

A SYNTHESIS OF A C₁-C₇ BUILDING BLOCK FOR THE ENANTIOMER OF HENNOXAZOLE A UTILIZING A REGIO-SELECTIVE RING OPENING OF A CYCLIC ACETAL†

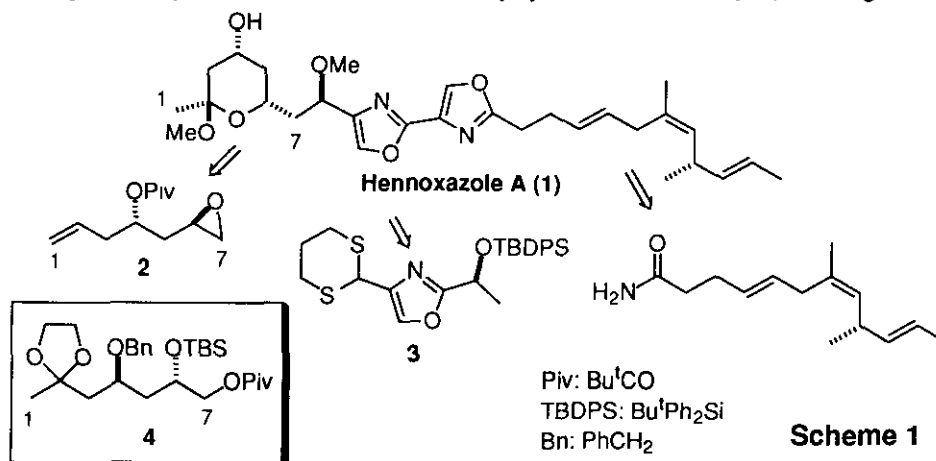
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Abstract - A C₁-C₇ building block (**4**) for the enantiomer of hennoxazole A (**1**), an antiviral and analgesic active marine natural product, was efficiently synthesized from (*S*)-malic acid utilizing the following key steps: (1) the stereoselective construction of an *anti*-1,3-diol, (2) the regioselective ring opening of a cyclic acetal, and (3) the oxidative transformation of the olefin into the ketal of the methyl ketone in a one-pot process.

Hennoxazole A (**1**), isolated from a marine sponge *Polyfibrospongia* sp.,¹ is an interesting addition to the growing family of pharmacologically active compounds of marine origin. It is active against herpes simplex virus type 1, and displays peripheral analgesic activity.¹ This biologically active compound possesses a structurally unique tetrahydropyran/hemiketal function adjacent to a bis-oxazole moiety as shown in the structure (**1**) (Scheme 1). Its structural uniqueness as well as intriguing biological activity led several groups^{2,3} to synthesize **1**. We have already synthesized^{3b} the C₁-C₇ building block (**2**) and

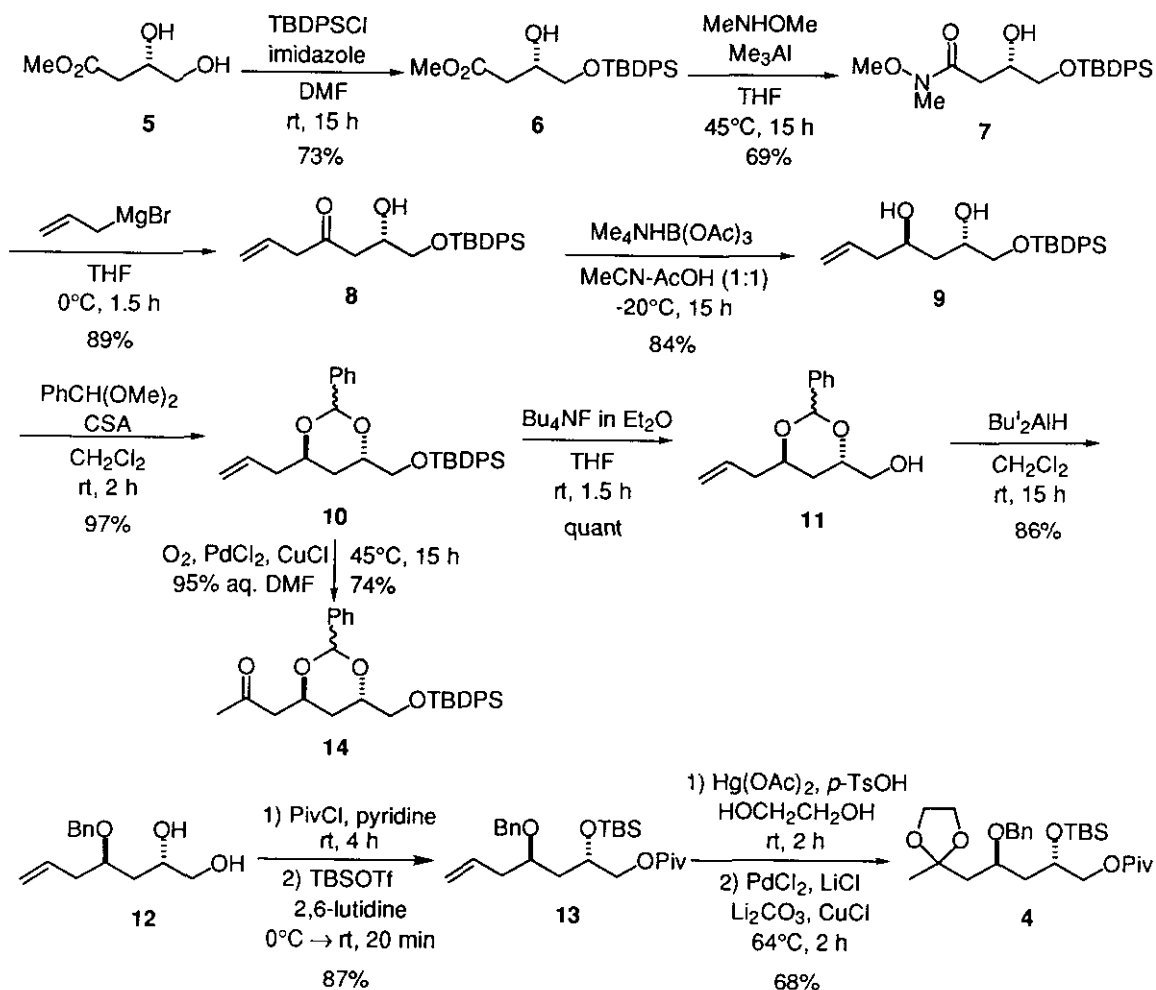


† Dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday.

the oxazole moiety (3). We now report the synthesis of another new C₁-C₇ building unit (4), which will ultimately produce the enantiomer of 1.² The key features are (1) the stereoselective construction of an *anti*-1,3-diol, (2) the regioselective ring opening of a cyclic acetal, and (3) the oxidative transformation of the olefin into the ketal of the methyl ketone in a one-pot process.

The starting material for 4 was methyl (*S*)-3,4-dihydroxybutyrate (5), prepared from (*S*)-malic acid in 2 steps.⁴ Regioselective silylation of 5 with *tert*-butyldiphenylsilyl chloride (TBDPSCl) gave the monosilyl ether (6), which was converted to the corresponding Weinreb amide (7) in 69% yield with an excess of *N,O*-dimethylhydroxylamine hydrochloride and trimethylaluminum,^{5,6} as shown in Scheme 2. Allylation of 7 was easily achieved with allylmagnesium bromide to give the allyl ketone (8). Stereoselective reduction of 8 was achieved by use of tetramethylammonium triacetoxyborohydride in acetonitrile-acetic acid to give the diol (9) in which the ratio of *anti*- to *syn*-isomers were 95:5. Differentiation of *anti*- and *syn*-1,3-diols was accomplished by the measurement of the ¹³C NMR spectra of the corresponding dimethyl acetal according to the known method.^{7,8} The *anti*-diol (9) thus obtained was converted to the benzylidene acetal (10) using benzaldehyde dimethylacetal in the presence of camphorsulfonic acid (CSA) in almost quantitative yield. Attempted reductive cleavage of the acetal ring in 10 under various conditions proved to be fruitless. However, after quantitative desilylation with tetrabutylammonium fluoride, the regioselective ring cleavage of the resulting alcohol (11) was achieved by use of 6 molar equivalents of diisobutylaluminum hydride (DIBAL) to give the diol (12) as a sole product. Obviously, the primary hydroxyl function of 11 will act as a tether⁹ so that initial complexation of DIBAL will give the corresponding aluminum alkoxide, which will facilitate the intramolecular attack, and then reduction followed by hydrolysis will give the diol (12). Selective protection of the primary hydroxyl group with a pivalate function and the secondary hydroxyl group with a *tert*-butyldimethylsilyl (TBS) function, respectively, afforded the fully protected compound (13). The final task remained was transformation of the terminal olefin to the α -methyl ketone or its acetal derivative. We first attempted the Wacker oxidation with 10 to 14 in an attempt to test the feasibility of the transformation. The first reagents tried were usual palladium(II) chloride and copper (II) chloride,¹⁰ but the desired transformation would not occur. After numerous attempts, however, replacing copper(II) chloride for copper(I) chloride led to the methyl ketone (14) by heating the reaction mixture at 45°C. Furthermore, we searched a method that would achieve oxidation with concomitant protection of the resulting carbonyl group. When the olefin (10) was subjected to the Hunt's ethylene ketalization with mercuric acetate-ethylene glycol and palladium(II) chloride,¹¹ the only isolable product was again the ketone (14). On the other hand, however, when the olefin (13) was successively treated with mercuric acetate-*p*-toluenesulfonic acid in ethylene glycol and palladium(II) chloride-copper(I) chloride-lithium chloride-lithium carbonate, a modified Hunt's ethylene ketalization, the desired C₁-C₇ building block (4) for the enantiomer of hennoxazole A (1) was obtained in 68% yield.¹²

Thus, we could prepare 4 in 10 steps from readily available diol (5) in an overall yield of ca. 19%. This efficient synthetic route will open the way to natural hennoxazole A (1) when (*R*)-malic acid is used as a starting material instead of its antipodal (*S*)-isomer. The synthetic works toward this end are now actively being carried out in our laboratories.



Scheme 2

ACKNOWLEDGMENTS

This work was partly supported by Grants-in-Aid from the Ministry of Education, Science, Sports and Culture, Japan. One of the authors (N.M.) thanks the Japan Society for the Promotion of Science for the fellowship.

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12. 4, a yellow oil; IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 3071, 2959, 2932, 2858, 2349, 1716, 1589, 1471, 1428, 1361, 1309, 1113, 910, 823, 739, 702, 648, 613; ^1H NMR (TMS/ CDCl_3), 0.08 (3H, s), 0.09 (3H, s), 0.89 (9H, s), 1.22 (9H, s), 1.25 (3H, s), 1.54-1.77 (2H, m), 2.07 (1H, m), 2.39 (1H, m), 3.73-3.97 (5H, m), 3.99-4.10 (3H, m), 4.52 (2H, AB q, $J=12$ Hz), 7.33 (5H, m).

Received, 3rd March, 1997