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Enantioselective Synthesis of Curacin A. 2. Total Synthesis of Curacin A by Condensation of C1-C7, C8-C17, and C18-C22 Segments

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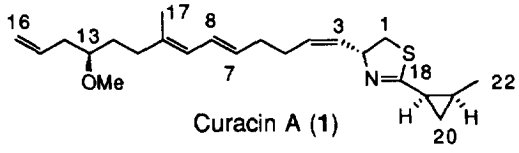
Abstract: Total synthesis of curacin A, a novel antimitotic antiproliferative antibiotic, was achieved by the connection of C1-C7, C8-C17, and C18-C22 segments by Julia coupling and iminoether condensation.

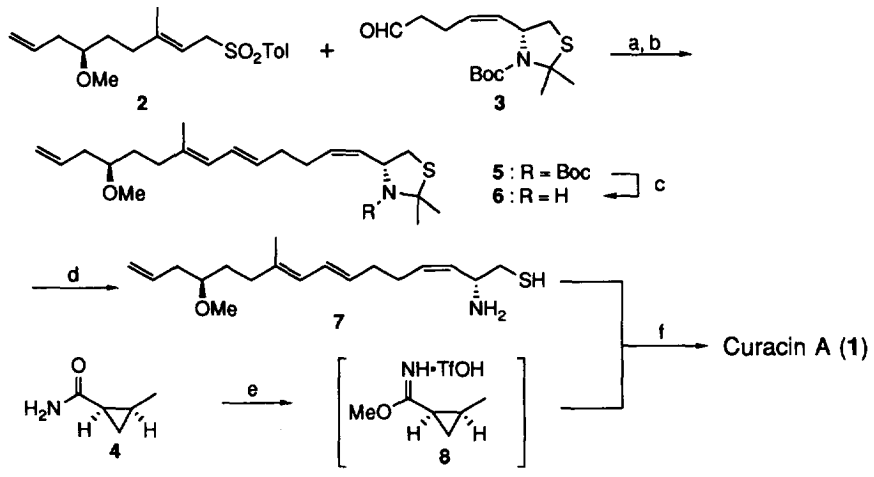
Curacin A (**1**), isolated by Gerwick *et al.* from the marine cyanobacterium *Lyngbya majuscula* is considered to be one of the interesting antitumor agents.[1] Structural feature and biological activity of curacin A have brought a considerable interest toward the total synthesis and structure-activity relationships.[2,3] In the preceding paper, we have described an efficient synthetic route to the segments C8-C17 (**2**), C1-C7 (**3**), and C18-C22 (**4**).[4] In this paper, we report the total synthesis of curacin A (**1**) by the condensation of three segments.



Curacin A (**1**)

The coupling of three segments of curacin A was accomplished in a straightforward manner (Scheme 1). Thus, Julia coupling of the sulfone **2** and the aldehyde **3** was first carried out to afford **5** in 50 % overall yield ($E : Z = 5 : 1$).[5] Although the stereoselectivity is moderate in the present Julia coupling, the minor isomer could be removed by medium pressure liquid chromatography after conversion to **6**. Conversion of thiazolidine **5** into free aminothiol **7** was next examined. Cleavage of the thiazolidine ring under acidic condition[6] (6N HCl in MeOH reflux) resulted in the formation of complex mixture of products, and was accomplished in a stepwise manner. Initially, Boc group was removed by 6N HCl in MeOH at 55 °C to give **6**,[7] and the resulting thiazolidine **6** was reacted with $AgNO_3$ in CH_3CN-H_2O. Then the silver mercaptide was treated with cysteamine to obtain aminothiol **7**. The crude aminothiol **7** thus obtained was finally reacted with iminoether **8**, prepared *in situ* from the amide **4** and TfOMe, to complete the total synthesis of curacin A. ^1H, ^{13}C NMR spectra of the synthetic curacin A {$[\alpha]_D$ 75° (c 0.44, $CHCl_3$), lit.[1] $[\alpha]_D$ 86° (c 0.64, $CHCl_3$)} were in good accordance with those reported by Gerwick *et al.*[1]

Scheme 1



Reagents: a) 2 and nBuLi, THF, -78 °C, 20 min, then 3, -78 °C, 30 min, then BzCl, Et_3N, DMAP, r.t., 10 h; b) Na(Hg), MeOH-THF, -12 °C, 2 h, two steps 50 %; c) 6N HCl, MeOH, 55 °C, 2 h; d) $AgNO_3$, CH_3CN-H_2O, r.t., 1 h, then cysteamine, r.t., 2 h; e) MeOTf, CH_2Cl_2, r.t., 14 h; f) MeOH, 55 °C, 2 days, 32 % from **5**.

The present approach can provide a facile route to variously substituted thiazoline derivatives. Structure-activity relationships of the related compounds are now in progress and will be reported in due course.

References and Notes

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7. **6**: $[\alpha]_D^{20}$ -41.2° (c 2.35, $CHCl_3$); IR (neat) 3401, 2971, 1640, 1439, 1096, and 965 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.26 (1H, dd, J = 15.0, 10.8 Hz), 5.75-5.86 (1H, m), 5.81 (1H, d, J = 10.8 Hz), 5.53-5.62 (2H, m), 5.37 (1H, dd, J = 10.8, 8.5 Hz), 5.04-5.12 (2H, m), 4.21 (1H, dddd, J = 9.4, 8.5, 6.0, 0.9 Hz), 3.34 (3H, s), 3.16-3.24 (2H, m), 2.68 (1H, dd, J = 10.3, 9.4 Hz), 2.01-2.33 (8H, m), 1.73 (3H, s), 1.68 (3H, s), 1.56-1.63 (2H, m), 1.57 (3H, s); ^{13}C NMR ($CDCl_3$) δ 136.9, 134.8, 132.8, 131.0, 128.5, 127.4, 124.6, 117.0, 79.9, 75.5, 60.9, 56.6, 43.2, 37.7, 35.4, 33.0, 32.7, 31.6, 31.4, 28.1, 16.6. HRMS calcd for $C_{21}H_{35}NOS$ 349.2437, found 349.2425.

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