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Concise Synthesis of the CDE Ring System of Tetrahydroisoquinoline Alkaloids Using Carbophilic Lewis Acid-Catalyzed Hydroamidation and Oxidative Friedel−Crafts Cyclization

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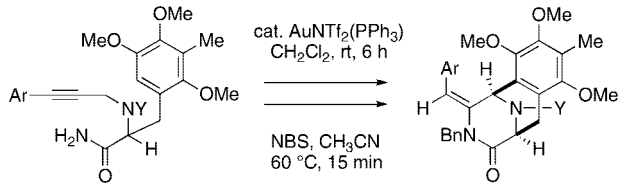

A concise synthesis of the CDE ring system of the tetrahydroisoquinoline antitumor alkaloids such as saframycins, renieramycins, and ecteinascidins has been developed. Both Au(I)-catalyzed intramolecular hydroamidation of alkynylamide and NBS-mediated oxidative Friedel−Crafts cyclization of the resulting 2-ketopiperazine were utilized as key reactions.

Tetrahydroisoquinoline alkaloids are a broad family of biologically active natural products, which include saframycins,[1] renieramycins,[2] and ecteinascidins[3] as shown in Figure 1. These

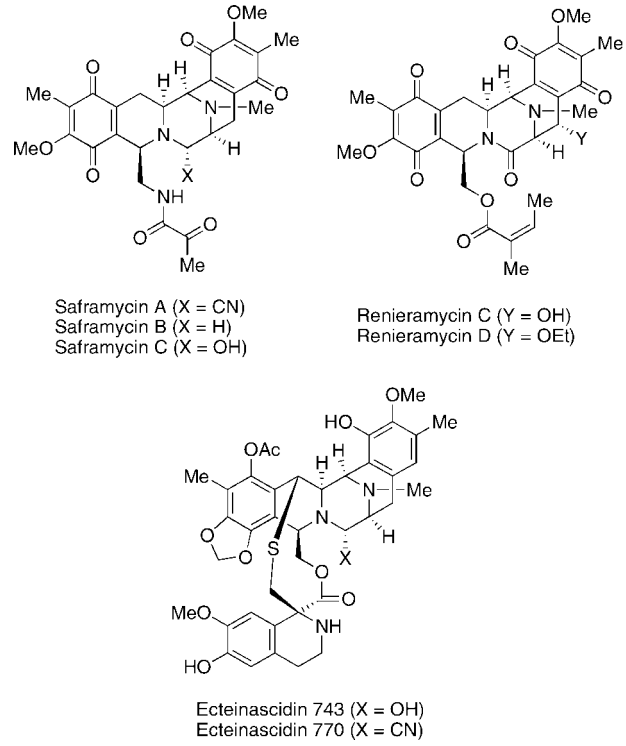

FIGURE 1. Biologically active tetrahydroisoquinoline alkaloids.

alkaloids possess potent antitumor, antibiotic, and antimicrobial activities through the inhibition of RNA, DNA, and protein synthesis.[4] In particular, ecteinascidin 743 (Et 743) is currently undergoing phase II/III clinical trials for the treatment of ovarian, endometrial, and breast cancer.[5] The antiproliferative activity of Et 743 is greater than that of taxol, camptothecin, mitomycin C, or cisplatin. However, the development of these compounds as antitumor drugs has been limited by their natural scarcity. Thus, total synthesis of these compounds presents a formidable and urgent challenge to the synthetic chemists in terms of the complexity of molecular architecture, the remarkable biological activities, and the restricted natural availability. Although, to date, a number of elegant synthetic studies on these pentacyclic alkaloids have been developed,[1−3,6] most of these approaches were based on a similar strategy with use of either double aldol condensation of 2,5-diketopiperazine and appropriate aryl aldehydes or stepwise Pictet−Spengler cyclization for the con-

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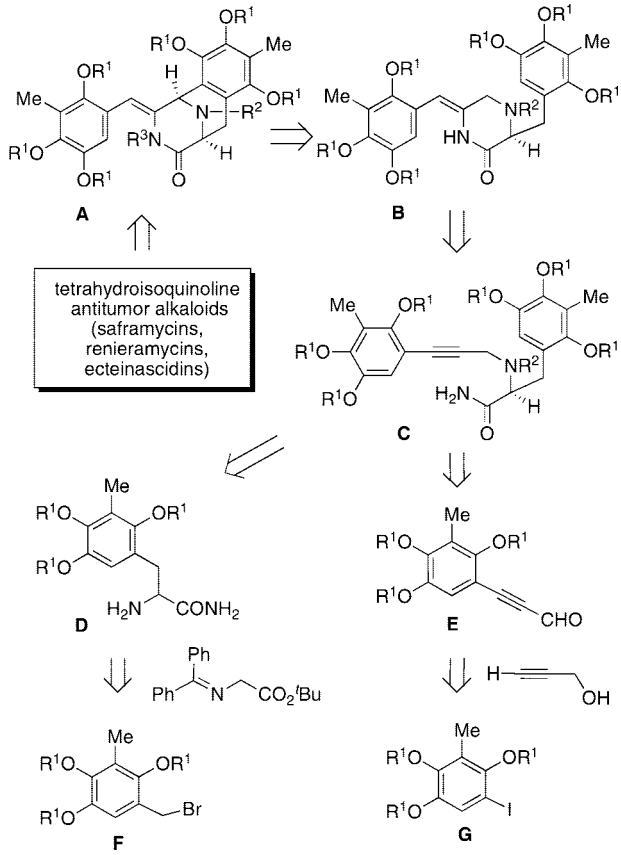
SCHEME 1. Retrosynthetic Analysis of Tetrahydroisoquinoline Antitumor Alkaloids

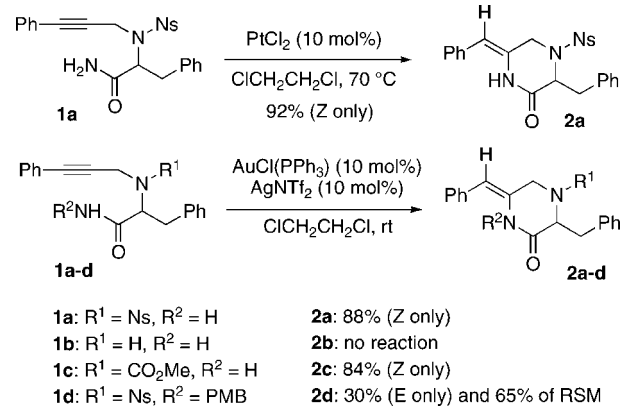


struction of the AB and DE tetrahydroisoquinoline ring systems.[1,2c–e,3a–c,6c–f]

Therefore, we planned to develop an alternative assembly for installation of the CDE ring system **A** as shown in Scheme 1. From our retrosynthetic analysis, both oxidative Friedel−Crafts cyclization (**B** to **A**) and intramolecular hydroamidation (**C** to **B**) would be key steps for success of this approach. The requisite compound **C** to test the key reactions can be synthesized by the reductive condensation of amino acid derivative **D** and alkynyl aldehyde **E**, which are easily accessible from **F** and **G** in the usual manner. Herein, we describe the concise synthesis of tricyclic fragment **A** of tetrahydroisoquinoline alkaloids by using Au(I)-catalyzed hydroamidation and NBS-mediated Friedel−Crafts cyclization as key reactions.

We have already reported that the Au(I)-catalyzed intramolecular hydroamidation of *N*-Boc(2-alkynylaryl)methylamine and *N*-Boc-2-(2-alkynylaryl)ethylamine in 1,2-dichloroethane (DCE) proceeded smoothly even at room temperature to give the corresponding hydroisoquinolines in good yields.[7] On the basis of these results, we first examined the 6-exo hydroamidation of *N*-Ns(alkynyl)amides **1a** in the presence of carbophilic Lewis acids such as $PtCl_2$[8] and $AuCl(PPh_3)/AgNTf_2$[9] (Scheme 2). Both Lewis acids gave the same product **2a** as a single (*Z*)-isomer in a similar chemical yield, but the Au(I)-catalyzed reaction took place under milder reaction conditions than that of $PtCl_2$. Therefore, the latter reactions of **1b**−**d** were carried out in the presence of 10 mol % of $AuCl(PPh_3)/AgNTf_2$ (Scheme 2).Although the reaction of amine derivative **1b** provided no desired product **2b**, carbamate **1c** underwent the hydroamidation to give the cyclic adduct (*Z*)-**2c** in 84% yield. In contrast to **1a**, the same reaction of secondary PMB amide **1d** as primary amide **1a** proceeded slowly to furnish the desired product **2d** in only 30% yield as an (*E*)-isomer together with a large amount of the recovered starting material (65%). The low yield of **2d** and the isomerization of (*Z*)-**2d** into (*E*)-**2d** might be attributed to the steric hindrance between *N*-PMB and phenyl groups on the trisubstituted olefin of **2d**. To improve the chemical yield of **2d**, other Lewis acids[10] such as $In(OTf)_3$, $NiCl_2$, $PdCl_2$, $AgNTf_2$, and $Cu(OTf)_2$ were investigated for the hydroamidation of **1d**, but no good results could be obtained. The configuration of the double bond of **2a**−**d** was determined to be *Z* by NOE experiment between the vinylic proton and the methylene proton of the C-5 position. The reaction demonstrated excellent stereoselectivity and none of *E*-isomer was detected.

SCHEME 2. The Lewis Acid-Catalyzed 6-Exo Hydroamination of Alkynylamides 1a−d



Having accomplished the structural optimization of alkynylamides **1** for the hydroamidation, our attention was next directed toward the synthesis of the requisite alkynylamide **13**. For the purpose, alkynylaldehyde **5** was prepared from aryl iodide **3**[11] and alkyne **4** by Sonogashira cross-coupling reaction and subsequent TPAP oxidation (Scheme 3).

Another coupling component **11** was synthesized from aryl alcohol **6**[12] by a 7-step sequence. After conversion of alcohol **6** into bromide **7**, successive treatment of **7** with imino ester **8** under the phase-transfer-catalyzed conditions and then with citric acid provided amino acid derivative **9** in good yield.[13] The resulting carboxylic acid, which was obtained from **9** via carbamate **10** by the protection and deprotection protocol, was transformed into the desired primary amide **11** by the mixed anhydride procedure with ammonia.

At this stage, we next undertook the coupling of two synthesized fragments **5** and **11** into **12**. Subjection of Cbz

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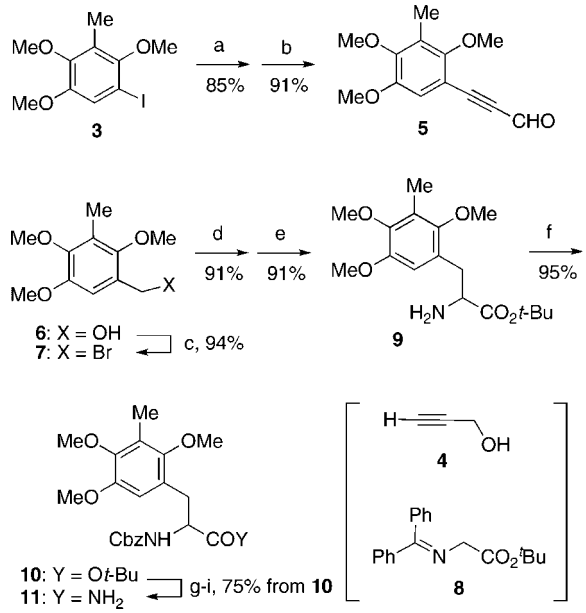
SCHEME 3. Synthesis of 5 and 11[a]

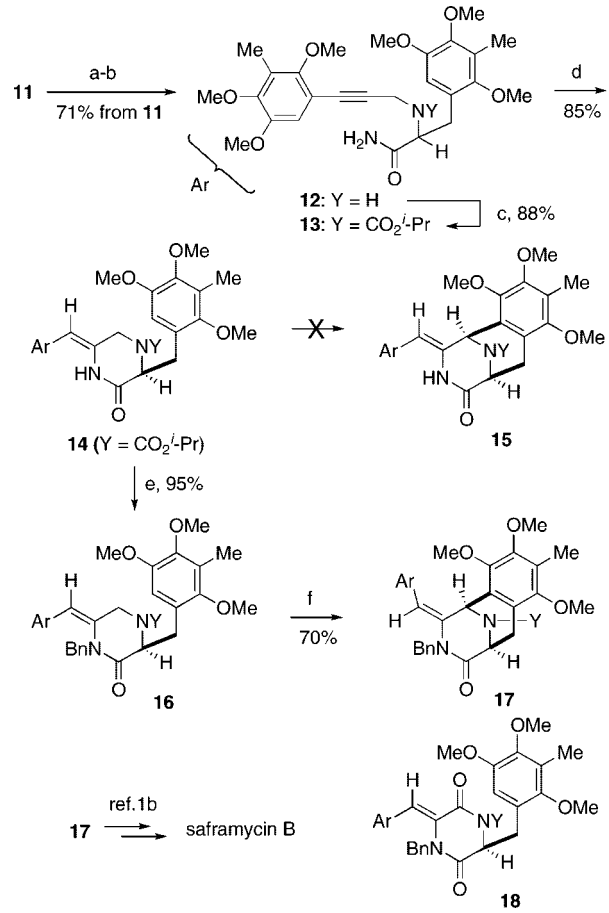


[a] Reagents and conditions: (a) **4**, $PdCl_2(PPh_3)_2$, CuI, Et_3N; (b) TPAP, NMO, MS_4A, CH_2Cl_2; (c) CBr_4, PPh_3, CH_2Cl_2; (d) **8**, Bu_4NHSO_4, 50% aq KOH, CH_2Cl_2; (e) 15% citric acid, THF; (f) CbzCl, Et_3N, CH_2Cl_2; (g) TFA, CH_2Cl_2; (h) EtOCOCl, Et_3N, CH_2Cl_2; (i) aq NH_3.

adduct **11** to hydrogenolysis with $Pd(OH)_2$ and reductive alkylation with aldehyde **5** afforded the coupling product **12** in 71% yield in two steps. After the carbamoylation of **12**, the key hydroamidation of **13** was carried out under the same conditions. As expected, the reaction occurred with excellent regio- and stereoselectivity to give the desired cyclized adduct **14** in 85% yield as a single isomer.

Having succeeded in construction of the C ring of tetrahydroisoquinoline alkaloids, we finally explored the oxidative Friedel−Crafts cyclization of **14** into tricyclic compounds such as **15** and **17**. The initial attempts were directed to the oxidation and halogenation of **14** with CAN, DDQ, NBS, and $RuCl_2(PPh_3)_3$/*t*-BuO_2H.[14] However, all attempts resulted in a complex mixture and failed to yield the desired product **15**. Then, our attention was next focused on the reactivity of benzyl adduct **16**, which has no proton on the nitrogen of the amido group. In contrast to **14**, the desired tricyclic compound **17** was produced in 15% yield along with 2,5-diketopiperazine **18** (15% yield), when **16** was subjected to the single-electron oxidation with CAN in methanol and then heating at 60 °C in the presence of HCO_2H (Scheme 4). Further elaboration of the oxidative Friedel−Crafts cyclization finally led to discovery of NBS[15] as the best oxidant, enhancing the chemical yield of **17** up to 70%. In both cases, we observed the isomerization of the enamide moiety from *Z*- to *E*-configuration, giving **17** as a single isomer.[1b,6d] The obtained product **17** is a known compound, from which total synthesis of saframycin B has been achieved by Kubo's group in 1988.[1b] The synthetic compound **17** was identical with the reported authentic sample from all spectral data (^1H NMR, ^{13}C NMR, IR, and MS). Therefore, this means that we have succeeded in a formal synthesis of saframycin B.

SCHEME 4. Synthesis of Tricyclic Product 17[a]



[a] Reagents and conditions: (a) H_2 (1 atm), $Pd(OH)_2$, MeOH; (b) **5**, MeOH, then $NaBH_4$; (c) *i*-PrOCOCl, *i*-Pr_2NEt, CH_2Cl_2; (d) $AuCl(PPh_3)$, $AgNTf_2$, CH_2Cl_2; (e) BnBr, NaH, DMF; (f) NBS, CH_3CN.

In conclusion, a concise synthesis of the CDE ring system of tetrahydroisoquinoline alkaloids such as saframycins, renieramycins, and ecteinascidins was established by using Au(I)-catalyzed intramolecular hydroamidation and NBS-mediated oxidative Friedel−Crafts cyclization as key reactions. Furthermore, we have also demonstrated a formal synthesis of saframycin B starting from alkynylamide **C** bearing two aryl substituents.

Experimental Section

Au(I)-Catalyzed Cyclization of 13 to 14. To a solution of **13** (60 mg, 0.10 mmol) in CH_2Cl_2 (0.5 mL) were added $AuCl(PPh_3)$ (5.0 mg, 0.010 mmol) and $AgNTf_2$ (4.8 mg, 0.010 mmol), and the mixture was stirred at room temperature for 6 h. After being quenched with an aqueous $NaHCO_3$ solution (0.5 mL), the mixture was extracted with $CHCl_3$ (3 × 1 mL) and the combined organic layers were dried over Na_2SO_4 and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 3/1 to 1/1) to give **14** (48 mg, 85%). ^1H NMR (500 MHz, $CDCl_3$) δ 6.67 (s, 1H), 6.61 (s, 1H), 5.27 (s, 1H), 4.96−4.86 (m, 2H), 4.18−4.00 (m, 2H), 3.98−3.84 (m, 4H), 3.81 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.68 (s, 3H), 3.66 (s, 3H), 3.33 (s, 3H), 2.21 (s, 3H), 2.19 (s, 3H), 1.34−1.26 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 155.7, 150.8, 149.1, 149.0, 148.3, 146.7, 133.5, 126.9, 126.2, 125.2, 124.9, 111.5, 110.9, 110.5, 77.2,

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69.6, 61.3, 60.7, 60.4, 60.2, 60.1, 56.0, 55.8, 44.8, 29.5, 22.0, 9.5, 9.3; IR ($CHCl_3$) 3235, 2983, 2840, 1772, 1700, 1635 cm^{-1}; MS (FAB) *m*/*z* 573 (MH^+, 8), 529 (5), 485 (10), 346 (10), 321 (10), 271 (15), 219 (55), 195 (100), 181 (17), 165 (15), 91 (25); HRMS (FAB) calcd for $C_{30}H_{41}N_2O_9$ (MH^+) 573.2812, found 573.2766.

Synthesis of 17. To a solution of **16** (33 mg, 0.050 mmol) in MeCN (0.10 mL) was added NBS (11 mg, 0.060 mmol), and the mixture was stirred at 60 °C for 15 min. After being quenched with an aqueous $NaHCO_3$ solution (0.5 mL), the mixture was extracted with $CHCl_3$ (3 × 1 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 3/1 to 1/1) to give **17** (23 mg, 70%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.11−6.99 (m, 3H), 6.79 (s, 1H), 6.72−6.62 (m, 2H), 6.08 (s, 1H), 5.71 (d, J = 14.9 Hz, 1H), 5.33−5.19 (m, 1H), 5.12−4.93 (m, 1H), 4.55 (d, J = 15.5 Hz, 1H), 3.99 (s, 3H), 3.79 (s, 3H), 3.69 (s, 3H), 3.45 (s, 3H), 3.39 (d, J = 17.2 Hz, 1H), 3.14−3.03 (m, 1H), 2.98 (s, 3H), 2.88 (s, 3H), 2.19 (s, 3H), 2.17 (s, 3H), 1.33 (d, J = 5.7 Hz, 3H), 1.28 (d, J = 5.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 152.9, 152.7, 150.7, 150.3, 149.2, 146.8, 146.4, 136.3, 134.6, 128.4, 126.7, 126.1, 125.4, 125.2, 125.1, 124.7, 121.7, 110.2, 107.6, 77.2, 69.6, 60.3, 60.1, 59.9, 59.5, 59.0, 56.5, 53.4, 45.8, 43.7, 28.2, 22.2, 9.3, 9.2; IR ($CHCl_3$) 2936, 2830, 1698, 1672, 1639 cm^{-1}; MS (FAB) *m*/*z* 661 (M^+, 100), 575 (5), 278 (22), 234 (33), 204 (15), 91 (22); HRMS (FAB) calcd for $C_{37}H_{45}N_2O_9$ (M^+) 660.3047, found 660.3027.

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Supporting Information Available: Detailed experimental procedures and product characterization data for all new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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