetin isomer **1**. We can exclude that it had a tetramic acid core derived from D-threonine since Opatz et al.[9] demonstrated that the optical rotation changes dramatically by more than 200° when going from L-threonine-derived to D-threonine-derived hymenosetin. It is worth noting that Westwood and Healy[10] could also prove through their synthetic studies that the decalin configuration of JBIR-22 had previously been assigned wrongly by Izumikawa et al.[25]

Stereoinduction by Other Metal 3-Acyltetramates. 3-Acyltetramic acids may also coordinate to metals, such as magnesium, via their exocyclic enol OH group and their 4′-keto oxygen.[20] Hence, we conducted IMDA reactions of **15** in the presence of compounds of such metals, expecting the formation of methiosetin isomers featuring the "enantiomeric" decalin moiety. So far, no optimum catalyst of this type could be identified. For instance, $Cu(OAc)_2$ and $MgCl_2/MgBr_2$ mixtures led to crude products whose IR spectra suggested a predominant ketone coordination (cf. Supporting Information, Figure S1). However, the reaction catalyzed by the former was very slow, and the reaction with the latter resulted only in a 6:4 mixture of two diastereoisomers of methiosetin (cf. Supporting Information). In addition, the counteranion of the metal catalyst also played a role by influencing the IMDA reaction rates and the stability of the TIPS protecting group. Table S3 shows the effect of various catalysts on the progress and stereochemical outcome of the IMDA reaction.

CONCLUSIONS

We synthesized the methiosetin stereoisomer **1** by controlling the stereoselectivity of the IMDA reaction of the (*E*2,*E*8,*E*10)-dodecatrienoyl residue of **15** via an aluminum or lanthanum (1-*O*,2′-*O*)-chelate complex of its 3-acyltetramic acid core. This stereoinduction relied on the presence of a bulky residue at C-5′, apparent from the failure of a similar stereoinduction in the case of the alanine-derived tetramic acid TA-289 **4**. We could also assign the absolute configuration of methiosetin isomer **1**. Although it comprises a decalin residue which is configured as was proposed for the natural isolate, it is not identical to it. The most plausible explanation is a wrong stereochemical assignment of the structure of the natural isolate. We provided evidence for other metal catalysts, such as copper acetate or magnesium halides, being able to induce the formation of a decalin residue that is the enantiomer of that in isomer **1** and thus probably the "natural" one. However, a large-scale screening will be necessary to pinpoint suitable metal catalysts that form exclusively tetramic acid chelate complexes employing the 4′-keto function and that give rise to a rapid IMDA reaction.

EXPERIMENTAL SECTION

General Remarks. IR spectra were recorded with an FT-IR spectrophotometer equipped with an ATR unit. Chemical shifts of NMR signals are given in parts per million (δ) downfield from tetramethylsilane for ^{1}H and ^{13}C. Mass spectra were obtained under EI (70 eV) conditions. High-resolution mass spectra were obtained with a UPLC/Orbitrap MS system in ESI mode. For chromatography silica gel 60 (230−400 mesh) was used. HPLC was performed on Prontosil RP 200-5-C18, 5 μm, 250 × 4 mm (analytic) and 250 × 20 mm (preparative) columns.

2-(5*E*,7*E*)-Nona-5,7-diene-1-yl)-1,3-dioxolane 10. A suspension of magnesium (3.1 g, 142.5 mmol) in THF (17 mL) was treated dropwise with a sixth of a solution of 2-(3-bromopropyl)-1,3-dioxolane **7** (13.9 g, 71.4 mmol) in THF (17 mL). Dibromoethane (0.25 mL, 0.25 mmol) was added to activate the metal, then the remaining solution of 2-(3-bromopropyl)-1,3-dioxolane was added dropwise over a period of 15 min. The resulting solution was stirred at 30 °C for 1.5 h and then added dropwise to a solution of sorbinic acetate **9** (8.84 g, 59.2 mmol) and CuBr−DMS complex (1.28 g, 18,0 mmol) in THF (85 mL) and cooled to −40 °C. The resulting deep purple solution was stirred at −40 °C for 3 h, allowed to warm to room temperature overnight, and then quenched with saturated aqueous NH_4Cl (170 mL). The mixture was extracted three times with diethyl ether, and the combined organic layers were washed with brine, dried, and concentrated. The residue was dissolved in a 3:1 mixture of MeOH/THF (500 mL), NaOH (30 g) was added, and the mixture was stirred for 1.5 h to hydrolyze residual sorbic acetate. Half-concentrated aqueous $NaHCO_3$ (400 mL) was added, the organic layer was separated, and the aqueous one was extracted four times with diethyl

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ether. The combined organic layers were washed with brine, dried, and concentrated. The remainder was purified by column chromatography (cyclohexane/ethyl acetate 9:1, R_f 0.34) to leave **10** (9.0 g, 78%) as a colorless oil: IR (ATR) ν_{max} 3015, 2927, 2859, 1436, 1409, 1211, 1130, 1059, 1033, 986, 942, 863, 737, 709 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29−1.42 (m, 4 H), 1.52−1.62 (m, 2 H), 1.65 (d, J = 6.4 Hz, 3 H), 1.99 (dt, J = 6.1, 6.4 Hz, 2 H), 3.71−3.81 (m, 2 H), 3.82−3.91 (m, 2 H), 4.76 (t, J = 4.9 Hz, 1 H), 5.38−5.58 (m, 2 H), 5.86−6.10 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.7, 23.5, 29.2, 32.3, 33.6, 64.6, 104.4, 126.5, 130.3, 131.4, 131.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{21}O_2^+$ 197.15361, found 197.15366.

(6*E*,8*E*)-Deca-6,8-dienal 11. A mixture of **10** (1.29 g, 6.55 mmol), THF (19 mL), water (23 mL), and acetic acid (12 mL) was heated at 90 °C for 1.5 h. Due to identical R_f values of **10** and **11**, the progress of the reaction was controlled by gas chromatography. After completion, the solution was cooled to room temperature, treated with saturated $NaHCO_3$ (50 mL), and extracted three times with hexanes. The combined organic layers were washed with brine, dried over $NaSO_4$, and concentrated. The remainder was purified by column chromatography (cyclohexane/ethyl acetate 9:1, R_f 0.34) to leave **11** (0.97 g, 97%) as a colorless oil: IR (ATR) ν_{max} 3017, 2932, 2720, 1725, 1449, 988 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.36−1.48 (m, 2 H), 1.64 (quint, J = 7.4 Hz, 2 H), 1.72 (d, J = 6.3 Hz, 3 H), 2.07 (dt, J = 7.4, 14.0 Hz, 2 H), 2.42 (dt, J = 1.8, 7.4 Hz, 2 H), 5.44−5.64 (m, 2 H), 5.92−6.07 (m, 2 H), 9.78 (t, J = 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.0, 21.6, 28.9, 32.2, 43.7, 127.2, 130.9, 131.0, 131.5, 202.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{10}H_{17}O^+$ 153.12739, found 153.12739.

3-[(Triphenylphosphoranylidene)acetyl]-(5*S*)-((1′*R*)-1′-triisopropylsilyloxyethyl)-1-methylpyrrolidine-2,4-dione 14. A solution of tetramic acid **12**[15,16] (570 mg, 1.8 mmol) in THF (24 mL) was treated with Ph_3PCCO **13** (604 mg, 2.0 mmol) and refluxed for 12 h. Evaporation under reduced pressure afforded ylide **14** quantitatively as a brownish foam of mp 81 °C: IR (ATR) ν_{max} 2941, 2864, 1656, 1612, 1550, 1463, 1437, 1190, 1103, 1067, 1015, 997, 882, 851, 783, 746, 719, 690, 570, 540 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.98−1.11 (m, 42 H), 1.39 (d, J = 6.6 Hz, 3 H), 1.44 (d, J = 6.6 Hz, 3 H), 3.019 (s, 3 H), 3.023 (s, 3 H), 3.36 (d, J = 3.0 Hz, 1 H), 3.43 (d, J = 3.0 Hz, 1 H), 4.44 (qd, J = 6.6, 3.0 Hz, 1 H), 4.45 (qd, J = 6.6, 3.0 Hz, 1 H), 5.23 (d, J_{P-H} = 20.3 Hz, 1 H, fast H/D exchange in $CDCl_3$; signal disappears overnight), 7.45−7.53 (m, 12 H), 7.57−7.68 (m, 18 H); ^{31}P NMR ($CDCl_3$, 161.7 MHz) (ylides/betaines ~3:1) δ 14.8/14.9 (P=CHCOH), 21.4/21.9 ($P^+CH_2CO^-$); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.2, 17.75/17.78, 21.8/22.3, 28.58/28.64, 51.2 (d, J = 109.9 Hz)/51.4 (d, J = 111.7 Hz), 67.7/68.3, 69.3/71.3, 91.1/94.9 (d, J = 12.7 Hz), 119.0 (d, J = 88.1 Hz), 124.5/124.7 (d, J = 91.7 Hz), 128.1, 128.2, 128.3, 128.73, 128.76, 128.83, 128.9, 129.3, 129.4, 129.9, 130.0, 131.61, 131.63, 131.7, 132.47, 132.50, 132.55, 132.57, 132.70, 132.79, 132.84, 133.5, 133.6, 134.61, 134.63, 172.5/173.4, 172.3/177.1, 189.7/192.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{36}H_{47}NO_4PSi^+$ 616.3007, found 616.2998.

(5*S*)-((1*R*)-Triisopropylsilyloxyethyl)-1-methyl-3-((2*E*,8*E*,10*E*)-dodecatrienoyl)-pyrrolidine-2,4-dione 15. A solution of ylide **14** (920 mg, 1.5 mmol) in CH_2Cl_2 (20 mL) was treated with KO*t*Bu (180 mg, 1.6 mmol). After complete dissolution of the base, decadienal **11** (210 mg, 1.38 mmol) was added, and the mixture was stirred overnight at room temperature and finally washed with 1 M aqueous $NaHSO_4$, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by reversed-phase column chromatography (C-18, rinsing with 85% MeOH, 0.1% HCOOH in the water fraction, elution of the product with pure MeOH) to afford **15** as a yellow oil (550 mg, 1.1 mmol, 81%): IR (ATR) ν_{max} 2938, 2866, 1709, 1645, 1583, 1461, 1375, 1327, 1215, 1139, 1097, 1068, 986, 910, 882, 828, 782, 731, 677 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.75−1.10 (m, 21 H), 1.33−1.50 (m, 4H), 1.40 (d, J = 6.6 Hz, 3 H), 1.69 (d, J = 6.3 Hz, 3 H), 1.98−2.10 (m, 2 H), 2.21−2.35 (m, 2 H), 3.09 (s, 3 H), 3.47 (d, J = 1.4 Hz, 1 H), 4.52 (qd, J = 6.6, 1.4 Hz, 1 H), 5.32−5.63 (m, 2 H), 5.84−6.06 (m, 2 H), 6.98−7.17 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.5, 17.9, 18.0, 22.6, 27.7, 28.9, 29.1, 32.2, 32.9, 68.2, 72.3, 100.2, 113.7, 121.6, 126.8/130.6/131.2/131.5, 149.4, 172.5, 174.4, 193.3; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{28}H_{48}NO_4Si^+$ 490.3347, found 490.3348; $[M + H]^+$ calcd for $C_{28}H_{48}NaNO_4Si^+$ 512.3166, found 512.3168; $[M - H]^-$ calcd for $C_{28}H_{46}NO_4Si^-$ 488.3202, found 488.3212.

(*R*)-4-Benzyl-3-((2*E*,8*E*,10*E*)-dodeca-2,8,10-trienoyl)-oxazolidin-2-one 19. A solution of (6*E*,8*E*)-deca-6,8-dienal **11** (0.97 g, 6.38 mmol) and ylide **18**[23] (4.47 g, 9.33 mmol) in toluene (100 mL) was heated at 80 °C for 24 h. The remainder upon concentration was purified by column chromatography (cyclohexane/ethyl acetate 3:1, R_f 0.47) to give **19** (1.3 g, 58%) as a colorless oil: $[\alpha]_D^{20}$ −31.1 (c 1.0, CH_2Cl_2); IR (ATR) ν_{max} 3016, 2926, 2855, 1774, 1682, 1634, 1498, 1455, 1386, 1352, 1290, 1209, 1196, 1110, 1099, 1077, 1054, 987, 923, 851, 806, 761, 750, 731, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.35−1.56 (m, 4 H), 1.71 (d, J = 6.2 Hz, 3 H), 2.10 (dt, J = 7.2, 14.2 Hz, 2 H), 2.28 (dt, J = 6.8, 13.0 Hz, 2 H), 2.77 (dd, J = 13.2, 9.6 Hz, 1 H), 3.32 (dd, J = 13.2, 3.2 Hz, 1 H), 4.11−4.22 (m, 2 H), 4.72 (ddd, J = 3.4, 7.0, 13.1 Hz, 1H), 5.45−5.63 (m, 2 H), 5.92−6.06 (m, 2 H), 7.11−7.37 (m, 7 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.9, 27.6, 28.9, 32.2, 32.5, 37.9, 55.3, 66.0, 120.0, 127.0, 127.3, 128.9, 129.4, 130.6, 131.4, 131.5, 135.4, 151.7, 153.4, 165.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{22}H_{28}O_3N^+$ 354.20615, found 354.20605.

(4*R*)-Benzyl-3-((1*R*,2*R*,4a*S*,8a*R*)-1,2,4a,5,6,7,8,8a-octahydro-2-methylnaphthalene-1-carbonyl)oxazolidin-2-one 20. A solution of triene **19** (475 mg, 1.34 mmol) in CH_2Cl_2 (38 mL) was cooled to −30 °C and treated dropwise with a 0.9 M solution of Me_2AlCl in hexane (3 mL, 2.69 mmol) over 10 min. The mixture was stirred for another 4.5 h at −30 °C, treated with 1 M hydrochloric acid (20 mL), and extracted four times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The remainder was purified by column chromatography (cyclohexane/ethyl acetate 4:1, R_f 0.63) to give **20** (474 mg, 99%) as a colorless oil: $[\alpha]_D^{20}$ −123 (c 0.98, CH_2Cl_2) (lit.[18] $[\alpha]_D^{20}$ −185 (c 0.96, CH_2Cl_2)); IR (ATR) ν_{max} 2926, 1776, 1694, 1449, 1384, 1372, 1349, 1322, 1292, 1261, 1234, 1215, 1194, 1148, 1101, 1087, 1049, 1020, 998, 909, 817, 792, 767, 729, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.79−0.90 (m, 1 H), 0.95 (d, J = 7.2 Hz, 3 H), 1.00−1.22 (m, 1 H), 1.24−1.47 (m, 2 H), 1.52−1.67 (m, 1 H), 1.71−1.82 (m, 4 H), 1.86−1.96 (m, 1 H), 2.63 (dd, J = 10.6, 13.1 Hz, 1 H), 2.73−2.88 (m, 1 H), 3.42 (dd, J = 3.3, 13.1 Hz, 1 H), 3.82 (dd, J = 5.9, 11.3 Hz, 1 H), 4.10−4.19 (m, 2 H), 4.72 (ddd, J = 3.4, 7.0, 13.9 Hz, 1 H), 5.41 (br d, J = 9.9 Hz, 1 H), 5.58 (ddd, J = 2.6, 4.6, 9.9 Hz, 1 H), 7.21−7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.7, 26.5, 26.6, 30.0, 30.8, 33.1, 36.5, 38.2, 41.8, 47.6, 55.3, 66.0, 127.2, 128.9, 129.3, 130.6, 130.8, 135.5, 153.0, 173.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{28}O_3N^+$ 354.20637, found 354.20554.

(1*R*,2*R*,4a*S*,8a*R*)-1,2,4a,5,6,7,8,8a-octahydro-2-methylnaphthalene-1-carboxylic acid thiopropyl ester 21. A solution of oxazolidin-2-one **20** (50 mg, 0.14 mmol) and propanethiol (0.1 mL, 1.1 mmol) in THF (0.9 mL) was cooled to 0 °C and treated dropwise with a 2.25 M solution of *n*-butyllithium in hexane (0.1 mL). The mixture was stirred at 0 °C for 10 min, quenched with water (7.5 mL) and extracted four times with *t*-butyl methyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The remainder was purified by column chromatography (cyclohexane/ethyl acetate 3:1, R_f 0.7) to leave **21** (35 mg, 99%) as a waxy solid; $[\alpha]_D^{20}$ − 41.9 (c 1.0, CH_2Cl_2). IR (ATR) ν_{max} 2962, 2921, 2873, 2852, 1694, 1684, 1447, 1375, 1291, 1241, 1088, 1084, 1018, 998, 953, 913, 893, 862, 847, 824, 804, 788, 739, 721, 554 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78−0.93 (m, 1 H), 0.85 (d, J = 7.2 Hz, 3 H), 0.93 (t, J = 7.3 Hz, 3 H), 0.99−1.11 (m, 1 H), 1.20−1.34 (m, 2 H), 1.43−1.56 (m, 1 H), 1.55 (sex, J = 7.3, 2 H), 1.61−1.75 (m, 4 H), 1.77−1.87 (m, 1 H), 2.45−2.61 (m, 1 H), 2.70−2.91 (m, 1 H), 2.78 (q, J = 7.3, 2 H), 5.33 (br d, J = 9.9 Hz, 1 H), 5.49 (ddd, J = 2.6, 4.6, 9.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.3, 17.3, 23.2, 26.4, 26.6, 29.5, 30.5, 33.0, 33.5, 37.0, 42.4, 58.5, 130.8, 130.85, 200.3; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{25}OS^+$ 253.16206, found 253.16194.

(1*R*,2*R*,4a*S*,8a*R*)-1,2,4a,5,6,7,8,8a-Octahydro-2-methylnaphthalene-1-carboxylic Acid 17. A solution of thioester **21** (351 mg, 1.39 mmol) in 4:1 dioxane/water (30 mL) was treated with $AgNO_3$

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(1500 mg, 8.83 mmol) and refluxed until no further starting material could be detected by TLC. The suspension was extracted four times with CH_2Cl_2, and the combined extracts were purified by suction over a plug of Celite. Condensation of the filtrate and column chromatography (cyclohexane/ethyl acetate 3:1, R_f 0.5) afforded **17** (251 mg, 93%) as a crystalline solid of mp 123.2 °C (from *n*-hexane): $[\alpha]_D^{20}$ −159.2 (*c* 0.97, CH_2Cl_2); IR (ATR) ν_{max} 2929, 2852, 1703, 1447, 1420, 1292, 1262, 1223, 1194, 948, 743, 717, 671, 582, 567 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83−0.98 (m, 1 H), 0.98 (d, *J* = 7.2 Hz, 3 H), 1.02−1.10 (m, 1 H), 1.19−1.46 (m, 4 H), 1.61−1.82 (m, 4 H), 1.95−2.06 (m, 1 H), 2.51−2.64 (m, 2 H), 5.37 (br d, *J* = 9.9 Hz, 1 H), 5.53 (ddd, *J* = 2.6, 3.9, 9.9 Hz, 1 H) 10.97 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.6, 26.5, 26.6, 30.0, 32.1, 33.0, 36.2, 42.0, 49.5, 130.5, 131.0, 180.6; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{17}O_2^-$ 193.12231, found 193.12279.

Carboxylic Acid 17 from Cleavage of Methiosetin Isomer 1. A solution of methiosetin isomer **1** (30 mg, 0.09 mmol) in MeOH (1 mL) was treated with H_2O_2 (30% in H_2O, 2 mL), 1 M NaOH solution in H_2O (1 mL), and H_2O (5 mL) and stirred at room temperature. After 4 and 8 h, the solution was treated once more with H_2O_2 (30% in H_2O, 1 mL) and 1 M NaOH solution in H_2O (0.5 mL). After 24 h, 1 M hydrochloric acid was added to adjust a pH value of 1−2. The resulting solution was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The remainder was purified by column chromatography (silica gel; cyclohexane/ethyl acetate 3:1, R_f 0.5) to afford **17** (6 mg, 35%) as colorless crystals: $[\alpha]_D^{20}$ −157.2 (*c* 0.50, CH_2Cl_2). All other data were identical to those of compound **17** obtained from thioester **21**.

(5*S*)-((1′*R*)-Hydroxyethyl)-1-methyl-3-((1*R*,2*R*,4a*S*,8a*R*)-1,2,4a,5,6,7,8,8a-octahydro-2-methylnaphthalene-1-carbonyl)pyrrolidone-2,4-dione (Methiosetin) 1. *Protocol A:* A solution of 3-dodecatrienoyltetramic acid **15** (200 mg, 0.4 mmol) in CH_2Cl_2 (10 mL) was treated dropwise with a 1 M solution of Me_2AlCl in hexane (2 equiv, 0.8 mL) and then stirred for 3 days. The mixture was washed with 1 M aqueous $NaHSO_4$, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (10 mL) at room temperature and treated with $BF_3 \times OEt_2$ (0.8 mmol, 211 μL, 48% in ether) under exclusion of air and moisture. After being stirred overnight, the solution was washed with 1 M aqeuous $NaHSO_4$, dried over Na_2SO_4, and concentrated under reduced pressure. The crude BF_2 complex was hydrolyzed by boiling in methanol for 2 h. The solvent was evaporated, and the residue was taken up in ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and evaporated. The free 3-acyltetramic acid was purified by preparative HPLC (Kinetex C-18, 5 μm, rinsing with 65% MeOH, 0.1% HCO_2H in the water fraction, elution of the product with 77% MeOH) to afford **1** as a yellow oil (38 mg, 0.11 mmol, 29%).

Protocol B: A solution of tetramic acid **15** (274 mg, 0.56 mmol) in CH_2Cl_2 (20 mL) was treated with $La(OTf)_3$ (328.2 mg, 0.56 mmol) and stirred at room temperature for 2 days. The mixture was washed with 1 M aqueous $NaHSO_4$, dried over Na_2SO_4, and concentrated under reduced pressure. The remainder was dissolved in THF (1 mL) in a plastic vial and was treated with HF (70% in pyridine, 100 μL, 3.6 mmol). After being stirred for 24 h, Et_3SiH (573 μL, 3.6 mmol) was added and the resulting mixture was stirred for another 30 min. The solution was poured into methanol/water (65/35, 20 mL), and 3-acyltetramic acid **1** was extracted and purified by preparative HPLC (Kinetex C-18, 5 μm, rinsing with 65% MeOH, 0.1% HCO_2H in the water fraction, elution of the product with 77% MeOH) to afford pure **1** as a yellow oil (110 mg, 0.33 mmol, 59%): $[\alpha]_D^{25}$ −63 (*c* 0.83, MeOH); IR (ATR) ν_{max} 3438 (br), 3010, 2968, 2925, 2854, 1705, 1644, 1606, 1485, 1449, 1394, 1374, 1333, 1281, 1257, 1212, 1124, 1088, 989, 946, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.90 (qd, *J* = 11.9, 3.4 Hz, 1 H), 0.96 (d, *J* = 7.0 Hz, 3 H), 1.14 (d, *J* = 6.7 Hz, 2 H), 1.27−1.40 (m, 2 H), 1.59 (dddd, *J* = 11.7, 11.3, 10.0, 2.8 Hz, 1 H), 1.66−1.77 (m, 4 H), 1.78−1.88 (m, 2 H), 2.47−2.58 (m, 1 H), 2.99 (s, 3 H), 3.70 (dd, *J* = 11.6, 5.8 Hz, 1 H), 3.80 (d, *J* = 4.6 Hz, 1 H), 4.18 (qd, *J* = 6.7, 4.6 Hz, 1 H), 5.41 (d, *J* = 9.9 Hz, 1 H), 5.55 (ddd, *J* = 9.9, 4.6, 2.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 17.6, 17.8, 26.5, 26.6, 27.1, 29.9, 33.0, 33.2, 36.0, 42.2, 46.6, 66.7, 68.5, 102.7, 130.8, 130.9, 174.1, 191.1, 194.8; ^1H NMR (MeOD, 500 MHz) δ 0.88 (dq, *J* = 12.2, 2.5 Hz, 1 H), 0.92 (d, *J* = 7.0 Hz, 1 H), 1.05−1.14 (m, 1 H), 1.31 (d, *J* = 6.7 Hz, 3 H), 1.56 (qd, *J* = 11.3, 2.5 Hz, 1 H), 1.74−1.78 (m, 2 H), 1.85 (d, *J* = 11.6 Hz, 1 H), 2.53 (td, *J* = 6.1, 5.2 Hz, 1 H), 3.06 (s, 2 H), 3.71 (br s, 1 H), 3.77 (dd, *J* = 11.5, 5.5 Hz, 1 H), 4.16 (qd, *J* = 6.7, 3.4 Hz, 1 H), 5.41 (d, *J* = 9.8 Hz, 1 H), 5.56 (ddd, *J* = 10.1, 4.6, 2.5 Hz, 1 H); HRMS (ESI) *m*/*z* $[M - H]^-$ calcd for $C_{19}H_{26}NO_4^-$ 332.1856, found 332.1871.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00750.

NMR spectra of **1**, **10**, **11**, **14**, **15**, **17**, and **19**−**21**; IR spectra of Al and Cu chelate complexes of IMDA precursor **15**; chemical shifts of carbon and hydrogen atoms of isolated natural methiosetin and synthetic **1**; influence of various metal catalysts on the IMDA reaction of **15**; HPLC chromatograms of IMDA products of **15** catalyzed by various Lewis acids (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rainer.schobert@uni-bayreuth.de.

Author Contributions

†M.W. and K.K. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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