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.



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 transesterification⁴ 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, CH₃OH) 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(PPh₃)₄, Na₂CO₃, dioxane, reflux),⁶ to form the coupling product 7 in 90% yield after recrystallization (mp 141–142 °C, $[\alpha]^{22}_{D} = +9.2^{\circ}, c = 1.50$, CHCl₃). Thermolysis of 7 for 30 min (4-chlorophenol, 180 °C) afforded the quinolone 8 (mp 153-157 °C, $[\alpha]^{22}_{D} = -61.3^{\circ}, c = 0.69$, CHCl₃) 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 2,6di-*tert*-butylpyridine in dichloromethane ($-78 \rightarrow 0$ °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 ($[\alpha]^{22}_{D} = +5.2^{\circ}$, c = 0.54, CHCl₃) 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 silvl 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-(tertbutyldimethylsilyl)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 a-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

⁽¹⁾ Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; Van Duyne, G. D.; Clardy, J. J. Am. Chem. Soc. 1990, 112, 3715 and references therein.

⁽²⁾ For studies directed toward the total synthesis of 1, see: (a) Taunton, J.; Wood, J. L.; Schreiber, S. L. J. Am. Chem. Soc. 1993, 115, 10378 and J.; Wood, J. L.; Schreiber, S. L. J. Am. Chem. Soc. 1993, 115, 103/8 and references therein. For related model systems, see: (b) Nicolaou, K. C.; Hwang, C.-K.; Smith, A. L.; Wendeborn, S. V. J. Am. Chem. Soc. 1990, 112, 7416. (c) Nishikawa, T.; Isobe, M.; Goto, T. Synlett 1991, 393. (d) Magnus, P.; Fortt, S. M. J. Chem. Soc., Chem. Commun. 1991, 544. (e) Nishikawa, T.; Ino, A.; Isobe, M.; Goto, T. Chem. Lett. 1991, 1271. (f) Wender, P. A.; Zercher, C. K. J. Am. Chem. Soc. 1991, 113, 2311. (g) Nicolaou, K. C.; Smith, A. L.; Wendeborn, S. V.; Hwang, C.-K. J. Am. Chem. Soc. 1991, 113, 3106. See also: (h) Yoon, T.; Shair, M. D.; Danishefsky, S. J.; Shulte, G. K. J. Org. Chem., in press. We are grateful to Professor Danishefsky for an advance conv of his manuscript. to Professor Danishefsky for an advance copy of his manuscript.

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⁽⁵⁾ Stereochemical assignments were determined by X-ray crystallographic analysis of the product 5.

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in DMF⁹ then provided the alcohol **13** in 96% yield. Swern oxidation of **13** (oxalyl chloride, DMSO, CH₂Cl₂, -40 °C; triethylamine, $-78 \rightarrow 0$ °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** ([α]²²_D = +579.8°, *c* = 0.48, CHCl₃) 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-nbutyltin 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 ($[\alpha]^{22}_{D} = +565.4^{\circ}, c =$ 0.40, CHCl₃) 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, $-78 \rightarrow 0$ °C, 85% yield). Treatment of 21 with 1.0 equiv of tri-n-butyltin hydride in wet dichloromethane containing Pd(PPh₃)₂Cl₂ as catalyst then afforded the quinone imine 3 ($[\alpha]^{22}_{D} = +1149^{\circ}, c = 0.500$, 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 carboncarbon 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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