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A Simple, Efficient Access to Functionalized Pyrrolobenzazepines Related to the ABC Core of Cephalotaxine

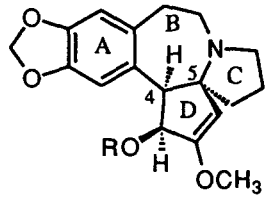
Eduardo R. de Oliveira[1], Françoise Dumas, Jean d'Angelo*

Unité de Chimie Organique Associé au CNRS, Centre d'Études Pharmaceutiques, Université Paris-Sud,

5, rue J.-B. Clément 92296, Châtenay-Malabry, France

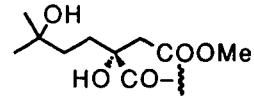
Abstract: Tetracyclic nitrile **19a** and ester **19b**, exhibiting the ABC core of cephalotaxine **1a**, were prepared through KH-induced cyclization of thioimides **14a** and **14b**, respectively. This new ring-closure methodology proved to be particularly efficient: thus nitrile **19a** was obtained in only 7 steps with a 17 % overall yield from commercially available, inexpensive safrole **2**. © 1997 Elsevier Science Ltd.

Cephalotaxine **1a**, the major alkaloid encountered in several *Cephalotaxus* species, has become an interesting synthetic target, because of the potent antileukemic activity found for some of its derivative esters (harringtonine **1b**, homoharringtonine **1c**).[2]

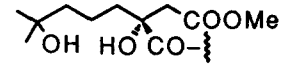


1a : R = H

1b : R =

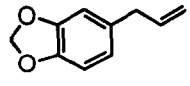


1c : R =



Several strategies have been evolved for the synthesis of cephalotaxine **1a**.[2] In this paper, we report on a simple, efficient methodology for the elaboration of the pyrrolobenzazepine-type core of **1a**, based on the ring B closure of AC subunits, by creating the C4-C5 linkage.

Preparation of the AC subunits. Eight [AC]-type compounds (**8a, 8b, 9, 10, 14a, 14b, 15** and **16**) were prepared and subjected to various cyclization conditions. The common intermediate in the synthesis of these precursors was bromide **4**[3], prepared as follows. Ozonolyzis[4] of inexpensive safrole **2** (*i*: O_3, CH_2Cl_2 - EtOH, -78 °C; *ii*: $NaBH_4$) furnished with a 78 % yield alcohol **3**, which was then converted into bromide **4** (Ph_3P, Br_2, CH_2Cl_2, 30 min at 20 °C, 83 % yield).



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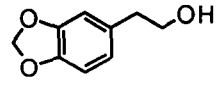

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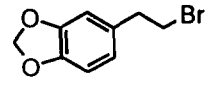
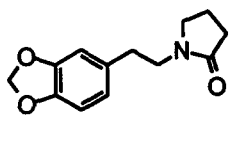


4

In the "lactam series" (AC subunits **8a, 8b, 9,** and **10**), the starting material was lactam **5**, prepared from **4** (pyrrolidone, NaH, benzene, 18 h at 20 °C, 58 % yield). Chloromethylation[5] of **5** led to **6 a**

FAX: 33 1 46 83 57 52 E-mail: jean.dangelo@cep.u-psud.fr

(paraformaldehyde, 12 *N* HCl, AcOH, $CaCl_2$, 1,2-dichlorethane, 16 h at 20 °C, 43 %), which was sequentially converted into nitrile **6b** (NaCN, acetone, 6 h at reflux, 72 %) and ester **6c** (conc. H_2SO_4 in MeOH, 22 h at reflux, 70 %). Condensation of Lawesson's reagent[6] with **6b** and **6c** (2 h at reflux in toluene) next furnished the corresponding thiolactams **7a** and **7b**[7] (94 % and 87 % yield, respectively).



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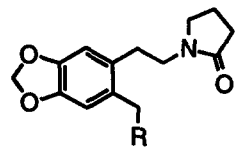
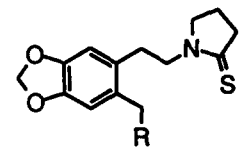


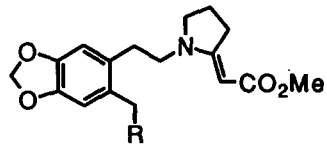
6, **a**: R = Cl,
b: R = CN,
c: R = CO_2Me



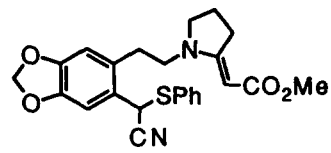
7, **a**: R = CN,
b: R = CO_2Me

Thiolactam **7a** was then tranformed into unsaturated ester **8a**[8], under the Eschenmoser-Rapoport reaction conditions[9] (*i*: $BrCH_2COOMe$, MeCN, 1 h at 20 °C; *ii*: Ph_3P in CH_2Cl_2, 2 min at 20 °C; *iii*: Et_3N, 1 h at 20 °C, 76 %). Similarly, **7b** was converted into diester **8b** with a 87 % yield.

Thioderivative **9** was synthesized with a 47 % yield from **8b** (*i*: KH, THF, 15 min at 20 °C; *ii*: Ph_2S_2, 15 min at 20 °C), and triester **10** with a 79 % yield from **7b** and bromomalonic acid methyl ester, in complete analogy with conversion **7a**→**8a**.



8, **a**: R = CN
b: R = CO_2Me



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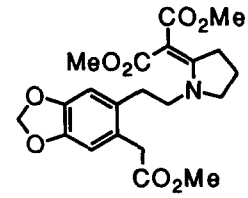
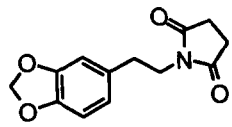


10

In the "imide series", the common imide intermediate **11** was prepared by condensing bromide **4** with succinimide (NaH, DMF-THF, 17 h at 40 °C, 80 %). Bromomethylation[10] of **11** (paraformaldehyde, HBr in AcOH, 2 h at 40 °C) gave **12** which was then converted into nitrile **13a** (NaCN, cat. NaI, acetone, 20 h at 20 °C, 70 % yield from **11**). Ester **13b** was prepared by methanolysis of **13a** (conc. H_2SO_4 in MeOH, 24 h at reflux, 70 %).



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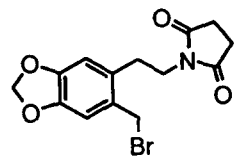

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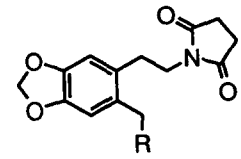
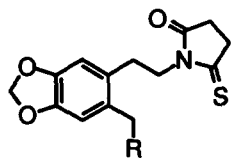
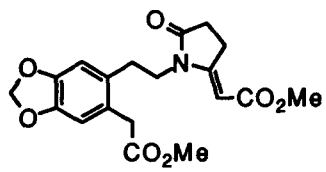


13, **a**: R = CN
b: R = CO_2Me

Compounds **14a**[11], **14b**[12] and **16** were prepared from corresponding imides **13a**, **13b** and **15**, as described for the related previous transformations, in 65 %, 72 % and 47 % yield, respectively. Diester **15** was obtained by condensing thioimide **14b** with phosphorane Ph_3P=CH-COOMe, under high pressure conditions (CH_2Cl_2, 14 kbar, 3 days at 45 °C, 84 %).



14, **a**: R = CN,
b: R = CO_2Me



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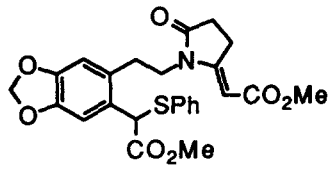
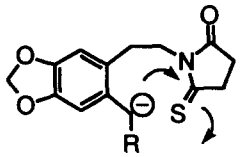
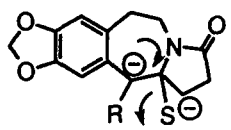


16

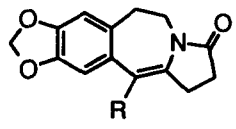
Attempted cyclizations of the AC subunits. All attempts at base-induced intramolecular Michael-type cyclization of substrates **8a**, **8b**, **10** and **15**, under a great variety of conditions, invariably failed: complex mixtures of unidentified products were formed, along with substantial amounts of starting materials. Disappointing results were also obtained in the radical-promoted cyclization of thio-derivatives **9** and **16** (9 h-addition of *n*-BuSnH, AIBN, benzene at reflux): the only isolated compounds were the "desulfurized" materials **8b** and **15**, respectively (40-50 % yield). In contrast, treatment of thioimides **14a** and **14b** with KH (10 eq, THF, 24 h at 20 °C) gave the corresponding tetracyclic derivatives **19a**[13] and **19b**[14] as single compounds, with 75 % and 22 % yield, respectively. This cyclization probably involves the attack of the benzylic anion of **14a,b** to the thioimide function (**17**), followed by displacement of sulfide anion (**18**).



17, **a**: R = CN
b: R = CO_2Me



18, **a**: R = CN
b: R = CO_2Me



19, **a**: R = CN
b: R = CO_2Me

This new cyclization reaction constitutes a remarkably simple and efficient access to the ABC core of cephalotaxine **1a**: nitrile **19a** was thus prepared in only 7 steps, with a 17 % overall yield, from safrole **2**. In comparison, according to the Danishefsky's procedure,[15] the ester analog **19b** was obtained in 16 steps, with a 1.6 % overall yield, from piperonal. Further extensions of the present ring-closure methodology are currently under investigation in our laboratory.

References and Notes

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3. **4**: colourless oil ; b. p. (0.5 Torr) 135-137 °C; ^{1}H NMR (200 MHz. $CDCl_3$) δ ppm: 3.06 (t, J = 7.4 Hz, 2H); 3.51 (t, J = 7.4 Hz, 2H); 5.93 (s, 2H); 6.7 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 33.1 (CH_2); 39.0 (CH_2); 100.9 (CH_2); 108.2 (CH); 108.9 (CH); 121.6 (CH); 132.5 (C); 146.4 (C); 147.6 (C).
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7. **7b**: oil; IR (neat) : 1737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.97 (t, J = 7.6 Hz, 2H); 2.88 (t, J = 7.8 Hz, 2H); 2.96 (t, J = 7.6 Hz, 2H); 3.56 (t, J = 7.6 Hz, 2H); 3.63 (s, 5H); 3.78 (t, J = 7.8 Hz, 2H); 5.87 (s, 2H); 6.65 (s, 1H); 6.69 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 19.7 (CH_2); 29.0 (CH_2); 38.1 (CH_2); 44.8 (CH_2); 49.1 (CH_2); 52.1 (CH_3); 55.7 (CH_2); 101.1 (CH_2); 109.8 (CH); 110.6 (CH); 125.7 (C); 130.1 (C); 146.5 (C); 147.0 (C); 172.1 (C); 201.0 (C).
8. **8a**: oil; IR (neat): 2242, 1684, 1600 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 1.88 (m, 2H); 2.79 (t, J = 7.3 Hz, 2H); 3.17 (m, 4H); 3.40 (t, J = 7.3 Hz, 2H); 3.60 (s, 2H); 3.64 (s, 3H); 4.58 (s, 1H); 5.97 (s, 2H); 6.66 (s, 1H); 6.83 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 21.1 (CH_2); 21.2 (CH_2); 28.6 (CH_2); 32.5 (CH_2); 47.1 (CH_2); 50.0 (CH_3); 53.4 (CH_2); 77.6 (CH); 101.5 (CH_2); 109.4 (CH); 109.9 (CH); 117.8 (C); 121.1 (C); 130.3 (C); 146.9 (C); 148.0 (C); 164.5 (C); 169.5 (C).
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10. van der Made, A. W.; van der Made, R. H. *J. Org. Chem.* **1993**, *58*, 1262-1263.
11. **14a**: white solid; m. p. 119-121 °C; IR: 2239, 1754 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 2,73 (m, 2H); 2,81 (m, 2H); 3.15 (m, 2H); 3.81 (s, 2H); 3.96 (m, 2H); 5.96 (s, 2H); 6.75 (s, 1H); 6.87 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 21.1 (CH_2); 28.7 (CH_2); 29.5 (CH_2); 38.6 (CH_2); 42.3 (CH_2); 101.5 (CH_2); 109.4 (CH); 110.4 (CH); 118.0 (C); 121.8 (C); 128.9 (C); 147.2 (C); 147.8 (C); 178.4 (C); 210.5 (C).
12. **14b**: white solid; m. p. 104-105 °C; IR: 1748, 1633 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.71 (m, 2H); 2.83 (m, 2H); 3.14 (m, 2H); 3.69 (s, 3H); 3.70 (s, 2H); 3.99 (m, 2H); 5.92 (s, 2H); 6.70 (s, 1H); 6.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 28.7 (CH_2); 29.6 (CH_2); 37.9 (CH_2); 38.6 (CH_2); 42.8 (CH_2); 52.0 (CH_3); 101.0 (CH_2); 110.0 (CH); 110.5 (CH); 125.9 (C); 129.5 (C); 146.6 (C); 146.9 (C); 172.1 (C); 178.4 (C); 210.5 (C).
13. **19a**: pale yellow solid; m. p. 199-201 °C; IR: 2202, 1741, 1625, 1601 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.69 (t, J = 7.6 Hz, 2H); 2.89 (br m, 2H); 3.18 (t, J = 7.6 Hz, 2H); 3.6-4.4 (br m, 2H); 5.97 (s, 2H); 6.59 (s, 1H); 7.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 26.5 (CH_2); 27. 8 (CH_2); 34.5 (CH_2); 44.5 (CH_2); 88.2 (C); 101.5 (CH_2); 108.0 (CH); 109.6 (CH); 119.1 (C); 124.0 (C); 132.5 (C); 146.8 (C); 147.0 (C); 152.9 (C); 175.6 (C).
14. **19b**: white solid; m. p. 145-147 °C (lit.[15]: m. p. 147-148 °C); IR: 1721, 1630, 1604 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.55 (t, J = 7.5 Hz, 2H); 2.88 (t, J = 4.7 Hz, 2H); 3.11 (br t, J = 7.5 Hz, 2H); 3.65-3.85 (br m, 2H); 3.78 (s, 3H); 5.93 (s, 2H); 6.58 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 25.4 (CH_2); 28.1 (CH_2); 34.2 (CH_2); 46.0 (CH_2); 52.0 (CH_3); 101.2 (CH_2); 108.0 (C); 108.7 (CH); 109.0 (CH); 126.3 (C); 134.1 (C); 145.4 (C); 146.3 (C); 146.4 (C); 169.7 (C); 176.2 (C).
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