Enantioselective Total Synthesis of (+)-Duocarmycin A, *epi*-(+)-Duocarmycin A, and Their Unnatural Enantiomers

Dale L. Boger,* Jeffrey A. McKie, Takahide Nishi, and Tsuyoshi Ogiku

Department of Chemistry
The Scripps Research Institute
10666 North Torrey Pines Road
La Jolla, California 92037

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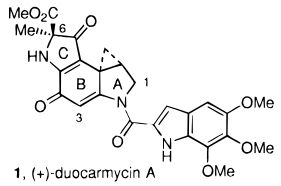
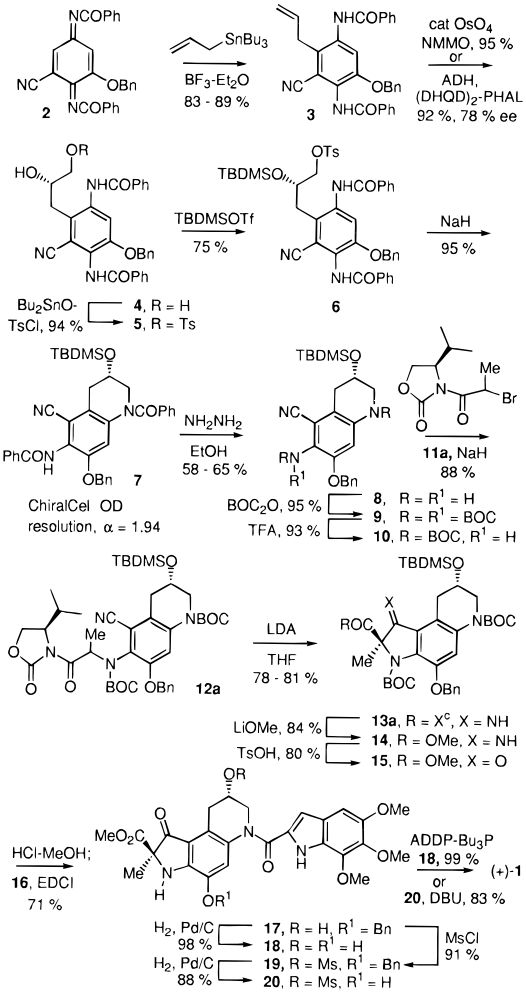
Duocarmycin A (**1**)[1] represents one of the newest additions and the structurally most challenging member of a class of naturally occurring potent antitumor antibiotics[2−4] that derive their properties through sequence-selective alkylation of duplex DNA.[5,6] In addition to **1** being the most reactive member of



the natural products and thus the most difficult to handle, synthetic approaches to the control of the relative and absolute stereochemistry of its two remote stereocenters have not been forthcoming. Herein, we report a divergent and diastereoselective total synthesis of natural (+)-duocarmycin A and its C6 diastereomer, (+)-*epi*-duocarmycin A, in which solutions to the remote stereocenter introductions are provided.[7,8]

Regiospecific Lewis acid-catalyzed addition[9] of allyltributyltin (0.5 equiv of BF_3-OEt_2, CH_2Cl_2, −20 °C, 3 h, 83−89%) to the activated *p*-quinodiimide **2**[10] cleanly provided **3** (Scheme 1). Catalytic dihydroxylation (catalytic OsO_4, 2 equiv of NMMO, acetone−H_2O 4:1, 25 °C, 12 h, 95%), followed by

Scheme 1



selective protection of the primary alcohol of **4** (1.1 equiv of Bu_2SnO, toluene−THF 10:1, reflux, $-H_2O$, 6 h; 1.2 equiv of TsCl, catalytic Et_3N, 25 °C, 12 h, 89%), provided **5**. Protection of the remaining secondary alcohol (1.5 equiv of TBDMSOTf, 2 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 3 h, 73%), followed by base-promoted intramolecular alkylation (2.0 equiv of NaH, THF, 0 °C, 2 h, 92−97%), provided the first key intermediate, **7**. Optically active **7** was obtained by catalytic asymmetric dihydroxylation[11] of **3** in the presence of $(DHQD)_2-PHAL$[12] (0.1 equiv, 0.01 equiv of OsO_4, 3 equiv of $K_3Fe(CN)_6$, 3 equiv of K_2CO_3, 3 equiv of $CH_3SO_2NH_2$, THF−H_2O 4:1, 16 h, 89−92%, 78% ee). Notably, the (*S*) absolute configuration of the newly introduced secondary hydroxyl group was determined to be opposite that predicted from the established models, and the complementary ligand, $(DHQ)_2-PHAL$, provided the corresponding (*R*) enantiomer (89%, 77% ee).[12] Further enrichment in the optical purity of the intermediates could be accomplished by direct chromatographic resolution of **7**, $[\alpha]^{25}_D$ −116° (*c* 0.5, CH_3OH), on a semipreparative ChiralCel OD column (2 cm × 25 cm, 25% *i*-PrOH−hexane), which provided a preparatively useful (150−250 mg/injection) and unusually effective separa-

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(10) *p*-Quinodiimide **2** was prepared in six steps from commercially available 2-hydroxy-4-nitroaniline: (1) 1.05 equiv of BnCl, 2.2 equiv of K_2CO_3, catalytic KI, DMF, 25 °C, 24 h, 90−94%; (2) 1.05 equiv of NBS, CH_3CN, 25 °C, 2 h, 100%; (3) 1.1 equiv of CuCN, DMF, 160 °C, 16 h, 95%; (4) 10 equiv of Fe, HOAc−H_2O, 120 °C, 15 min, 52% or Al(Hg), Et_2O−EtOH-H_2O, 0 to 25 °C, 2 h, 95−100%; (5) 2.5 equiv of BzCl, 4 equiv of K_2CO_3, 0.3 equiv of DMAP, THF, 25 °C, 16 h, 92−96%; (6) 1.0 equiv of $Pb(OAc)_4$, $CHCl_3$, 0 to 25 °C, 4 h, 84%.

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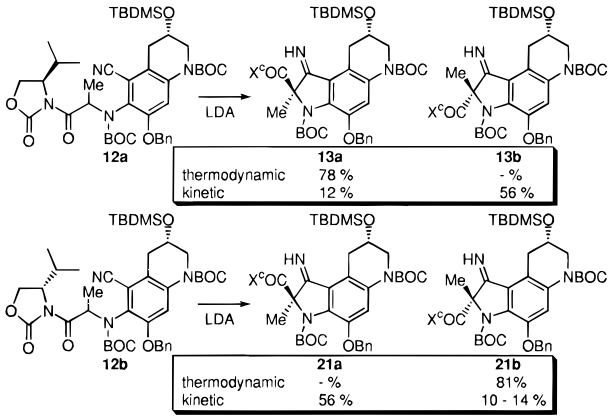
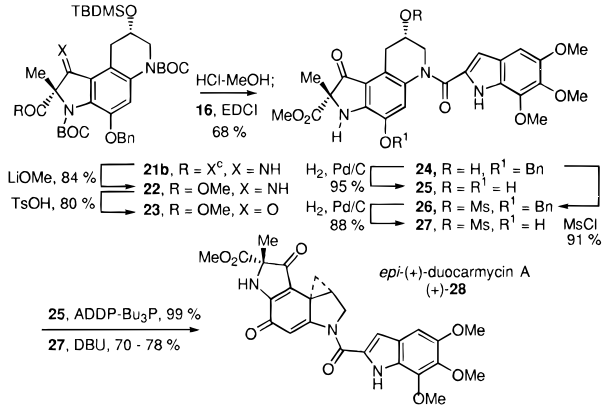
Scheme 2



Scheme 3



tion of the enantiomers (t_R = 48.2 (3*R*) and 93.4 (3*S*) min, 5 mL/min flow rate, α = 1.94, >99.9% ee).[13] Removal of the two benzoyl protecting groups (NH_2NH_2−EtOH 10:1, 140 °C, 20 h, sealed tube, 58−65%), followed by immediate reprotection of the free amine **8** with BOC_2O (6 equiv, catalytic DMAP, THF, reflux, 4 h, 95%; 5 equiv of TFA, CH_2Cl_2, −30 to 0 °C, 3 h, 93%), provided **10** and set the stage for introduction of the C ring and its remaining C6 quaternary center.

Alkylation of **10** with the oxazolidinone **11**[14] (1.5 equiv of NaH, DMF, 0 °C, 1 h, 88%), followed by condensation of **12a** under thermodynamically controlled reaction conditions achieved by inverse addition of base to the substrate (6 equiv of LDA, THF, −78 to −50 °C, 0.5 h, 78%), cleanly provided the (3*S*,6*R*) diastereomer **13a** (≥8−10:1) as the nearly exclusive closure product and a small amount of recovered **12a** (7%), (Scheme 2). Alternatively, condensation of **12b** containing the enantiomer of the acyl oxazolidinone under kinetically controlled reaction conditions,[14] achieved by slow addition (30 min) of substrate to base maintained at −78 °C (4−6 equiv of LDA, THF, −78 °C, 10 min, 56%), cleanly provided **21a**, also possessing the desired (3*S*,6*R*) stereochemistry.[15] Notably, the diastereomeric pairs **21a/21b** (SiO_2, α = 2.3, 30% EtOAc−hexane) or **13a/13b** (SiO_2, α = 1.4, 20% EtOAc−hexane) bearing Evans's optically active acyl oxazolidinones were readily separable by chromatography, thereby providing the pure diastereomers (>99.9% de). That the latter constitutes the kinetic product and the former the thermodynamic product of a reversible closure was established by resubjecting the kinetic product **21a** to the reaction conditions (1.5 equiv of LDA, −78 °C, 6 h) with equilibration to the thermodynamic product **21b** (8:1). The stereochemical outcome is consistent with the derivation of the kinetic product from the reaction of a chelated (*Z*)-enolate, while the latter equilibration process provides the most stable of the two possible diastereomers (ΔE = 0.76 and 0.4 kcal/mol, MM2 and AM1, respectively). Both results are dependent on the size of the adjacent N-protecting group (BOC > CHO) and its interaction with the chiral auxiliary substituent in either the diastereomeric transition states (kinetic product, chelated (*Z*)-enolate) or the final products (nonchelated *anti* carbonyl conformation). Methanolysis of **13a** or **21a** (30 equiv of $LiOCH_3$, THF−CH_3OH, 0 °C, 0.5 h, 78−84%), which served to remove the oxazolidinone to provide **14**, followed by imine hydrolysis (2 equiv of TsOH−H_2O, THF−H_2O 8:1, 0 °C, 3 h, 76−80%), afforded **15**. Acid-catalyzed deprotection of **15** (4 M HCl−CH_3OH, 0 °C, 1 h), which served to remove both BOC and the TBDMS protecting groups, followed by coupling with 5,6,7-trimethoxyindole-2-carboxylic acid (**16**,[16] 3 equiv of EDCI, DMF, 25 °C, 4 h, 68%), provided **17**. Removal of the benzyl ether (H_2, 10% Pd−C, CH_3OH, 25 °C, 30 min, 95−98%), followed by direct transannular spirocyclization of the alcohol **18** upon Mitsunobu activation (1.5 equiv of ADDP, 1.5 equiv of Bu_3P, C_6H_6, 50 °C 1 h, 99%), provided (+)-duocarmycin A (**1**), identical in all respects with authentic material, $[\alpha]^{25}_D$ +291° (*c* 0.01, CH_3OH).[17] Alternatively, treatment of **17** with MsCl (3 equiv, pyridine, 0 °C, 1 h, 87−91%), followed by hydrogenolysis of the benzyl ether (H_2, 10% Pd−C, CH_3OH, 25 °C, 30 min, 82−88%) and spirocyclization effected by treatment with DBU (2 equiv, CH_3CN, 25 °C, 2 h, 70−83%), also provided (+)-duocarmycin A in conversions that proved more dependable on a small scale.

Similarly, closure of **12b** under conditions of thermodynamic control or condensation of **12a** under kinetic control, where product equilibration is minimized, provided **21b** (81%) or **13b** (56%), respectively, possessing the (3*S*,6*S*) stereochemistry (Scheme 2). Methanolysis of **21b** or **13b** and conversion of **22** to *epi*-(+)-duocarmycin A (**28**), $[\alpha]^{25}_D$ +155° (*c* 0.02, CH_3OH),[17] was accomplished as detailed for (+)-**1** (Scheme 3). Thus, the diastereoselective preparation of **1** or its epimer **28** was achieved on the basis of a divergent Dieckmann-like condensation in which either C6 absolute configuration could be introduced through choice of kinetic or thermodynamic reaction conditions on the same intermediate (*e.g.*, **12a**) *or* through choice of complementary auxiliaries (*e.g.*, **12a/12b**). By means of the same approach but employing (3*R*)-**8**, the unnatural enantiomers of **1**, $[\alpha]^{25}_D$ −284° (*c* 0.025, CH_3OH), and **28**, $[\alpha]^{25}_D$ −156° (*c* 0.025, CH_3OH), were also prepared.

Extensions of these studies to the preparation of key partial structures of **1** and their comparative examination are in progress and will be reported in due course.

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Supporting Information Available: Physical and spectroscopic characterization of all synthetic intermediates is provided (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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(13) This latter procedure, which benefits from an unusually large separation, was employed to further enrich the mixture obtained from ADH or to resolve racemic material and dependably assured the optical purity of the samples (>99.9% ee).

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(17) (+)-Duocarmycin A: lit.[1] $[\alpha]^{25}_D$ +282° (*c* 0.1, CH_3OH), lit.[7] $[\alpha]^{25}_D$ +332° (*c* 0.14, $CHCl_3$). *epi*-(+)-Duocarmycin A: lit.[7] $[\alpha]^{25}_D$ +161° (*c* 0.07, $CHCl_3$).