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Total Synthesis of Mirabazole B

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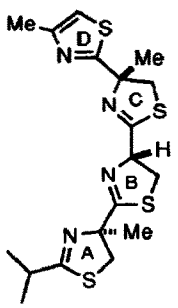
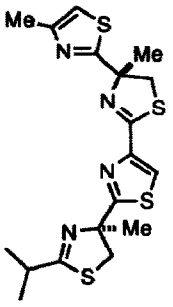
Abstract: Mirabazole B (**3**) has been prepared in eleven steps from α-methylcysteine.

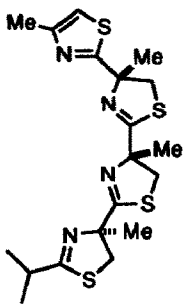
The mirabazoles (**1-4**) are a group of thiazoline/thiazole-containing marine alkaloids isolated from the blue-green alga *Scytonema Mirabile*.[1]



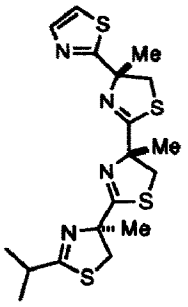
1: Mirabazole A



2: Didehydromirabazole A



3: Mirabazole B

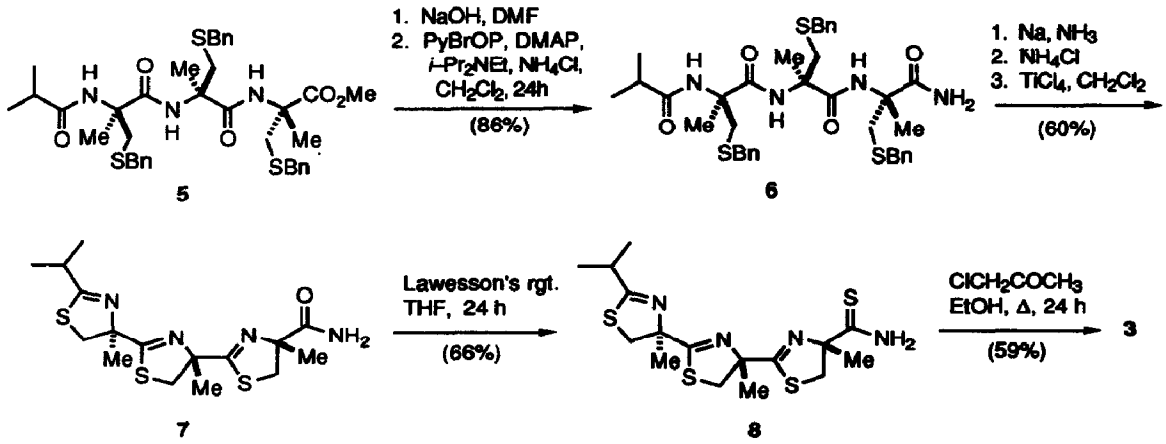


4: Mirabazole C

These natural products and the structurally similar tantazoles[2] and thiangazole[3] have recently stimulated considerable synthetic interest[4,5,6,7] because of their unique structures and biological activity. We have previously developed a strategy for synthesis of mirabazoles in which the four heterocyclic rings are simultaneously formed by $TiCl_4$-mediated cyclodehydration of an appropriate tripeptide diamide. This procedure was applied for a synthesis of the structure originally assigned to mirabazole C[5] and for a synthesis of the newly-assigned structure.[8] In this approach, cyclization to form the three substituted thiazoline rings proceeds easily, but the terminal unsubstituted ring is formed more slowly and requires repeated submission to the cyclization conditions. The oxidative instability of the free thiols makes manipulation of the partially cyclized material difficult and in most cases leads to complicated reaction mixtures and low product yields. To avoid this cyclization difficulty, we have made a slight modification of our synthetic strategy, such that only the substituted thiazoline rings are formed in the $TiCl_4$-mediated cyclodehydration step. In this Letter, we report a total synthesis of mirabazole B (**3**) using this modified strategy.

The synthesis begins from the previously-described tripeptide **5**,[5] which is converted into primary amide **6** by saponification and coupling of the resulting acid with ammonium chloride using PyBrOP.[9] The benzyl groups are then removed by treatment with sodium in ammonia and the crude debenzylation product is immediately subjected to the $TiCl_4$-mediated cyclodehydration conditions; trithiazoline amide **7** is obtained in 60% yield. This material is converted by treatment with Lawesson's reagent into thioamide **8**. The final thiazoline ring is then formed by condensation of **8** with chloroacetone (Hantzsch condensation).[10] Mirabazole B (**3**) is thereby produced in 59% yield. The synthetic material

was compared with an authentic sample of the natural product in Professor Moore's laboratory and found to be identical by ^{1}H NMR spectroscopy and HPLC mobility. The reported specific rotation for the natural alkaloid is $[\alpha]_D$ −166 (c = 0.09, $CHCl_3$)[1] and that found for the synthetic material is $[\alpha]_D$ −150 (c = 0.067, $CHCl_3$).



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