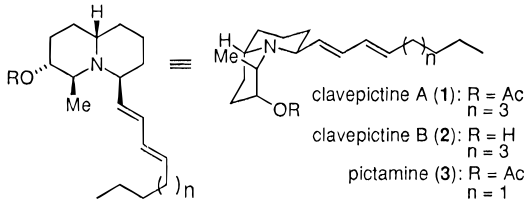
Enantioselective Total Synthesis of the Marine Alkaloid Clavepictines A and B

Naoki Toyooka, Yasuhito Yotsui, Yasuko Yoshida, and Takefumi Momose*

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan

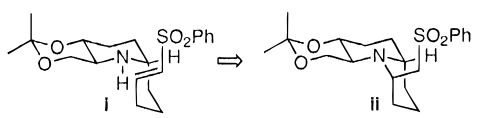
Received May 7, 1996

Clavepictines A (**1**) and B (**2**), isolated from the tunicate *Clavelina picta*, are the first quinolizidine alkaloids from a tunicate and possess a substantial cytotoxic activity against human solid tumor cell lines.[1] Although their relative stereochemistry has been determined on the basis of extensive NMR studies for **1** in conjunction with an X-ray diffraction analysis for **2**, the absolute stereochemistry is unknown.[1] Pictamine (**3**) has been isolated from the same marine species, and its gross structure has been determined to be a bis-nor analog of **1**.[2]



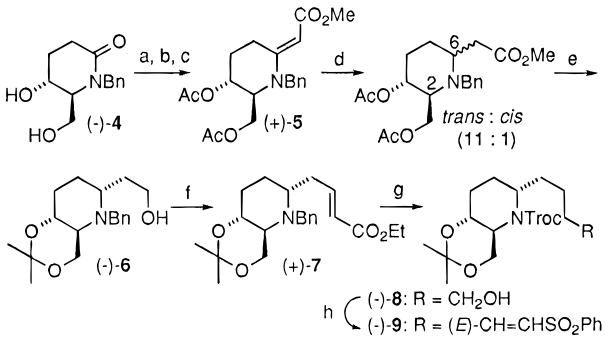
Although a notable progress toward access to the deoxy core of the above *cis*-quinolizidine alkaloids *via* reduction of the corresponding iminium salt has been made by Hart,[3] the total synthesis has not been achieved to date.

Herein we disclose the first enantioselective total synthesis of (+)-**1** and (−)-**2** and determination of the absolute configuration of the natural products. The synthetic strategy involved is based on an intramolecular ring closure[4] of the functionalized piperidine (**i**) to form a *cis*-quinolizidine (**ii**) bearing all the chiral centers and appropriate functionality needed for the synthesis of **1** and **2**.



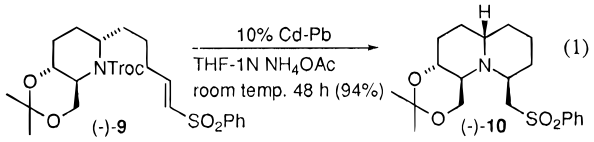
The enantiopure diol (−)-**4**[5] was converted to the vinylogous urethane (+)-**5** ($[\alpha]^{26}_D$ +70.2)[6] by the Eschenmoser's sulfide contraction reaction *via* the diacetate ($[\alpha]^{26}_D$ −55.0) and the thiolactam ($[\alpha]^{26}_D$ −137.0). Reduction of (+)-**5** with $NaBH_3CN$ under an acidic condition at 0 °C gave a ca. 11:1 diastereomeric mixture of the *trans*-2,6- and *cis*-2,6-piperidines.[7] Reduction of the mixture with $LiAlH_4$ followed by treatment of the resulting triol with 2,2-dimethoxypropane in the presence of *p*-TsOH and molecular sieves (5A) afforded the diastereomerically pure acetonide (−)-**6** ($[\alpha]^{26}_D$ −20.9). Swern oxidation of (−)-**6** and Wittig−Horner reaction of the resulting aldehyde provided the homologated ester (+)-**7** ($[\alpha]^{26}_D$ +62.6). Catalytic hydrogenation of (+)-**7** over $Pd(OH)_2$, $LiAlH_4$ reduction, and protection of the amine with TrocCl yielded alcohol (−)-**8** ($[\alpha]^{26}_D$ −9.3), which on Swern oxidation and subsequent Wittig−Horner reaction gave ester (−)-**9** ($[\alpha]^{26}_D$ −3.77) (Scheme 1).

Scheme 1[a]



[a] Key: (a) Ac_2O, pyridine (88%); (b) Lawesson's reagent, THF, reflux (99%); (c) $BrCH_2CO_2Me$ then Ph_3P, Et_3N, MeCN, reflux (92%); (d) $NaBH_3CN$, TFA, 0 °C (84% combined yield); (e) $LiAlH_4$, THF, reflux; 2,2-dimethoxypropanone, *p*-TsOH, MS (5A), CH_2Cl_2, room temperature (75%); (f) Swern oxidation; $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF (80%); (g) H_2, $Pd(OH)_2$, EtOH; $LiAlH_4$, THF, reflux; TrocCl, K_2CO_3, $CHCl_3-H_2O$ = 10:1 (65%); (h) Swern oxidation; $(EtO)_2P(O)CH_2SO_2Ph$, NaH, THF (80%).

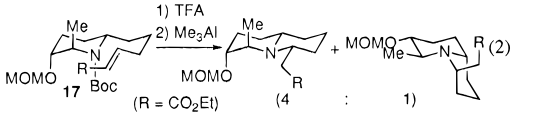
With the requisite ester (−)-**9** in hand, we next focused our attention on the construction of the *cis*-quinolizidine core by using the intramolecular Michael reaction as the key step. Deprotection of the Troc group in (−)-**9** with 10% Cd−Pb[8] at room temperature took place smoothly, and subsequent intramolecular cyclization proceeded nicely to afford the quinolizidine (−)-**10** ($[\alpha]^{26}_D$ −44.5)[9] in 94% yield as the only cyclized product (eq 1).



(1)

The stereochemistry of (−)-**10** was initially assigned on the basis of the following NMR argument. The observation of an NOE between H_a and H_b on the NOESY experiment for (−)-**10** suggested a *cis* relation between the substituents at the C_4- and C_6-position. Moreover, analysis of the coupling pattern (doublet of multiplets)

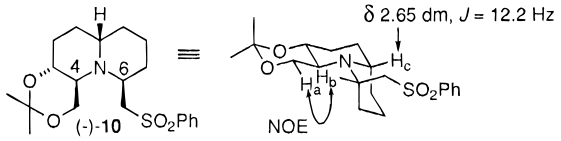
(1) Raub, M. F.; Cardellina, J. H., II; Choudhary, M. I.; Ni, C.-Z.; Clardy, J.; Alley, M. C. *J. Am. Chem. Soc.* **1991**, *113*, 3178−3180.
(2) Kong, F.; Faulkner, D. J. *Tetrahedron Lett.* **1991**, *32*, 3667−3668.
(3) Hart, D. J.; Leroy, V. *Tetrahedron* **1995**, *51*, 5757−5770.
(4) The intramolecular conjugate addition reaction with nitrogen nucleophiles has been recognized as a powerful tool for construction of piperidine ring systems; see: Akiyama, E.; Hirama, M. *Synlett* **1996**, 100−102 and references cited therein.
(5) Toyooka, N.; Yoshida, Y.; Momose, T. *Tetrahedron Lett.* **1995**, *36*, 3715−3718. An alternative stereoselective chiral synthesis of the dibenzyl ether of (−)-**4** from D-serine was reported; see: Campbell, J. A.; Lee, W. K.; Rapoport, H. *J. Org. Chem.* **1995**, *60*, 4602−4616.
(6) Satisfactory analytical and spectral data were obtained for all new compounds. Optical rotations were taken in chloroform unless otherwise stated.
(7) The *trans*(2,6)-selectivity based on the $A^{(1,2)}$ strain, and a stereoelectronic effect has been reported for the reduction of an iminium salt of this type of piperidine; see: Cook, G. R.; Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 3575−3584.
(8) Dong, Q.; Anderson, C. E.; Ciufolini, M. A. *Tetrahedron Lett.* **1995**, *36*, 5681−5682.
(9) Fixation of the ring conformation (i.e., presence of the acetonide protecting group) was indispensable for exclusive formation of **10**. For example, cyclization of **17** resulted in the formation of a ca. 4:1 mixture of *trans*- and *cis*-quinolizidines (eq 2).



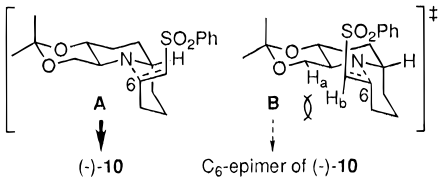
(2)

S0022-3263(96)00817-1 CCC: $12.00

and the coupling constant (J = 12.2 Hz) of the bridgehead proton (H_c) indicated that H_c was situated axially with respect to the ring bearing the (benzenesulfonyl)methyl and equatorially to the second ring, implying a *cis* ring fusion.[10] This assignment was confirmed by an X-ray diffraction analysis,[11] and the result suggested that the absolute configuration of (−)-**10** was 3*R*,4*S*,6*S*,10*S*.

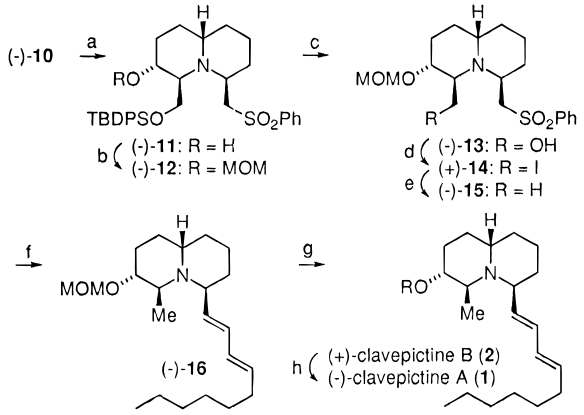


This high-kinetic stereoselectivity on the Michael cyclization can be rationalized as shown below. Comparison of two kinds of folded chairlike transition states (**A** and **B**) leading to (−)-**10** and its C_6-epimer, respectively, reveals a potential steric repulsion involving the H_a and H_b protons for **B**. Therefore, the cyclization occurs *via* the transition state **A** to give the desired product (−)-**10**.



Completion of the synthesis of **1** and **2** is shown in Scheme 2. Treatment of (−)-**10** with 10% HCl in EtOH followed by TBDPSCl and imidazole gave alcohol (−)-**11** ([α]$^{26}_D$ −1.01). Protection of the secondary hydroxyl in (−)-**11** with MOMCl afforded ether (−)-**12** ([α]$^{26}_D$ −4.58), and deprotection with HF−pyridine provided alcohol (−)-**13** ([α]$^{26}_D$ −3.06). Iodination of (−)-**13** to give (+)-**14**

Scheme 2[a]



[a] Key: (a) 10% HCl, EtOH, reflux; TBDPSCl, imidazole, DMF, 80 °C (85%); (b) MOMCl, Hünig base, $CHCl_3$, reflux (93%); (c) 40% HF, pyridine, THF (95%); (d) I_2, Ph_3P, imidazole, benzene (89%); (e) *n*-Bu_3SnH, AIBN, toluene, reflux (94%); (f) *n*-BuLi, *trans*-2-nonenal, −80 to −50 °C; 5% Na−Hg, Na_2HPO_4, MeOH, rt (53%); (g) concd HCl, MeOH, reflux (82%); (h) Ac_3O, pyridine (90%).

([α]$^{26}_D$ +30.9) and radical reduction of (+)-**14** afforded quinolizidine (−)-**15** ([α]$^{26}_D$ −10.95). Finally, the decadienyl moiety was installed by the Julia coupling. Thus, treatment of (−)-**15** with *n*-BuLi at −80 °C followed by addition of *trans*-2-nonenal to the resulting anion at −80 to 50 °C gave the β-hydroxy sulfone, which on sodium amalgam reduction provided the diene (−)-**16** ([α]$^{26}_D$ −20.7). Deprotection of the MOM protecting group with concentrated HCl in refluxing MeOH resulted in (+)-clavepictine B (**2**) [[α]$^{26}_D$ +25.7 (*c* 0.61, CH_2Cl_2) (lit.[1] [α]$_D$ +27.1 (*c* 0.03, CH_2Cl_2))], and acetylation of (+)-**2** afforded (−)-clavepictine A (**1**) [[α]$^{26}_D$ −74.5 (*c* 0.55, CH_2Cl_2) (lit.[1] [α]$^{26}_D$ −75.6 (*c* 0.7, CH_2Cl_2))]. The spectral data for synthetic (−)-**1** and (+)-**2** were identical with those for natural products.[1]

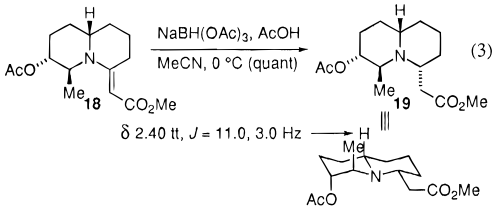
In summary, the first total synthesis of (−)-**1** and (+)-**2** was accomplished by using the intramolecular Michael reaction as a crucial step that enabled us to construct the *cis*-quinolizidine ring having correct chiral centers of the above alkaloids. Furthermore, the absolute stereochemistry of both alkaloids was verified to be 3*R*,4*S*,6*S*,-10*S* by the present synthesis; pharmacological studies on the alkaloids and congeners synthesized are now being conducted concurrently at the NCI, and the results will be described in due course.

Acknowledgment. We are grateful to Doctor John H. Cardellina, II, National Cancer Institute, for kindly providing us with ^{1}H and ^{13}C NMR spectra of natural (−)-**1** and (+)-**2**.

Supporting Information Available: General experimental procedures and compound characterization data (9 pages).

JO9608174

(10) We have investigated the alternative construction of a *cis*-quinolizidine according to the Hart protocol,[3] and as in the case of the reduction of an iminium ion generated from **18** with $NaB(OAc)_3H$, undesired *trans*-quinolizidine **19** was formed exclusively in quantitative yield. Comparison of the coupling pattern (triplet of triplets) and coupling constant (11.0, 3.0 Hz) of the bridgehead proton of **19** to (−)-**10** revealed the *trans* ring juncture of **19** (eq 3).



(11) Crystallographic data for (−)-**10**: orthorhombic, space group $P2_12_12_1$, with a = 14.160(3) Å, b = 15.825(3) Å, c = 8.616(3) Å, V = 1930.5(9) Å^3, and Z = 4 (D_{calcd} = 1.306 g cm^{-3}), μ (Mo Kα) = 1.92 cm^{-1} absorption corrected by ω scans; 966 with $I > 3.00\sigma(I)$ were used in refinement; R = 5.2%, R_w = 6.4%. The authors have deposited the atomic coordinates for (−)-**10** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.