ORGANIC LETTERS

2003
Vol. 5, No. 3
333−335

Novel Rearrangement of a 2-Aryl-3-alkyl-3*H*-indol-3-ol to a 1,4,5,6-Tetrahydro-2,6-methano-1-benzazocin-3(2*H*)-one with Implications for the Biosynthesis of Aspernomine

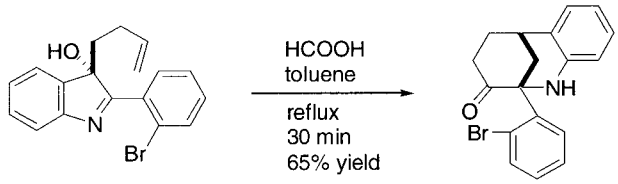
Yahua Liu,[†] William W. McWhorter, Jr.,*[,†] and Chad E. Hadden[‡]

Medicinal Chemistry Research and Global Pharmaceutical Science, Pharmacia Corporation, Kalamazoo, Michigan 49001

william.w.mcwhorter@pharmacia.com

Received November 25, 2002

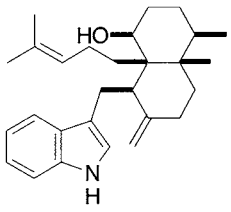
ABSTRACT



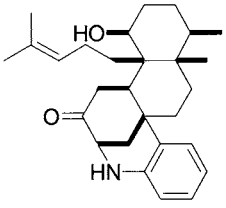
5 7

Nominine (1) and aspernomine (2) are two biologically important indole diterpenoids that arise from a common digeranylindole precursor. The skeletal relationship of these two natural products was not heretofore understood. We have observed a novel rearrangement of 2-(2-bromophenyl)-3-(3-butenyl)-3*H*-indol-3-ol (5) to 7, which contains the uncommon 1,4,5,6-tetrahydro-2,6-methano-1-benzazocin-3(2*H*)-one ring system, under acidic conditions. This rearrangement suggests that aspernomine (2) may arise biosynthetically from nominine (1).

In 1989, Gloer and co-workers reported the isolation of the novel indole diterpenoid, nominine (**1**).[1] Nominine (**1**) was isolated from the sclerotia of the fungus *Aspergillus nomius* and was shown to have potent antiinsectan activity against the crop pest *Heliothis zea*.[1] In 1992, Gloer and co-workers followed up the report of the nominine structure with the report of an additional antiinsectan metabolite from *A. nomius*: aspernomine (**2**).[2] Aspernomine (**2**) was demonstrated to have a fascinating and previously undescribed ring system.[2] Gloer and co-workers indicated that aspernomine (**2**) and nominine (**1**) arise biogenetically from a common digeranylindole precursor,[2] but they were unable, at that time, to explain the great skeletal differences between these two natural products.



1



2

We have observed the rearrangement of 2-(2-bromophenyl)-3-(3-butenyl)-3*H*-indol-3-ol (**5**) to the uncommon 1,4,5,6-tetrahydro-2,6-methano-1-benzazocin-3(2*H*)-one ring system containing **7** under acidic conditions. This observation enables us to suggest a mechanism by which nominine (**1**) may be converted into aspernomine (**2**).

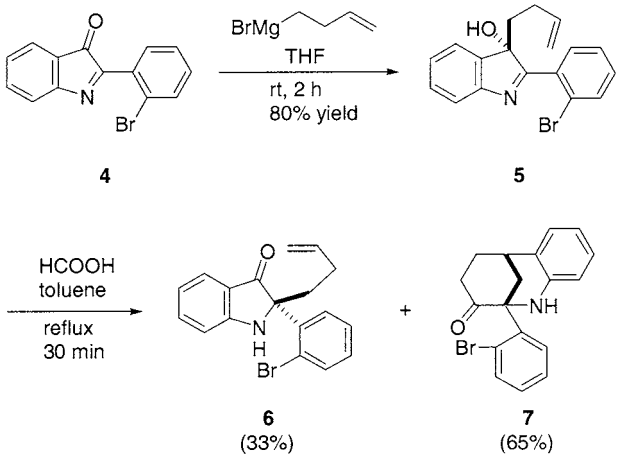
During the course of research on the total synthesis of hinckdentine A (**3**),[3] we added 3-butenylmagnesium bromide to 2-(2-bromophenyl)-3*H*-indol-3-one (**4**),[4] which had been prepared from 2-(2-bromophenyl)-indole,[5] to obtain 2-(2-

[†] Medicinal Chemistry Research.
[‡] Global Pharmaceutical Science.

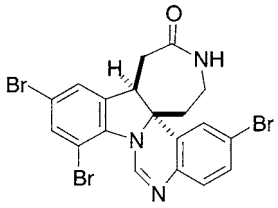
(1) Gloer, J. B.; Rinderknecht, B. T.; Wicklow, D. T.; Dowd, P. F. *J. Org. Chem.* **1989**, *54*, 2530.
(2) Staub, G. M.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Am. Chem. Soc.* **1992**, *114*, 1015.

10.1021/ol0202417 CCC: $25.00
Published on Web 01/11/2003

Scheme 1



bromophenyl)-3-(3-butenyl)-3*H*-indol-3-ol (**5**) (Scheme 1).[6] Treating **5** with formic acid in toluene at reflux for 30 min brought about the formation of two products.[7] The first product was the expected pinacol-like rearrangement product **6**. The second and major product was the novel rearrangement product 2-(2-bromophenyl)-1,4,5,6-tetrahydro-2,6-methano-1-benzazocin-3(2*H*)-one (**7**).

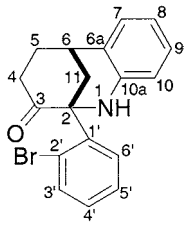


3

The structure of **7** was determined by NMR experiments. The ^{1}H, ^{13}C, DEPT, COSY, HMQC, HMBC, and ^{1}H−^{15}N HMBC NMR spectra were used to assign the peaks. The ^{1}H and ^{13}C NMR assignments are shown in Table 1. The three-bond correlations from the HMBC spectra were used to determine the structure of rearrangement product **7**.

Table 1. ^{1}H (599.75 MHz), ^{13}C (150.82 MHz), and ^{15}N (60.78 MHz) NMR Data of **7** in $CDCl_3$ at 300 K

	δ_H [J (Hz)]	$\delta_{C/N}$	HMBC (^{1}H)
1	4.38 (br s)	85.4	7 or 9, 10, 11
2		65.8	1, 3′, 4 (δ 2.69), 6, 6′, 11
3		206.2	4, 5, 11 (δ 2.07)
4	2.24 (dd, J = 17.4 and 6.8), 2.69 (dd, J = 17.4 and 5.8)	35.7	5, 6, 11 (δ 2.07)
5	2.18 (m), 2.40 (m)	33.9	4, 6, 11
6	3.24 (dd, J = 5.8 and 2.9)	32.9	4 (δ 2.69), 5, 7, 10, 11
6a		124.5	1, 4, 5, 6, 7, 8, 10, 11
7	7.15 (d, J = 7.3)	128.3	1, 6, 8, 9, 11 (δ 3.05)
8	6.83 (ddd, J = 7.5, 7.3, and 1.0)	119.4	7, 9, 10
9	7.16 (ddd, J = 7.5, 7.3, and 1.5)	129.1	7, 8
10	6.73 (dd, J = 7.5 and 1.0)	115.5	1, 8, 9
10a		143.0	6, 7, 8, 9, 10
11	2.07 (dd, J = 13.1 and 3.1), 3.05 (dd, J = 13.1 and 2.7)	35.0	1, 5, 6
1′		141.4	1, 3′, 4 (δ 2.69), 4′, 5′, 11
2′		122.8	3′, 4′, 5′, 6′
3′	7.65 (dd, J = 7.9 and 1.3)	134.8	4′, 5′, 6′
4′	7.24 (ddd, J = 7.9, 7.7, and 1.7)	129.7	5′, 6′
5′	7.42 (ddd, J = 7.9, 7.7, and 1.3)	128.1	3′, 4′
6′	7.80 (dd, J = 7.9 and 1.7)	128.2	4′, 5′



7

All of the important three-bond ^{1}H−^{13}C and ^{1}H−^{15}N correlations are shown in Figure 1. These correlations taken as a whole demonstrate conclusively that the structure of rearrangement product **7** is as shown. Of particular note are

(3) (a) Blackman, A. J.; Hambly, T. W.; Picker, K.; Taylor, W. C.; Thirasasana, N. *Tetrahedron Lett.* **1987**, *28*, 5561. (b) Liu, Y.; McWhorter, W. W. *J. Am. Chem. Soc.* Accepted for publication.

(4) Prepared by the procedure in: Richman, R. J.; Hassner, A. *J. Org. Chem.* **1968**, *33*, 2548.

(5) Dalton, L.; Humphrey, G. L.; Cooper, M. M.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2417.

(6) Preparation of 2-(2-bromophenyl)-3-(3-butenyl)-3*H*-indol-3-ol (**5**): 2-(2-Bromophenyl)-3*H*-indol-3-one (**4**) (286 mg, 1 mmol) was dissolved in dry THF (100 mL) that had been refluxed over sodium and benzophenone for 8 h and freshly distilled. Under the protection of nitrogen and at room temperature, a solution of 3-butenylmagnesium bromide in THF (0.5 M, 2.2 mL, 1.1 mmol) was added dropwise and slowly. After stirring for 2 h, the reaction mixture was concentrated under reduced pressure at 25−28 °C to a very small volume, diluted with EtOAc (120 mL), and washed with 10% NH_4Cl solution (40 mL). The aqueous wash was extracted with EtOAc (3 × 20 mL). The combined EtOAc extracts were washed with brine (30 mL) and dried over Na_2SO_4 for 50 min. Evaporation of solvent and then silica gel chromatography with 9:2 hexane/EtOAc afforded **5** (273 mg, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (m, 2H, CH_2), 2.07 (m, 2H, CH_2), 2.43 (br s, 1H, OH), 4.91 (dd, J = 10.0 and 1.5 Hz, 1H, =CH_2), 4.96 (dd, J = 17.2 and 1.5 Hz, 1H, =CH_2), 5.70 (m, 1H, =CH), 7.31−7.36 (2H, ArH), 7.41−7.45 (2H, ArH), 7.48 (d, J = 8.1 Hz, 1H, ArH), 7.66 (d, J = 7.7 Hz, 1H, ArH), 7.75 (dd, J = 8.1 and 1.0 Hz, 1H, ArH), 7.79 (dd, J = 7.7 and 1.7 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3, 35.1, 88.2, 115.0, 121.8, 122.3, 122.8, 127.1, 127.2, 129.8, 130.0, 131.0, 133.9, 134.4, 137.3, 139.3, 152.6, 181.0; HRESIMS calcd for $C_{18}H_{17}BrNO$ (MH^+) 342.0494, found 342.0508.

(7) Rearrangement of 2-(2-bromophenyl)-3-(3-butenyl)-3*H*-indol-3-ol (**5**): To a solution of **5** (171 mg, 0.5 mmol) in toluene (20 mL) was added 88% aqueous formic acid (4 mL). After stirring and refluxing for 30 min, the reaction mixture was cooled to room temperature and carefully poured into saturated Na_2CO_3 solution (150 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (4 × 40 mL). The combined organic solution layers were washed with brine (20 mL) and dried over Na_2SO_4. Evaporation of solvent and silica gel chromatography with 11:1 hexane/EtOAc afforded **6** (56.4 mg, 33%) and **7** (111 mg, 65%). **Compound 6**: IR 3363 (N−H), 3067 (=C−H), 2974, 2924, 2855, 1695, 1614, 1618, 1509, 1564, 1487, 1467, 1324, 1295, 1282, 913, 890, 752, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84 (m, 1H, CH_2), 2.16 (m, 1H, CH_2), 2.30 (ddd, J = 12.4, 11.2 and 5.0 Hz, 1H, CH_2), 2.56 (ddd, J = 12.4, 11.5 and 4.4 Hz, 1H, CH_2), 4.92 (dd, J = 10.2 and 3.1 Hz, 1H, =CH_2), 4.96 (dd, J = 17.0 and 3.1 Hz, 1H, =CH_2), 5.77 (m, 1H, =CH), 6.10 (br s, 1H, NH), 6.83 (ddd, J = 7.5, 7.1 and 0.6 Hz, 1H, ArH), 6.88 (ddd, J = 8.3, 1.7 and 0.6 Hz, 1H, ArH), 7.16 (ddd, J = 7.6, 7.3 and 1.7 Hz, 1H, ArH), 7.30 (ddd, J = 7.7, 7.5 and 1.3 Hz, 1H, ArH), 7.47 (ddd, J = 7.7, 7.1 and 1.3 Hz, 1H, ArH), 7.63−7.66 (2H, ArH), 7.69 (ddd, J = 8.9, 1.3 and 0.8 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 36.8, 72.6, 112.4, 115.4, 119.1, 121.3, 123.0, 125.1, 128.0, 129.5, 129.6, 135.7, 138.0, 138.0, 138.0, 160.4, 201.9; HRESIMS calcd for $C_{18}H_{17}BrNO$ (MH^+) 342.0494, found 342.0508. Anal. Calcd for $C_{18}H_{16}BrNO$: C, 63.17; H, 4.71; N, 4.09. Found: C, 63.46; H, 4.85; N, 3.86. **Compound 7**: IR 3304 (N−H), 3055, 2967, 2931, 2932, 2855, 1686 (C=O), 1607, 1589, 1488, 1467, 1454, 1433, 1394, 1321, 1307, 1266, 1239, 1222, 1134, 1115, 1025, 720,

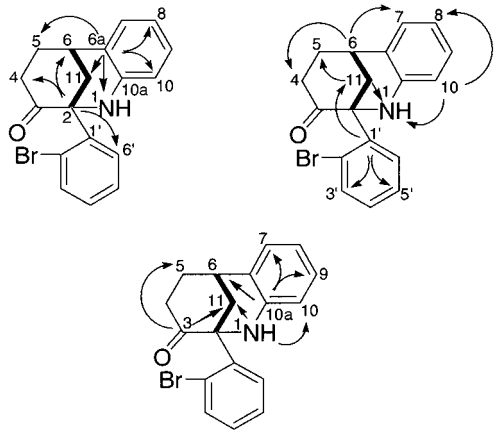
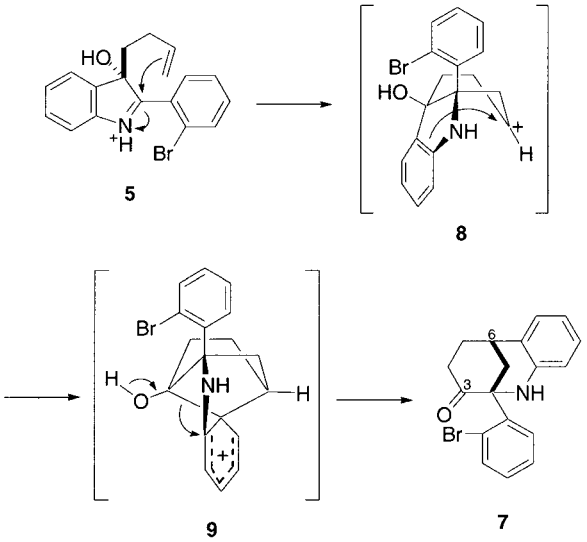


Figure 1. Three-bond $^{1}H-^{13}C$ and $^{1}H-^{15}N$ correlations.

the correlations for C.3 and C.6, the centers from which and to which the migration has taken place, respectively. The carbonyl carbon (C.3) correlates with the H.5 and H.11, but not with any aromatic protons, while H.4 and most importantly the aromatic H.7 correlate to the methine proton bearing C.6 (bridge head center).

We believe that the rearrangement of **5** to **7** takes place as shown in Scheme 2. Markovnikov addition of the

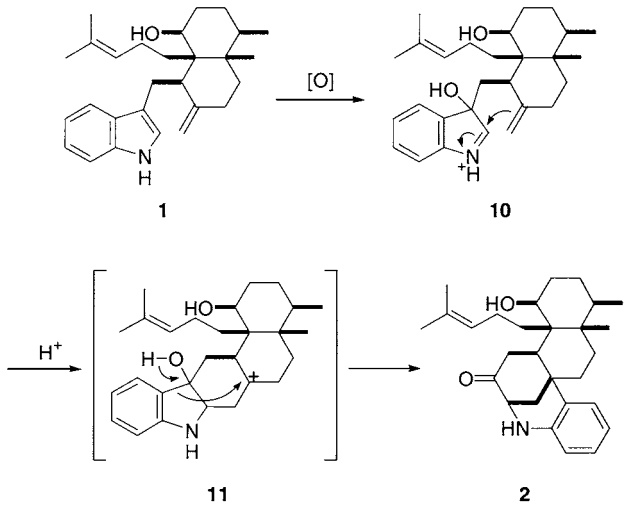
Scheme 2



protonated imine to the monosubstituted double bond of **5** yields intermediate **8**. The bulky bromophenyl group causes the double bond and the imine to approach one another such that the newly formed six-membered ring initially adopts a boatlike conformation. Electrophilic attack of the secondary carbocation on the π-bond of the electron-rich aromatic ring, with which it is aligned across the boatlike six-membered ring, yields intermediate **9**, which in turn readily collapses to yield **7**.

It is interesting to note that aspernomine (**2**) and nominine (**1**) may be related to one another by a similar type of rearrangement. If nominine (**1**) is oxidized[8] to the corresponding 3*H*-indol-3-ol (**10**), it contains all of the structural features of **5** that are necessary for the rearrangement. Treatment of **10** with acid could then lead to rearrangement to aspernomine (**2**) via **11** as shown in Scheme 3. This

Scheme 3



rearrangement may be indicative of steps in the biosynthetic pathway of aspernomine (**2**) and suggests that aspernomine (**2**) could be derived biosynthetically from nominine (**1**). Moreover, this proposed conversion of nominine into aspernomine hints at a potential biomimetic synthetic route for the preparation of aspernomine (**2**).

Thus, we have observed the formation of 2-(2-bromophenyl)-1,4,5,6-tetrahydro-2,6-methano-1-benzazocin-3(2*H*)-one (**7**) from 2-(2-bromophenyl)-3-(3-butenyl)-3*H*-indol-3-ol (**5**) by a novel acid-induced rearrangement reaction. The structure of **7** has been conclusively determined by NMR experiments. The observed rearrangement suggests a possible biosynthetic relationship between the structures of nominine (**1**) and aspernomine (**2**).

Acknowledgment. We are grateful to Pharmacia Corporation for supporting a postdoctoral fellowship for Y.L. We thank the Analytical Chemistry Department of Pharmacia for acquiring the infrared spectra and the high-resolution mass spectra.

Supporting Information Available: ^{1}H NMR spectra of **5**−**7** and the ^{13}C NMR spectrum, DEPT NMR spectra, $^{1}H-^{1}H$ COSY, HMQC, and HMBC of **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0202417

672, 634 cm^{-1}; ^{1}H, ^{13}C, and ^{15}N NMR (see Table 1); HRESIMS calcd for $C_{18}H_{17}BrNO$ (MH^{+}) 342.0494, found 342.0487. Anal. Calcd for $C_{18}H_{16}BrNO$: C, 63.17; H, 4.71; N, 4.09. Found: C, 63.04; H, 4.78; N, 4.00. mp 217.0−219.5 °C.

(8) See: Nakagawa, M.; Matsuki, K.; Hasegawa, K.; Hino, T. *J. Chem. Soc., Chem. Commun.* **1982**, 742 and references therein.