Highly Convergent Route to Dynemicins of Wide Structural Variability. Enantioselective Synthesis of Quinone Imine Precursors to Natural and Nonnatural Dynemicins

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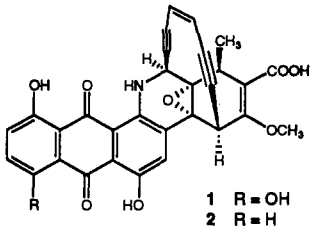
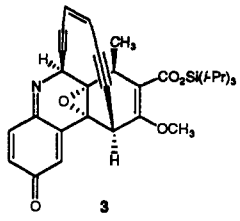
As a consequence of their potent antitumor activity and unique structural characteristics, dynemicin A (**1**) and deoxydynemicin A (**2**) constitute one of the most interesting and complex classes of natural products discovered in recent times.[1,2] In an effort to develop a synthetic route to the dynemicins, we adopted a strategy involving the quinone imine **3** as a key intermediate. Although not apparent on the basis of literature precedent,[3] it was conjectured at the outset of our studies that **3** would be a stable substance and would be suitably activated to deliver the entire right-hand portion of the dynemicins, comprising the strained (*Z*)-enediyne, epoxide, and vinylogous carbonic acid functional groups, to a variety of acceptor substrates. We describe herein a concise and enantioselective synthetic route to the quinone imine **3**, as well as the synthesis of several quinone imines that are precursors to nonnatural dynemicins.



1 R = OH
2 R = H



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Enantiodifferentiation was achieved at the outset of our synthetic route by employing menthol as a chiral auxiliary/resolving agent. Menthyl acetoacetate (1.06 equiv), prepared on the half-kilo scale in 94% yield by thermal transesterification[4] of *tert*-butyl acetoacetate with (−)-menthol, was condensed with ethyl crotonate (1 equiv) in *tert*-butyl alcohol in the presence of potassium *tert*-butoxide (1.04 equiv), forming the two possible *trans*-disubstituted 1,3-cyclohexanediones as a 1:1 mixture. A single recrystallization of the crude product mixture (benzene) afforded the diastereomerically pure 1,3-diketone **4** (mp 180−181 °C, $[\alpha]^{22}_D = +66.9°$, $c = 0.77$, CH_3OH) in 36% yield.[5] In a typical procedure, 150 g of menthyl acetoacetate was transformed into 65 g of the optically pure, crystalline diketone **4**. Treatment of **4** with anhydrous methanol and camphorsulfonic acid formed the enol ether **5** regioselectively in 71% yield.[5] Deprotonation of **5** with sodium hydride in ether and trapping of the resultant enolate with triflic anhydride at −78 °C afforded the corresponding enol triflate **6** in 95% yield. This product was efficiently coupled with *tert*-butyl 2-borono-4-methoxycarbanilate ($Pd(PPh_3)_4$, Na_2CO_3, dioxane, reflux),[6] to form the coupling product **7** in 90% yield after recrystallization (mp 141−142 °C, $[\alpha]^{22}_D = +9.2°$, $c = 1.50$, $CHCl_3$). Thermolysis of **7** for 30 min (4-chlorophenol, 180 °C) afforded the quinolone **8** (mp 153−157 °C, $[\alpha]^{22}_D = -61.3°$, $c = 0.69$, $CHCl_3$) in 84% yield. The solvent is believed to play an important role in this reaction, perhaps as a weak Bronsted acid. Reactions conducted in *o*-dichlorobenzene at the same temperature, for example, did not proceed to any appreciable extent. Quinolone **8** was transformed into the corresponding trifluoromethanesulfonate derivative with triflic anhydride and 2,6-di-*tert*-butylpyridine in dichloromethane (−78 → 0 °C, 86%). Epoxidation of the enol ether double bond using *m*-chloroperoxybenzoic acid (*m*-CPBA) in methanol at reflux afforded selectively the α-oriented alcohol **9** in 67% yield. Reductive cleavage of the trifluoromethanesulfonate group to form the quinoline **10** ($[\alpha]^{22}_D = +5.2°$, $c = 0.54$, $CHCl_3$) was accomplished in 97% yield by heating **9** in dioxane at reflux containing formic acid (2.6 equiv), triethylamine (4.0 equiv), and $Pd(PPh_3)_4$ (0.04 equiv).[7] To exchange the aryl methyl ether group for the more labile *tert*-butyldimethylsilyl group, **10** was treated initially with ethylmagnesium bromide (1.1 equiv) in tetrahydrofuran (THF) at 0 °C (to prevent nucleophilic attack on the dimethyl ketal group) and the resulting magnesium alkoxide was heated with excess sodium ethyl mercaptide in *N*,*N*-dimethylformamide (DMF) at reflux for 1.5 h.[8] The diol product of the latter reaction was isolated in 71% yield; protection of the phenol (*tert*-butyldimethylsilyl chloride, imidazole, DMF)[9] afforded the silyl ether **11** (91%).

At this juncture, the enediyne bridge was introduced using a modification of the methodology of Yamaguchi and coworkers.[10] A critical feature of this step concerns the stereochemistry of the carbon−carbon bond formation, where the desired product must result from addition of the magnesium acetylide to the same face of the *N*-acylpyridinium intermediate as that occupied by the methyl group. This requirement was easily met, and with high stereoselectivity (>20:1), when the addition reaction was conducted with the magnesium salt of alcohol **11**. Thus, the alcohol **11** was treated with ethylmagnesium bromide (0.9 equiv) in THF at 0 °C, and the resulting alkoxide was combined with (*Z*)-1-(bromomagnesio)-6-(*tert*-butyldimethylsilyl)hex-3-ene-1,5-diyne (2.0 equiv) in the presence of allyl chloroformate (1.6 equiv) to form the adduct **12** in 89% yield (10-g scale). The high stereoselectivity of this addition reaction is believed to be due to the involvement of a reactive half-chair conformation in which magnesium is chelated to the alkoxide and one or both methoxyl oxygens, placing the methyl group in a pseudoequatorial orientation. Selective epoxidation of the allylic alcohol **12** proceeded smoothly with *m*-CPBA in a two-phase mixture of dichloromethane and pH 7 aqueous phosphate buffer solution at 0 °C to provide the α-epoxide in 88% yield. Removal of both *tert*-butyldimethylsilyl groups occurred upon treatment of the latter product with tetrabutylammonium fluoride in THF (100%); reprotection of the phenol with *tert*-butyldimethylsilyl chloride and imidazole

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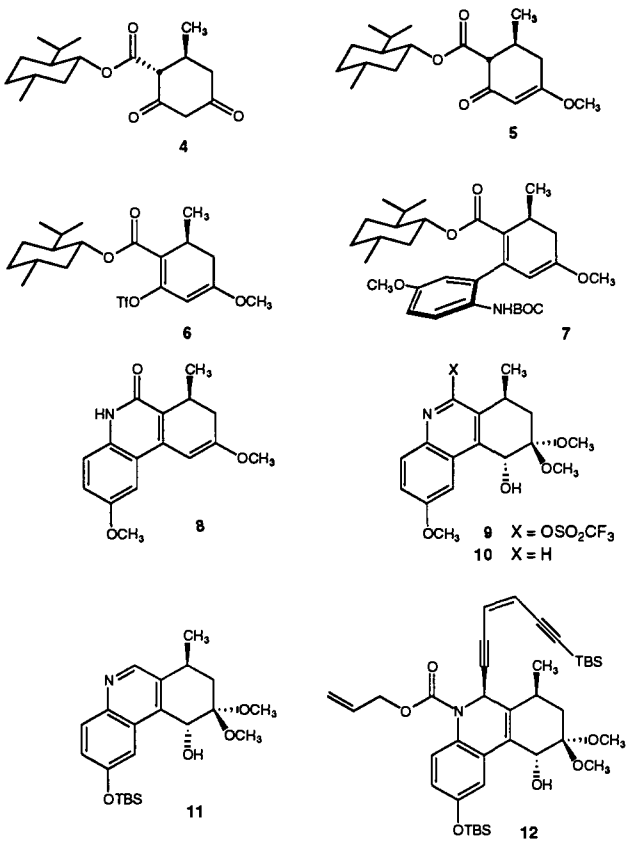
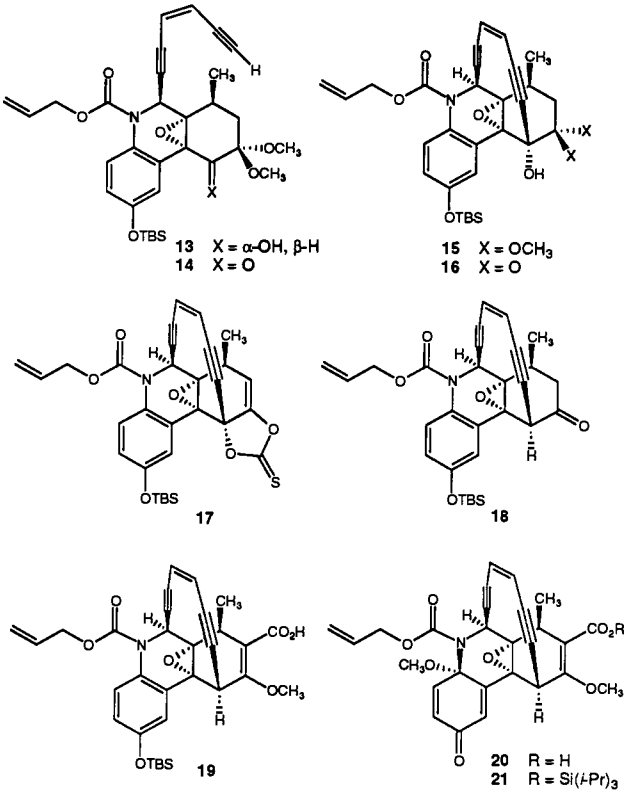


in DMF[9] then provided the alcohol **13** in 96% yield. Swern oxidation of **13** (oxalyl chloride, DMSO, CH_2Cl_2, −40 °C; triethylamine, −78 → 0 °C) afforded the ketone **14** in high yield (92%) and set the stage for closure of the enediyne bridge. Toward this end, addition of 1.1 equiv of potassium hexamethyldisilazide solution to a solution of ketone **14** in THF at −78 °C containing 3 equiv of cerium(III) chloride[11d] produced the strained addition product **15** ($[\alpha]^{22}_D = +579.8°$, $c = 0.48$, $CHCl_3$) in 94% yield after purification by flash column chromatography.[12]

Completion of the A ring was initiated by hydrolysis of the dimethyl ketal group of **15** with *p*-toluenesulfonic acid hydrate in acetone at 23 °C, furnishing the ketone **16** in 83% yield. Exposure of the latter product to excess 1,1′-thiocarbonyldiimidazole and (*N,N*-dimethylamino)pyridine (DMAP, 1.5 equiv) in dichloromethane at reflux produced the cyclic thionocarbonate **17** in 85% yield. When **17** was heated with tri-*n*-butyltin hydride (1.4 equiv) and a catalytic amount of azobisisobutyronitrile in deoxygenated toluene at 70 °C, the ketone **18** was obtained in 97% yield.[2b,13] The seemingly straightforward sequence of carboxylation α to the ketone within **18** and methyl enol ether formation proved to be one of the most difficult operations in the route. After extensive experimentation, it was discovered that mild conditions for ketone carboxylation,[14] involving stirring a solution of **18** in acetonitrile under a carbon dioxide atmosphere in the presence of magnesium bromide (2.5 equiv) and triethylamine (15 equiv), led to efficient conversion of **18** to the corresponding α-keto acid. Addition of a solution of the sensitive keto acid in ether to a suspension



of potassium *tert*-butoxide (4 equiv) in ether at −78 °C and transfer of the resulting solution to a solution of methyl triflate (5 equiv, freshly distilled) in toluene at −20 °C afforded the enol methyl ether carboxylic acid **19** ($[\alpha]^{22}_D = +565.4°$, $c = 0.40$, $CHCl_3$) in 49% yield for the two-step sequence. Cleavage of the *tert*-butyldimethylsilyl ether group of **19** with triethylamine hydrogen fluoride complex in acetonitrile at 23 °C and oxidation of the resulting phenol with 1.1 equiv of iodosobenzene in methanol at 23 °C afforded the protected quinone imine **20** in 89% yield.[15] Removal of the allyl carbamate group of **20** to reveal the quinone imine was found to proceed with greater efficiency when the carboxyl group was protected as the corresponding triisopropylsilyl ester **21** (triisopropylsilyl triflate, triethylamine, THF, −78 → 0 °C, 85% yield). Treatment of **21** with 1.0 equiv of tri-*n*-butyltin hydride in wet dichloromethane containing $Pd(PPh_3)_2Cl_2$ as catalyst then afforded the quinone imine **3** ($[\alpha]^{22}_D = +1149°$, $c = 0.500$, benzene, 60% yield). As anticipated, the quinone imine **3** proved to be stable to chromatography on silica gel, to routine manipulations, and to storage. The same sequence of steps, desilylation, oxidation, and deprotection, transformed intermediates **15**, **18**, and **19** methyl ester into the analogous quinone imines in 50−70% yield for the sequence. These compounds are each stable materials that are nevertheless activated toward a variety of carbon−carbon bond forming reactions in the C ring, most notably Diels−Alder cycloaddition reactions, and have been transformed into both natural and nonnatural dynemicins, as described in a subsequent paper.

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Supplementary Material Available: Tabulated ^1H NMR and IR data and reproductions of ^1H NMR spectra for intermediates **3-21** and crystal structure data for compound **5** (63 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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