Convergent Synthesis of Methylenomycin B *via* Selenium-assisted Intramolecular S_N2' Cyclization

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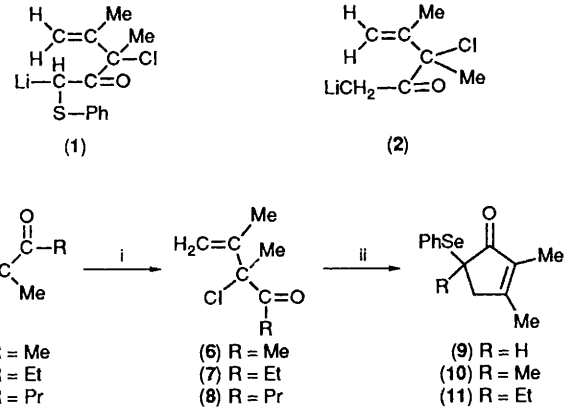
A highly convergent and efficient synthesis of methylenomycin B has been achieved by the reaction of the lithium enolate of 4-chloro-4,5-dimethyl-5-hexen-3-one with phenylselenenyl bromide followed by selenoxide elimination.

One of the important objectives in modern organic synthesis is to develop new methods for the construction of organic molecules that proceed with high chemo-, regio-, and stereoselectivity. We recently reported a novel route to substituted cyclopent-2-en-1-one by the reaction of ethyl 2-chloro-2,3-dialkylbut-3-enoates with sulphur[1] and nitrogen[2] stabilized carbanions. Furthermore, base induced cyclization of several fully substituted α-chloro-β,γ-unsaturated ketones was shown to generate cyclopentenones in high yield.[3] These cyclizations were proposed to proceed through an intramolecular S_N2' reaction wherein heteroatom assistance by sulphur and nitrogen was strongly implicated. While the enolate (**1**) cyclized to cyclopentenone at −70 °C, keto-enolate (**2**) required warming to room temperature to effect the cyclization.

The isolation of methylenomycins A and B from a streptomycete strain and the elucidation of their structure in 1974[4] was followed by disclosure of their synthesis by several groups.[5—8] The interest that the methylenomycins have elicited is due to their promising profile of antibiotic and antineoplastic activity. Methylenomycin B, for example, is active against both gram-positive and gram-negative bacteria and is cytotoxic *in vitro* in the KB assay.[4,9]

Most of the reported syntheses of this antibiotic proceed through 2,3-dimethyl-cyclopent-2-en-1-one[10] as the key intermediate for introducing the exocyclic double bond. Although, we recently reported a highly efficient synthesis of this intermediate by base-induced cyclization of 3-chloro-3,4-dimethyl-hex-4-en-2-one,[3] we sought a more direct synthesis.

We now report the extension of this reaction to selenium-

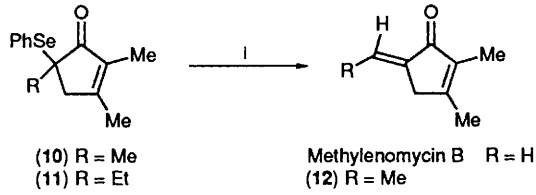


Scheme 1. *Reagents and conditions:* i, $Ca(OCl)_2$, AcOH, CH_2Cl_2, 78—82%; ii, LDA, THF, PhSeBr, −70 °C to 0 °C; 48—54%.

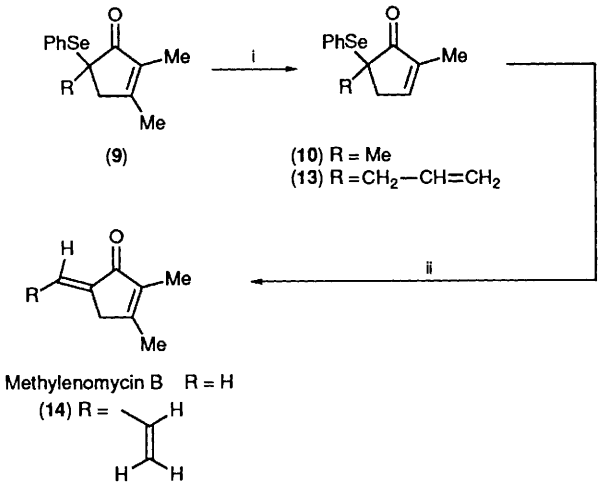
substituted keto-enolates similar to (**1**) resulting in a highly convergent total synthesis of the antibiotic methylenomycin B. Thus, the readily available 4,5-dimethyl-4-hexen-3-one[11] (**4**) was converted to 4-chloro-4,5-dimethyl-5-buten-3-one (**7**) using hypochlorous acid.[3,12] Addition of this ketone to one equivalent of lithium di-isopropylamide(LDA)/tetrahydrofuran (THF) at −70 °C followed by the rapid addition of phenylselenenyl bromide[13] in THF gave, after work-up, the methylenomycin B precursor 2,3,5-trimethyl-5-phenylseleneno-2-cyclopenten-1-one (**10**) in 48% isolated yield. The sequence of reactions was also successfully performed with two other enones [(**3**) and (**5**)][14] to yield the cyclopentenones (**9**) and (**11**) in comparable yields. (45—56%) (Scheme 1).†

The reaction most likely proceeds in two steps. The enolate derived from (**7**) reacts with phenylselenenyl bromide at −70 °C to give the phenylselenenyl ketone which undergoes a S_N2' cyclization to give the cyclopentenone. The selenium must favourably assist this cyclization because the cyclopentenone can be isolated within a few minutes of mixing the reagents. As pointed out, keto-enolate (**2**) which is devoid of sulphur or selenium does not undergo this reaction at low temperature. Another intriguing aspect of this cyclization is that a second equivalent of LDA is not required for this cyclization. It is possible that the seleno-ketone intermediate is sufficiently acidic to be deprotonated by the di-isopropylamine present in the reaction mixture. In fact, addition of a second equivalent of LDA after the addition of phenylselenyl bromide does not increase the yield. Furthermore treating ketone (**7**) with 2 equivalents of LDA followed by addition of phenylselenenyl bromide resulted in very low yield of the cyclopentenone (20%).

Reaction of the seleno-ketones (**10**) and (**11**) with 30% hydrogen peroxide (3 equiv.) at 0 °C gave *via syn* selenoxide elimination,[15,16] methylenomycin B and the methylenomycin analogue (**12**) respectively (88—92%). (Scheme 2).‡



Scheme 2. *Reagents and conditions:* i, H_2O_2, acetone, 0 °C; 88—82%.



Scheme 3. *Reagents and conditions:* i, LDA, THF, RBr, −70 °C to room temp.; 86—90%; ii, H_2O_2 acetone, 0 °C; 72%—88%.

It must be pointed out that the modest yield in the crucial cyclization step permits an overall yield of only 35%. Despite this, starting from enone (**4**), the method permits one to prepare gram quantities of this antibiotic in a single day. Since enone (**4**) can be easily prepared in multigram scale from inexpensive starting materials, this route may be comparable to the best known route to methylenomycin B[7] which gives an overall yield of 64%. However, the method uses α-lithio-α-(methoxymethyl)allene[17] as the starting material and the rather involved synthesis of this allene makes it unattractive on a large scale. As shown in Scheme 2 we were able to prepare the methylenomycin B analogue (**12**) in comparable yield starting from the readily available 5,6-dimethyl-5-hepten-4-one (**5**). This implies that other alkyl-substituted methylenomycins can readily be accessed by this route.

Furthermore, an alternative approach to methylenomycin B and analogues was also discovered (Scheme 3).§ Thus, 5-phenylseleneno-cyclopentenone (**9**) was alkylated with LDA/THF/MeI to give the methylenomycin-precursor (**10**) in 86% yield. The cyclopentenone (**9**) can also be alkylated with allyl bromide to give the 5-allyl-cyclopentenone (**13**) in 90% yield. Selenoxide elimination of (**13**) using 30% H_2O_2 gave the highly conjugated dienone (**14**) in 72% yield.[18] Surprisingly, the dienone (**14**) is stable to flash column chromatography and can be stored in the freezer for several months without decomposition (as indicated by ^1H NMR).

† The structures of compounds (**3**)—(**11**) were verified by ^{13}C and ^1H NMR and IR spectroscopy and elemental analysis.

‡ Spectral data for methylenomycin B: ^1H NMR, δ 6.05 (s, 1 H), 5.30 (s, 1 H), 3.05 (s, 2 H), 2.05 (s, 3 H) and 1.80 (s, 3 H); ^{13}C NMR, δ 196.85, 164.20, 141.77, 138.14, 114.84, 36.94, 16.68, and 8.24. Mass spectrum, 122 (*m/z*), 107, 91, and 79. Spectral data for (**12**): ^1H NMR, 6.65 (q of t, 1 H), 3.00 (s, 2 H), 2.05 (s, 3 H), 1.80 (d, 3 H) and 1.70 (s, 3 H). ^{13}C NMR, δ 196.11, 162.09, 138.14, 135.86, 127.96, 34.99, 16.57, 14.84 and 8.18. Mass spectrum, 136 (*m/z*), 121. Satisfactory elemental analyses were obtained for the above two compounds.

§ Spectral data for (**13**): ^1H NMR, δ 7.10—7.70 (m, 5 H), 5.40—5.80 (m, 1 H), 4.80—5.20 (m, 2 H), 2.40—2.80 (m, 4 H), 1.80 (s, 3 H) and 1.60 (s, 3 H). For (**14**): ^{13}C NMR, δ 196.81, 162.19, 138.74, 135.00, 132.83, 128.98, 125.30, 35.26, 16.63 and 8.28. ^1H NMR, δ 6.30—7.00 (m, 2 H), 5.40—5.75 (m, 2 H), 3.10 (s, 2 H), 2.05 (s, 3 H) and 1.80 (s, 3 H). Satisfactory elemental analyses were obtained for (**13**) and (**14**).

A ^{1}H NMR analysis of this compound indicated that the central carbons of the diene have a *trans* arrangement of vinyl hydrogens and that the vinyl hydrogen closest to the ring carbonyl oxygen is *cis* to the oxygen as indicated by the proton chemical shift (δ 6.90). Similarly, for enone (**12**), the relationship between the methyl group on the exocyclic double bond and the carbonyl ring oxygen was *trans*(*anti*) as evidenced by the downfield proton resonance shift (δ 6.65) of the vinyl proton from TMS [this being the only isomer produced by the *syn* elimination of the selenoxide (**11**)].

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