Pergamon

Tetrahedron Letters, Vol. 38, No. 39, pp. 6909-6912, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01592-X

A New Method for the Formation of the Imidazo[4', 5'; 3,4] pyrido[2,3-b]indole Ring : Formal Synthesis of the Alkaloids from Marine Origin Grossularines -1 and 2.

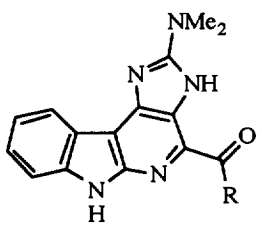
Pedro Molina*, Pilar M. Fresneda*, Miguel A. Sanz

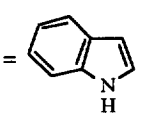
Departamento de Química Orgánica, Facultad de Química,
Universidad de Murcia, Campus de Espinardo, E-30071, Murcia, Spain.

Abstract : A new synthesis of the 2-dimethylamino-4-hydroxy-6-methoxymethyl-3H-imidazo[4', 5' :3,4] pyrido[2,3-b]indole, used as key intermediate in the total synthesis of the alkaloids grossularines -1 and -2, based on the step-wise formation of the pyridine and imidazole rings, is described.

Marine organisms are among the most promising sources of new and biologically active molecules. Certain secondary metabolites are non-traditional guanidine-based alkaloids[1] that possess a broad spectrum of powerful biological activities.The guanidine moiety is most frequently found in the guise of a 2-aminoimidazole ring that is generally substituted with alkyl groups on carbon or nitrogen.[2]

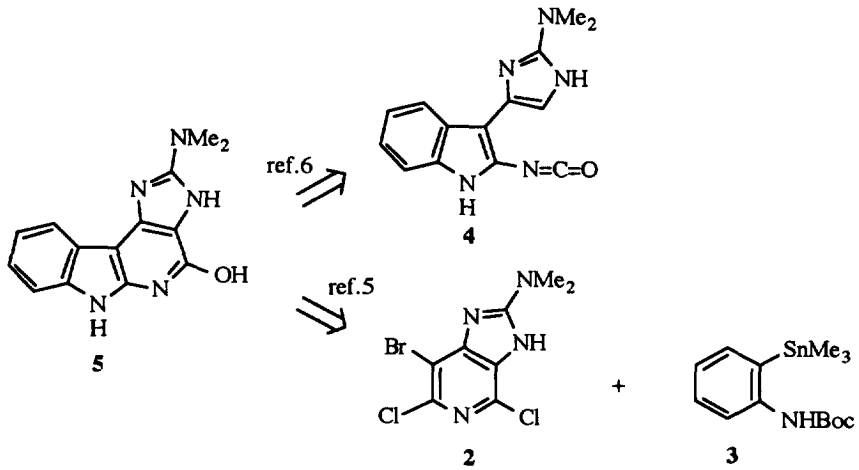
Marine alkaloids grossularines -1 **1a** and -2 **1b**, possessing a cyclic guanidine moiety in the form of 2-dimethylaminoimidazole subunit, were isolated in 1984 from the marine tunicate *Dendrodoa grossularia* (Stylidae) collected in the coast of Britany.[3] These compounds, which are the first examples of naturally ocurring pyrido[2,3-b]indoles (α-carbolines), exhibit marked cytotoxicity toward murine and human tumor cells.[4]



1a Grossularine -1 R = 

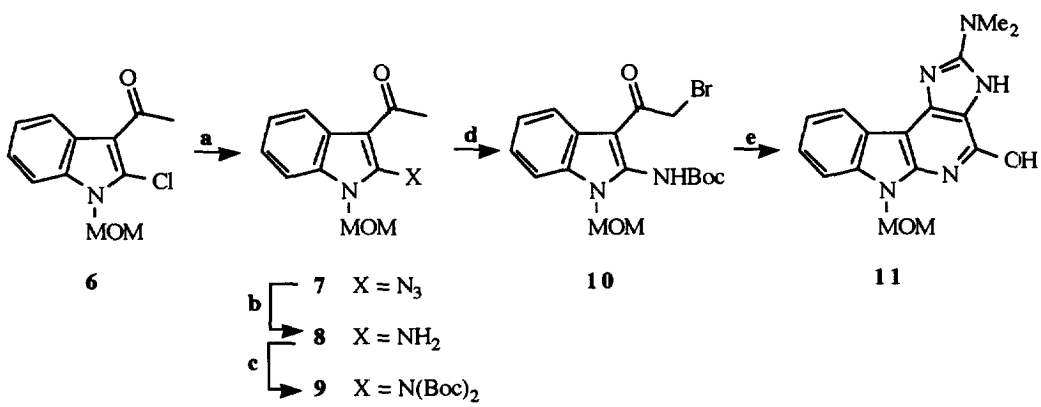
1b Grossularine -2 R = 4-HO.C_6H_4

Recently, two approaches have been developed for the construction of the tetracyclic imidazo[4', 5' : 3, 4]pyrido[2,3-b]indole framework of the titled compounds. The first is based on the palladium-catalyzed cross coupling between the appropriately substituted imidazo[4, 5-c]pyridine **2** and the stannane aniline **3** followed by base-promoted intramolecular cyclization of the resulting biaryl compound to construct the α-carboline ring system.[5] In the second approach, the formation of the α-carboline ring is based on the thermal electrocyclic ring-closure of a 2-azahexatriene system, including the indole 2,3-bond and the imidazole 4,5-bond. The starting material **4** was prepared by cross-coupling reaction between 3-iodoindole-2-carboxylate and the directed metallation-derived imidazole followed by hydrolysis of the ester group and further Curtius rearrangement with diphenyl phosphorazidate (DPPA).[6] In the first total synthesis of compounds **1**, the key intermediate **5** was elaborated into the target compounds through a sequence involving triflate formation and subsequent arylation by way of the Stille or Suzuki cross-coupling methodologies with or without carbon monoxide insertion.[7]



Following our programme directed toward the synthesis of imidazole-containing alkaloids from marine origin,[8] we wish to report an efficient synthesis of the intermediate **5**, successfully used in the above mentioned synthesis of the alkaloids grossularines -1 and 2. Our approach is based on the step-wise formation of the imidazole and pyridine rings starting from an appropiate 2,3-disubstituted indole.

The N-protected indole **6** was prepared in 85% yield from 3-acetyl-2-chloroindole[9] and methoxymethyl chloride in the presence of sodium hydride. Conversion of **6** into the azido indole **7** was performed in 65% yield by reaction with sodium azide in DMSO at room temperature. Staudinger reaction of **7** with triphenylphosphine in diethyl ether at room temperature, and further treatment with THF/H_2O in the presence of catalytic amounts of hydrochloric acid provided **8** in 85% yield.Treatment of **8** with the system Boc_2O/DMAP at room temperature afforded **9** in 85% yield, which underwent bromination at room temperature with concomitant N-Boc deprotection to give **10** in 70% yield.[10] The reaction of **10** with N, N- dimethylguanidine in ethanol at room temperature directly gave **11** in 80% yield.[11]



Reagents and Conditions: a) NaN_3, DMSO, 45°C, 65 %; b) Ph_3P, Et_2O, r.t. then THF, H_2O, HCl, r.t., 85 %; c) $(Boc)_2O$, DMAP, r.t., 85%; d) Br_2, $CHCl_3$, 50°C→ r.t., 70%; e) DMAG, EtOH, r.t., 80%.

Taking into account that a) the formation of isocyanates from carbamates usually requires either strong acid conditions or high temperatures[12] and b) electrocyclization of the isocyanate **4** to give **11** is carried out at high temperature,[7] we reasonably thought that the conversion **10** → **11** does not involve the formation of the intermediate isocyanate. A tentative mechanism for this conversion could involve initial formation of a dihydropyridone ring by nucleophilic attack of the enolate ion derived from the bromomethylacetyl substituent at position 3 on the carbamate group at position 2 and further formation of the imidazole ring accross the remaining α-bromocarbonyl moiety.

Formation of compound **11** constitutes a formal total synthesis of grossularines -1 and -2, since **11** may be easily converted into the target molecules in a straightforward manner.

Acknowledgements:
We gratefully acknowledge the financial support of the Dirección General de Investigación Científica y Técnica (PB95-1019). One of us (M.A.S.) also thanks the Ministerio de Educación y Cultura for a scholarship.

References and Notes:

1. Albizati, K. F.; Martin, V. A.; Agharahimi, M. R.; Stolze, D. A.*Synthesis of Marine Natural Products in Biorganic Marine Chemistry* ; Scheuer, P. J. Ed.; Springer: Berlin, 1992; Vol. 6 pp 158-248.
2. For recent reports of biologically active 2-aminoimidazole alkaloids, see: Kobayashi, J.; Tsuda, M.; Murayama, T.; Nakamura, H.; Ohizumi, Y.; Ishibashi, M.; Iwamura, M.; Otha, T.; Nozoe, S.*Tetrahedron* **1990**,*46*, 5579. Commerço, A.; Gueremy, C. *Tetrahedron Lett.* **1991**, *32*, 1416. He, H.; Faulkner, D. J.; Lee, A.; Clardy, J. *J. Org. Chem.* **1992**, *57*, 2176. Faulkner, D. J.; *Nat. Prod. Rep.* **1992**, *9* , 323. Alvi, K. A.; Peters, B. M.; Hunter, L. M.; Crews, P. *Tetrahedron* **1993**, *49*, 329. Little, T. L.; Webber, S.E*J. Org. Chem.* **1994**, *59*, 7299. Chan, G.W.; Mong, S.; Hemling, M. E.; Freyer, A. J.; Offen, P.H.; DeBrosse, C. W.; Sarau, H. M.; Westley, J. W. *J. Nat. Prod.* **1993**, *56*, 116.
3. Moquin, C.; Guyot, M. *Tetrahedron Lett.* **1984**, 5047. Moquin-Pattey. C.; Guyot, M. *Tetrahedron* **1989**, 3445.
4. Helbecque, N.; Berbier, J. L.: Henichard, J. P.; Moquin-Pattey, C.; Guyot, M. *Cancer Biochem. Biophys.* **1987**, *9*, 271.
5. Achab, S.; Guyot, M.; Potier, P. *Tetrahedron Lett.* **1993**, 2127.
6. Achab, S.; Guyot, M.; Potier, P. *Tetrahedron Lett.* **1995**, 2615. Choshi, T. Yamada, S.; Sugino, E.; Kuwada, T.; Hibino, S.*Synlett.* **1995**, 147.
7. Choshi, T. Yamada, S.; Sugino, E.; Kuwada, T.; Hibino, S. *J. Org. Chem.* **1995**, *60*, 5899.
8. Molina, P.; Fresneda, P. M.; Almendros, P. *Tetrahedron Lett.* **1992**, *3*, 4491. Molina, P.; Almendros, P.; Fresneda, P. M. *Tetrahedron* **1994**, *50*, 2241. Molina, P.; Almendros, P.; Fresneda, P. M. *Tetrahedron Lett.* **1994**, *35*, 2235.
9. Monge, A.; Palop, J. ; Ramirez, C.; Font, M.; Fernandez-Alvarez E. *Eur. J. Med. Chem.* **1991**, *26*, 179.
10. *Typical Procedure* : To a solution of **6** (1.5 g, 6.3 mmol) in DMSO (30 ml) NaN_3 (1.0 g, 16.6 mmol) was added. The mixture was stirred at 45°C for 24 h then poured into ice/H_2O and extracted with Et_2O (4 x 50 ml). The combined organic layers were dried over $MgSO_4$, concentrated and the crude was chromatographed on a silica gel column using Et_2O/n-hexane as eluent to give **7** as oil. To a cooled at 0°C solution of Ph_3P (0.53 g, 2.04 mmol) in dry Et_2O (10 ml), a solution of **7** (0.5 g, 2.04 mmol) in the some solvent (10 ml) was added dropwise under N_2. The mixture was allowed to warm to room temperature and stirred for 12 h. The solvent was removed under reduced pressure and the crude was dissolved in THF (20 ml) and 5% HCl (20 ml) was aaded. The mixture was stirred at room temperature for 24 h. The solution was concentrated to dryness and the solid was extracted with Et_2O (2x20 ml). The remaining solidwas treated with hot EtAcO (3x25 ml) and filtered. The filtrate was concentrated and cooled to give **8** (m. p. 186-188°C). To a cooled solution of Boc_2O (2.2 g, 9.2 mmol) in dry THF (25 ml) a solution of **8** (1.0 g, 4.6 mmol) and 4-dimethyl aminopyridine (1.12 g, 9.2 mmol) in the same solvent was added dropwise. The resultant solution was stirred at room temperature for 18 h and then concentrated to dryness. The residue was taken up in Et_2O (50 ml),

washed with 0.1N HCl (20 ml), H_2O (20 ml) and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure to give a solid, wich recrystallized from EtAcO / n-hexane gave **9** (m. p. 122-125°C). To a solution of **9** (o.1 g, 0.24 mmol) in dry $CHCl_3$ (15 ml) was added a solution of Br_2 (0.038 g, 0.24 mmol) in the same solvent (5 ml). The resultant solution was stirred at room temperature for 12 h, then washed with saturated $NaHCO_3$ aqueouse, and H_2O (10 ml). The organic layer was dried over $MgSO_4$, concentrated and chromatographed on a silica gel column using EtAcO / n-hexane (6:4) as eluent to give **10** (m.p. 108°C)

Compound 7. (65%) ^{1}H n.m.r. (200 MHz, $CDCl_3$) δ 2.79 (s, 3H, CH_3CO),3.18 (s, 3H, CH_3O), 5.50 (s, 2H, CH_2O), 7.37-7.25 (m, 2H, H-5 + H-6), 7.5-7.4 (m, 1H, H-7), 7.9-7.8 (m, 1H, H-4).^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 31.1 (CH_3CO), 56.3 (CH_3O), 73.0 (CH_2O), 107.0 (C-2), 110.4 (C-7), 119.9 (C-4), 122.8 and 122.9 (C-5 or C-6), 125.0 (C-3a), 133.4 (C-7a), 140.6 (C-2), 193.3 (C=O). IR ($CHCl_3$) ν : 2140(s), 1722 (s) 1649 (s). MS:m/z (%) (FAB positive, NBA) 245 (M+H, 65).

Compound 8. (85%) ^{1}H n.m.r. (200 MHz, DMSO-d_6) δ 2.44 (s, 3H, CH_3CO), 3.23 (s, 3H, CH_3O), 5.47 (s, 2H, CH_2O), 7.01 (ddd, 1H, J=7.8, 7.5, 1.5 Hz, H-6), 7.09 (ddd, 1H, J=7.5, 7.5, 0.9 Hz, H-5), 7.32 (d, 1H, J= 7.5, H-7), 8.04 (s, 2H, NH_2).^{13}C n.m.r. (50 MHz, DMSO-d_6) δ 29.7 (CH_3CO), 55.3 (CH_3O), 71.5 (CH_2O), 95.7 (C-3), 109.1 (C-7), 117.7 (C-4), 119.9 (C-6), 121.7 (C-5), 125.9 (C-3a), 133.8 (C-7a), 154.1 (C-2), 190.4 (CO). IR (nujol) ν : 3304(m), 3277(m), 1636 (s). MS: m/z (%) (EI positive) 219 (M+1, 6), 218 (M, 51), 143 (100).

Compound 9. (85%) ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.42 (s, 18H, ($(CH_3)_3C$), 2.54 (s, 3H, CH_3CO), 3.30 (s, 3H, CH_3O), 5.38 (s, 2H, CH_2O), 7.26-7.38 (m, 2H, H-5+ H-6), 7.48-7.56 (m, 1H, H-7), 8.28-8.34 (m, 1H, H-4). $_{13}$C n.m.r . (75 MHz, $CDCl_3$) δ 27.8 ($(CH_3)_3C$), 24.6 (CH_3CO), 56.4 (CH_3O), 73.9 (CH_2O), 84.3 ($(CH_3)_3C$), 110.1 (C-7), 112.4 (C-3), 122.6 (C-4), 122.9 and 124.0 (C-5 or C-6), 125.0 (C-3a), 134.3 9C-7a), 136.8 (C-2), 149.9 (COO^{t}Bu), 192.8 (CO). IR (nujol) ν : 1805 (s), 1728 (s), 1640 (s). MS : m/z (%) (EI positive) 420 (M+2, 3), 419 (M+1, 21), 418 (M, 100), 218 (91).

Compound 10 . (70%) ^{1}H n.m.r. (200 MHz, $CDCl_3$) δ 1.44 (s, 9H, ($(CH_3)_3C$), 3.03 (s, 3H, CH_3O, 4.39 (s, 2H, CH_2Br), 5.49 (s, 1H, CH_2O), 7.1-7.3 (m, 2H, H-5 + H-6), 7.37-7.46 (m,1H, H-7), 7.51-7.65 (m, 1H, H-4). ^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 27.9 ($(CH_3)_3C$), 35.0 (CH_2Br), 56.2 (CH_3O), 76.5 (CH_2O), 82.6 ($(CH_3)_3C$) , 102.1 (C-3), 118 (C-7), 120.0 (C-4), 122.9 and 123.2 (C-5 or C-6), 123.7 (C-3a), 133.8 (C-7a), 143.9 (C-2), 152.6 (COO^{t}Bu), 187.4 (CO). IR (nujol) ν : 3268 (m), 1733 (s), 1620 (s). MS : m/z (%) (EI positive) 398 (M+2, 33), 396 (M, 34) 296 (75).

11. *General Procedure for the Preparation of* **11** : To a solution of the indole derivative **10** (0.397 g. 1mmol) in anhydrous ethanol (50 ml) was added dropwise a solution of N,N-dimethylguanidine (0.174 g, 2 mmol) in the same solvent (100 ml) at 0°C under nitrogen. The reaction mixture was allowed to warm at room temperature and stirred for 3 h. The solvent was removed under reduced pressure and the residual material was chromatographed on a silica gel column eluting with dichloromethane /ethanol (9:1) to give **11** (0.25 g, 80%). ^{1}H n.m.r.(300 MHz, DMSO-d_6) δ 3.10 (s, 6H, $(CH_3)_2$N3.24 (s, 3H, CH_3O), 5.75 (s, 2H, CH_2O), 7.19 (dt, J=7.5, 7.5, 0.9 Hz, H- 9), 7.30 (dt, J=7.5, 7.5, 0.9 Hz, H-8), 7.54 (d, J=8.1Hz, H-7), 8.12 (d, J=7.5Hz, H-10). ^{13}C n.m.r. (75 MHz, DMSO-d_6) δ 38.0 $(CH_3)_2$N, 55.6 (CH_3O), 72.0 (CH_2O), 99.4 (q), 109.9 (C-7), 116.0 (q), 119.8 (C-9), 120.7 (C-10), 121.0 (q), 121.9 (q), 122.9 (C-8), 136.9 (q), 148.2 (q), 151.5 (q), 154.6 (q). IR (nujol) ν : 3344(m), 1684(m), 1597(s). MS: m/z(%) (FAB positive, NBA) 312 (M+H, 100); (EI posi tive) 312 (M+1, 23), 311 (M, 100), 280 (49), 266 (22).

12. Molina, P.; Tarraga, A. *Comprehensive Organic Functional Group Transformations* ; Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W. Ed.; Vol. 5; Moody, C. J., vol. Ed.; Pergamon : Cambridge, 1995; p 976.

(*Received in UK* 7 *July* 1997; *revised* 29 *July* 1997; *accepted* 1 *August* 1997)