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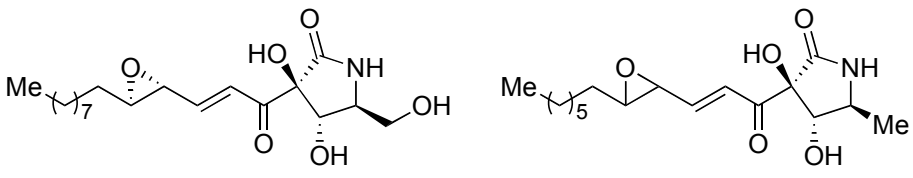
TOTAL SYNTHESIS OF (−)-PRAMANICIN‡

Shin-ya Aoki, Taro Tsukude, Yukari Miyazaki, Ken-ichi Takao, and Kin-ichi Tadano*

Department of Applied Chemistry, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan
tadano@applc.keio.ac.jp

Abstract – The total synthesis of natural (−)-pramanicin, a highly oxygenated γ-lactam-type antifungal agent, is described. The enantiospecific total synthesis of this natural product commenced with 5-deoxy-1,2-*O*-isopropylidene-α-D-xylo-furanose as an enantiopure starting material.

(−)-Pramanicin (−)-(**1**) (Figure 1), isolated from the fungus *Stagonospora* species by Schwartz and coworkers in 1994,[1] showed moderate antifungal activity against various fungal strains, including *Candida* sp. and *Cryptococcus neoformans*, as well as antibacterial activity against *Bacillus subtilis*. Later, Kwan and coworkers reported that (−)-**1** has a cytotoxic effect on vascular endothelial cells, resulting in the loss of vasorelaxant function.[2] Recently, Basaga and coworkers reported that (−)-**1** induces apoptosis in Jurkat leukemia cells.[3] The structure of (−)-**1**, including its relative stereochemistry, was determined by a combination of 1-D and 2-D NMR techniques, mass spectral analysis, and chemical modification.[1] Harrison and coworkers explored the incorporation experiment of labeled acetates and serine into (−)-**1**, which reveals that the carbon framework of (−)-**1** is derived from eight acetate and a serine residue.[4] Through a biosynthetic experiment, the absolute configuration of (−)-**1** was determined. Furthermore, Barrett and coworkers reported the total synthesis of the antipode (+)-(**1**), establishing the absolute stereochemistry of pramanicin.[5] The structurally related natural product TMC-260 (**2**) was isolated in 2003 from the fermantation broth of *Acremonium kiliense* Grüetz TC 1703 as an inhibitor of



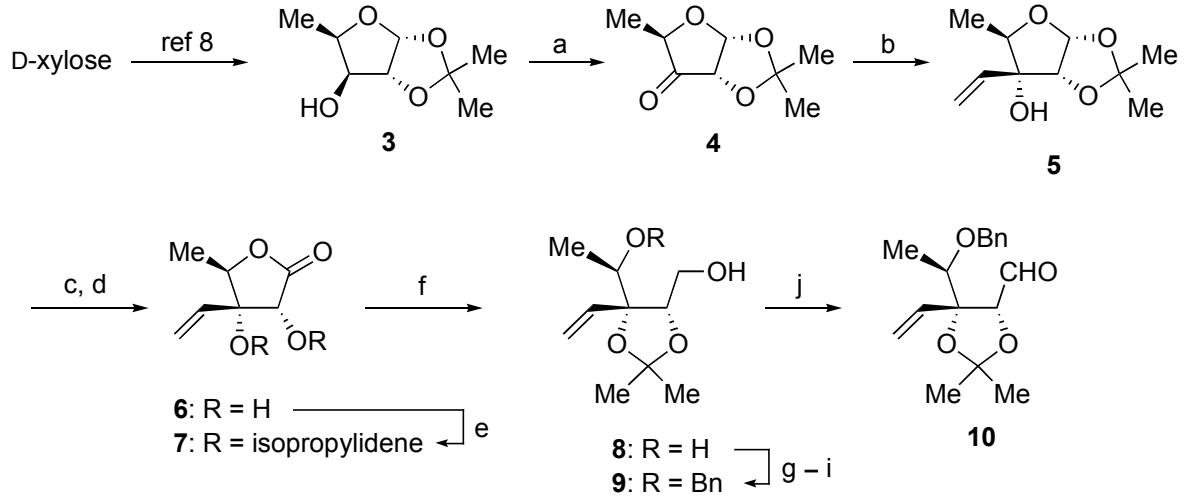
(−)-pramanicin (-)-(**1**) TMC-260 (**2**)

Figure 1. Structures of (−)-pramanicin (-)-**1** and TMC-260 **2**

‡ This paper is dedicated to Dr. Satoshi Omura (The Kitasato Institute, and Kitasato Institute of Life Science, Kitasato University) with respect and admiration on the occasion of his 70th birthday.

interleukin-4 signal transduction.[6] These two natural products (−)-(**1**) and (**2**) consist of a highly oxygenated and γ-alkylated γ-lactam with a lipophilic side chain containing a γ,δ-epoxyenone structure. We describe herein the total synthesis of natural (−)-pramanicin (−)-(**1**) using a carbohydrate derivative as a chiron.[7]

Our total synthesis began with the known 5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (**3**), prepared conveniently from D-xylose.[8] Oxidation of **3** with PCC, followed by a vinyl Grignard addition to the 3-ulose (**4**), provided the desired β-oriented adduct (**5**) as a single diastereomer (Scheme 1).[9] The vinyl nucleophile exclusively attacked the convex face of the trioxabicyclo[3.3.0]octane structure of **4**. Acidic hydrolysis of the acetal moiety in **5** and subsequent chemoselective oxidation of the hemiacetal hydroxyl group with *N*-iodosuccinimide (NIS) provided γ-lactone-α,β-diol (**6**). The diol in **6** was protected as the isopropylidene acetal affording **7**, which was reduced with $LiAlH_4$ to provide an acyclic 1,4-diol (**8**). A three-step protection/deprotection sequence from **8** via the primary trityl ether provided the secondary benzyl ether (**9**). Dess−Martin oxidation[10] of **9** produced a five-carbon aldehyde (**10**).

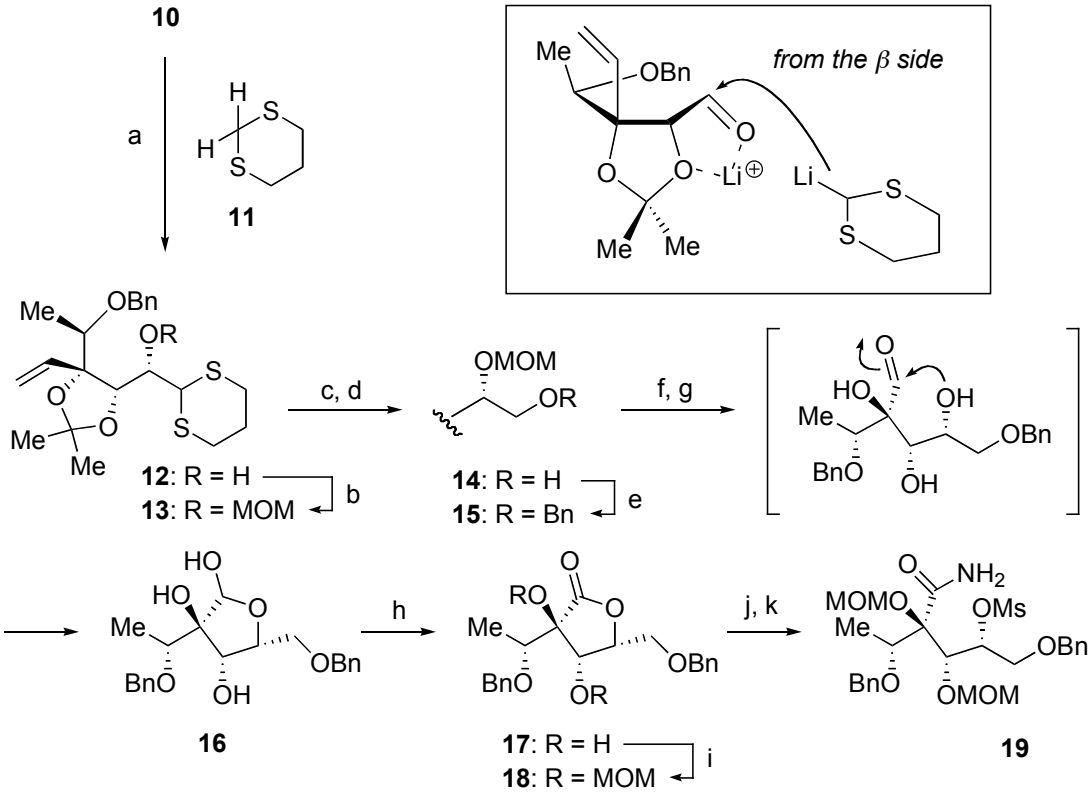


Reagents and conditions: a) PCC, MS4A, CH_2Cl_2; b) CH_2=CHMgBr, THF, −18 °C, 73% for 2 steps; c) 80% aq. AcOH, 80 °C; d) NIS, *n*-Bu_4NI, CH_2Cl_2, 77% for 2 steps; e) $Me_2C(OMe)_2$, acetone, CSA, reduced pressure (ca. 300 hPa), 40 °C, 72%; f) $LiAlH_4$, THF, 0 °C, 94%; g) TrCl, DMAP, pyr, reflux; h) BnBr, NaH, DMF; i) CSA, MeOH, 89% for 3 steps; j) Dess−Martin periodinane, CH_2Cl_2, 99%.

Scheme 1

The addition of the 2-lithiated 1,3-dithiane, prepared from 1,3-dithiane (**11**) and *n*-BuLi (execss) in THF at −18 °C, to **10** produced the 1,3-dithiane (**12**) as a single stereoisomer in an excellent yield of 97% (Scheme 2). The configuration of the newly introduced stereogenic center in **12** shown as depicted was established later. This exclusive stereoselective addition of the 2-lithiated 1,3-dithiane to **10** can be explained using a depicted lithium-ion-associated five-member chelation-controlled transition state, in which the nucleophile attacks from the less hindered β-side leading to **12**. Protection of the secondary hydroxyl group in **12** as a methoxymethyl (MOM) ether and subsequent conversion of the 1,3-dithiane moiety in the MOM ether (**13**) into the primary hydroxyl group was achieved with methyl iodide in wet

CH_3CN at 50 °C, followed by treatment with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ in a mixed solvent of DMPU and cyclohexene (1:1, v/v), providing **14**. Protection of the hydroxyl group in **14** as a benzyl ether afforded **15**.[11] Ozonolysis of the carbon–carbon double bond in **15**, followed by simultaneous hydrolysis of the isopropylidene acetal and the MOM group, provided γ-lactol (**16**). The lactol carbon in **16** was oxidized with NIS to provide γ-lactone-α,β-diol (**17**). The two hydroxyl groups in **17** were protected as *O*-MOM ethers to provide fully protected γ-lactone (**18**). Treatment of **18** with liquid NH_3 (sealed tube) at room temperature provided a ring-opened amidation product quantitatively, which was subjected to chemoselective *O*-mesylation to provide the *O*-mesylate (**19**).

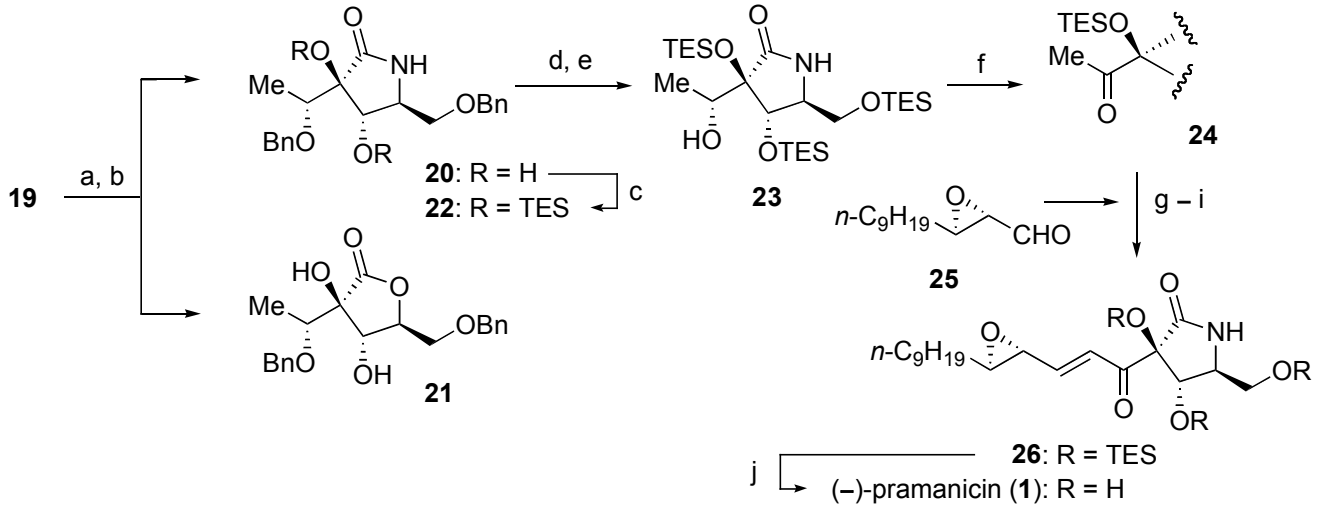


Reagents and conditions: a) **11** (6.0 equiv), *n*-BuLi (6.0 equiv), THF, −18 °C, then **10**, 97%; b) MOMCl, *i*-Pr_2NEt, CH_2Cl_2 reflux, 96%; c) MeI, CH_3CN/H_2O (4:1, v/v), 50 °C; d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, DMPU/cyclohexene (1:1, v/v), 0 °C; e) BnBr, NaH, DMF, 0 °C, 86% for 3 steps; f) O_3, CH_2Cl_2, −78 °C; Ph_3P; g) 60% aqueous CF_3CO_2H; h) NIS, *n*-Bu_4NI, CH_2Cl_2, 92% for 3 steps; i) P_2O_5, $CH_2(OMe)_2$, $CHCl_3$, 0 °C, 79%; j) *i*-PrOH/liquid NH_3 (1:1, v/v) in a sealed tube; k) MsCl, Et_3N, 1,2-dimethoxyethane, −18 °C, 83% for 2 steps.

Scheme 2

The desired γ-lactamization via S_N2–displacement of the mesyloxy group by the amide anion generated from **19** was then explored (Scheme 3). Treatment of the mesylate (**19**) with NaH (3.0 molar equiv) in DMSO at room temperature and subsequent acidic cleavage of the MOM ethers provided two cyclization products, i.e., the desired γ-lactam (**20**)[12] (52%) and the γ-lactone (**21**)[13] (44%). In this S_N2-type cyclization step, the attack of the amide anion (N^-) (desired) and that of the imidate anion (O^-) (undesired)

competed. We examined other basic conditions for the attempted γ-lactamization, however, the yield of **20** could not be improved.[14] The liberated hydroxyl groups in **20** were protected as TES ethers to provide **22**. Deprotection of the benzyl groups in **22** by hydrogenolysis, followed by regioselective *O*-silylation, provided a tri-*O*-triethylsilyl (TES) derivative (**23**). The remaining hydroxyl group in **23** was oxidized to produce methyl ketone (**24**). On the other hand, enantiomeric (2*S*,3*R*)-2,3-epoxydodecanal (**25**) (>99% ee, HPLC analysis) as the side-chain precursor was synthesized from *n*-decylaldehyde according to the reported procedure.[5] The attempted aldol reaction of **24** and **25** was best achieved as follows. Deprotonation of **24** with KHMDS (2.0 molar equiv) in THF at −78 °C, followed by the addition of **25** (3.0 molar equiv), provided the desired aldol adducts as a 3:2 diastereomeric mixture (^{1}H NMR analysis). Acetylation of the aldol mixture, followed by treatment with hot pyridine, afforded the γ,δ-epoxyenone (**26**) in 43% yield from **24**. Removal of the *O*-TES groups in **26** completed the total synthesis of (−)-pramanicin (−)-(**1**). The spectroscopic data (mp, IR, ^{1}H and ^{13}C NMR, HRMS) and optical property of synthetic (−)-**1** matched well those reported for natural (−)-**1** in all respects.[15] In summary, we have accomplished the total synthesis of natural (−)-pramanicin (−)-(**1**) for the first time by using a carbohydrate-based chiron approach.



Reagents and conditions: a) NaH, DMSO; b) 8 M HCl/MeOH (1:1, v/v) , 52% for **20** and 44% for **21** for 2 steps; c) TESOTf, pyr, 40 °C, 95%; d) H_2, 10% Pd on C, EtOAc; e) TESCl, pyr, CH_2Cl_2, −18 °C, 93% for 2 steps; f) Dess–Martin periodinane, CH_2Cl_2, 91%; g) KHMDS, THF, −78 °C then **25**; h) Ac_2O, pyr; i) pyr, 90 °C, 43% for 3 steps; j) HF·pyridine complex, pyr, 88%.

Scheme 3

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7. We have achieved total syntheses of some highly oxygenated γ-lactam-type natural products starting from D-glucose. For pseurotins A, F_2, and azaspirene, see: (a) S. Aoki, T. Oi, K. Shimizu, R. Shiraki, K. Takao, and K. Tadano, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 1703. (b) S. Aoki, T. Oi, K. Shimizu, R. Shiraki, K. Takao, and K. Tadano, *Heterocycles*, 2004, **62**, 161. (c) S. Aoki, T. Ohi, K. Shimizu, R. Shiraki, K. Takao, and K. Tadano, *Heterocycles*, 2002, **58**, 57. For PI-091, see: (d) R. Shiraki and K. Tadano, *Rev. Heteroatom Chem.*, 1999, **20**, 283. (e) R. Shiraki, A. Sumino, K. Tadano, and S. Ogawa, *J. Org. Chem.*, 1996, **61**, 2845. (f) R. Shiraki, A. Sumino, K. Tadano, and S. Ogawa, *Tetrahedron Lett.*, 1995, **36**, 5551.
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9. All new compounds were fully characterized by spectroscopic means [^{1}H NMR (300 MHz in $CDCl_3$ or CD_3OD) and ^{13}C NMR (75 MHz in $CDCl_3$ or CD_3OD), IR] and gave satisfactory HRMS spectrum. Yields referred to homogeneous samples purified by chromatography on silica gel.
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11. Compound (**15**) was converted into known (2*S*)-2,3-bis(benzyloxy)propanol (1,2-di-*O*-benzyl-*sn*-glycerol) by the following reaction sequence: 1) cleavage of the MOM group (CSA/MeOH, 76%); 2) benzylation of the resulting hydroxyl group (BnBr/NaH/DMF, 74%); 3) hydrolysis of the isopropylidene acetal (80% aqueous AcOH/60 °C, 94%); 4) oxidative cleavage of the resulting diol ($NaIO_4$/MeOH–H_2O); and 5) reduction of the resulting aldehyde ($NaBH_4$/MeOH, 81% for 2 steps). Comparison of the optical properties between the synthetic sample {$[\alpha]_D^{23}$ −17.0 (c 0.23, $CHCl_3$)} and the reported one for (2*S*)-2,3-bis(benzyloxy)propanol {$[\alpha]_D^{21}$ −17.2 (*c* 1, $CHCl_3$)} [C. A. A. van Boeckel, G. M. Visser, and J. H. van Boom, *Tetrahedron*, 1985, **41**, 4557] concluded the (*S*)-configuration for the newly introduced stereogenic center in **12**.
12. Compound (**20**) was obtained as colorless crystals: mp 152.0−152.4 °C; TLC R_f 0.35 (EtOAc/hexane, 1:1); $[\alpha]_D^{23}$ −39.5 (*c* 0.500, $CHCl_3$); IR (neat) 3400, 2920, 1695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (d, 3H, *J* = 6.4 Hz), 2.91 (d, 1H, *J* = 7.1 Hz), 3.01 (br s, 1H), 3.35 (dd, 1H, *J* = 8.3, 9.4 Hz), 3.66 (ddd, 1H, *J* = 3.2, 7.1, 8.3 Hz), 3.74 (dd, 1H, *J* = 3.2, 9.4 Hz), 4.00 (q, 1H, *J* = 6.4 Hz), 4.06 (t, 1H, *J* = 7.1 Hz), 4.51 (s, 2H), 4.52, 4.70 (AB q, each 1H, *J* = 11.5 Hz), 5.93 (br s, 1H), 7.27−7.43 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 58.4, 71.4, 71.7, 73.5, 78.9, 79.2 × 2, 127.8 × 3, 128.0 × 3, 128.1

× 2, 128.6 × 2, 137.3, 137.5, 173.9; HRMS calcd for $C_{21}H_{25}NO_5$ (M^+) *m/z* 371.1733, found 371.1732.

13. Compound (**21**) was obtained as colorless crystals: mp 89.7–90.8 °C; TLC R_f 0.44 (EtOAc/hexane, 1:1); $[\alpha]_D^{24}$ +30.3 (*c* 1.60, $CHCl_3$); IR (neat) 3450, 2920, 1790 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (d, 3H, *J* = 6.4 Hz), 2.80 (d, 1H, *J* = 5.8 Hz), 3.21 (s, 1H), 3.68, 3.74 (2 dd, each 1H, *J* = 3.2, 11.5 Hz), 4.11 (q, 1H, *J* = 6.4 Hz), 4.40 (dt, 1H, *J* = 6.4, 3.2 Hz), 4.42 (dd, 1H, *J* = 5.8, 6.4 Hz), 4.52, 4.71 (AB q, each 1H, *J* = 11.3 Hz), 4.55, 4.61 (AB q, each 1H, *J* = 12.0 Hz), 7.26–7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2, 68.3, 71.2, 73.6, 75.4, 76.7, 78.6, 81.6, 127.8 × 3, 127.90 × 2, 127.94 × 2, 128.5 × 3, 137.2, 137.4, 175.4; HRMS calcd for $C_{21}H_{24}O_6$ (M^+) *m/z* 372.1573, found 372.1581.
14. We examined the following reaction conditions: a) NaH, DMF, 0 °C (36% for **20**, 52% for **21**); b) NaH, DMPU (**20**: 33%, **21**: 53%); c) NaH, benzene (**20**: 35%, **21**: 42%). Under the following reaction conditions, the γ-lactone (**21**) was a sole product: a) saturated aqueous Na_2CO_3, 1,2-dichloroethane, 60 °C (87%); b) LiH, DMF, 50 °C (94%); c) Cs_2CO_3, MeOH (94%).
15. (–)-Pramanicin (–)-(**1**) was obtained as colorless crystals: mp 118.6–120.5 °C; TLC R_f 0.13 (EtOAc); $[\alpha]_D^{24}$ –34.0 (*c* 0.150, CH_3OH) {$[\alpha]_D^{25}$ –35 (*c* 0.21, CH_3OH)[1] for natural (-)-**1**; $[\alpha]_D^{25}$ +28.8 (*c* 0.21, CH_3OH)[5] for synthetic (+)-**1**}; IR (KBr) 3360, 2940, 1715, 1690, 1635 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 0.89 (t, 3H, *J* = 6.6 Hz), 1.29 (br s, 12H), 1.46 (m, 2H), 1.60 (m, 2H), 2.93 (ddd, 1H, *J* = 2.0, 5.1, 6.1 Hz), 3.31 (m, 1H), 3.47 (ddd, 1H, *J* = 2.7, 5.4, 7.1 Hz), 3.54 (dd, 1H, *J* = 5.4, 11.5 Hz), 3.79 (dd, 1H, *J* = 2.7, 11.5 Hz), 4.15 (d, 1H, *J* = 7.1 Hz), 6.64 (dd, 1H, *J* = 7.1, 15.6 Hz), 7.05 (dd, 1H, *J* = 0.7, 15.6 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 14.4, 23.7, 27.0, 30.45, 30.51, 30.56, 30.64, 33.1 × 2, 57.8, 60.3, 62.0, 62.9, 78.9, 88.1, 127.9, 145.1, 175.0, 197.9; HRMS calcd for $C_{19}H_{31}NO_6$ (M^+) *m/z* 369.2151, found 369.2149.