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First total synthesis of a new pyrrolizidine alkaloid, amphorogynine A

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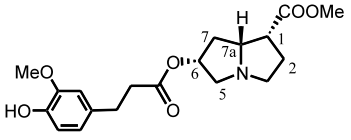
Abstract—An efficient and stereodefined strategy is described for the first asymmetric synthesis of a new type of pyrrolizidine alkaloids, amphorogynine A and its 1-*epi*-isomer. The key 2,4-disubstituted pyrrolidine ring was constructed by elaboration of the chiral lactam derivative incorporating the D-malic acid-derived skeleton through asymmetric *cis*-allylation of the functionalized allysilane.

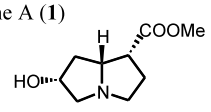
Amphorogynine A together with structurally related compounds, amphorogynines B, C, and D, was first isolated in 1998 by Païs and co-workers from the leaves of *Amphorogyne spicata* Stauffer and Hürlimann (Santalaceae) in a research for alkaloids in New Caledonian plants.[1] After structural characterization by the same group based on spectroscopic methods using chemical correlations, these were revealed to be a new class of pyrrolizidine alkaloids possessing a 1,6-disubstituted structure (Fig. 1).[1] These alkaloids differ from the position of the substituents on the pyrrolizidine ring. Whereas amphorogynines possess a hydroxyl group at the C(6) position, the well known necines generally bear this substituent at the C(7) position of the pyrrolizidine.[2] Since such alkaloids showing substituted functions at both C(1) and C(6) only have not been reported previously,[3] their structural and stereochemical complexity coupled with their diverse and potentially useful characteristics would make them hereafter inviting targets for synthesis. The synthesis of this type of compounds poses interesting and often unsolved problems of sterecontrol. Consequently, no report concerning the total synthesis of **1** along with related natural products has appeared to date.

With these considerations in mind, we wish to communicate the details of the first asymmetric synthesis of **1** and its 1-epimer (6-*epi*-amphorogynine B) by means of requisite stereoselective allylation of the α-hydroxypyrrolidine intermediate elaborated from D-malic acid.

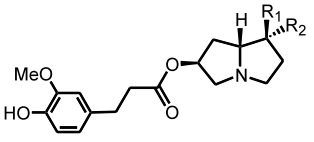
As shown in Scheme 1, *N*-MPM(*p*-methoxybenzyl)-imide **6** obtained from D-malic acid (**5**) was reduced regioselectively with $NaBH_4$[4] and readily effected by $BF_3{\cdot}OEt_2$-induced reductive deoxygenation with Et_3SiH[5] to afford the acetoxylactam intermediate. After



Amphorogynine A (**1**)



Amphorogynine D (**4**)



Amphorogynine B (**2**): R_1 = COOMe, R_2 = H
Amphorogynine C (**3**): R_1 = H, R_2 = COOMe

Figure 1.

Keywords: amphorogynine; pyrrolizidine alkaloid; allylation; lactam; malic acid.
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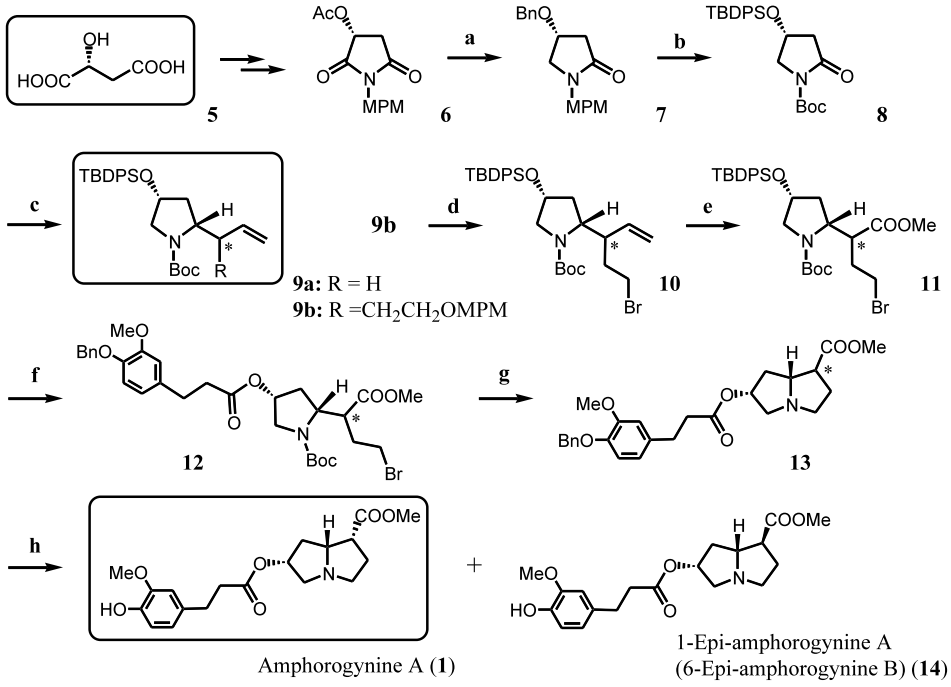
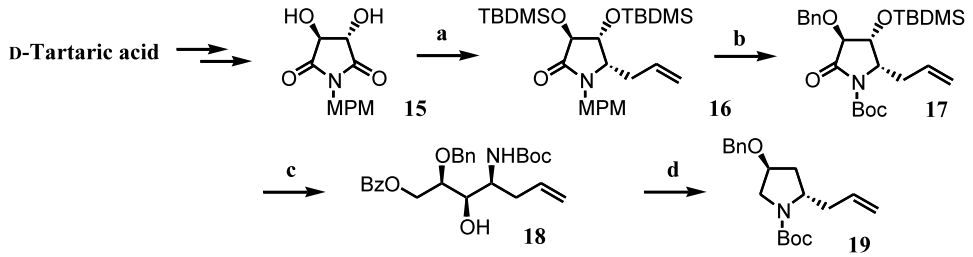


Scheme 1. *Reagents and conditions*: (a) **1**, $NaBH_4$, MeOH, 0°C; 2, $BF_3{\cdot}OEt_2$, Et_3SiH, CH_2Cl_2, 0°C; 69% (two steps); **3**, K_2CO_3, MeOH; 97%; **4**, BnBr, Ag_2O; DMF; 92%; (b) **1**, CAN, CH_3CN–H_2O (9:1); 93%; **2**, $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2, 0°C; quant.; **3**, Pd (black), 4.4% HCOOH–MeOH, 45°C; quant.; **4**, TBDPSCl, imidazole, CH_2Cl_2; 94%; (c) **1**, $NaBH_4$, MeOH, 0°C; **2**, $CH_2{=}CHCH_2SiMe_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78°C; 72%; (**9a**) (two steps); $MPMO(CH_2)_2CH{=}CHCH_2SiMe_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78°C; 47%; (**9b**) (two steps); (d) **1**, DDQ, CH_2Cl_2–H_2O (11:1), 0°C; 90%; **2**, CBr_4, PPh_3, CH_2Cl_2; 96%; (e) **1**, OsO_4, NMO, acetone–H_2O, 0°C; **2**, $NaIO_4$, ether–THF–H_2O (1:1:2); 88% (two steps); **3**, Br_2, $NaHCO_3$, MeOH–H_2O (9:1); 89%; (f) **1**, Bu_4NF, THF, 0°C; 87%; **2**, 3-(*p*-benzyloxy-*m*-methoxyphenyl)propanoic acid, EDCI, DMAP, CH_2Cl_2; 0°C; 70%; (g) **1**, $BF_3{\cdot}OEt_2$, CH_2Cl_2; −15°C; **2**, $NaHCO_3$, H_2O; 85% (two steps); (h) H_2, Pd/C, CH_3COOEt; 58% (amphorogynine A (**1**)); 26% (1-*epi*-amphorogynine A (6-*epi*-amphrogynine B)) (**14**).

exchange of the acetyl group to the benzyl moiety, the lactam **7** thus obtained was transformed into the expected *N*-Boc derivative **8**, $[\alpha]_D^{26}$+16.5° (*c* 1.03, $CHCl_3$), by four steps through both subsequent *N*- and *O*-deprotection and reprotection sequence (54% overall yield from D-malic acid) for further convenient transformation of the functional groups. Initial experiments have been performed on a coupling reaction via *N*-acyliminium ion promoted by $BF_3{\cdot}OEt_2$ at −78°C between allyltrimethylsilane and α-hydroxypyrrolidine derivative derived from the partial reduction of **8**.[6] These conditions brought about the desired allylated pyrrolidine **9a** as a sole product with complete *cis*-stereoselectivity.[7] These results are in accord with expectations based on the preceding reports.[6a,9] We were delighted to find that the use of the functionalized allyltrimethylsilane reagent (E/Z = 3.1/1.0) prepared from 3-buten-1-ol according to the Seyferth's procedure[10] also underwent fast reaction to afford the corresponding coupling product **9b** with complete *cis*-relationship again[11] in the pyrrolidine ring, but with about 55% d.e. at the allylic position (determined by ^1H NMR), which would be ascribed to the ratio of the starting geometrical isomers.

For the purpose of the construction of a pyrrolizidine ring system, **9b** was in turn submitted to deprotection of the MPM moiety followed by introduction of the bromo function as the leaving group.[12] The olefinic part in the pyrrolidine derivative **10** thus obtained was then cleaved via dihydroxylation to give the aldehyde intermediate, which was successively subjected to bromine-induced oxidation,[13] leading to the corresponding methyl ester **11** in 89% yield. The remaining side unit in amphorogynines prepared from vanillin was then introduced in the presence of EDCI (1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride and DMAP[14] after desilylation. Finally, the coupling product **12** was effected by deprotection with $BF_3{\cdot}OEt_2$[15] together with concomitant cyclization, followed by debenzylation of the resulting pyrrolizidine **13** with 5% Pd on carbon to produce the desired compound, amphorogynine A (**1**), accompanying with its 1-epimer (6-*epi*-amphorogynine B) **14**. These were readily separated by column chromatography on silica gel and demonstrated that the less mobile compound ($CHCl_3$/MeOH = 3:1; TLC R_f 0.55) corresponded to the natural product **1** (58%), $[\alpha]_D^{26}$+52.1° (*c* 0.57, $CHCl_3$) {lit. $[\alpha]_D$+53° (*c* 1, $CHCl_3$)[1]}, and the more mobile substance ($CHCl_3$/MeOH = 3:1; TLC R_f 0.60) was the 1-*epi*-isomer **14**[16] of amphorogynine A (6-*epi*-amphorogynine B) (26%), $[\alpha]_D^{27}$−15.7° (*c* 0.38, $CHCl_3$), based on their spectral data,[1] respectively. The spectral data of synthetic (+)-**1** were completely identical to those of the reported natural product.[1]

In summary this work constitutes the first synthesis of the natural pyrrolizidine alkaloid, amphorogynine A,



Scheme 2. *Reagents and conditions*: (a) **1**, TBDMSCl, imidazole, DMF; **2**, $NaBH_4$, MeOH; **3**, Ac_2O, pyridine, DMAP; **4**, $CH_2{=}CHCH_2SnBu_3$, $MgBr_2$, toluene; quant. (four steps); (b) **1**, conc. HCl, MeOH; **2**, BnBr, Ag_2O, CH_3COOEt; 58% (two steps); **3**, CAN, CH_3CN–H_2O (9:1); **4**, TBDMSCl, imidazole, DMF; **5**, $(Boc)_2O$, Et_3N, DMAP; 64% (three steps); (c) **1**, $NaBH_4$, MeOH; **2**, BzCl, Et_3N, CH_2Cl_2; **3**, Bu_4NF, THF; 71% (three steps); (d) **1**, Im_2CS, THF, 40°C; **2**, Bu_3SnH, AIBN, toluene, 70°C; 38% (two steps); **3**, K_2CO_3, MeOH; **4**, MsCl, Et_3N, CH_2Cl_2; **5**, *t*-BuOK, THF; 68% (three steps).

and verifies the structure proposed in the literature for this natural product, since no report concerning the total synthesis of amphorogynines has appeared to date.

Acknowledgements

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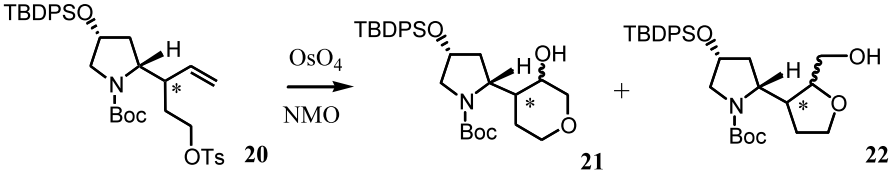
References

1. Huong, D. T. T.; Martin, M.-T.; Litaudon, M.; Sévenet, T.; Païs, M. *J. Nat. Prod.* **1998**, *61*, 1444.
2. (a) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129 and references cited therein; (b) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **2000**, *65*, 5785; (c) Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **2000**, *65*, 2875; (d) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046; (e) Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1994**, *59*, 5672; (f) Wróbel, J. T. In *Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26 Chapt. 7.
3. Hartmann, T.; Witte, L. In *Alkaloids Chemical and Biological Perspectives*; Pelletier, W. S., Ed.; Elsevier: Amsterdam, 1995; Vol. 9, p. 155.
4. (a) Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *J. Am. Chem. Soc.* **1989**, *111*, 2588; (b) Hart, D. J.; Yang, T.-K. *J. Org. Chem.* **1985**, *50*, 253; (c) Chamberlin, A. R.; Chung, Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653; (d) Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron* **1992**, *48*, 3313.
5. (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976; (b) Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Org. Chem.* **1987**, *52*, 1273; (c) Yoda, H.; Kawauchi, M.; Takabe, K. *Synlett* **1998**, 137; (d) Yoda, H.; Nakajima, T.; Takabe, K. *Tetrahedron Lett.* **1996**, *37*, 5531; (e) Yoda, H.; Yamazaki, H.; Kawauchi, M.; Takabe, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2669 and references cited therein.
6. (a) Thaning, M.; Wistrand, L.-G. *Acta Chem. Scand.* **1992**, *46*, 194; (b) Thaning, M.; Wistrand, L.-G. *Acta Chem. Scand.* **1989**, *43*, 290; (c) Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K. *J. Org. Chem.* **1986**, *51*, 2590.
7. The absolute stereochemistry of the newly created carbon center in **9a** was unambiguously proved to be *S* after derivatisation of **9a** to the benzyl ether by comparing its spectral data with those of the *trans*-*N*-Boc-pyrrolidine **19**, which was in turn elaborated from D-tartaric acid-derived C_2-imide **15** employing *cis*-selective allylation reaction[8] as shown in Scheme 2.
8. Ryu, Y.; Kim, G. *J. Org. Chem.* **1995**, *60*, 103.
9. Renaud and Seebach[9a] have also observed a similar stereochemical behavior in the synthesis of 2,4-*cis*-substituted pyrrolidines;[9b] (a) Renaud, P.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1704; (b) Boto, A.; Hernández, R.; Suárez, E. *J. Org. Chem.* **2000**, *65*, 4930; (c) Schuch, C. M.; Pilli, R. A. *Tetrahedron: Asymmetry* **2002**, *13*, 1973 and references cited therein. These results indicate that allylic $A^{1,3}$-interactions involving the substitutent α to the nitrogen atom and the *N*-Boc group may determine the preferential conformation of the *t*-butoxycarbonyl function in the *N*-acyliminium ion intermediate. On the other hand, Ogasawara and his co-workers recently reported that upon reaction with allyltrimethylsilane in the presence of zinc(II) chloride, *N*-Boc-5-acetoxy-2-methoxypiperidine afforded the unexpected *trans*-selective allylation product predominantly (11:1) based on the anchimeric assistance of the acetate group; Tanaka, H.; Sakagami, H.; Ogasawara, K. *Tetrahedron Lett.* **2002**, *43*, 93; Sakagami, H.; Kamikubo, T.; Ogasawara, K. *Chem. Commun.* **1996**, 1433.
10. (a) Seyferth, D.; Wursthorn, K. R.; Mammarella, R. E. *J. Org. Chem.* **1977**, *42*, 3104; (b) Seyferth, D.; Wursthorn, K. R.; Lim, T. F. O.; Sepelak, D. J. *J. Organometal. Chem.* **1979**, *181*, 293.
11. *Cis*-stereochemistry in the pyrrolidine ring of **9b** was determined based on its spectral data of synthetic (+)-**1**.
12. To begin with, experiments have been performed on a dihydroxylation reaction mediated by OsO_4 employing the tosylated compound **20** as shown below. The reaction, however, resulted in the preparation of the corresponding simultaneously cyclized products of **21** and **22** as an inseparable mixture.



13. (a) Williams, D. R.; Klingler, F. D.; Allen, E. E.; Lichtenthaler, F. W. *Tetrahedron Lett*. **1988**, *29*, 5087; (b) Lichtenthaler, F. W.; Jarglis, P.; Lorenz, K. *Synthesis* **1988**, 790.
14. Kikuchi, H.; Saito, Y.; Komiya, J.; Takaya, Y.; Honma, S.; Nakahata, N.; Ito, A.; Oshima, Y. *J. Org. Chem*. **2001**, *66*, 6982.
15. (a) Yoda, H.; Kawauchi, M.; Takabe, K. *Synlett* **1998**, 137; (b) Yoda, H.; Oguchi, T.; Takabe, K. *Tetrahedron Lett*. **1997**, *38*, 3283.
16. ^{1}H and ^{13}C NMR data ($CDCl_3$) for **14**. ^{1}H NMR δ 1.71–2.36 (4H, m), 2.37–2.96 (7H, m), 2.98–3.44 (2H, m), 3.57–3.94 (1H, m), 3.84 (3H, s), 3.89 (3H, s), 4.98–5.63 (1H, m), 5.98 (1H, br), 6.62 (1H, d, $J=8$ Hz), 6.66 (1H, s), 6.79 (1H, d, $J=8$ Hz). ^{13}C NMR δ 30.5, 30.8, 36.1, 37.6, 49.9, 51.8, 54.2, 55.7, 59.7, 66.6, 76.5, 111.1, 114.7, 120.6, 131.9, 144.3, 146.8, 172.6, 173.9.