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Study on Fungitoxic 3-Amino-2-piperidinone-containing Lipids: Total Syntheses of Cepaciamides A and B

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Abstract: Total syntheses of cepaciamides A and B were accomplished. In the preparation of two fatty acid segments, (*S*)-malic acid was used as a chiral source to introduce (2*S*)-configuration. A known chiral cyclopropane derivative was introduced in the segment of cepaciamide A. The formation of (*Z*)-olefin in the segment of cepaciamide B was achieved by means of partial reduction of the acetylenic bond. Esterification between fatty acid segments and amide segment with DCC/DMAP and subsequent oxidative deprotection of the MPM group with CAN gave cepaciamides.

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In the preceding paper,[1] we have described the revised structure of cepaciamide A (**1a**) and the structural determination of cepaciamide B (**2a**) closely related to **1a** (Fig. 1). Cepaciamides are novel fungitoxic 3-amino-2-piperidinone-containing lipids against *Botrytis cinerea* and *Penicillium expansum*, which cause the storage rot of beet roots, and are considered to be a promising biocontrol agent.[2] However, it is difficult to obtain a sufficient amount of cepaciamides from *Pseudomonas cepacia* D-202 because of its low productivity. Furthermore, a large amount of various phospholipids, which occur closely near the cepaciamide fraction, interfere with isolation and purification. In order to examine the structure-activity relationship of cepaciamides and their derivatives, stereochemically pure compounds must be supplied synthetically. We describe here the total syntheses of cepaciamides A (**1a**) and B (**2a**).

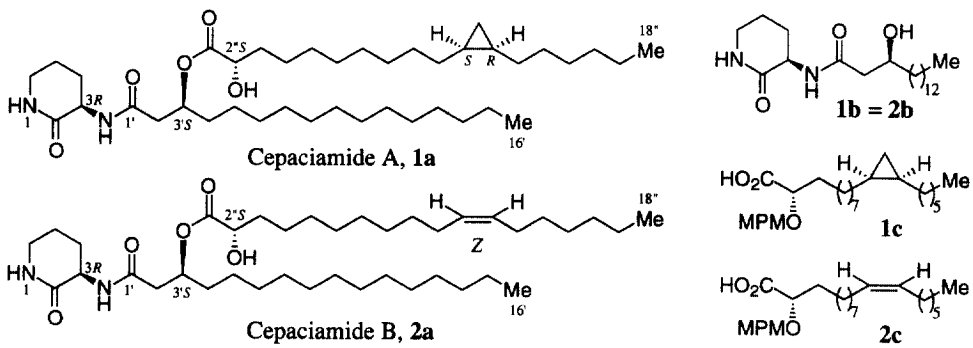

Fig. 1 Structures of cepaciamides and their segments

Since the common amide-segment (**1b** = **2b**) for cepaciamides has been prepared as described in the preceding paper,[1] carboxylic acid-segments (**1c** and **2c**) are required. While use of a non-protected segment[1] for the direct synthesis of **2a** failed, use of a TBDPS-protected segment[1] for esterification with DCC/DMAP gave an ester in moderate yield (65%). However, subsequent desilylation with TBAF or HF-pyridine gave **2a** in only 0-3% yield. From these preliminary results, we selected an MPM protective group which would be deprotected oxidatively on our substrates in a neutral medium. In the syntheses of **1c** and **2c**, (*S*)-malic acid **3a** was used instead of (*R*)-glycidol as a chiral source to introduce (2*S*)-configuration because **3a** is considered to be optically pure and cheaper than (*R*)-glycidol.[3]

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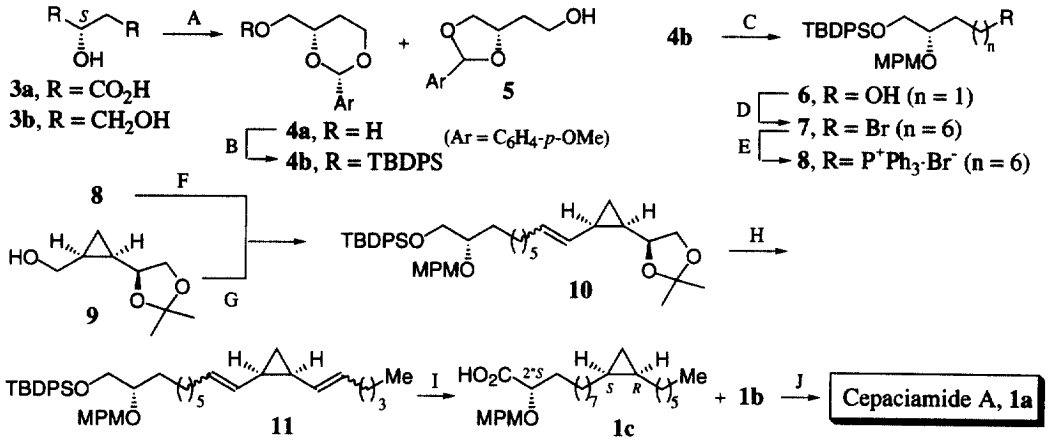
Total Synthesis of Cepaciamide A

(*S*)-Malic acid **3a** was reduced with $BH_3 \cdot SMe_2$ and $B(OMe)_3$ to give triol **3b**[4] which was converted to *p*-methoxybenzylidene acetals **4a** (1,3-acetal, as a single diastereomer)[5] and **5** (1,2-acetal, as a mixture of two diastereomers) in *ca.* 10:1 ratio[6] (Scheme 1). The ratio was increased up to *ca.* 30:1 by column chromatography. Protection of **4a** by the TBDPS group gave **4b** which could be obtained as a single diastereomer by column chromatography. DIBAL-H reduction[7] of **4b** gave primary alcohol **6** as the sole product because **4b** was regioselectively reduced from the less-hindered site. The structure of **6** was confirmed from the ^{1}H-^{1}H-COSY spectrum of the acetate of **6**. Cross-coupling between a tosylate of **6** and a Grignard reagent in the presence of CuI proceeded to give a C_5-elongated derivative which was converted to bromide **7** *via* deprotection and subsequent bromination. By treating **7** with triphenylphosphine in refluxing CH_3CN, phosphonium salt **8** was obtained quantitatively. The phosphonium ylide generated from **8** was subjected to Wittig reaction with an aldehyde obtained from known chiral cyclopropane **9**[8] to give olefin **10** as a mixture of geometric isomers (*E*:*Z* = *ca.* 1:5). Further elongation of the C_5-unit was achieved by Wittig reaction for an aldehyde which was derived from **10** *via* deprotection and subsequent oxidative cleavage of a diol. Thus, C_{19}-diene **11** equipped with all requisite carbons was obtained as a mixture of four geometric isomers. A further four-step conversion, including diimide reduction[9] of diene and oxidation to carboxylic acid, gave **1c** as the segment of **1a**.



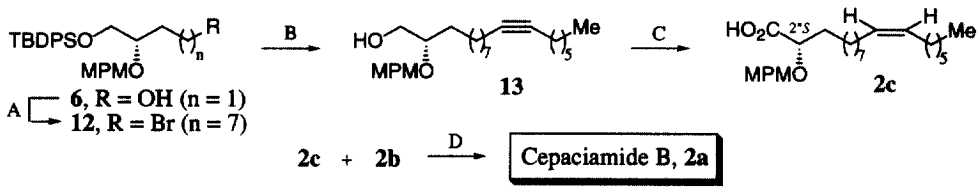
Scheme 1: [A] (1) $BH_3 \cdot SMe_2$, $B(OMe)_3$ / THF, quant., (2) *p*-methoxybenzaldehyde, PPTS / benzene, 92%, [B] TBDPSCl, imidazole / DMF, 100%, [C] DIBAL-H / toluene, 82 %, [D] (1) TsCl, pyr. / CH_2Cl_2, 97%, (2) $MgBr(CH_2)_5OTHP$, CuI / THF, (3) PPTS / EtOH (4) CBr_4, Ph_3P / CH_2Cl_2, 88%, 3 steps, [E] Ph_3P / CH_3CN, quant., [F] *n*-BuLi / THF, [G] Swern oxid., (82% as Wittig reaction), [H] (1) PPTS / EtOH, 72%, (2) $NaIO_4$ / THF-H_2O, (3) Ph_3P^+-$(CH_2)_4CH_3 \cdot Br^-$, *n*-BuLi / THF, 93%, [I] (1) TBAF / THF, 99%, (2) $KO_2CN{=}NCO_2K$, AcOH / pyridine, 97%, (3) Swern oxid., (4) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene / *t*-BuOH-H_2O, 98%, 2 steps, [J] (1) DCC, DMAP / toluene, 80%, (2) CAN / CH_3CN-$CHCl_3$-H_2O, 80%.

Esterification between **1c** and previously synthesized **1b**[1] was carried out with DCC and DMAP to give the desired ester in 80% yield. Final oxidative deprotection of the MPM group was first attempted with DDQ in CH_2Cl_2-H_2O[10] to give **1a** in only 24% yield. This reaction took a relatively long time (20 h) in contrast to general cases of MPM-deprotection. Ceric (IV) ammonium nitrate (CAN) in CH_3CN-$CHCl_3$-H_2O[11] was next used for depotection. In this case, the reaction was completed in 30 minutes to give **1a** as a colorless oil in 80% yield. The spectral data of synthetic **1a** were identical with those of natural **1a**.[12] In this way, the first total synthesis of **1a**, which is regarded as diastereomerically pure, was accomplished.

Total Synthesis of Cepaciamide B

Carboxylic acid segment **2c** was synthesized from common intermediate **6** (Scheme 2). According to the same procedure as for preparation of **7**, except for using the C_6-unit as the Grignard reagent, bromide **12** was obtained from **6**. Lithium acetylide of 1-octyne (C_8-unit) was alkylated with **12** to give the C_{18}-alkyne equipped

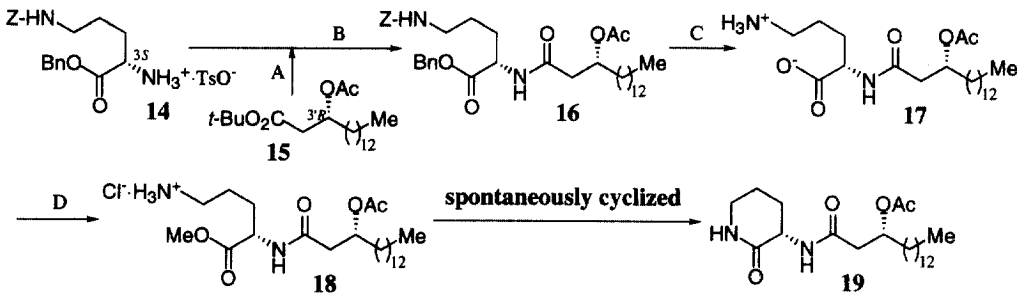
with all requisite carbons whose TBDPS group was deprotected with TBAF to give **13**. By a further three-step conversion, including partial reduction to (*Z*)-olefin and oxidation to carboxylic acid, **2c** as the carboxylic acid segment of **2a** was obtained. Esterification between **2c** and **2b** (= **1b**)[1] was carried out to give the desired ester in 76% yield under the same conditions as used in the synthesis of **1a**. Final oxidative deprotection of the MPM group with CAN[11] gave **2a** as a colorless oil in 76% yield. Although there are no spectral data of natural **2a** alone, the ^{1}H-NMR spectrum of synthetic **2a** corresponded to that of the mixture of **1a** and **2a**. Other spectral data substantiated the structural validity of **2a**.[13] In this way, the first total synthesis of **2a**, which is regarded as diastereomerically pure, was accomplished.



Scheme 2: [A] (1) TsCl, pyr. / CH_2Cl_2, 97%, (2) $MgBr(CH_2)_6OTHP$, CuI / THF, (3) PPTS / EtOH (4) CBr_4, Ph_3P / CH_2Cl_2, 79%, 3 steps, [B] (1) *n*-BuLi, 1-octyne / THF-HMPA, (2) TBAF / THF, 86%, 2 steps, [C] (1) H_2, Lindlar cat. / EtOAc, 100%, (2) Swern oxid. (3) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene / *t*-BuOH-H_2O, 97%, 2 steps, [D] (1) DCC, DMAP / toluene, 76% (2) CAN / CH_3CN-$CHCl_3$-H_2O, 76%.

Synthesis of Ornithine-Amide

It is suspected from the occurrence of ornithine-containing lipids[14] closely related to cepaciamides that cepaciamides are artifacts. Therefore, an ornithine-amide was synthesized in order to examine its property. Known (*S*)-ornithine derivative **14**[15,16] was coupled with a carboxylic acid derived from (3*R*)-ester **15**[1] to give amide **16**. Catalytic hydrogenolysis gave ornithine-amide **17** which was converted to methyl ester **18** with diazomethane in acidic medium. While **17** did not cyclize in the range of room temperature to 60 ℃ or during chromatographic purification on silica gel with $CHCl_3$-MeOH as an eluent, whose system was used for separation of natural products, the corresponding ester **18** cyclized spontaneously to give 3-amino-2-piperidinone-amide **19**. Such conversions have been utilized in determining the stereochemistry of the ornithine-part by the CD spectrum.[17,18] Ornithine-containing lipids so far isolated have been shown not to cyclize during chromatographic operation similar to ours,[14,17,18] and only (*S*)-ornithine was identified from some ornithine-containing lipids. Therefore, it is strongly suggested that cepaciamides are not artifacts.



Scheme 3: [A] TFA / CH_2Cl_2, [B] (1) DEPC, Et_3N / CH_2Cl_2, 85% from **14**, [C] H_2, 10% Pd-C / MeOH, 93%, [D] CH_2N_2 / Et_2O-1M HCl, 99%

In conclusion, the first total syntheses of cepaciamides A (**1a**) and B (**2a**) were accomplished, and the synthetically obtained cepaciamides are regarded as diastereomerically pure. Furthermore, our method makes it possible to synthesize all stereoisomers of cepaciamides, their analogs, and ornithine-containing lipids required for study of the structure-activity relationship.

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References and Notes

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12. **1a**: FDMS *m/z* 663 (MH^+, 91.7), 662 (M^+, 100); HRMS calcd. for $C_{40}H_{74}N_2O_5$ (M^+) *m/z* 662.5598, found 662.5590; $[\alpha]_D^{22}$ -28.5° (*c* 1.08, $CHCl_3$); IR (film) 3307, 3060, 2924, 2854, 1732, 1652, 1554, 1494, 1467, 1362, 1332, 1271, 1214, 1104, 1021, 987, 759, 723, 667, cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ -0.34 (1H, dd, *J* = 9.5, 5.3 Hz), 0.55 (1H, dt, *J* = 8.2, 3.9 Hz), 0.64 (2H, m), 0.87 (3H, t, *J* = 6.6 Hz), 0.88 (3H, t, *J* = 6.6 Hz), 1.13 (2H, m), 1.18-1.48 (44H, m), 1.53-1.78 (5H, m), 1.92 (2H, m), 2.49 (1H, d, *J* = 14.5 Hz), 2.51 (1H, m), 2.54 (1H, dd, *J* = 14.5, 4.9 Hz), 3.35 (2H, m), 3.60 (1H, d, *J* = 5.7 Hz, OH), 4.15 (1H, m), 4.20 (1H, ddd, *J* = 11.8, 5.8, 5.4 Hz), 5.27 (1H, quint., *J* = 5.5 Hz), 5.85 (1H, s, NH), 6.61 (1H, d, *J* = 5.4 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 10.9, 14.1, 15.7, 15.8, 21.1, 22.7, 25.1, 25.2, 27.1, 28.7, 29.31, 29.34, 29.42, 29.47, 29.53, 29.55, 29.62, 29.64, 29.65, 29.68, 30.17, 30.22, 31.91, 31.94, 33.7, 34.5, 41.1, 41.8, 50.8, 71.3, 72.4, 169.7, 171.5, 174.3 (Some methylene-carbon signals overlap); Since **1a** partially solidifies or crystallizes out of its oil evaporated, attempts to recrystallize **1a** from various solvent-systems are now in progress.
13. **2a**: FDMS *m/z* 649 (MH^+, 100), 648 (M^+, 96.4); HRMS calcd. for $C_{39}H_{72}N_2O_5$ (M^+) *m/z* 648.5442, found 648.5416; $[\alpha]_D^{21}$ -26.3° (*c* 1.09, $CHCl_3$); IR (film) 3304, 3078, 3005, 2924, 2854, 1732, 1652, 1558, 1494, 1467, 1362, 1332, 1270, 1207, 1106, 989, 756, 722, 667, cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.88 (6H, t, *J* = 6.6 Hz), 1.15-1.38 (40H, m), 1.42 (2H, m), 1.53-1.78 (5H, m), 1.92 (2H, m), 2.02 (4H, m), 2.49 (1H, d, *J* = 14.5 Hz), 2.51 (1H, m), 2.54 (1H, dd, *J* = 14.5, 4.9 Hz), 3.35 (2H, m), 3.57 (1H, d, *J* = 5.7 Hz, OH), 4.15 (1H, m), 4.20 (1H, ddd, *J* = 11.8, 5.8, 5.4 Hz), 5.27 (1H, quint., *J* = 5.5 Hz), 5.34 (2H, m), 5.83 (1H, s, NH), 6.60 (1H, d, *J* = 5.4 Hz); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ 14.1, 21.1, 22.6, 22.7, 25.1, 25.2, 27.0, 27.2, 29.0, 29.2, 29.4, 29.42, 29.5, 29.6, 29.7, 29.8, 31.7, 31.9, 33.8, 34.4, 41.1, 41.7, 50.7, 71.3, 72.4, 129.8, 129.9, 169.7, 171.7, 174.2 (Some methylene-carbon signals overlap); Since **2a** partially solidifies or crystallizes out of its oil evaporated, attempts to recrystallize **2a** from various solvent-systems are also in progress.
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