# A SYNTHESIS OF A $C_1$-$C_7$ BUILDING BLOCK FOR THE ENANTIOMER OF HENNOXAZOLE A UTILIZING A REGIO-SELECTIVE RING OPENING OF A CYCLIC ACETAL†

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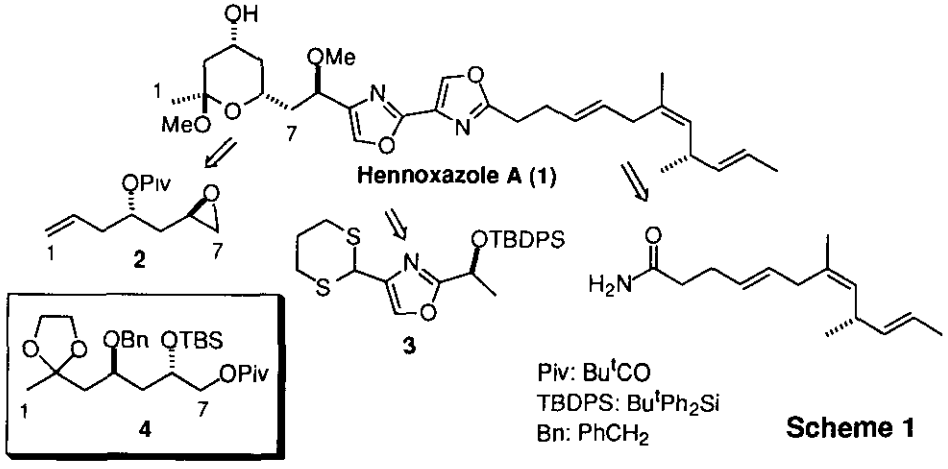
***Abstract*** - A $C_1$-$C_7$ building block (**4**) for the enantiomer of hennoxazole A (**1**), an antivirus and analgesic active marine natural product, was efficiently synthesized from (*S*)-malic acid utilizing the following key steps: (1) the stereoselective construction of an *anti*-1,3-diol, (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 $C_1$-$C_7$ building block (**2**) and



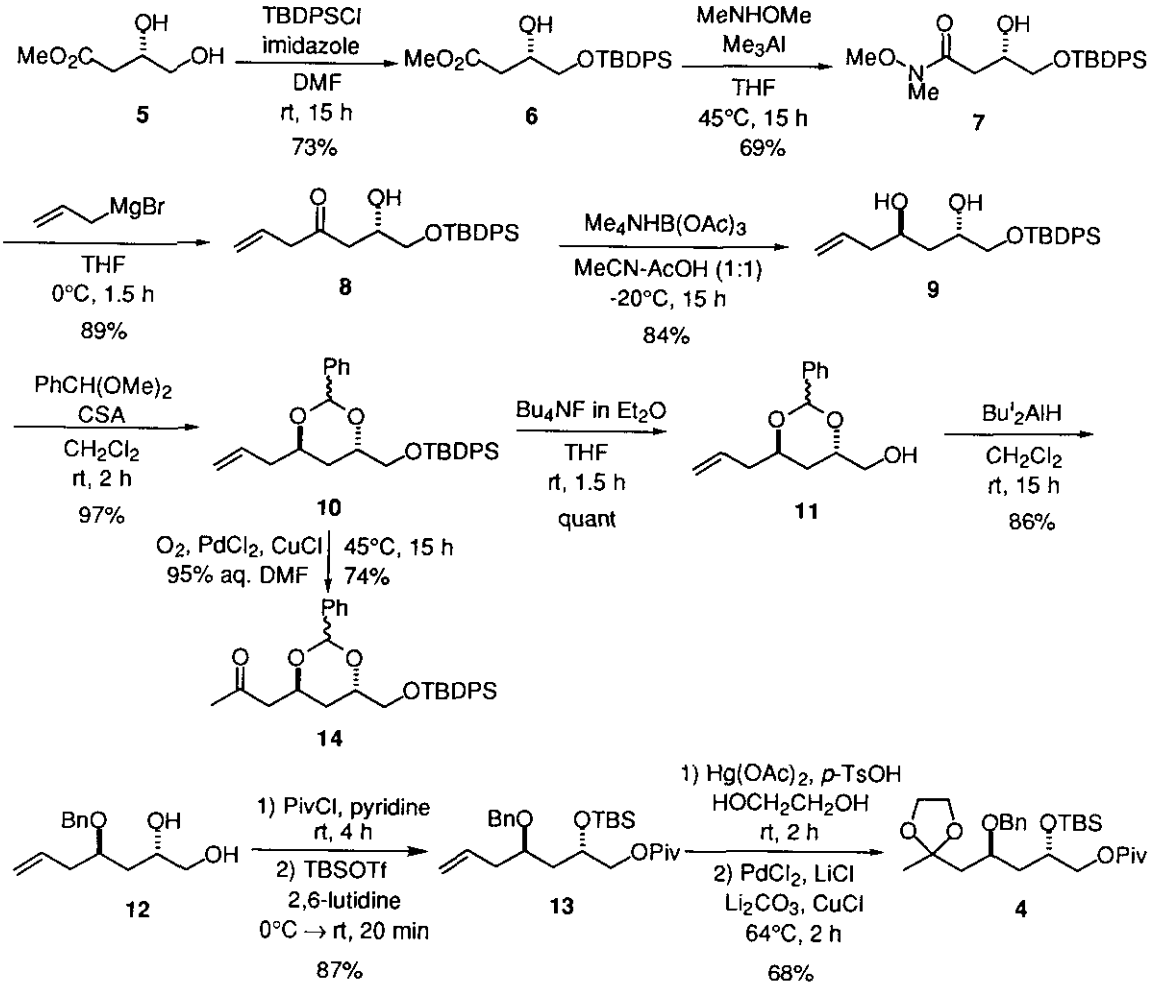

**Scheme 1**

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

the oxazole moiety (**3**). We now report the synthesis of another new $C_1$-$C_7$ 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 $^{13}C$ 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 varions 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 tether[9] 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℃. 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 $C_1$-$C_7$ 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.

## REFERENCES AND NOTES

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6. The starting ester (**5**) was sometimes contaminated with methyl (*S*)-2,4-dihydroxybutyrate whose separation was difficult. However, after conversion to the Weinreb amides, the desired amide (**7**) could be purified by careful column chromatography on silica gel followed by recrystallization (ether/hexane).
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8. The $^{13}C$ NMR spectrum of the dimethyl acetal from the anti-diol (**9**) confirmed the nature of the diol, with peaks at 100.108 corresponding to the acetal carbon and 24.890 and 24.997 corresponding to the *gem*-dimethyl's.
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12. **4**, a yellow oil; IR $\nu_{max}^{neat}$ $cm^{-1}$ : 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