Total Synthesis of (+)-Macbecin I

James S. Panek* and Feng Xu

Department of Chemistry, Boston University
Boston, Massachusetts 02215

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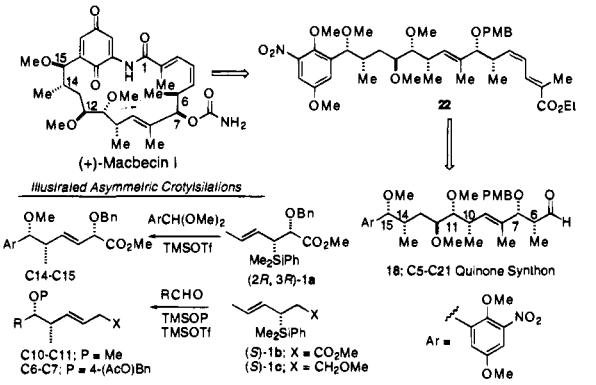
(+)-Macbecin I, an antitumor antibiotic, is a member of a class of natural products known as the benzoquinone ansamycins.[1] The structure and absolute configuration have been determined by Muroi and co-workers by partial degradation and X-ray crystallographic analysis. Other members of this group include geldamycin[2] and ansamitocin.[3] Certain members have been shown to exhibit selective inhibitory activity against protein tyrosine kinases (PTKs) and have the unusual ability to reverse the characteristics of oncogene expression.[4] The critical role of PTKs in the regulation of cellular growth and the potential use of these agents as biological probes provided the incentive for our synthetic studies. Earlier studies in this area have resulted in two total syntheses[5] and one formal synthesis of (+)-macbecin I.[6] A retrosynthetic analysis of (+)-macbecin I is shown in Scheme 1, with the first disconnection, opening of the macrocycle, providing the functionalized macbecin precursor **22**. Cleavage of the C4−C5 double bond removes the (*E,Z*)-dienoate, leading to the C5−C21 quinone synthon **18**. We envisioned that this advanced intermediate, possessing three pairs of *syn*-related methyl−oxygen vicinal stereogenic centers at C6−C7, C10−C11, and C14−C15, could be constructed with asymmetric crotylsilation methodology using the illustrated chiral silane reagents **1a**−**c**.[7]

The synthesis of macbecin I was initiated with a TMSOTf-catalyzed condensation reaction between the (*E*)-crotylsilane reagent **1a** and the dimethoxy aryl acetal **2** (Scheme 2). In accordance with our previous reports concerning the use of these chiral silanes in additions to acetals, the homoallylic ether[8] **3** was constructed in 92% yield (>30:1 *syn/anti*) with high diastereoselectivity.[9] This asymmetric crotylsilation established the absolute stereochemical relationships between C14/C15 and C11 within the target molecule, along with the functionalized nitro aromatic fragment.

The C12 stereocenter was introduced with an alkoxy-directed hydroboration reaction on the α-benzyloxy ester **3**.[10] Treatment of **3** with $BH_3{\cdot}SMe_2$ (1.05 equiv, 0 °C → room temperature, 16 h), then NaOOH (5.0 equiv), afforded the desired 1,3-diol **4** (85% isolated yield, diastereoselection >8.5−11:1 *anti/syn* C11−C12). Methylation of the C12 hydroxyl of **4** was carried out with a three-step procedure: (i) silation of the primary hydroxyl with TBSCl (1.05 equiv), imidazole (4.0 equiv); (ii) methylation of the secondary hydroxyl with MeOTf (3.0 equiv), 2,6-di-*tert* butylpyridine (5.0 equiv), followed by (iii) desilation with *n*-Bu_4NF (0.5 equiv). This sequence provided **7** in 87% yield. Removal of the benzyl ether with BCl_3 (1.5 equiv, −78 °C), afforded the 1,2-diol **8**, which was immediately subjected to an oxidative cleavage with $NaIO_4$, affording the α-methoxy aldehyde **9** in 66% yield.

Scheme 1



The second of three crotylsilation reactions was used for the installation of the C10−C11 stereocenters. Aldehyde **9**, TMSOMe (2.0 equiv), and the silane reagent (*R*)-**1b** (2.0 equiv) in anhydrous CH_2Cl_2 at −78 °C were treated with TMSOTf (2.0 equiv) to afford the homoallylic ether **10** in 80% yield.[11] This *syn* bond construction reinstalled the C11 stereocenter and introduced the C10 methyl group with diastereoselection ~12:1 favoring the *syn* diasteromer at C10−C11, allowing for the direct introduction of the C11 methyl ether. This double stereodifferentiating reaction is most likely a result of a fully matched pair of reaction partners, as the C11−C12 stereocenters emerge with an *anti* stereochemical relationship from a nonchelate-controlled Felkin addition (OMe prependicular to C=O).[12] The C8−C9 trisubstituted double bond was constructed through a three-step sequence begining with the ozonolysis of the *trans*-olefin of **10**, followed by treatment of the derived aldehyde with (carbethoxymethylene)triphenylphosphorane,[13] to afford the α,β-unsaturated ester **12**, which was achieved in 61% (two steps). Subsequent DIBAL-H reduction and Swern oxidation[14] afforded α,β-unsaturated aldehyde **14** (88%, two steps). From the outset, it was our intention to install the C7 hydroxyl-bearing stereocenter with a protecting group that could be oxidatively removed in the final stages. The third *syn*-crotylsilation reaction for the introduction of the C6−C7 stereocenters was accomplished by a double stereodifferentiating reaction between aldehyde **14** and (*S*)-**1c**[15] (1.5 equiv). This three-component reaction system employed 4-acetoxybenzyl trimethylsilyl ether (1.2 equiv) under the influence of a catalytic amount of TMSOTf (0.5 equiv), to afford the desired *syn* homoallylic ether bearing a *p*-acetoxybenzyl ether with diastereoselectivity reaching >20:1 *syn/anti* at C6−C7.[16] The 4-acetoxy group was exchanged for a methyl ether, positioning the C7 OPMB for oxidative removal in the final deprotection step.[17] The successful use of this intermediate in the synthesis required a selective cleavage of the *trans*-disubstituted double bond. This transformation was accom-

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(16) The OsO_4-promoted dihydroxylation of the *trans*-disubstituted olefin derived from (*S*)-**1b** resulted in lactone formation, thus, silane (*S*)-**1c** [$[\alpha]^{23}_D$ = +28.4° (*c* = 0.88, CH_2Cl_2)] prepared in two steps: (i) LAH, (ii) MeOTf, 2,6-di-*tert*-butylpyridine in 73% yield. See supporting information for details.

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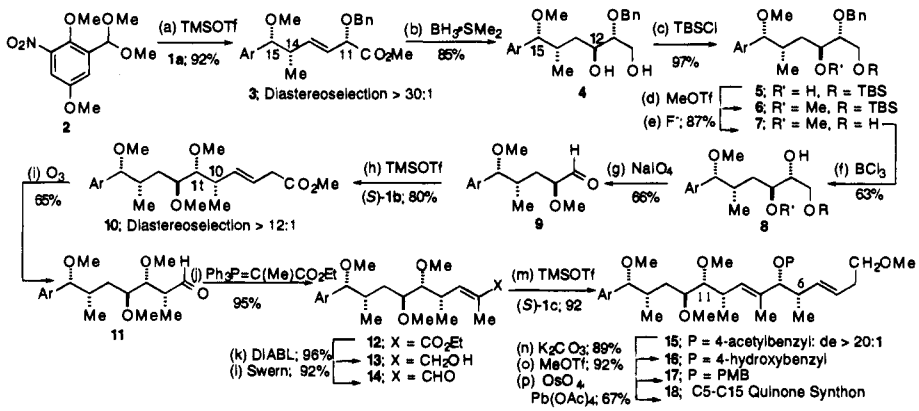
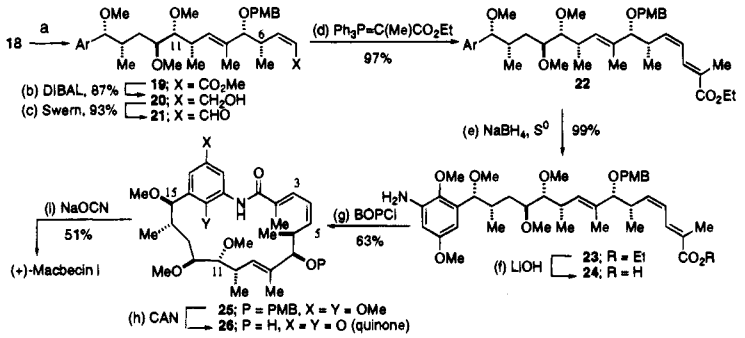
Scheme 2[a]



[a] Key: (a) TMSOTf, CH_2Cl_2, −78 °C; (b) BH_3·SMe_2, THF, 0 °C → room temperature; (c) TBSCl, imidazole, 0 °C, DMF; (d) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2; (e) *n*-Bu_4NF, THF; (f) BCl_3, CH_2Cl_2, −78 °C; (g) $NaIO_4$, $NaHCO_3$, acetone/H_2O; (h) TMSOMe, TMSOTf, (*S*)-**1b**, CH_2Cl_2, −78 °C → −50 °C; (i) O_3, Py, MeOH, −78 °C → room temperature; (j) Ph_3P=C(Me)CO_2Et, toluene, reflux; (k) DIBAL, THF, −78 °C; (l) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C → room temperature; (m) 4-acetoxybenzyl trimethylsilyl ether, TMSOTf, (*S*)-**1c**, CH_2Cl_2, −78 °C; (n) K_2CO_3, MeOH; (o) *t*-BuOK, MeOTf, DMF, 0 °C; (p) catalytic OsO_4, TMNO, then $Pb(OAc)_4$, K_2CO_3, PhH, 5 min.

Scheme 3[a]



[a] Keys: (a) $(CF_3CH_2O)_2P(O)CH_2COOMe$, $KN(SiMe_3)_2$, 18-crown-6, THF, −78 °C; (b) DIBAL, THF, −78 °C; (c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C → room temperature; (d) Ph_3P=C(Me)CO_2Et, toluene, reflux; (e) $NaBH_4$, sulfur, THF, reflux; (f) LiOH, THF/MeOH/H_2O; (g) BOPCl, EtN(*i*-Pr)$_2$, toluene, 85 °C; (h) CAN, THF/H_2O; DDQ, THF/H_2O; (i) NaOCN, TFA, CH_2Cl_2.

plished in the presence of the trisubstituted double bond by a two-step process, employing a dihydroxylation with OsO_4 (0.1 mol %) and MNO (1.0 equiv).[18] The diol was used without purification in a subsequent oxidative cleavage using $Pb(OAc)_4$ (1.2 equiv), to afford the corresponding aldehyde **18**, completing the construction of all seven stereocenters of macbecin.

Completion of the synthesis of macbecin is summarized in Scheme 3, and was initiated with the assembly of the C1−C4 (*Z,E*)-dienoate system. A (*Z*)-selective Horner−Emmons olefination reagent, employing the conditions described by Still, produced the (*Z*)-unsaturated ester in 82% yield as 15:1 mixture of olefin isomers.[19] The olefination was followed by a DIBAL-H reduction (THF, −78 °C) and Swern oxidation to afford aldehyde **21**. Treatment of **21** with (carbethoxymethylene)triphenylphosphorane gave the (*E,Z*)-dienoate **22**, completing the assembly of the macbecin carbon framework. The introduction of the arylamine was achieved in quantitative yield through the use of sulfurated borohydride.[20] The nitro ester was treated with the combination of $NaBH_4$ (5.0 equiv) and elemental sulfur (15.2 equiv) in refluxing THF, to obtain arylamine **23** in quantitative yield. Subsequent hydrolysis of the ethyl ester with LiOH (10 equiv, THF/MeOH/H_2O) gave the amino acid. Treatment of the unpurified hydrolysis product **24** with Hünig's base, BOPCl,[21] afforded C7 OPMB-protected macrocycle **25**.

Macbecin was secured by two sequential oxidations [(i) CAN, THF/H_2O (10:1), −10 °C (quinone oxidation); (ii) DDQ (1.5 equiv), THF/H_2O (20:1), 0 °C, C7 OPMB deprotection], to afford decarbamoylmacbecin **26** in 39% isolated yield. The acylation of the C7 hydroxy group (NaOCN, TFA) provided synthetic (+)-macbecin I, whose spectroscopic and physical properties were identical in all respects (^1H and ^{13}C NMR, IR, $[\alpha]_D$, MS, and TLC) with those previously reported. In conclusion, the synthesis was completed in 25 steps and underscores the utility of our developing silane reagents, as it documents the first total synthesis of macbecin without the use of metal enolate-based technology for the construction of the stereochemical relationships.

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Supporting Information Available: General experimental procedures as well as spectral data for all intermediates and final products (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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