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Synthesis of antifungal *N*-isoprenyl-indole alkaloids from the fungus *Aporpium caryae*†

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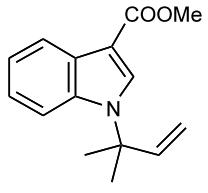
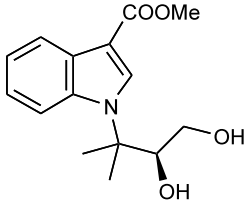
Abstract—The synthesis of two antifungal alkaloids **1** and **2** is described. It involves the *N*-isoprenyl-indole brominated key-intermediate **3** prepared by introduction of the isoprenyl group on the indole core itself.

Basidiomycetes are known to produce a series of biologically active compounds.[1] Recently from the wood-inhabiting fungus *Aporpium caryae*, two indole metabolites **1** and **2**, possessing antifungal activity, have been isolated.[2] These compounds are characterized by a *N*-isoprenyl-indole substructure which is common to other natural aminoacids and alkaloids produced by terrestrial or marine microorganisms and showing interesting bioactivities. Cyclomarins aminoacids[3] and the antitumor dihydroxyquinone Asterriquinone[4] are some valuable examples.



1



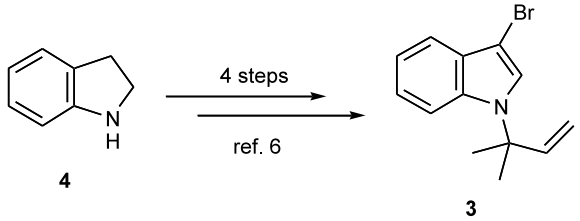
2

Recently these compounds have been objects of synthetic studies and just last year, Sugiyama et al. reported the synthesis of **1** and **2** from the 3-bromo-derivative **3**, obtained from indoline (**4**) (Scheme 1).[5] In this strategy the isoprenyl unit was introduced on the indoline and the indole core was then formed after oxidation.

Herein we wish to report a novel synthesis of metabolites **1** and **2** through the intermediate **3**, based on the direct isoprenylation of the nitrogen atom of the indole core. This strategy might be useful in general for synthesis of *N*-isoprenyl-indole natural compounds where it is advisable to start from an indole-type precursor.

Primarily we effected the bromination of indole affording 3-bromo-indole (**6**). Many methods to accomplish this transformation are available in literature.[6] We gained the best results (96%) with Br_2 in DMF.[6a] In our hands, bromination with 2 mol. equiv. of Me_3SiBr and dimethyl sulfoxide, differently to what reported,[6b] gave 2,3-dibromo-indole as shown by comparison of ^1H and ^{13}C NMR data,[6c] instead of **6**.

Successively, as depicted in Scheme 2, the bromo-compound **3** was obtained from **6** in four steps. Being position 3 occupied, nitrogen became the better nucleophilic site: 3-bromo-indole's sodium salt could be easily alkylated with methyl 3-bromo-propionate to furnish α-methyl ester **7**.[7]



4 **3**

Scheme 1.

Keywords: natural products; antifungal indole alkaloids; *N*-isoprenyl indole; Sharpless dihydroxylation.

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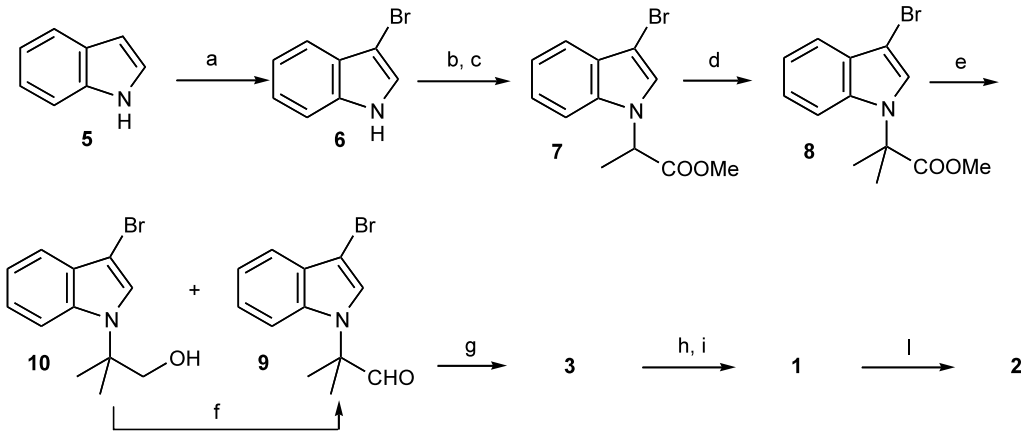

Scheme 2. *Reagents and conditions*: (a) Br_2, DMF, rt, 96%; (b) NaH, DMF, rt; (c) $CH_3CH(Br)COOMe$, 50°C, 93%; (d) *t*-BuOK, MeI, THF, rt, 72%; (e) DIBALH (1.3 equiv.), CH_2Cl_2, −78°C, 61% (9), 34% (**10**); (f) TPAP, NMO, CH_2Cl_2, mol. sieves, rt, 91%; (g) $Ph_3PCH_3^+Br^-$, NaH, THF, rt, then **9**, rt, 70%; (h) *t*-BuLi, THF, −100°C; (i) ClCOOMe, −78°C, 89%; (j) OsO_4 (1 mol%), $(DHQ)_2PYR$ (1.1 mol%), $K_3Fe(CN)_6$, K_2CO_3, H_2O/*t*-BuOH 1:1, 0°C, quantitative yield, 69% ee.

The introduction of a second α-methyl group by treatment of the ester enolate with CH_3I, proved to be harder than expected. No reaction was observed employing many bases, such as *n*-BuLi, LDA, NaHMDS, LiCl/LDA/DMPU and NaH at different temperatures. We were able to obtain good results only by slow addition of *t*-BuOK, 1 M THF solution, to a mixture of **7** and CH_3I, at room temperature. Furthermore, reaction time proved to be decisive: optimal yield (72%) was found after 15 min. Lower yield (50%) was observed after 4 h and a worsening (33%) after 72 h.

Selective reduction with DIBALH (1.3 mol. equiv.) of the resulting α,α-dimethyl ester **8**, gave a mixture of the related aldehyde **9** and alcohol **10**, respectively, in 61 and 34% yields. TPAP-catalyzed oxidation[8] allows to recycle alcohol **10** and therefore to obtain **9** in 92% overall yield from **8**.

The target intermediate **3**[9] was obtained by Wittig methylenation of **9**: in order to reach satisfying yield, use of NaH as base was found to be better than *n*-BuLi. Hence we accomplished synthesis of **8** from indole in five steps and 41% overall yield.

3-Lithium-indoles, formed from related 3-bromo-compounds by lithium–halogen exchange, can react, as broadly described, with a number of electrophiles affording several 3-substituted indole analogues.[10] As reported by Sugiyama et al. as well,[5] treatment of organolithium derivative of **3** with ClCOOMe gave natural product **1** and successive Sharpless asymmetric dihydroxylation furnished the related diol **2**. Spectral data of compounds **1** and **2** were identical to those reported for the natural products.[2,11] As well as on other 3,3-dimethyl-monoenes, the best enantiomeric excesses in asymmetric OsO_4 mediated dihydroxylation were obtained with 2,5-diphenyl-4,6-pyrimidine ligands.[12] 69% ee (*S*)-**6** was obtained by employing $(DHQ)_2PYR$, its absolute configuration being determined by comparison of the optical rotation power sign with that reported in literature for the natural compound. The unnatural enantiomer, (*R*)-**6**, was formed in 89% ee when $(DHQD)_2PYR$ was used instead.[13]

In conclusion, antifungal compounds **1** and **2** were efficiently prepared, respectively, in six and seven steps and 36% overall yield starting from indole (**5**). Further applications of compound **3** as intermediate in the synthesis of other *N*-isoprenyl-indole natural compounds are currently subject of our studies.

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References

1. Arnone, A.; De Gregorio, G.; Vajna de Pava, O. *Tetrahedron* **1998**, *54*, 10199–10204.
2. Levy, L. M.; Cabrera, G. M.; Wright, J. E.; Seldes, A. M. *Phytochemistry* **2000**, *54*, 941–943.
3. Renner, M. K.; Shen, Y.-C.; Cheng, X.-C.; Jensen, P. R.; Frankmoelle, W.; Kauffmann, C. A.; Fenical, W.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1999**, *121*, 11273–11276.
4. Yamamoto, Y.; Nishimura, K.-i.; Kiriyama, N. *Chem. Pharm. Bull.* **1976**, *24*, 1853–1859.
5. Sugiyama, H.; Yokokawa, F.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **2001**, *42*, 7277–7280.
6. (a) Bocchi, V.; Palla, G. *Synthesis* **1982**, 1096–1097; (b) Bellesia, F.; Ghelfi, F.; Pagnoni, U. M.; Pinetti, A. *J. Chem. Res. (S)* **1989**, *1*, 182–183; (c) Brennan, M. R.; Erickson, K. L.; Szmale, F. S.; Tansey, M. J.; Thornton, J. M. *Heterocycles* **1986**, *24*, 2879–2885; (d) Norton, R. S.; Wells, R. J. *J. Am. Chem. Soc.* **1982**, *104*, 3628–3635.
7. (a) Nilsson, I.; Isaksson, R. *Acta Chem. Scand. B* **1985**, *39*, 531–547; (b) Schuster, H. F.; Coppola, G. M. *J. Heterocycl. Chem.* **1994**, *31*, 1381–1384.

8. Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13–19.
9. Satisfactory analytical data (^{1}H, ^{13}C NMR and ESMS spectra) were obtained for all new compounds. Compound **3**: colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=7.56$ (m, 1H), 7.51 (m, 1H), 7.31 (s, 1H), 7.17 (m, 1H), 7.15 (m, 1H), 6.13 (dd, 1H, $J=10.7$, 17.4 Hz), 5.24 (d, 1H, $J=10.7$ Hz), 5.18 (d, 1H, $J=17.4$ Hz), 1.75 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=143.5$, 134.8, 128.5, 124.2, 121.7, 119.8, 119.3, 113.8 (×2), 89.3, 59.6, 27.8; ESMS: m/z 264/266 $[MH]^+$, daughter ions of m/z 264: 196, 186.
10. (a) Amat, M.; Hadida, S.; Sathyanarayana, S.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 10–11; (b) Amat, M.; Seffar, F.; Bosch, J. *Synthesis* **2001**, 267–275; (c) Belley, M.; Scheigetz, J.; Dubé, P.; Dolman, S. *Synlett* **2001**, 222–225; (d) Kawasaki, I.; Katsuma, H.; Nakayama, Y.; Yamashita, M.; Ohta, S. *Heterocycles* **1998**, *48*, 1887–1901; (e) Vedejs, E.; Barda, D. A. *Org. Lett.* **2000**, *2*, 1033–1035; (f) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757–761; (g) Wenkert, E.; Angell, E. C.; Ferreira, V. F.; Michelotti, E. L.; Piettre, S. R.; Sheu, J.-H.; Swindell, C. S. *J. Org. Chem.* **1986**, *51*, 2343–2351; (h) Gribble, G. W.; Barden, T. C. *J. Org. Chem.* **1985**, *50*, 5900–5902.
11. Compound **1**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=8.19$ (m, 1H), 8.04 (s, 1H), 7.54 (m, 1H), 7.24 (ddd, 1H, $J=7.1$, 6.9, 1.1 Hz), 7.18 (ddd, 1H, $J=8.1$, 7.1, 1.4 Hz), 6.12 (dd, 1H, $J=10.8$, 17.4 Hz), 5.27 (d, 1H, $J=10.8$ Hz), 5.18 (d, 1H, $J=17.4$ Hz), 3.92 (s, 1H), 1.79 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=165.9$, 143.2, 136.1, 132.3, 128.2, 122.1, 121.9, 121.8, 114.7 (×2), 106.5, 60.3, 51.2, 28.1; ESMS: m/z 244 $[MH]^+$, daughter ions of m/z 244: 176, 162, 144.
Compound **2**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=8.20$ (m, 1H), 7.99 (s, 1H), 7.67 (m, 1H), 7.26 (m, 1H), 7.21 (m, 1H), 4.50 (dd, 1H, $J=7.5$, 3.8 Hz), 3.85 (s, 1H), 3.54–3.44 (m, 2H overlapped), 2.61 (bs, 1H exchanged), 2.00 (bs, 1H exchanged) 1.78 (s, 3H), 1.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=166.0$, 135.6, 133.7, 128.2, 122.4, 122.1, 121.9, 114.1, 106.2, 75.0, 62.5, 62.4, 51.2, 24.3, 24.1; ESMS: m/z 278 $[MH]^+$, daughter ions of m/z 278: 260, 246, 176, 144.; $[\alpha]_D=-3.7$ (c 1.0, $CHCl_3$).
12. Paquette, L. A.; Barriault, L.; Pissarnitski, D.; Johnston, J. N. *J. Am. Chem. Soc.* **2000**, *122*, 619–631.
13. The enantiomeric excesses of the diols (*S*)- and (*R*)-**2** were determined by treating the monobenzoate derivatives with (*R*)-MTPA–Cl and evaluating the diastereomeric ratio of the MTPA esters obtained by integration of the characteristic ^{1}H NMR peaks.