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Total Synthesis of Ecteinascidin 743

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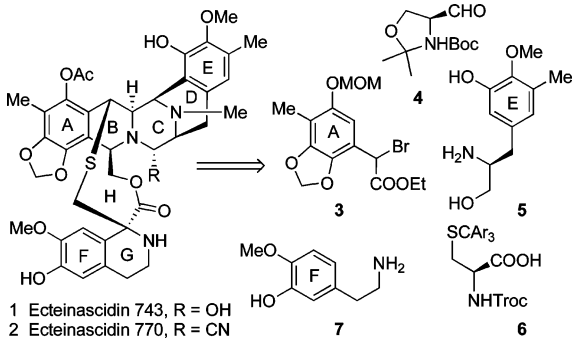
Ecteinascidin 743 (Et 743, **1**, Scheme 1), isolated from the Caribbean tunicate *Ecteinascidia turbinate*,[1] possesses potent cytotoxic activity against a variety of tumor cell lines in vitro and against several rodent tumors and human tumor xenografts in vivo. It is currently in phase II/III clinical trials in Europe and in the United States for ovarian, endometrium, and breast cancer as well as several types of sarcoma.[2] The antiproliferative activity of Et 743 is greater than that of Taxol, camptothecin, adriamycin, mitomycin C, cisplatin, bleomycin, and etopside by 1−3 orders of magnitude. The complexity of molecular architecture, the remarkable biological activities, and the restricted natural availability (1.0 g from about 1.0 ton of tunicate) made it an attractive synthetic target for total synthesis.[3] To date, two total syntheses have been accomplished by Corey et al.[4] and Fukuyama et al.[5] A semisynthesis from cyanosafracin B has been developed by Cuevas, Manzanares, and co-workers at PharmaMar.[6] In addition, other synthetic approaches have been reported from a number of research groups.[7] We report herein a highly convergent total synthesis of **1** that would potentially be amenable to large-scale production of this important antitumor agent. As shown in Scheme 1, Et 743 is retrosynthetically disconnected into five building blocks (**3** to **7**) of almost equal size.

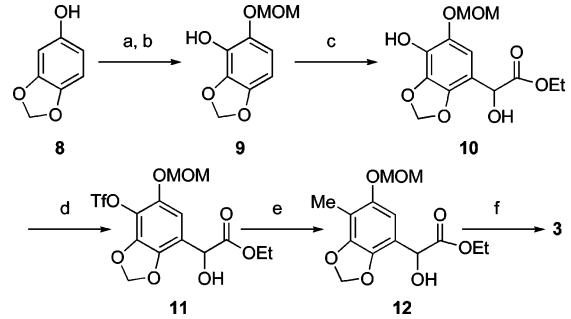
Synthesis of α-bromo-α-aryl substituted ethyl acetate **3** is depicted in Scheme 2. Masking the hydroxyl group of sesamol **8** by MOMCl followed by a sequence of regioselective lithiation/boration/oxidation according to Fukuyama[5b] afforded phenol **9**. Friedel−Crafts reaction of **9** with ethyl glyoxalate under the conditions we developed recently for the Pictet−Spengler reaction (LiCl, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)/toluene = 1:4, room temperature, rt)[8] furnished α-hydroxy ester **10** in excellent yield. Triflation of **10** with triflic anhydride under classic conditions provided a complex reaction mixture. However, using 4-nitrophenyltriflate as sulfonylating agent developed in this laboratory,[9] we found that chemoselective trifluoromethanesulfonylation of phenol **10** proceeded smoothly to afford triflate **11**. Palladium-catalyzed Suzuki−Miyaura cross-coupling[10] between **11** and trimethyl boroxine provided **12** in 93% yield. Treatment of benzyl alcohol **12** with thionyl bromide in the presence of benzotriazole[11] afforded the corresponding benzyl bromide **3** in excellent yield.

Synthesis of the D−E fragment **16** is shown in Scheme 3. Condensation of Garner's aldehyde (*S*)-**4**[12] with L-3-hydroxy-4-methoxy-5-methyl phenylalanol (**5**), which was prepared from 3-methyl catechol in eight steps,[13] provided under optimized conditions (AcOH, CH_2Cl_2/CF_3CH_2OH, molecular sieves 3 Å) the desired tetrahydroisoquinoline **13** in 84% yield as the only isolable product at the expense of other regio- (C-19 vs C-15, Et 743 numbering) and diastereoisomers.[14,15] The NOEs observed between protons H15/C_{16}-Me, H15/H14, H13/H11 of compound **14** supported both the regio- and stereochemistry assigned for compound **13**. Interestingly, the stereochemistry at C_{11} was controlled solely by the absolute configuration of amino alcohol **5** since condensation of **5** and (*R*)-**4** gave also the C_{11}−C_{13} cis diastereoisomer in excellent yield. It seems reasonable to assume that, under this circumstance, both C_{11} and C_{13} substituents adopted pseudoequatorial positions leading to the observed cis selectivity after ring closure.

Scheme 1

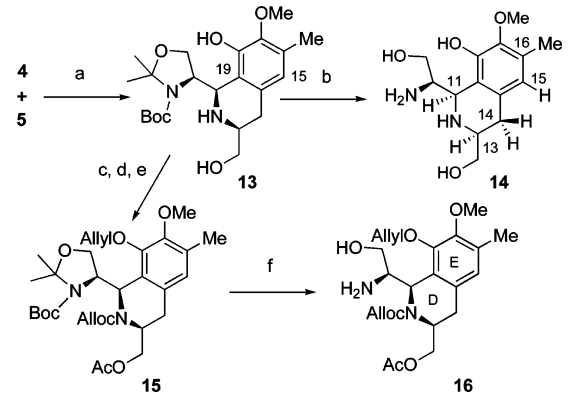


Scheme 2 [a]



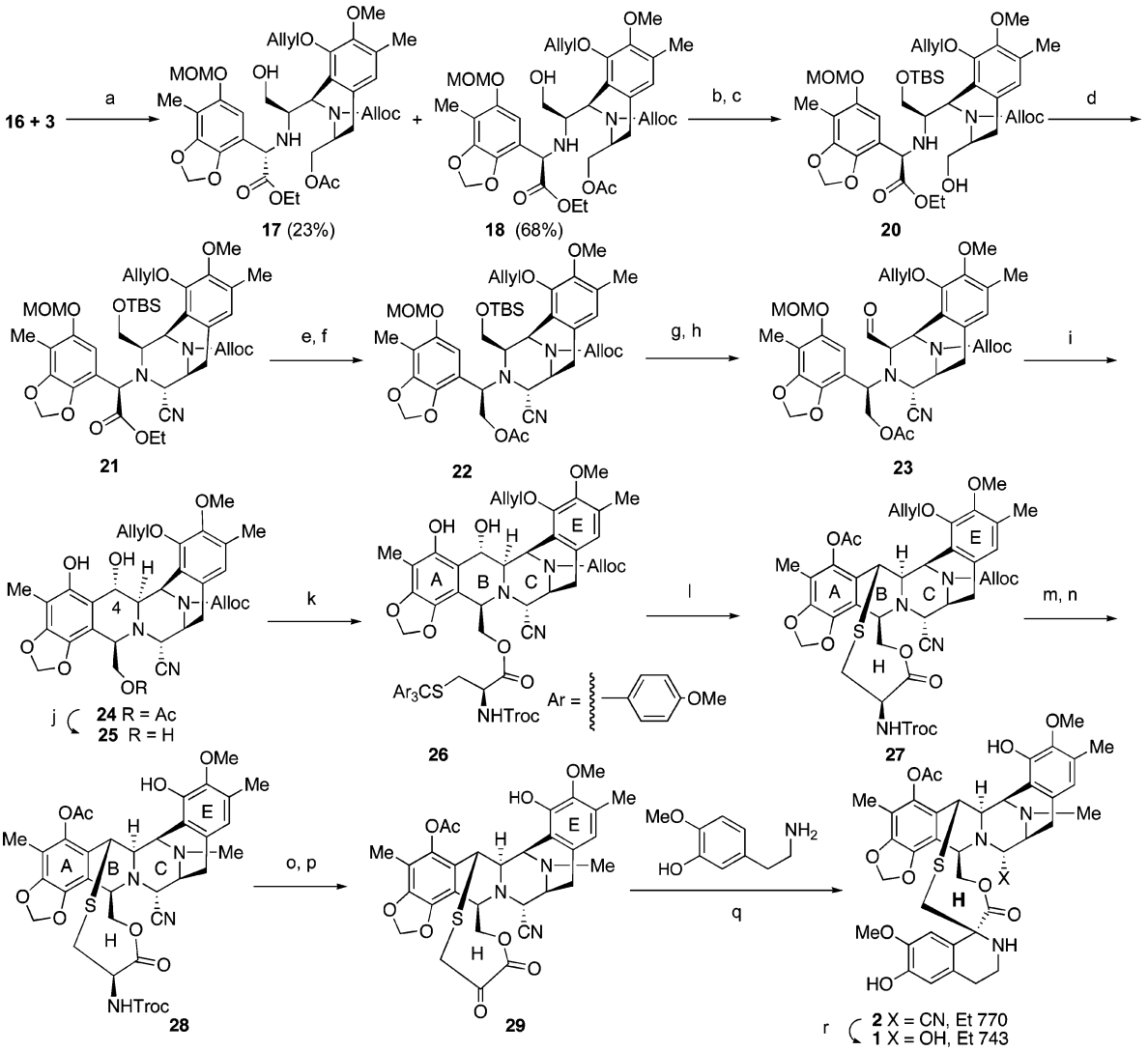
[a] Reagents and conditions: (a) MOMCl, NaH, Et_2O/DMF, 0 °C to rt, 96%; (b) *n*-BuLi, $B(OMe)_3$, THF then AcOH, H_2O_2, 0 °C to rt, 95%; (c) LiCl, 3 Å molecular sieves, HFIP/toluene, ethyl glyoxalate, rt, 97%; (d) 4-nitrophenyltriflate, K_2CO_3, DMF, rt, 94%; (e) trimethyl boroxine, K_3PO_4, $Pd(PPh_3)_4$, dioxane, reflux, 93%; (f) $SOBr_2$, benzotriazole, CH_2Cl_2, rt, 91%.

Scheme 3 [a]



[a] Reagents and conditions: (a) AcOH, CH_2Cl_2/CF_3CH_2OH (7:1), 3 Å molecular sieves, rt, 20 h, 84%; (b) 6 N HCl, in MeOH, rt, 95%; (c) AllocCl, $NaHCO_3$, CH_2Cl_2, rt, 2 h, 88%; (d) AllylBr, Cs_2CO_3, DMF, rt, 3 h, 86%; (e) Ac_2O, pyridine, DMAP, CH_2Cl_2, rt, 1 h, 92%; (f) TFA in CH_2Cl_2, rt, 72%.

Scheme 4 [a]

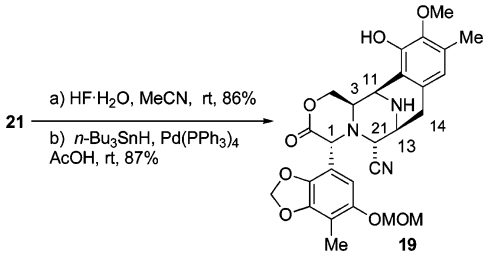


[a] Reagents and conditions: (a) TEA, MeCN, 0 °C, 91%; (b) TBSCl, imidazole, DMF, rt, 97%; (c) K_2CO_3, MeOH, rt, 94%; (d) Dess−Martin reagent, rt, then TMSCN, $ZnCl_2$, rt, 78%; (e) $LiBH_4$, MeOH, THF, 0 °C, 80%; (f) Ac_2O, pyridine, DMAP, CH_2Cl_2, 92%; (g) HF·H_2O, MeCN, rt, 91%; (h) Dess−Martin reagent, rt, 93%; (i) TFA, CH_2Cl_2, rt, 95%; (j) K_2CO_3, MeOH, rt, 96%; (k) EDCI, DMAP, CH_2Cl_2, rt, 95%; (l) TFA, TFE, rt, then Ac_2O, pyridine, DMAP, CH_2Cl_2, 77%; (m) *n*-Bu_3SnH, $PdCl_2(PPh_3)_2$, AcOH, CH_2Cl_2, rt, 87%; (n) $NaBH_3CN$, AcOH, HCHO, rt, 96%; (o) AcOH, Zn, rt, 92%; (p) 4-formyl-1-methylpyridinium benzenesulfonate, DBU, saturated aqueous oxalic acid, DMF−CH_2Cl_2, rt, 53%; (q) NaOAc, EtOH, rt, 97%; (r) $AgNO_3$, MeCN−H_2O, rt, 92%.

This experimentally simple, yet highly efficient, synthesis of the D−E fragment is one of the key steps in our efforts toward the development of a practical synthesis of Et 743. Masking the secondary amine of **13** as *N*-allyloxycarbamate followed by chemoselective allylation of the phenol and acetylation of the remaining primary alcohol provided compound **15**. Simultaneous removal of *N*-Boc and isopropylidene protective groups was realized under acidic conditions (TFA, rt) to afford amino alcohol **16** in 72% yield.

The accomplishment of the total synthesis of Et 743 is described in Scheme 4, starting from the assembly of two segments, **3** and **16**. After much experimentation varying the solvents (MeCN, trifluoroethanol, THF), bases (TEA, pyridine, DBU, Ag_2O), and temperatures (from −45 °C to rt), the coupling of **3** and **16** (1:1 ratio) was realized in MeCN in the presence of triethylamine (2.0 equiv) at 0 °C. Under these conditions, two coupled products **18** and **17** were isolated in 68 and 23% yield, respectively. The observed diastereoselectivity in the N-alkylation of racemic bromide **3** could be tentatively explained by a S_N1 mechanism via an *ortho*-quinone methide intermediate.[16] The absolute configuration of the newly created chiral center of the major stereoisomer was determined to be *R* by its transformation to the corresponding lactone (cf. Scheme 5, vide infra).

Scheme 5



Compound **20** has all the requisite functionalities to build the polycyclic ring system of Et 743. The sequence of construction that we adopted in the present synthesis involved the formation of C-ring, B-ring, and then H-ring. Ring C was constructed onto the D−E segment as follows. Masking of the primary hydroxyl group of **18** as TBS ether and hydrolysis of the acetate under mild basic

conditions afforded compound **20**. Oxidation of the hydroxyl group using Dess−Martin reagent[17] followed by zinc chloride-catalyzed Strecker reaction provided amino nitrile **21** as one single stereoisomer, thus accomplishing the construction of the bicyclo[3.3.1] system with high efficacy.

The configuration of **21** was determined as follows. Treatment of an acetonitrile solution of **21** with $HF{\cdot}H_2O$ effected a sequential O-desilylation and in situ lactonization leading to, after removal of *N*-Alloc and *O*-allyl protective groups, the rigid tetracyclic compound **19** (Scheme 5). The characteristic NOEs observed between H1/H21 and H21/H14 (Et 743 numbering) indicated that the configuration of **19**, hence that of **21**, is (1*R*,3*R*,11*R*,13*S*,21*R*).

With the absolute configuration of **21** being assigned, the synthesis was pursued by installation of ring B with a correct oxidation state at C_4 (Scheme 4). Reduction of the ester function and subsequent acetylation of the resulting primary alcohol afforded compound **22**. O-Desilylation followed by Dess−Martin oxidation of the C_4 hydroxyl group afforded aldehyde **23**. The Pomerantz−Fritsch-type cyclization[7d,e,18] of **23** took place smoothly under acidic conditions (TFA in dichloromethane) to afford the A−B−C−D−E polyheterocycle **24** with concomitant removal of the phenolic MOM-protecting group. Although of no consequence, the cyclization is highly stereoselective (dr > 20/1) and the configuration at C_4 of the major isomer was tentatively assigned as *S* based on the coupling constant (compound **25**: $J_{H3-H4} = 10.1$ Hz) and in analogy to the work done by Fukuyama and co-workers.[5b] Saponification of **24** followed by coupling of the resulting alcohol **25** with (*R*)-*N*-Troc-(*S*-4,4′,4″-trimethoxyltrityl) Cys (**6**) under standard conditions afforded compound **26** in 94% yield. With the hexacyclic compound **26** in hand, a one-pot S-deprotection/cyclization to the 1,4-bridged 10-membered ring via formation of C−S bond was sought next.[5b,7f,8] Gratifyingly, by simply dissolving **26** in TFE containing 1% of TFA, the bridged macrocycle **27** was produced in 77% isolated yield after masking the phenol as the corresponding acetate. In this operationally simple experiment, a complex reaction sequence involving *S*-trityl deprotection, 1,4-β elimination leading to *ortho*-quinone methide and macrocyclization via an intramolecular Michael addition occurred in a highly ordered manner, to accomplish the key C−S bond-forming process. Simultaneous removal of *N*-Alloc and *O*-allyl functions under Guibé's conditions,[19] followed by reductive N-methylation, provided the key intermediate **28** in excellent overall yield.

Following Corey's protocol, compound **28** was converted to Et 743 in four steps. Removal of the *N*-Troc protective group under reductive conditions[20] afforded the corresponding amino ester that was oxidized to ketoester **29**. Pictet−Spengler reaction of **29** with 3-hydroxy-4-methoxyphenethylamine afforded ecteinascidin 770 (**2**) in 97% yield.[1f] Finally, treatment of Et 770 (**2**) with $AgNO_3$ in $MeCN/H_2O$ provided ecteinascidin 743 (**1**) in 92% yield. Synthetic Et 770 and Et 743 exhibited physical, spectroscopic, and spectrometric characteristics (^1H, ^{13}C NMR, IR, $[\alpha]_D$, and HRMS) identical to those reported for the natural products.

In conclusion, a total synthesis of ecteinascidin 743 (**1**) has been achieved in 31 steps in the longest linear sequence and 1.7% overall yield from 3-methyl catechol (23 steps and 3% overall yield from the point of assembly). Notable features of our convergent approach include: (a) Rapid construction of D−E segment by highly diastereoselective Pictet−Spengler condensation of Garner's aldehyde **4** with substituted phenylalanol **5**, (b) diastereoselective N-alkylation of racemic benzyl bromide **3** by enantiomerically pure amino alcohol **16**, and (c) one-pot deprotection/cyclization of the S-protected precursor **26** leading to a 1,4-bridged 10-membered ring. The synthesis is straightforward without using sophisticated reaction conditions and should potentially be amenable to large-scale production.

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

References

(1) (a) Wright, A. E.; Forleo, D. A.; Gunawardana, G. P.; Gunasekera, S. P.; Koehn, F. E.; McConnell, O. J. *J. Org. Chem*. **1990**, *55*, 4508−4512. (b) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Stroh, J. G.; Keifer, P. A.; Sun, F.; Li, L. H.; Martin, D. G. *J. Org. Chem.* **1990**, *55*, 4512−4515. (c) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Stroh, J. G.; Keifer, P. A.; Sun, F.; Li, L. H.; Martin, D. G. *J. Org. Chem*. **1991**, *56*, 1676; additions and corrections. (d) Sakai, R.; Rinehart, K. L.; Guan, Y.; Wang, A. H. J. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 11456−11460. (e) Sakai, R.; Jares-Erijman, E. A.; Manzanares, I.; Elipe, M. V. S.; Rinehart, K. L. *J. Am. Chem. Soc*. **1996**, *118*, 9017−9023. (f) Suwanborirux, K.; Charupant, K.; Amnuoypol, S.; Pummangura, S.; Kubo, A.; Saito, N. *J. Nat. Prod*. **2002**, *65*, 935−937.

(2) Rinehart, K. L. *Med. Drug Rev*. **2000**, 1−27.

(3) For a recent comprehensive review in the field, see: Scott, J. D.; Williams, R. M. *Chem. Rev*. **2002**, *102*, 1669−1730.

(4) (a) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc*. **1996**, *118*, 9202−9203. (b) Martinez, E. J.; Corey, E. J. *Org. Lett*. **2000**, *2*, 993−996.

(5) (a) Endo, A.; Kan, T.; Fukuyama, T. *Synlett* **1999**, 1103−1105. (b) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc*. **2002**, *124*, 6552−6554.

(6) (a) Cuevas, C.; Pérez, M.; Martín, M. J.; Chicharro, J. L.; Fernández-Rivas, C.; Flores, M.; Francesch, A.; Gallego, P.; Zarzuelo, M.; De La Calle, F.; Gracía, J.; Polanco, C.; Rodríguez, I.; Manzanares, I. *Org. Lett*. **2000**, *2*, 2545−2548. (b) Menchaca, R.; Martínez, V.; Rodríguez, A.; Rodríguez, N.; Flores, M.; Gallego, P.; Manzanares, I.; Cuevas, C. *J. Org. Chem*. **2003**, *68*, 8859−8866.

(7) (a) Saito, N.; Tashiro, K.; Maru, Y.; Yamaguchi, K.; Kubo, A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 53−69. (b) Saito, N.; Kamayachi, H.; Tachi, M.; Kubo, A. *Heterocycles* **1999**, *51*, 9−12. (c) Saito, N.; Tachi, M.; Seki, R.; Kamayachi, H.; Kubo, A. *Chem. Pharm. Bull*. **2000**, *48*, 1549−1557. (d) Zhou, B.; Edmondson, S.; Padron, J.; Danishefsky, S. J. *Tetrahedron Lett*. **2000**, *41*, 2039−2042. (e) Zhou, B.; Guo, J.; Danishefsky, S. J. *Tetrahedron Lett*. **2000**, *41*, 2043−2046. (f) Zhou, B.; Guo, J.; Danishefsky, S. J. *Org. Lett.* **2002**, *4*, 43−46. (g) Herberich, B.; Kinugawa, M.; Vazquez, A.; Williams, R. M. *Tetrahedron Lett*. **2001**, *42*, 543−546. (h) Jin, W.; Williams, R. M. *Tetrahedron Lett*. **2003**, *44*, 4635−4639. (i) Jin, W.; Metobo, S.; Williams, R. M. *Org. Lett.* **2003**, *5*, 2095−2098. (j) Magnus, P.; Matthews, K. S.; Lynch, V. *Org. Lett.* **2003**, *5*, 2181−2184. (k) Tang, Y.-F.; Liu, Z.-Z.; Chen, S.-Z. *Tetrahedron Lett*. **2003**, *44*, 7091−7094.

(8) (a) De Paolis, M.; Chiaroni, A.; Zhu, J. *J. Chem. Soc., Chem. Commun.* **2003**, 2896−2897. (b) Chen, X.; Chen, J.; De Paolis, M.; Zhu, J. *J. Org. Chem*. **2005**, *70*, 4397−4408.

(9) Neuville, L.; Bigot, A.; Tran Huu Dau, M. E.; Zhu, J. *J. Org. Chem*. **1999**, *64*, 7638−7642.

(10) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457−2483.

(11) Chaudhari, S. S.; Akamanchi, K. G. *Synlett* **1999**, 1763−1765.

(12) (a) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361−2364. (b) Garner, P.; Park, J. M. *J. Org. Chem.* **1988**, *53*, 2979−2984. (c) Garner, P.; Park, J. M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 4395−4398.

(13) De Paolis, M.; Chen, X.; Zhu, J. *Synlett* **2004**, 729−731.

(14) For a general review of the Pictet−Spengler reaction, see: (a) Cox, E. D.; Cook, J. M. *Chem. Rev*. **1995**, *95*, 1797−1842. For 1,3-cis selective Pictet−Spengler reaction see: (b) Massiot, G.; Mulamba, T. *J. Chem. Soc., Chem. Commun*. **1983**, 1147−1149. (c) Bailey, P. D.; Hollinshead, S. P.; McLay, N. R.; Morgan, K.; Palmer, S. J.; Prince, S. N.; Reynolds, C. D.; Wood, S. D. *J. Chem. Soc., Perkin Trans. 1* **1993**, 431−439.

(15) For synthesis of (−)-saframycin by the directed condensation of suitably protected α-amino aldehyde precursors, see: (a) Myers, A. G.; Kung, D. W.; Zhong, B.; Movassaghi, M.; Kwon, S. *J. Am. Chem. Soc.* **1999**, *121*, 8401−8402. (b) Myers, A. G.; Kung, D. W. *J. Am. Chem. Soc.* **1999**, *121*, 10828−10829.

(16) For a recent comprehensive review in the field, see: Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367−5405.

(17) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 902−903. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277−7287.

(18) Bobbitt, J. M.; Kiely, J. M.; Khanna, K. L.; Ebermann, R. *J. Org. Chem*. **1965**, *30*, 2247−2250.

(19) Guibé, F. *Tetrahedron* **1998**, *54*, 2967−3042.

(20) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbruggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852−853.

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