Tetrahedron Letters 50 (2009) 3753–3755

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 5-deoxypterocarpens, pterocarpens, and coumestans by intramolecular Heck reaction

Danilo P. Sant'Ana, Vagner D. Pinho, Marta C. L. S. Maior, Paulo R. R. Costa *

Laboratório de Química Bioorgânica (LQB), Núcleo de Pesquisa de Produtos Naturais, Centro de Ciências da Saúde, Bl H, Ilha da Cidade Universitária, Universidade Federal do Rio de Janeiro 21941-590, Brazil

ARTICLE INFO

Article history:
Received 21 October 2008
Revised 19 December 2008
Accepted 6 January 2009
Available online 10 January 2009

ABSTRACT

Two 5-deoxypterocarpens, one pterocarpen, and one coumestan were prepared from deoxychromenes, chromenes, and *ortho*-iodophenols. The key step in the described synthetic approach is an intramolecular Heck reaction leading to the formation of the C-ring present in the structure of these compounds.

1. Introduction

Since the report of Lerner and co-workers[1,2] describing the first nonsteroidal compound with antiestrogen activity (MER25), attention has been focused on the development of new antihormone analogues to control breast, prostate, and uterine cancers. These efforts led to the discovery of Tamoxifen (**1**, Fig. 1), which was used for the treatment of breast cancer and, in some countries, to induce ovulation.[3] Recently, 5-deoxypterocarpen **2** and pterocarpen **3**, along with a series of structurally related tetracyclic compounds, were patented as bioligands of estrogenic receptors, and several potential benefits for the health were claimed for this group of compounds.[4] A number of bioactive pterocarpen have also been isolated from plants.[5] Moreover, some coumestans, such as coumestrol, also have estrogenic action[6] and other interesting pharmacological properties.[7]

Despite the important biological properties shown by these compounds, few approaches are available in the literature to synthesize them.[4,8–10,4,11,12] In this letter, we describe the preparation of 5-desxipterocarpen **4a**,**b**, pterocarpen **5**, and the corresponding coumestan **6** through a new intramolecular Heck reaction.

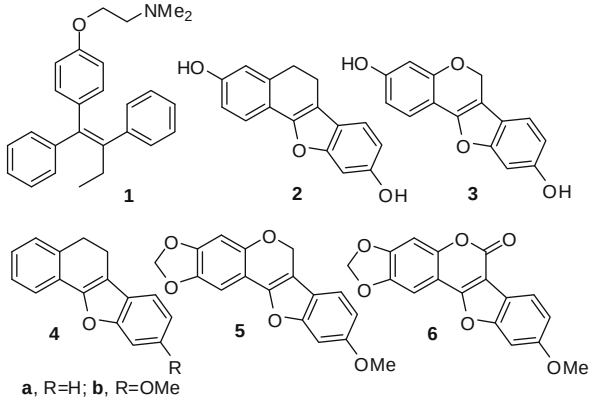
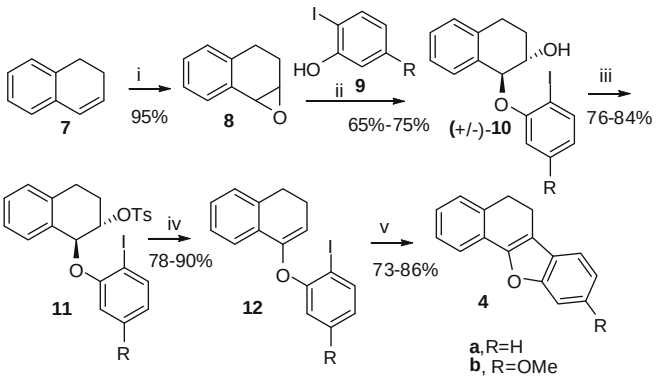


Figure 1. Estrogenic compounds (**1**–**3**) and new derivatives prepared in this work.

2. Results

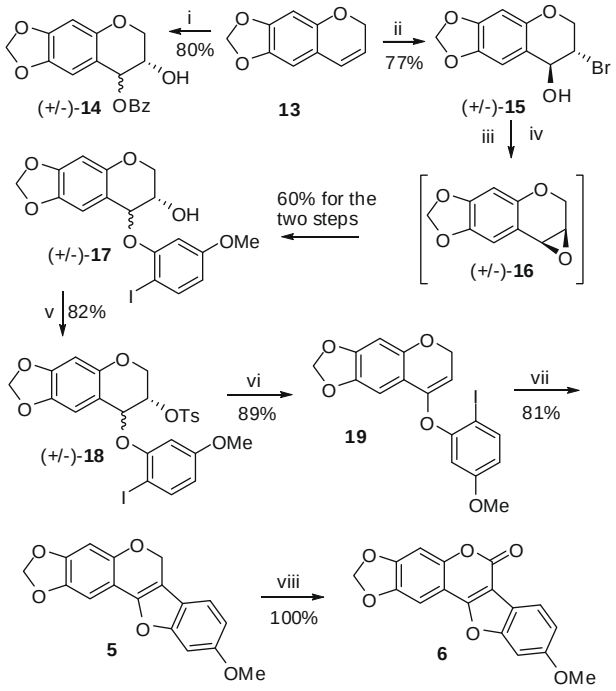
In Scheme 1, the synthesis of **4a** and **4b** is shown. Commercially available 1,2-dihydronaphthalene **7** was allowed to react with *meta*-chloroperbenzoic acid under buffered conditions, leading to epoxide **8**.[13] The epoxide ring was regioselectively opened[14] by reaction with commercially available *ortho*-iodophenol (**9a**) and **9b**, which was easily prepared from resorcinol.[15] The resulting alcohols **10a** and **10b** were tosylated under standard conditions, leading to **11a** and **11b**, respectively. Reaction of these tosylates



Scheme 1. Synthesis of **4a**,**b** through intramolecular Heck reaction in **12a**,**b**. Reagents and conditions: (i) MCPBA, $NaHCO_3$ 0.5 M, CH_2Cl_2, 0 °C to rt, 1.5 h; (ii) **11** (1.5 equiv, NaOH 100 °C, 2 h; (iii) TsCl, pyridine, $CHCl_3$ 1:3, rt, 12 h; (iv) *t*BuOK, THF 0 °C to rt, 1 h; (v) $Pd(AcO)_2$ (5 mol %); TBACl, $NaHCO_3$, DMF, 100 °C, 5–12 h.

* Corresponding author. Tel.: +55 21 256 26791; fax: +55 21 2562 6512.
E-mail address: lqb@nppn.ufrj.br (P.R.R. Costa).

0040-4039/$ - see front matter © 2009 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2009.01.004



Scheme 2. Synthesis of **5** and **6** through intramolecular Heck reaction of **19**. (i) MCPBA, $NaHCO_3$ 0.5 M, CH_2Cl_2, 0 °C to rt, 1.5 h; (ii) NBS, H_2O, DMSO, 0 °C to rt, 15 min; (iii) NaH (2 equiv) THF, rt, 20 min; (iv) **11b**, rt, 12 h; (v) TsCl, pyridine, $CHCl_3$ 1:3, rt, 12 h; (vi) *t*BuOK, THF 0 °C to rt, 1 h; (vii) $Pd(AcO)_2$ (5 mol %) TBACl, $NaHCO_3$, DMF, 100 °C, 2 h; (viii) DDQ, THF, t.a., 2 h.

with *t*BuOK furnished the corresponding key intermediates, olefins **12a** and **12b**. These compounds cyclized to the corresponding 5-desoxipterocarpens **4a** and **4b** in the presence of 5 mol % of $Pd(OAc)_2$.[16] A similar strategy was described by Santosh and co-workers for the synthesis of pterocarpans through radical cyclization promoted by nBu$_3$SnH.[17]

Our next goal was the synthesis of pterocarpen **5** and coumestan **6** (Scheme 2). Chromene **13**, required for this synthesis, was prepared from sesamol, as described in the literature.[18] Under the same conditions used for epoxidation of **7**, **13** led exclusively to benzoate **14**. Alternatively, chromene **13** led to bromohydrin **15** regioselectively by reaction with NBS in DMSO/H_2O.

This compound was transformed, in one pot, to alcohol **17** as a mixture of epimers (3:1) at the benzylic carbon by reacting with sodium hydride in THF in the presence of phenol **9b**.[19] It seems reasonable to accept that epoxide **16** is an intermediate in this transformation.

Alcohol **17** (mixture of epimers) was tosylated leading to **18** (mixture of epimers).

The desired key intermediate, olefin **19**, was formed when **18** reacted with *t*BuOK in THF at rt. Pterocarpen **5** was obtained from **19** through an intramolecular Heck reaction in the presence of 5 mol % of $Pd(OAc)_2$.[16] Finally, coumestan **6** was prepared in quantitative yield by oxidation of **5** with DDQ in THF.

In conclusion, the strategy described herein allowed the preparation of 5-deoxypterocarpens **4a**,**b**, a pterocarpen (**5**), and a coumestan (**6**) in 40%, 31%, 27%, and 27% overall yield, respectively, starting from olefins **9** and **13**. The use of this strategy to prepare new compounds, including naturally occurring pterocarpens, pterocarpans, and coumestans is under investigation in our laboratory.

3. General procedure for intramolecular Heck reactions

A mixture of $Pd(AcO)_2$ (5 mol %), $NaHCO_3$ (2.5 equiv), TBACl (1 equiv), olefins **12a**, **12b** or **19** in DMF was heated to 100 °C under a nitrogen atmosphere until starting material disappeared (**12a**: 12h; **12b**: 5h; and **19**: 2h). The cooled solution was partitioned between dichloromethane and water. The organic layer was washed with water (3 times), dried, filtered, and evaporated. The material obtained was purified by silica gel chromatography, except for **5**, which was purified by basic alumina.

4. 5-Deoxypterocarpen 4a

^{1}H NMR ($CDCl_3$), δ (ppm): 7.64 (1H, d, J = 7.4 Hz); 7.48 (2H, m); 7.28–7.16 (5H, m); 3.07 (2H, t, J = 7.8 Hz); 2.92 (2H, t, J = 7.6)—^{13}C NMR ($CDCl_3$), δ (ppm): 155.2(C); 151.6(C); 135.8(C); 128.3(C); 128.9(CH), 127.6(C); 127.5(CH); 126.7(CH); 123.9(CH); 122.6(CH); 120.4(CH); 119.0(CH); 113.9(C); 111.3(CH); 28.56(CH_2); 19.20(CH_2)—MS: m/z = 220.

5. 9-Methox-5-deoxypterocarpen 4b

^{1}H NMR ($CDCl_3$), δ (ppm): 7.59 (1H, d, $3J$ = 7.4 Hz); 7.35 (1H, d, J = 8.6 Hz); 7.29–7.14 (3H, m); 7.07 (1H, d, $4J$ = 2.4 Hz); 6.88 (1H, dd, ^3J = 8.6 Hz, J = 2.4 Hz); 3.87 (3H, s); 3.08 (2H, t, J = 8.0 Hz); 2.92 (2H, t, J = 7.8)—^{13}C NMR ($CDCl_3$), δ (ppm): 157.9(C); 156.2(C); 150.9(C); 135.2(C); 127.9(CH), 127.8(C); 126.9(CH); 126.7(CH); 121.8(C); 119.2(CH); 119.8(CH); 114.1(C); 111.4(CH); 96.35(CH); 55.69(CH3); 26.6(CH_2); 19.34(CH_2)—MS: m/z = 250.

6. 1,3-Dioxolo-9-methoxypterocarpen 5

^{1}H NMR ($CDCl_3$), δ (ppm): 7.21 (1H, d, J = 8.6 Hz); 7.05 (1H, d, J = 2.0 Hz); 6.97 (1H, s); 6.87 (1H, dd, J = 8.6 Hz, J = 2.0 Hz); 6.51 (1H, s); 5.93 (2H, s); 5.48 (2H, s); 3.86 (3H)—^{13}C NMR ($CDCl_3$), δ (ppm): 157.7(C); 156.3(C); 149.2(C); 147.9(C), 147.6(C); 142.2(C); 119.2(C); 118.6(CH); 111.8(CH); 109.6(C); 106.0(C); 101.3(CH_2); 100.3(CH); 99.3(CH); 99,6(CH); 66.4(CH_2); 55.8(CH_3)—MS: m/z = 296.

7. 1,3-Dioxolo-9-methoxycoumestan 6

^{1}H NMR ($CDCl_3$), δ (ppm): 8.03 (1H, d, J = 2.2 Hz); 7.32 (1H, s); 7.21 (1H, d, $4J$ = 0.6); 7.12 (1H, dd, J = 2.2 Hz, J = 0.6 Hz); 7.03 (1H,s); 6.15 (2H,s); 3.89 (3H)—^{13}C NMR ($CDCl_3$), δ (ppm): 159.3(C); 156.4(C); 151.1(C); 150.4(C); 145.2(C), 132.5(C); 121.7(CH); 120.2(C); 116.6(C); 113.3(CH); 106.3(C); 102.4(CH_2); 100.0(C); 99.2(CH); 99.1(CH); 99.6(CH); 55.9(CH_3)—MS: m/z = 310.

Acknowledgments

We thank CAPES, FAPERJ, FINEP, and CNPq for financial support and CNPq for fellowships to the authors. We also thank Professor Alcides J. M. da Silva for the sample of chromene **13**.

References and notes

1. Lerner, L. J.; Holthaus, F. J.; Thompson, C. R. *Endocrinology* **1958**, *63*, 295–318.
2. Jordan, V. C. *Pharmacol. Rev.* **1984**, *36*, 245–276.
3. Shelly, W.; Draper, M. W.; Krishnan, V., et al *Obstet. Gynecol. Surv.* **2008**, *63*, 163–181.
4. Miller, C.P.; Collini, M.D.; Morris, R.L.; Singhaus, R.R., Jr. US Patent 2006/0004087 A1.
5. Veitch, N. C. *Nat. Prod. Rep.* **2007**, *24*, 417–464.
6. Bickoff, E. M.; Livingston, A. L.; Booth, A. N. *Arch. Biochem. Biophys.* **1960**, *88*, 262–266.
7. Kaushik-Basu, N.; Bopda-Waffo, A.; Talele, T. T.; Basu, A.; Costa, P. R. R.; da Silva, A. J. M.; Sarafianos, S. G.; Nöel, F. *Nucleic Acids Res.* **2008**, *36*, 1482–1496; Pôças, E. S. C.; Touza, N. A.; Pimenta, P. H. C.; Leitão, F. B.; Netto, C. D.; da Silva, A. J. M.; Costa, P. R. R.; Noël, F. *Bioorg. Med. Chem.* **2008**, *16*, 8801–8805; da Silva, A. J. M.; Coelho, A. L.; Simas, A. B. C.; Moraes, R. A. M.; Pinheiro, D. A.; Fernandes, F. F. A.; Arruda, E. Z.; Costa, P. R. R.; Melo, P. A. *Bioorg. Med. Chem.* **2004**, *14*, 431–435; da Silva, A. J. M.; Melo, P. A.; Silva, N. M. V.; Brito, F. V.; Buarque, C. D.; de Souza, D.

V.; Rodrigues, V. P.; Poças, E. F. C.; Nöel, F.; Albuquerque, E. X.; Costa, P. R. R. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 283–286.
8. Wanzlick, H.; Heidepri, H.; Gritzky, R. *Chem. Ber.* **1963**, *96*, 305.
9. Laschober, R.; Kappe, T. *Sinthesis-Stuttgar* **1990**, 387–388.
10. Antus, S.; Gottsegen, A.; Kolonits, P., et al *J. Chem. Soc., Perkin Trans. 1* **1982**, 1389–1394.
11. Furstner, A.; Heilmann, E. K.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 4760–4763.
12. Khupse, R. S.; Erhardt, P. W. *J. Nat. Prod.* **2008**, *71*, 275–277.
13. Anderson, W. K.; Veysoglu, T. *J. Org. Chem.* **1973**, *38*, 2267–2268.
14. Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737–799.
15. Das, B.; Krishnaiah, M.; Venkateswarlu, K., et al *Tetrahedron Lett.* **2007**, *48*, 81–83.
16. Ma, D.; Cai, Q.; Xie, X. *Synlett* **2005**, 1767–1770.
17. Gopalsamy, A.; Balasubramanian, K. K. *J. Chem. Soc., Chem. Commun.* **1988**, 28–29; Santhosh, K. C.; Gopalsamy, A.; Balasubramanian, K. K. *Eur. J. Org. Chem.* **2001**, 3461–3466.
18. Coelho, A. L.; Vasconcellos, M. L. A. A.; Rabi, J. A.; Costa, P. R. R. *Synthesis-Stuttgart* **1992**, *10*, 914.
19. Camps, F.; Coll, J.; Messeguer, A., et al *Tetrahedron Lett.* **1980**, *21*, 2361–2364.