Communications to the Editor

A Concise, Stereocontrolled Synthesis of (−)-Saframycin A by the Directed Condensation of α-Amino Aldehyde Precursors

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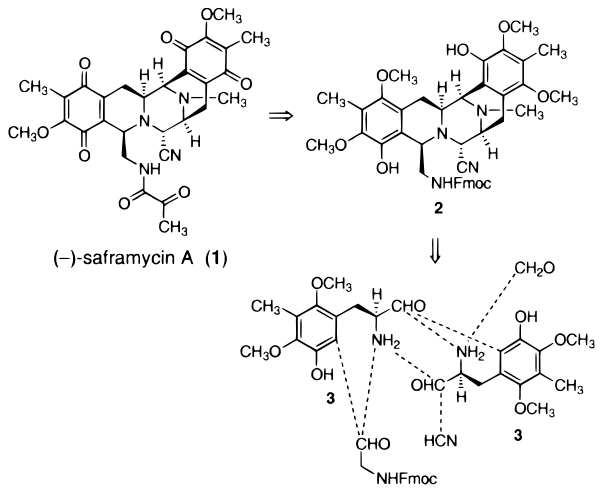
In this work we describe a short and enantioselective synthetic route to the potent antitumor agent (−)-saframycin A (**1**), a bisquinone alkaloid of microbial origin.[1,2] The route employs a new and powerful synthetic strategy involving the directed condensation of optically active α-amino aldehydes. This strategy evolved from retrosynthetic analysis of **1**, as shown, where a series of transformations initiated by the condensation of an aldehyde with an amine (e.g., reductive amination, Pictet−Spengler, and Strecker reactions) was envisioned to assemble the target **1** from five simple components: hydrogen cyanide, formaldehyde, and three α-amino aldehydes [two of which (structure **3**) are the same, hence the latent symmetry of **1**]. The complexity of the analysis arises in the determination of the precise order and stereochemistry of bonding events that will link the precursors (seven bonds must be formed), and upon consideration of the fundamental issues of stability, reactivity, and protection strategies surrounding the proposed use of optically active α-amino aldehydes as synthetic intermediates. Recently, we reported the development of a series of "*C*-protected" optically active α-amino aldehydes that incorporates an amino nitrile group as a masked aldehyde.[3] Morpholino nitrile derivatives, exemplified by structure **5**, were found to be particularly useful synthetic intermediates, undergoing condensation reactions with optically active *N*-protected α-amino aldehydes with little to no epimerization of either component, thus establishing the basis for the directed assembly of (−)-saframycin A detailed herein.

Compounds **4** and **5**, *N*- and *C*-protected versions of the same chiral α-amino aldehyde (**3**), were prepared in high enantiomeric excess from the same product of asymmetric alkylation of (−)-pseudoephedrine glycinamide, as previously described.[3,4] Addition of *N*-protected α-amino aldehyde **4** (96% ee, 1.05 equiv) to *C*-protected α-amino aldehyde **5** (92% ee, 1 equiv)[5] in dichloromethane at 23 °C in the presence of sodium sulfate cleanly provided the imine **6** (presumed trans) without detectable epimerization of either α-stereocenter (^{1}H NMR analysis, >90% yield. Addition of a saturated solution of anhydrous lithium bromide in dimethoxyethane to the imine intermediate and warming to 35 °C brought about Pictet−Spengler cyclization to provide a ∼5:1 mixture of cis and trans tetrahydroisoquinolines, respectively. Flash column chromatography afforded the desired cis product (**7**) in 65−72% yield and 99% ee. The optical purity of **7** was assayed by HPLC analysis (Chiralcel OD) of the corresponding bis(benzoyl) derivative against an authentic sample of its enantiomer, derived from (+)-pseudoephedrine via *ent*-**4** and *ent*-**5**. Lithium ion proved to be optimal for mild and selective Lewis acid activation of the imine function without reaction of the morpholino nitrile. The cis−trans selectivity of the cyclization

Scheme 1



reaction varied markedly as a function of solvent and activating agent; for example, use of lithium perchlorate in diethyl ether provided the trans product exclusively. It is also noteworthy that the transformation of **6** to **7** is the only step in the synthetic route that was conducted above ambient temperature.

Introduction of the *N*-methyl group at this stage of the synthesis was found to be optimal. Stirring **7** at 23 °C in the presence of formalin (2.0 equiv) and sodium triacetoxyborohydride (1.5 equiv) in acetonitrile provided the corresponding *N*-methylated compound in 94% yield; the morpholino nitrile function was unaffected by the reductive conditions. The *N*-Fmoc and *O*-TBS protective groups were then cleaved. While these deprotections could be performed simultaneously by the action of fluoride or hydroxide, sequential removal of the silyl ether with acetic acid-buffered tetrabutylammonium fluoride (2.4 and 1.1 equiv, respectively) followed by cleavage of the carbamate with DBU (1.3 equiv) provided **8** with greater efficiency (92%). Notably, compound **8** showed no propensity for the primary amine to add to the masked aldehyde under such conditions as exposure to silica gel or upon standing in the protic medium 2,2,2-trifluoroethanol, further highlighting the stability of the morpholino nitrile protective group.

Addition of the third and final α-amino aldehyde component, *N*-Fmoc glycinal (1.5 equiv), to amine **8** (1 equiv) in the presence of sodium sulfate in deoxygenated dichloromethane at 23 °C

(1) Reviews: (a) Arai, T.; Kubo, A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1983; Vol. 21, Chapter 3. (b) Remers, W. A. In *The Chemistry of Antitumor Antibiotics*; Wiley-Interscience: New York, 1988; Vol. 2, Chapter 3.

(2) Previous syntheses of the saframycins: (±)-Saframycin B: (a) Fukuyama, T.; Sachleben, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 4957−4958. (b) Kubo, A.; Saito, N.; Yamato, H.; Masubuchi, K.; Nakamura, M. *J. Org. Chem.* **1988**, *53*, 4295−4310. (±)-Saframycin A: (c) Fukuyama, T.; Yang, L.; Ajeck, K. L.; Sachleben, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 3712−3713. (−)-Saframycin A: (d) Martinez, E. J.; Corey, E. J. *Org. Lett.* **1999**, *1*, 75−77. See also: (e) Zhou, B.; Edmondson, S.; Danishefsky, S. J. *Tetrahedron Lett.* Submitted for publication. (f) Zhou, B.; Danishefsky, S. J. *Tetrahedron Lett.* Submitted for publication.

(3) Myers, A. G.; Kung, D. W.; Zhong, B.; Movassaghi, M.; Kwon, S. *J. Am. Chem. Soc.* **1999**, *121*, 8401−8402.

(4) Myers, A. G.; Schnider, P.; Kwon, S.; Kung, D. W. *J. Org. Chem.* **1999**, *64*, 3322−3327.

(5) The sequence of reactions shown in Scheme 2 has been conducted independently with both the (*R*)- [depicted] and (*S*)-morpholino nitrile diastereomers. The yields and selectivities in both sequences were nearly identical and in no event was scrambling of the morpholino nitrile stereochemistry observed. We have also successfully executed the sequence using a ∼1:1 mixture of the (*R*)- and (*S*)-diastereomers, converging on the intermediate **2**, this being the preferred route for large-scale synthesis of **1** and **2**.

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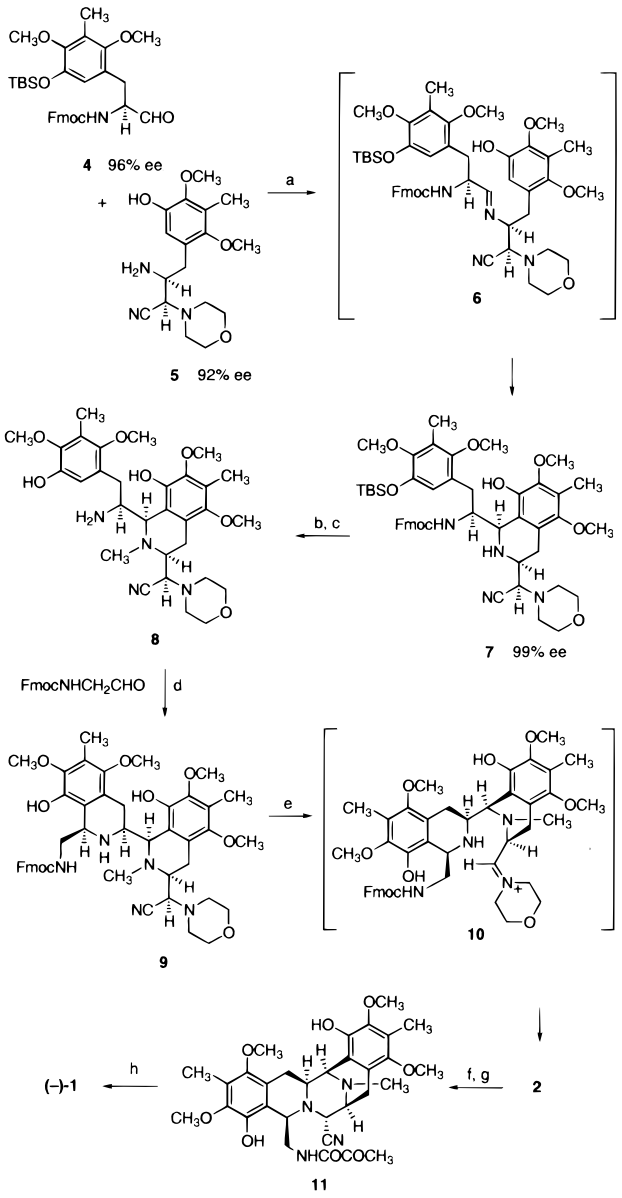
Scheme 2[a]



[a] Reaction conditions: (a) Na_2SO_4, CH_2Cl_2, 23 °C, >90%; LiBr, DME, 35 °C, 65−72%. (b) CH_2O-H_2O, $NaBH(OAc)_3$, CH_3CN, 23 °C, 94%. (c) HOAc, TBAF, THF, 23 °C; DBU, CH_2Cl_2, 23 °C, 92%. (d) Na_2SO_4, CH_2Cl_2, 23 °C, 66%. (e) $ZnCl_2$, TMSCN, $CF_3CH_2OH-THF$, 23 °C, 86%. (f) DBU, CH_2Cl_2, 23 °C, 88%. (g) $ClCOCOCH_3$, $PhNEt_2$, CH_2Cl_2, 0 °C, 89%. (h) PhIO, CH_3CN-H_2O, 0 °C, 66%.

produced an imine intermediate that underwent Pictet−Spengler cyclization, also at 23 °C, to provide a ≥9:1 mixture of cis and trans tetrahydroisoquinolines, respectively. The desired cis isomer (**9**) was isolated in 66% yield. The reaction solvent was again critical for selective formation of the desired cis tetrahydroisoquinoline; protic solvents afforded predominantly the trans diastereomer (e.g., in methanol, trans:cis >5:1). With the "trimer" of α-amino aldehydes assembled (**9**), the *C*-terminus morpholino nitrile blocking group was then cleaved with anhydrous zinc chloride[6] (3.0 equiv) in a mixture of trifluoroethanol and tetrahydrofuran (2:1) at 23 °C, producing the key pentacyclic intermediate **2** in 86% yield. This transformation presumably proceeded by the sequential formation of iminium ion **10**, cyclization (addition of the secondary amine to the iminium ion), expulsion of morpholine, and trapping of the resultant iminium ion by cyanide. It was necessary to introduce exogenous cyanide (trimethylsilyl cyanide, 2.0 equiv) to ensure complete amino nitrile formation; in the absence of added cyanide, small amounts (5−10%) of the hemiaminal corresponding to hydrolysis of amino nitrile **2** were observed, presumably due to adventitious water. Finally, the *N*-Fmoc protective group of **2** was cleaved with DBU (1.3 equiv) at 23 °C in 88% yield, and the resulting primary amine was acylated with pyruvoyl chloride (3.0 equiv) in the presence of *N*,*N*-diethylaniline (1.1 equiv) at 0 °C to afford **11** (89%). Oxidative demethylation of the hydroquinones with iodosobenzene (2.5 equiv) in acetonitrile−water (1:1, 0 °C) furnished synthetic (−)-saframycin A in 66% yield (127 mg of (−)-**1**).[7] The synthetic material was found to be identical in all respects (^1H NMR, ^{13}C NMR, IR, HPLC, TLC analysis, and optical rotation) with an authentic sample of natural saframycin A, kindly provided by Professor T. Arai.

In summary, we have developed a practical and efficient synthesis of (−)-saframycin A that proceeds in just 8 steps from the α-amino aldehyde precursors **4** and **5**, in ∼15% overall yield. The synthesis illustrates a simple strategy for alkaloid assembly that involves the directed condensation of α-amino aldehyde precursors in a manner not unlike oligopeptide synthesis (here, with $C \rightarrow N$ directionality). The present route is suitable for the production of **1** in quantity; to date, more than 1 g of **2** and 200 mg of (−)-**1** have been prepared.

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Supporting Information Available: Experimental procedures and listings of spectral data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA993079K

(6) Guibe, F.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1982**, *23*, 5055−5058.

(7) Two unstable byproducts, tentatively assigned as the regioisomeric *o*-,*p*- and *p*-,*o*-quinones, were also isolated in a combined yield of ∼15%.