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Enantioselective Synthesis of Curacin A. 1. Construction of C1-C7, C8-C17, and C18-C22 Segments

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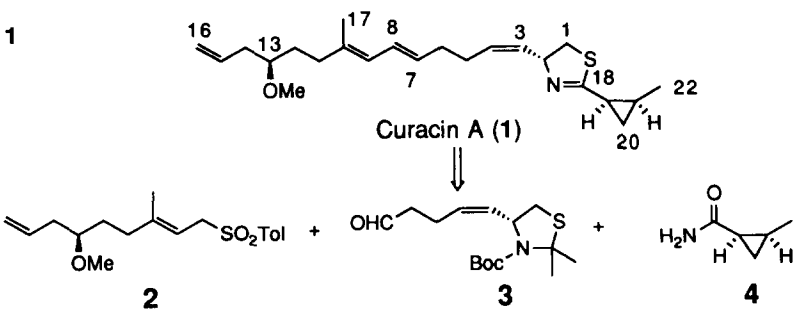
Abstract: Total synthesis of curacin A, a novel antimitotic antiproliferative antibiotic, was achieved by the connection of C1-C7, C8-C17, and C18-C22 segments. Enantioselective preparation of each segments were accomplished by asymmetric allylation, chiral synthon method, and asymmetric hydrolysis by using pig liver esterase, respectively.

Curacin A (**1**), a novel antimitotic antiproliferative antibiotic, was isolated by Gerwick *et al.* from the marine cyanobacterium *Lyngbya majuscula*.[1] It showed some selective inhibitory activity for colon, renal, and breast cancer-derived cell lines, and is considered to be one of the interesting antitumor agents. Structural feature of curacin A is characterized by the disubstituted thiazoline skeleton, chiral cyclopropane ring, and long aliphatic chain containing four C-C double bonds and one methoxyl group. Absolute configuration of curacin A was initially elucidated by degradative study by Gerwick and White *et al.*[2] and was confirmed by the total synthesis by White *et al.*[3] In addition, the synthesis of four stereoisomers of thiazoline-cyclopropane part was recently reported by Iwasaki *et al.*[4] Independently, we have also succeeded in the total synthesis of curacin A. The present communication focuses on a facile and enantioselective construction of segments C8-C17 (**2**), C1-C7 (**3**), and C18-C22 (**4**).[5] The accompanying paper describes the total synthesis of curacin A (**1**).[6]

Scheme 1

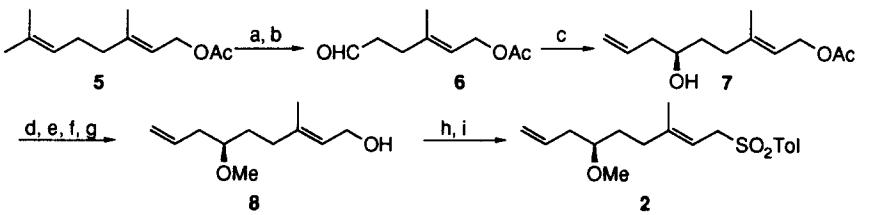


Retrosynthetic analysis was outlined in Scheme 1. From preliminary experiments, thiazoline ring was found to be rather labile under various conditions including oxidation and reduction. Consequently, the construction of thiazoline ring was planned at the final stage of the synthesis. Disconnection of curacin A

generated three fragments, C8-C17 (**2**), C1-C7 (**3**), and C18-C22 (**4**) segments. The key steps of our strategy were construction of C7-C8 *E* olefin by Julia coupling reaction[7] and condensation of aminothiol with cyclopropyl iminoether derivative. The chiral center in segment **2** might be controlled by asymmetric allylation developed by Brown *et al.*[8] The segment **3** could be prepared from L-cysteine by using Wittig reaction. The segment **4** could be derived in an enantioselective manner from the readily available chiral cyclopropane dicarboxylic acid monomethyl ester.[9]

Our initial approach was examined for the synthesis of segment **2** as shown in Scheme 2. The aldehyde **6** was prepared from geranyl acetate (**5**) by regioselective epoxidation followed by oxidative cleavage of the epoxide with orthoperiodic acid.[10] The asymmetric allylation of aldehyde **6** with allyldiisopinocampheylborane, prepared from commercially available (-)-*B*-methoxydiisopinocampheylborane with allylmagnesium bromide, proceeded cleanly at -100 °C under salt free condition[8] to give homoallylic alcohol **7** in 80 % yield (>90 % ee). The enantiomeric excess was determined by ^{1}H NMR analysis after converting to its MTPA ester. Deacetylation of **7**, followed by selective silylation of diol with *t*-butyldimethylsilyl chloride afforded the *O*-momosilylated alcohol, which was transformed into the allylic alcohol **8** by a two-step sequence involving methylation of hydroxyl group at C13 and desilylation (87 % overall yield). The absolute chemistry of **8** was confirmed after converting to known curacin A fragment[2] (diimide reduction of vinyl group and following ozonolysis). After bromination of **8**, the bromide was converted to the sulfone **2** by the treatment with tetrabutylammonium *p*-toluenesulfinate[11] in THF at room temperature in 80 % yield.[12]

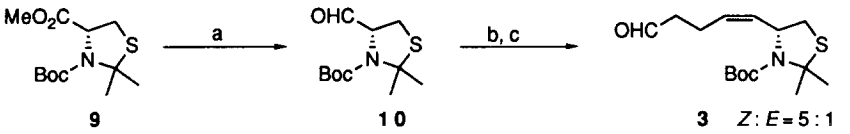
Scheme 2



Reagents: a) mCPBA, CH_2Cl_2, r.t., 12 h, 84 %; b) H_5IO_6, THF-H_2O, r.t., 1.5 h, 97 %; c) (-)-*B*-methoxydiisopinocampheylborane, allylmagnesium bromide, salt free condition, ether, -100 °C, 2 h, 80 %; d) K_2CO_3, MeOH-H_2O, r.t., 3 h, 98 %; e) TBDMSCl, imidazole, DMF, 0 °C, 3 h, 97 %; f) NaH, MeI, DMF, r.t., 3 h; g) 1N HCl, THF, r.t., 3 h, two steps 91 %; h) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 1 h; i) tetrabutylammonium p-toluenesulfinate, THF, r.t., 3 h, two steps 80 %.

The synthesis of C1-C7 segment **3** is shown in Scheme 3. Thiazolidine carboxylic acid methyl ester **9**, prepared from L-cysteine in three steps, was converted to the aldehyde **10** by half reduction with diisobutylaluminum hydride.[13] The aldehyde **10** was then reacted with the phosphonium ylide generated from the 3-cyanopropyltriphenylphosphonium bromide[14] and LDA to afford the *Z*-isomer as major product (87 % 2 steps, $Z : E = 5 : 1$). The isomeric mixture could be separated by silica gel column chromatography. After the half reduction of nitrile derivative with diisobutylaluminum hydride, the desired segment **3** was provided in 80 % yield.[15] The enantiomeric purity of compound **3** could not be determined by spectroscopic and HPLC analysis. However, we think that the racemization at C2 is negligible since the aldehyde **3** obtained by several runs showed a similar $[\alpha]_D$ value within an experimental error.

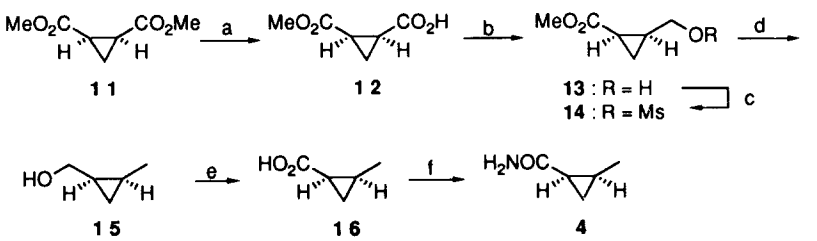
Scheme 3



Reagents: a) DIBAL, toluene, -78 °C, 5h; b) 3-cyanopropyltriphenylphosphonium bromide, LDA, THF, -78 °C-r.t., 2 h, two steps 87 %; c) DIBAL, ether, -78 °C-r.t., 2 h, 80 %.

C18-C22 segment **4** was prepared by the following procedure. Enantiomerically pure cyclopropane monoester **12** was obtained by a pig liver esterase-mediated asymmetric hydrolysis of the corresponding *meso* diester **11**.[9] Chemoselective reduction of the carboxyl group in **12** was carried out using borane methylsulfide complex in the presence of trimethylborate to afford **13**[9b], and the latter was converted to the mesylate **14** in 83 % overall yield. The enantiomeric excess of compound **13** was determined after converting to its MTPA ester (> 95 % ee). After reduction of **14** with lithium aluminum hydride, the resulting alcohol **15** was oxidized to the carboxylic acid **16** with a catalytic amount of ruthenium chloride in the presence of four equivalents of sodium periodinate.[16] The carboxylic acid **16** was then transformed to the carboxamide **4** *via* mixed anhydride method.[17]

Scheme 4



Reagents: a) PLE, $NaHPO_3$, $NaHCO_3$, H_2O, r.t., 3 days, 90 %; b) BH_3•SMe_2, $(MeO)_3B$, THF, r.t., 21 h, 91 %; c) MsCl, Et_3N, CH_2Cl_2, 0 °C, 3 h, 91 %; d) $LiAlH_4$, ether, r.t., 6 h, 66 %; e) $RuCl_3$•nH_2O, $NaIO_4$, CCl_4-CH_3CN-H_2O, r.t., 10 h; f) $ClCO_2Me$, Et_3N, THF, 0 °C, 2 h, then NH_4OH, r.t., 2 h, two steps 52 %.

As described above, preparation of three segments **2**, **3**, and **4** of curacin A was achieved in stereo- and enantioselective manners.[18] Coupling of segments toward the total synthesis is the subject of the accompanying paper.[6]

References and Notes

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12. The structure of the segment **2** was characterized as follows: $[\alpha]_D^{20}$ +10.6° (c 1.19, $CHCl_3$); IR (neat) 3073, 2976, 2928, 2826, 1663, 1642, 1597, 1445, 1316, 1238, 1150, and 1088 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73 (2H, d, J = 8.2 Hz), 7.32 (2H, d, J = 8.2 Hz), 5.78 (1H, dddd, J = 16.9, 10.4, 7.1, 7.1 Hz), 5.20 (1H, t, J = 8.0 Hz), 5.08 (1H, d, J = 16.9 Hz), 5.07 (1H, d, J = 10.4 Hz), 3.78 (2H, d, J = 8.0 Hz), 3.33 (3H, s), 3.12-3.19 (1H, m), 2.44 (3H, s), 1.96-2.32 (4H, m), 1.46-1.53 (2H, m), 1.33 (3H, s); ^{13}C NMR ($CDCl_3$) δ 146.1, 144.4, 135.8, 134.5, 129.5, 128.5, 117.1, 110.5, 79.6, 56.5, 56.1, 37.5, 35.3, 31.4, 21.6, 16.2. Anal. Calcd for $C_{18}H_{26}O_3S$: C, 67.04; H, 8.13; S, 9.94. Found: C, 66.66; H, 8.13; S, 9.60.
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15. The structure of the segment **3** was characterized as follows: $[\alpha]_D^{20}$ +38.6° (c 1.18, $CHCl_3$); IR (neat) 2976, 2932, 1725, 1692, 1454, 1358, 1171, and 1065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.78 (1H, s), 5.73 (1H, dd, J = 10.7, 9.3 Hz), 5.37 (1H, dt, J = 10.7, 7.2 Hz), 5.12 (1H, bt, J = 7.8 Hz), 3.28 (1H, dd, J = 11.6, 6.1 Hz), 2.4-2.6 (5H, m), 1.77 (3H, s), 1.76 (3H, s), 1.44 (9H, s); ^{13}C NMR ($CDCl_3$) δ 201.8, 152.4, 132.2, 128.1, 80.1, 70.1, 60.8, 43.7, 34.0, 30.4, 29.8, 28.5, 20.3. Anal. Calcd for $C_{15}H_{25}NO_3S$: C, 60.17; H, 8.42; N, 4.68; S, 10.71. Found: C, 59.92; H, 8.35; N, 4.63; S, 10.60.
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17. The structure of the segment **4** was characterized as follows: mp 117.5-118°C; $[\alpha]_D^{20}$ +6.6° (c 0.97, $CHCl_3$); IR (KBr) 3389, 3217, 1690, 1640, 1611, 1443, and 1292 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.80 (1H, bs), 5.70 (1H, bs), 1.51 (1H, ddd, J = 8.5, 7.7, 5.5 Hz), 1.18-1.28 (1H, m), 1.18 (3H, d, J = 5.3 Hz), 0.88-0.96 (2H, m); ^{13}C NMR ($CDCl_3$) δ 174.1, 19.9, 15.1, 12.8, 11.9. Anal. Calcd for C_5H_9NO: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.41; H, 9.34; N, 14.03.
18. All new compounds gave satisfactory ^1H NMR, ^{13}C NMR, and MS spectra.

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