ORGANIC LETTERS

2003
Vol. 5, No. 10
1741−1744

Dichloroketene–Chiral Olefin-Based Approach to Pyrrolizidines: Highly Stereocontrolled Synthesis of (+)-Amphorogynine A

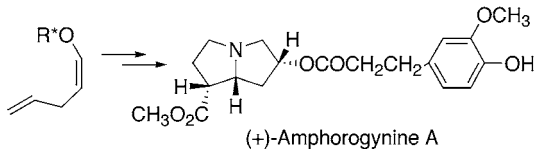
Caroline Roche, Philippe Delair,* and Andrew E. Greene*

Université Joseph Fourier de Grenoble, Chimie Recherche (LEDSS), 38041 Grenoble Cedex, France

philippe.delair@ujf-grenoble.fr; andrew.greene@ujf-grenoble.fr

Received March 2, 2003

ABSTRACT



A highly stereoselective route to (+)-amphorogynine A, a novel pyrrolizidine recently isolated from the New Caledonian plant *Amphorogynine spicata*, has been realized. The key step in the approach is a diastereoselective [2 + 2] dichloroketene–chiral enol ether cycloaddition (dr ≥ 93:7) to access a dichlorocyclobutanone intermediate, which is converted into the alkaloid natural product via a pyrrolidinone derivative.

The pyrrolizidines are numerous and widespread in nature. To date, more than 370 of these alkaloids, which appear to function as protective agents for plants, have been isolated from over 560 species, for the most part belonging to the botanical families *Asteraceae*, *Boraginaceae*, *Fabaceae*, and *Orchidaceae*.[1]

In 1998, a research group at ICSN in France reported[2] the isolation and structural and stereochemical elucidation of four new pyrrolizidines from the New Caledonian plant *Amphorogynine spicata* (Santalaceae). These alkaloids (**1a**−**d**, Figure 1) represent a previously unknown class of pyrrolizidines, characterized by substitution at C-1 and C-6.

In this paper, we disclose the first synthesis of a member of this new group, that of amphorogynine A (**1a**). The success of this total synthesis serves to demonstrate that dichloroketene−chiral enol ether cycloaddition,[3] previously used to prepare indolizidines,[4] can also be effective for the preparation of pyrrolizidines.

Our nonchiral-pool approach to this natural product is outlined retrosynthetically in Scheme 1. On the basis of

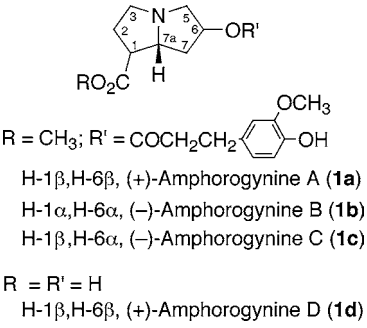


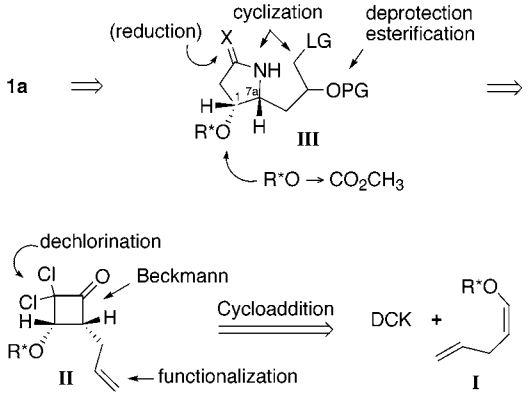
Figure 1. Novel pyrrolizidines from *Amphorogynine spicata*.

(1) For reviews on pyrrolizidines, see: Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773−781. Hartmann, T.; Witte, L. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Elsevier Science, Ltd.: Oxford, 1995; Vol. 9, Chapter 4. *Naturally Occurring Pyrrolizidine Alkaloids*; Rizk, A.-F. M., Ed.; CRC Press: Boston, 1991. *Pyrrolizidine Alkaloids*; World Health Organization: Geneva, 1988.

(2) Huong, D. T. T.; Martin, M.-T.; Litaudon, M.; Sévenet, T.; Païs, M. *J. Nat. Prod.* **1998**, *61*, 1444−1446.

10.1021/ol034369f CCC: $25.00
Published on Web 04/24/2003

Scheme 1. Retrosynthesis of Amphorogynine A (**1a**)



previous studies, it was expected that pyrrolidine or pyrrolidinone **III** could be induced to cyclize to provide a bicyclo[3.3.0]azaoctane, which on functional group transformations might be converted into amphorogynine A (**1a**). Intermediate **III** would result from regioselective Beckmann ring expansion, dechlorination, and double-bond functionalization of cyclobutanone **II**, which might be secured diastereoselectively by facially selective [2 + 2] dichloroketene−chiral enol ether cycloaddition.

The (*S*)-enantiomer of 1-(2,4,6-triisopropylphenyl)ethanol,[5] a previously used and highly effective chiral auxiliary, was chosen as the starting material on the basis of precedent[4,6] and conformational analysis,[7] which clearly indicated the C_α-*re* face of the envisaged (*Z*)-enol ether to be the more accessible (Figure 2).

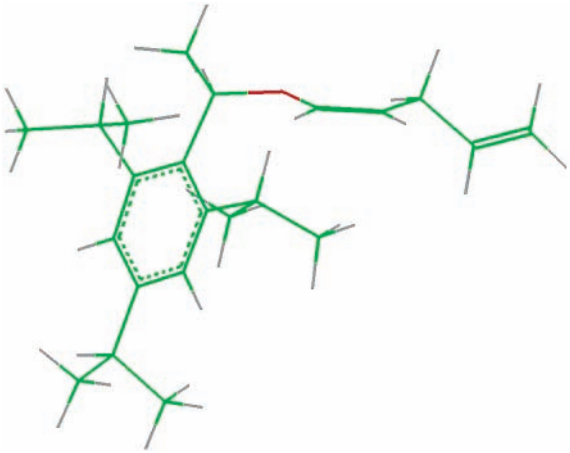
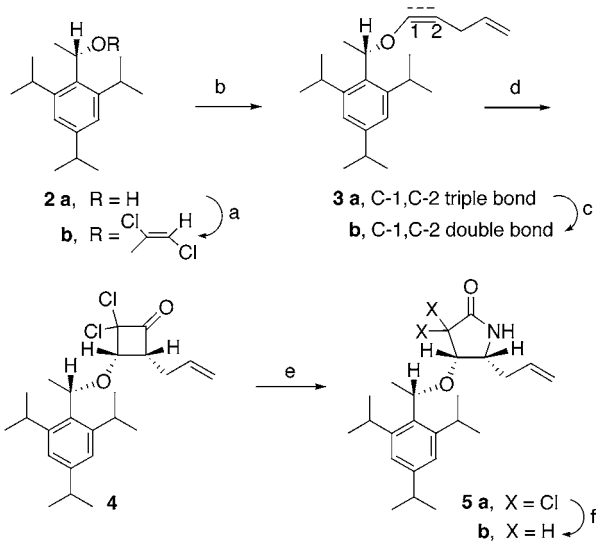


Figure 2. Lowest-energy conformation of enol ether **3b**.[7]

This enantiopure alcohol (**2a**) in the presence of potassium hydride and trichloroethylene was converted[8] into dichloroenol ether **2b** (79%), which on treatment with 2.1 equiv of butyllithium and then excess allyl iodide produced the unstable ynol ether **3a** (Scheme 2). Without purification, this

Scheme 2[a]



[a] Reagents: (a) KH, THF; $Cl_2C{=}CHCl$ (79%). (b) C_4H_9Li, THF; allyl iodide, HMPA. (c) Pd/$BaSO_4$, H_2, C_5H_5N, 1-hexene. (d) Cl_3CCOCl, Zn−Cu, $(C_2H_5)_2O$. (e) $NH_2OSO_2C_6H_2(CH_3)_3$, CH_2Cl_2; Al_2O_3, CH_3OH. (f) Zn−Cu, NH_4Cl, CH_3OH (42% from **2b**, 84% yield per step).

material was carefully hydrogenated with palladium on barium sulfate in the presence of 1-hexene in pyridine[8,9] to afford enol ether **3b** together with small amounts of subsequently removed over-reduced material and trans isomer. Dichloroketene, generated in situ,[10] entered smoothly into cycloaddition with this enol ether with high facial selectivity (93:7, ^{1}H NMR) and total regioselectivity for the electron-rich double bond to yield α,α-dichlorocyclobutanone **4**. Electronic effects (chlorine substituents) and Baeyer strain present in **4** produced a rapid, highly regioselective ring expansion reaction under Tamura's Beckmann conditions[11] to generate **5a**, which on dechlorination[12] afforded lactam **5b** in 42% overall yield from **2b** (84% yield per step).

Osmium tetroxide-catalyzed dihydroxylation of the double bond in **5b**, followed by highly selective monotosylation of

(3) Greene, A. E.; Charbonnier, F. *Tetrahedron Lett.* **1985**, *26*, 5525−5528.

(4) Pourashraf, M.; Delair, P.; Rasmussen, M.; Greene, A. E. *J. Org. Chem.* **2000**, *65*, 6966−6972. Rasmussen, M.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2001**, *66*, 5438−5443.

(5) Delair, P.; Kanazawa, A.; B. M. de Azevedo, M.; Greene, A. E. *Tetrahedron: Asymmetry* **1996**, *7*, 2707−2710.

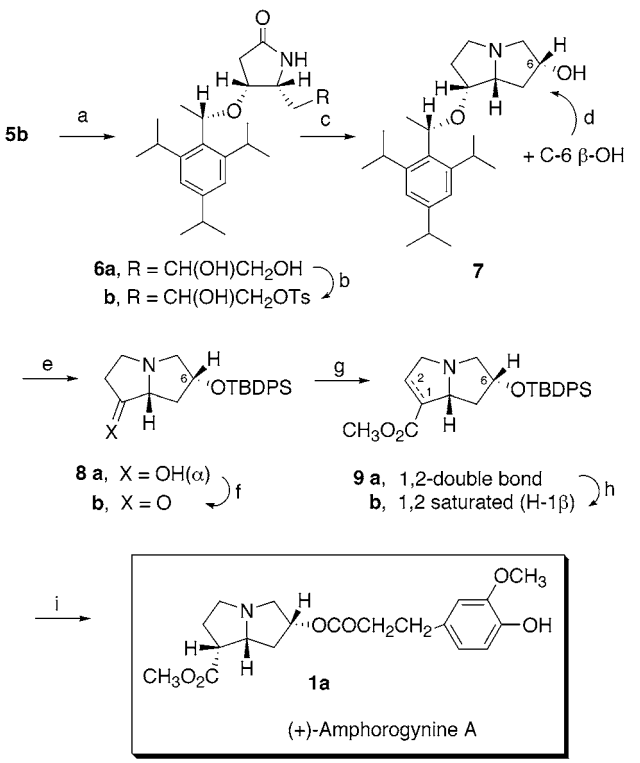
(6) B. M. de Azevedo, M.; Greene, A. E. *J. Org. Chem.* **1995**, *60*, 4940−4942. Kanazawa, A.; Delair, P.; Pourashraf, M.; Greene, A. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1911−1912. Nebois, P.; Greene, A. E. *J. Org. Chem.* **1996**, *61*, 5210−5211. Kanazawa, A.; Gillet, S.; Delair, P.; Greene, A. E. *J. Org. Chem.* **1998**, *63*, 4660−4663. Delair, P.; Brot, E.; Kanazawa, A.; Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1383−1386.

(7) Molecular modeling was performed on a SGI02 workstation running Insight II Discover 2000 (ACCELRYS, San Diego). The structure was energy minimized with the force field cvff.frc. and the minimization algorithm VA09A. The molecular dynamics study was performed at 1000 K in a vacuum (dielectric constant fixed at 1; 400 000 steps of 1 fs) and consisted of generation of 500 structures. For **3b**, the conformation is lowest in energy by 1.5 kcal/mol. (The next lowest in energy would also be expected to undergo cycloaddition largely on the C_α-*re* face.)

(8) Kann, N.; Bernardes, V.; Greene, A. E. *Org. Synth.* **1997**, *74*, 13−22.

the in situ-generated dibutylstannoxane derivative,[13] produced in good yield hydroxy tosylate **6b** (55:45 mixture of hydroxy epimers), which cyclized on reduction with borane-dimethyl sulfide to give pyrrolizidine **7** together with its C-6 epimer (Scheme 3). The latter could be converted to the former through oxidation−reduction (50% combined yield). The identity of **7** (HCl salt), purified by crystallization from dichloromethane−pentane, was fully confirmed by X-ray diffraction analysis.[14]

Scheme 3[a]



[a] Reagents: (a) OsO_4, $(CH_3)_3NO$, $(CH_3)_3COH/H_2O$ (74%). (b) $(C_4H_9)_2SnO$, CH_3OH; TsCl, $(C_2H_5)_3N$ (87%). (c) $BH_3{\cdot}S(CH_3)_2$, THF. (d) $(ClCO)_2$, $(CH_3)_2SO$, CH_2Cl_2; $(C_2H_5)_3N$; $NaBH_4$, C_2H_5OH (50% from **6b**). (e) TBDPSCl, imidazole, DMAP, DMF; TFA, CH_2Cl_2 (74%). (f) $(ClCO)_2$, $(CH_3)_2SO$, CH_2Cl_2; $(C_2H_5)_3N$. (g) LiHMDS, THF; CPT (68% from **8a**); $Pd(OCOCH_3)_2$, $(C_6H_5)_3P$, $(C_2H_5)_3N$, CO, $CH_3OH-DMF$ (65%). (h) 10% Pd/C, H_2, CH_3OH (93%). (i) TBAF, THF (82%); *O*-TBDMS hydroferulic acid, DIC, DMAP, CH_2Cl_2 (70%); TBAF, THF (77%).

t-Butyldiphenylsilylation of **7**, followed by inductor cleavage with trifluoroacetic acid, provided the monoprotected diol **8a** (74%), which was oxidized under Swern conditions to afford in good yield the unstable ketone **8b**. The enol triflate, derived with LiHMDS and the Comins triflimide (*N*-(5-chloro-2-pyridyl)triflimide, CPT),[15] was subjected to palladium-catalyzed carbomethoxylation to generate the conjugated ester **9a** in 65% yield. In view of the folded geometry and the endo-face-encumbering silyl group in **9a** (Figure 3),[7] hydrogenation was expected to take place predominantly on the exo face of the molecule; in fact, the saturated ester **9b** was the unique product of the reaction (93% yield).

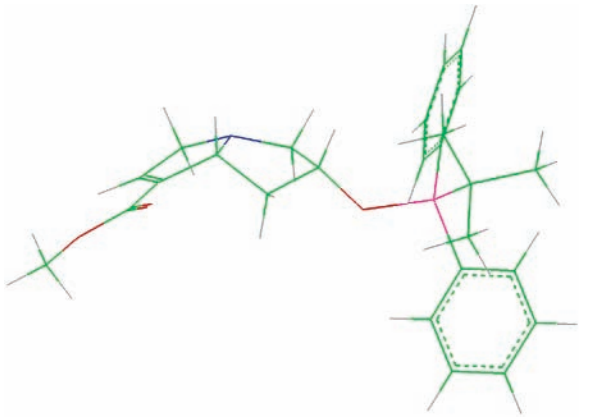


Figure 3. Lowest-energy conformation of ester **9a**.[7]

The concluding steps of the synthesis proved to be uneventful. Desilylation at C-6 in **9b** was readily accomplished in 82% yield with tetrabutylammonium fluoride in THF to give the free alcohol, which was esterified with *t*-butyldimethylsilyl-protected hydroferulic acid (70%).[16] Desilylation of the phenolic protecting group then produced in 77% yield enantiopure (+)-amphorogynine A, which provided high-field ^1H and ^{13}C NMR and IR spectra superimposable with those of an authentic sample of the natural product.[17,18]

In summary, a highly stereocontrolled approach to a new class of pyrrolizidines, based on diastereofacially selective [2 + 2] cycloaddition of dichloroketene with a chiral enol ether, has been demonstrated by the synthesis of (+)-

(9) Ho, T.-L.; Liu, S.-H. *Synth. Commun.* **1987**, *17*, 969−973.
(10) Hassner, A.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3173−3179. Brady, W. T.; Lloyd, R. M. *J. Org. Chem.* **1979**, *44*, 2560−2564. For reviews on dichloroketene, see: Hyatt, J. A.; Raynolds, P. W. *Org. React.* **1994**, *45*, 159−646. Tidwell, T. T. *Ketenes*; Wiley: New York, 1995.
(11) Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1−17.
(12) Johnston, B. D.; Slessor, K. N.; Oehlschlager, A. C. *J. Org. Chem.* **1985**, *50*, 114−117.
(13) For a similar transformation, see: Ley, S. V.; Brown, D. S.; Clase, J. A.; Fairbanks, A. J.; Lennon, I. C.; Osborn, H. M. I.; Stokes, E. S. E.; Wadsworth, D. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2259−2276. See also: Martinelli, M. J.; Vaidyanathan, R.; Pawlak, J. M.; Nayyar, N. K.; Dhokte, U. P.; Doecke, C. W.; Zollars, L. M. H.; Moher, E. D.; Khau, V. V.; Kosmrlj, B. *J. Am. Chem. Soc.* **2002**, *124*, 3578−3585.
(14) Analysis was accomplished on microcrystals at the European Synchrotron Radiation Facility. This study will be published separately.
(15) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299−6302.
(16) See: Solladié, G.; Gressot-Kempf, L. *Tetrahedron: Asymmetry* **1996**, *7*, 2371−2379. Hydroferulic acid is available from Lancaster Synthesis, Bischheim, Strasbourg, France.
(17) Mp 103−104 °C (*n*-$C_7H_{16}-CH_3OH$); $[\alpha]^{20}_D$ +42 (*c* 0.9, $CHCl_3$). Lit.[2] mp 108 °C; lit.[2] $[\alpha]^{20}_D$ +53 (*c* 1, $CHCl_3$). Our authentic sample: mp 102−103 °C; $[\alpha]^{20}_D$ +44 (*c* 0.6, $CHCl_3$).
(18) Note added in revision: A chiral-pool approach to amphorogynine A has just appeared. See: Yoda, H.; Egawa, T.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 1643−1646.

amphorogynine A. The approach is currently being applied in our laboratory to access other pyrrolizidine natural products.

Acknowledgment. We thank Professor P. Dumy for his interest in our work, Drs. T. Sévenet and M. Païs for a sample of natural (+)-amphorogynine A, and Drs. M.-L. Dheu-Andries, D. Flot, and C. Philouze and Ms. B. Escudé for their technical support. Financial support from the CNRS (UMR 5616) is gratefully acknowledged.

Supporting Information Available: Characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034369F