Tetrahedron Letters, Vol. 33, No. 42, pp. 6247-6250, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Synthesis of a Tetracyclic Substructure of Manzamine A

Jeffrey A. Campbell and David J. Hart*

Department of Chemistry, The Ohio State University, 120 W. 18th Ave., Columbus, Ohio 43210, USA

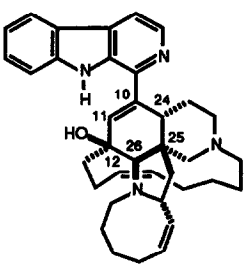
Abstract: *A synthesis of tetracyclic manzamine A substructure **28** is described. The route involves (1) a new approach to perhydroisoquinolines, (2) a Mitsunobu reaction that proceeds with net retention of configuration using a new N-acyl sulfonamide (**16**) and (3) a high yield preparation of a $\Delta^{3,4}$-azocine via an intramolecular N-alkylation.*

Manzamine A (**1**) is one member of a family of alkaloids that includes manzamines B (**2**), C (**3**), E (**4**), F (**5**) and other β-carbolines (Figure 1).[1,2] The structure of manzamine A is secure (X-ray) and it has interesting biological activity as it inhibits growth of P-388 mouse leukemia cells (IC_{50} = 0.07 μg mL^{-1}).[3] Several studies directed toward the pyrrolo-[2,3-*i*]isoquinoline core of **1** have been reported. Simpkins and Oishi have examined cycloaddition reactions of 5,6-dihydro-2-pyridones [simultaneous construction of the C(10)-C(24) and C(25)-C(26) bonds].[4] Nakagawa and Hino have examined related cycloadditions.[5] Pandit has reported an excellent enantioselective route that involves an intramolecular Diels-Alder reaction [simultaneous construction of the C(10)-C(11) and C(24)-C(25) bonds].[6] Martin has reported a different intramolecular Diels-Alder approach [simultaneous construction of the C(24)-C(25) and C(12)-C(26) bonds], an approach also being pursued by Leonard and Marko.[7-9] In addition, Baldwin has proposed an ingenious biogenetic path to the manzamines, the final stages of which have recently been accomplished in the laboratory by Kobayashi.[10,11] Several years ago, we published an approach to the tricyclic core of **1** that revolved around a free radical cyclization reaction.[12] This letter describes the first synthesis of the tetracyclic perhydro-1*H*-azocino[1'2':1,5]pyrrolo[2,3-*i*]isoquinoline substructure of manzamine A.

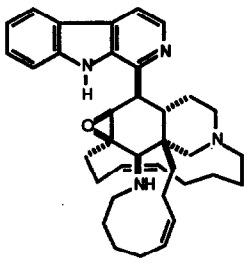
We began by developing the perhydroisoquinoline synthesis outlined in Scheme 1. Thus, iodolactone **7** was prepared in 70% overall yield from benzoic acid (**6**) using a reductive alkylation-halolactonization sequence. Keck allylation of **7** gave **8** in 68% yield with 96:4 diastereoselectivity.[13,14] Opening of the lactone with the magnesium salt of *p*-anisidine followed by Steglich acylation of the resulting alcohol gave **9** in 91% yield.[15] Oxidative cleavage of the mono-substituted double bond, treatment of the resulting mixture of carbinol lactam and enamide with methanol and acid, and reduction of the resulting N,O-acetal afforded perhydroisoquinoline **10** in 65% yield.[16,17] This sequence represents a new route to substituted perhydroisoquinolines.

We next turned to construction of the azocine as outlined in Schemes 1 and 2. Removal of the methyl ether and oxidation of the resulting alcohol gave aldehyde **12** (**10** → **11** → **12**) in 77% yield.[18,19] Treatment of **12** with the appropriate acetylide gave **13** as a 68:32 mixture of diastereomers at C(34) in 63% combined yield (87% based on converted **12**).[20] These diastereomers were inseparable, but hydrogenation of **13** gave an easily separable mixture of *cis* allylic alcohols **14** (68%) and **15** (32%).[21] The stereochemical assignments for **14** and **15** were based on X-ray crystallographic analysis of an intermediate derived from **14** (*vide infra*).

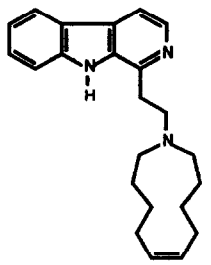
Figure 1



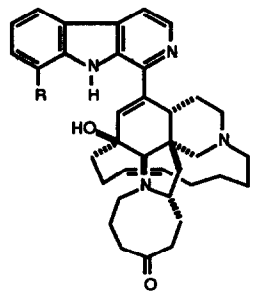
1 Manzamine A



2 Manzamine B



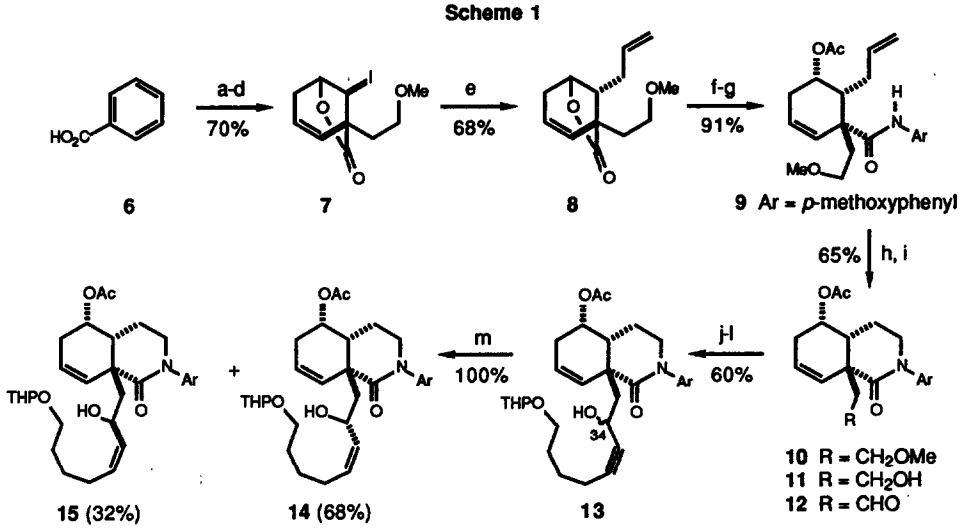
3 Manzamine C



4 Manzamine E R = H
5 Manzamine F R = OH

Treatment of **14** with imide **16** under typical Mitsunobu conditions gave allylic amine derivative **17** in 86% yield.[22,23] Removal of the BOC and THP groups was followed by conversion of the resulting alcohol (**18**) to tosylate **19** in 86% overall yield.[24] Treatment of **19** with KH and tetra-*n*-butylammonium iodide gave azocine **20** in a notably high 91% yield.[25] The structure of **20** was proven by X-ray crystallography.[26]

Scheme 1

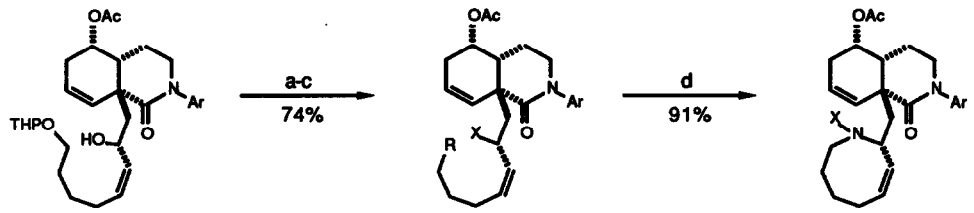


(a) Li, NH_3 (b) $BrCH_2CH_2OMe$ (c) $(PhO)_2P(=O)N_3$, Et_3N, pyrrolidine (d) I_2, THF, H_2O (e) $CH_2{=}CHCH_2SnBu_3$, AIBN, PhH, Δ (f) *p*-$MeOC_6H_4NHMgBr$ (g) Ac_2O, 4-DMAP, pyridine (h) OsO_4 (cat), $NaIO_4$ (i) $NaBH_3CN$, CF_3CO_2H (j) BBr_3 (k) Swern oxidation (l) $LiC{\equiv}C(CH_2)_4OTHP$ (m) $Pd/BaSO_4$, pyridine, H_2

It is notable that the conversion of **14** to **17** appears to proceed with overall retention of configuration. This stereochemical assignment is based on the following information. Treatment of allylic alcohol **15** with formic acid under Mitsunobu conditions gave a formate. Hydrolysis of this formate gave not the expected alcohol **14**, but returned the starting

alcohol **15**. This can be explained by invoking neighboring group participation by the amide, a process with some recent precedence.[27] We imagine that the same double inversion sequence is taking place in the conversion of **14** to **17**.[28]

Scheme 2



14
(Ar = *p*-methyoxyphenyl)

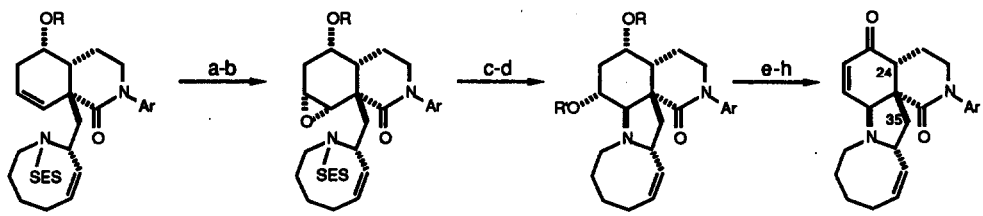
17 X = N(CO_2-*t*-Bu)($SO_2CH_2CH_2TMS$) R = CH_2OTHP
18 X = $NHSO_2CH_2CH_2TMS$ R = CH_2OH
19 X = $NHSO_2CH_2CH_2TMS$ R = CH_2OTs

20 X = $SO_2CH_2CH_2TMS$
21 X = H

(a) $HN(SO_2CH_2CH_2TMS)CO_2$-*t*-Bu (**16**), Ph_3P, DEAD (b) CH_3SiCl_3, NaI, CH_3CN (c) *p*-TsCl, Et_3N, 4-DMAP, CH_2Cl_2
(d) KH, *n*-$Bu_4N^+I^-$,18-C-6, toluene, Δ, [**19**] = 0.005 M (e) CsF, DMF, Δ

The conversion of **20** to a tetracycle potentially suitable for elaboration into manzamine A is outlined in Scheme 3. Conversion of **20** to amine **21** was accomplished in 95% yield using cesium fluoride in DMF, but attempts to convert **21** to tetracycles via electrophile-initiated cyclizations were not promising. Thus, ester **20** was hydrolyzed and the resulting homoallylic alcohol was epoxidized to afford **23** in 64% overall yield.[29] Protection of the alcohol as a methoxymethyl ether (**23** → **24**) was accomplished in 86% yield. Deprotection of azocine **24** was accompanied by epoxide opening to afford **25** (72%).[23] Acylation of the hydroxyl group (**25** → **26**, 93%),[14] cleavage of the methoxymethyl ether (65%),[24] oxidation of the resulting alcohol **27**,[19] and chromatography of the resulting crude material over alumina gave enone **28** (quantitative from **27**) (Scheme 3).[30]

Scheme 3



20 R = Ac
22 R = H

23 R = H
24 R = MOM

25 R = MOM R' = H
26 R = MOM R' = Ac
27 R = H R' = Ac

28

(a) LiOH (b) $VO(acac)_2$, *t*-BuOOH, Δ (c) CH_3OCH_2Cl, Hunig's base (d) CsF, DMF, Δ (e) Ac_2O, 4-DMAP, Et_3N
(f) Me_3SiCl, NaI, CH_3CN (g) Swern (h) basic alumina

In summary, a synthesis of tetracyclic manzamine A substructure **28** has been accomplished. It is our hope that this enone has functionality suitable for introduction of the β-carboline and 13-membered ring azacycle in the alkaloid target. In a more general sense, this study (1) provides a new route to perhydroisoquinolines that features a stereoselective free

radical allylation, (2) provides an example of a Mitsunobu reaction that occurs with retention of configuration, most likely due to neighboring group participation of a tertiary lactam, (3) introduces a new N-acyl sulfonamide (**16**) for use in Mitsunobu reactions, and (4) provides precedent for high yield azocine preparation in a system where conformational degrees of freedom are limited by the presence of a *Z*-alkene.

Acknowledgement: We thank the National Institutes of Health (GM-27647) for generous support.

References and Notes

1. Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986**, *108*, 6404.
2. Manzamines B and C: Sakai, R.; Kohmoto, S.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *Tetrahedron Lett.* **1987**, 5493. Manzamines E and F: Ichiba, T.; Sakai, R.; Kohmoto, S.; Saucy, G.; Higa, T. *Tetrahedron Lett.* **1988**, 3083. Keramamine A (Manzamine A): Nakamura, H.; Deng, S.; Kobayashi, J.; Ohizumi, Y.; Tomotake, Y.; Matsuzaki, T.; Hirata, Y. *Tetrahedron Lett.* **1987**, 621. For related alkaloids including manzamines H and J as well as their likely biosynthetic precursors, ircinals A and B, see reference 11.
3. At least a portion of the biological activity of the manzamines appears to reside in the β-carboline group. For example, manzamine C inhibits growth of P-388 mouse leukemia cells (IC_{50} = 3.0 μg mL^{-1}). A total synthesis of manzamine C has been described: Torisawa, Y.; Hashimoto, A.; Nakagawa, M.; Hino T. *Tetrahedron Lett.* **1989**, 6549.
4. Imbroisi, D. O.; Simpkins, N. S. *Tetrahedron Lett.* **1989**, 4309. Imbroisi, D. O.; Simpkins, N. S. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1815.
5. Torisawa, Y.; Nakagawa, M.; Arai, H.; Lai, Z.; Hino, T.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1990**, 3195. Nakagawa, M.; Lai, Z.; Torisawa, Y.; Hino, T. *Heterocycles* **1990**, *31*, 999.
6. Brands, K. M. J.; Pandit, U. K. *Tetrahedron Lett.* **1989**, 1423. Brands, K. M. J.; Meekel, A. A. P.; Pandit, U. K. *Tetrahedron* **1991**, *47*, 2005.
7. Martin, S. F.; Rein, T.; Liao, Y. *Tetrahedron Lett.* **1991**, 6481.
8. Leonard, J.; Fearnley, S. P.; Hickey, E. M. B.; *Synlett.* **1992**, 272.
9. Marko, I. E.; Chesney, A. *Synlett.* **1992**, 275.
10. Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, 2059.
11. Kondo, K.; Shigemori, H.; Kikuchi, Y.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 2480.
12. Hart, D. J.; McKinney, J. A. *Tetrahedron Lett.* **1989**, 2611.
13. Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829.
14. The stereoselectivity in the free radical allylation is the same as that observed in comparable reductions reported by: Muralidharan, V. B.; Ganem, B. *J. Org. Chem.* **1982**, *47*, 5041. Also see Keck, G. E.; Yates, J. B. *J. Org. Chem.* **1982**, *47*, 3590. Although only one enantiomer is shown, all compounds presented in Schemes 1-3 were racemic.
15. Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569.
16. Pappo, R.; Allen, D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.
17. Basha, A.; Orlando, J.; Weinreb, S. M. *Syn. Commun.* **1977**, 549.
18. McOmie, J. F.; Watts, M. L.; West, D. E. *Tetrahedron* **1968**, *24*, 2289.
19. Mancuso, A. J.; Huang, S.-L. Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
20. The required acetylide was prepared from 5-hexyn-1-ol in 92% yield.
21. Cram, D. J.; Allinger, N. L. *J. Am. Chem. Soc.* **1956**, *78*, 2518.
22. Mitsunobu, O. *Synthesis* **1981**, 1.
23. This sequence uses a hybrid of methodologies developed by Weinreb: Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D. Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, 5709. Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, 2099. The preparation of imide **16** will be described elsewhere.
24. Olah, G. A.; Husaing, A.; Singh, B. P.; Mehotra, A. K. *J. Org. Chem.* **1983**, *48*, 3667. Olah, G.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.
25. For a review of azocine chemistry see Perlmutter, H. D.; Trattner, R. B. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1982; Vol. 31, pp 115-167.
26. We thank Dr. Judith Gallucci for determining the crystal structure of **20** at our departmental crystallography facility.
27. Lipshutz, B. H.; Miller, T. A. *Tetrahedron Lett.* **1990**, 5253.
28. Alternate plans for using **15** in the synthetic scheme are being explored.
29. Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.
30. Enone **28** and all other new compounds were characterized by ^1H NMR, ^{13}C NMR, IR and mass spectrometry, and stereochemical assignments were supported by appropriate difference nOe experiments. For example, maintenance of the *cis*-fused perhydroisoquinoline in **28** was established by a 10% nOe observed at H_{24} upon irradiation of $H_{35\beta}$.

(Received in USA 6 July 1992; accepted 28 July 1992)