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Partial synthesis of camptothecin analogs. Part 3: Easy approach to a quinoline–lactone system†

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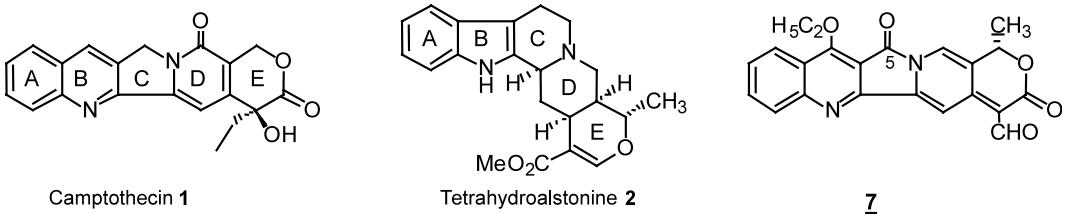
Abstract—Quinoline-lactone **7** related to anticancer alkaloid camptothecin has been synthesized from tetrahydroalstonine (**2**) in four steps through an original rearrangement.

In previous papers[1,2] we described the facile biomimetic transformation of the indole moiety of tetrahydroalstonine (**2**) into the quinoline system of the anticancer alkaloid camptothecin (**1**)[3] (Fig. 1).

However, in the way of preparing camptothecin analogs we were faced with two kinds of difficulties, i.e. formation of lactam function at ring D and of lactone at ring E. It appeared that the C-5 benzylic position inexorably led to an unwanted lactam function at ring C what is not really a disadvantage when considering the interest of unknown analogs of the natural product. More awkward was the transformation of the dihydropyran ester of tetrahydroalstonine (**2**) into the lactone ring which is essential for biological activities. Indeed it required decarboxylation of the acid form **2** into a lactol followed by a capricious oxidation. In this reaction the ester function is lost whereas it is the exact level of oxidation to form a lactone after opening the ring E of **2** into a α-formyl ester and a secondary alcohol. In this paper we report that this more logical strategy, impossible in the indole series of tetrahydroalstonine **2**, proved to be efficient in the camptothecin quinoline series.

When quinoline **3**[1] was treated with *meta*-chloroperbenzoic acid (*m*-CPBA), the corresponding N(b) oxide was obtained. Surprisingly if a borane complex was formed prior to addition of *m*-CPBA (Scheme 1), pyrrole **4**[4] was quantitatively obtained. The latter afforded acylalkoxydihydropyridines **6** when oxidized with DDQ in dioxan. The transient formation of an acylpyridinium salt **5** is a reasonable explanation for the formation of these over-oxidized compounds isolated after trapping with CH_3OH or C_2H_5OH. Interestingly, compound **6a**[5] could be isolated in 55% yield in a one-pot procedure from **3** using $TiCl_4$ and then DDQ. In this case the intermediary formation of pyrrole **4** is probably excluded. Coordination of N(b) with $TiCl_4$ enhances H-21α and H-3 acidities allowing facile oxidation and aromatization.

When placed in basic medium, compound **6a** rearranged into a strongly orange solid whose structure



Camptothecin **1** Tetrahydroalstonine **2** **7**

Figure 1.

Keywords: camptothecin; tetrahydroalstonine; rearrangement; oxidation.

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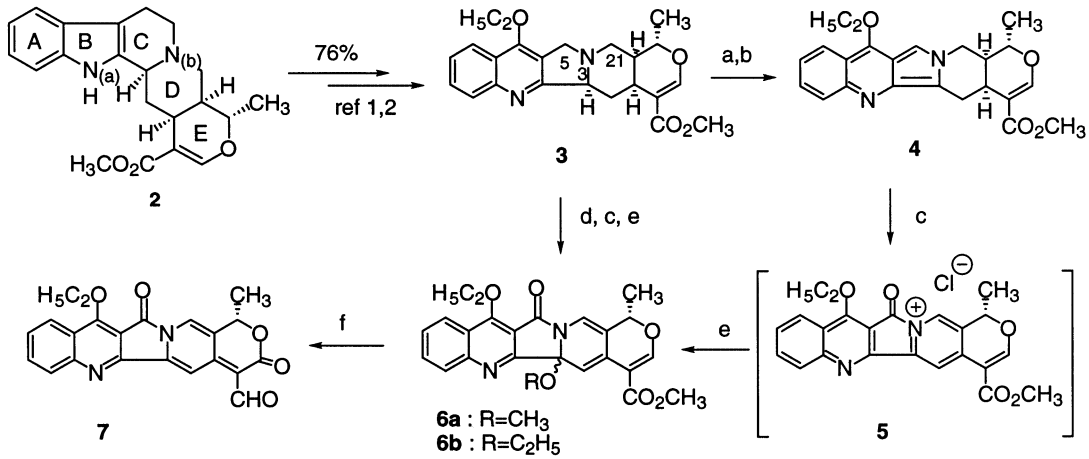
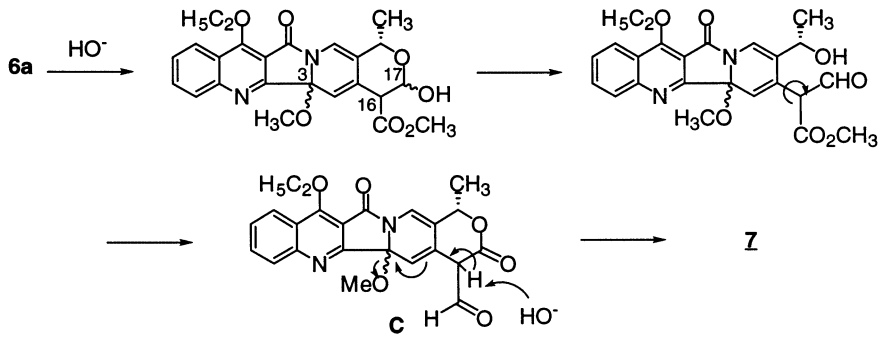


Scheme 1. *Reagents and conditions*: (a) $BF_3{\cdot}Et_2O$, THF, −78°C (100%); (b) *m*-CPBA, THF/CH_2Cl_2, −78°C (100%); (c) DDQ, dioxane, 60°C; (d) $TiCl_4$, THF/CH_2Cl_2, −78°C; (e) ROH; (f) LiOH, THF/H_2O (100%).



Scheme 2.

revealed to be lactam **7**.[6] This postulated rearrangement we were looking for, occurred according to the possible mechanism depicted in Scheme 2. The driving force of the reaction is probably the π electron delocalisation on the whole structure with the concomitant alcoholate elimination.

In conclusion we achieved a rapid and worthy preparation of lactone **7** from tetrahydroalstonine (**2**) (42% overall yield in four steps) according to original reactions. This key compound represents an important breakthrough for the synthesis of new analogs of camptothecin.

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4. Compound **4**: red amorphous solid; ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm), *J* (Hz): 8.38 (dd, $^3J=7.9$, $^4J=0.6$, 1H), 8.03 (d, $J=8.3$, 1H), 7.76 (ddd, $^3J^3J'=7.0$, $^4J=1.3$, 1H), 7.63 (s, 1H), 7.53 (dd, $^3J=7.7$, $^3J'=7.3$, 1H), 6.30 (d, $^3J=1.7$, 1H), 5.04 (qd, $^2J=7.0$; $^3J=7.02$, 1H), 4.49 (d, $^2J=13.8$, 1H), 3.84 (m, 2H), 3.70 (s, 3H), 3.05 (m, 1H), 2.77 (m, 1H), 2.21 (m, 1H), 1.68 (t, $^3J=6.6$, 3H), 1.42 (d, $^3J=6.0$, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm): 167.4; 166.9; 154.8; 141.2; 135.3; 133.0; 126.4; 124.7; 122.5; 118.3; 116.5; 112.8; 109.8; 109.4; 107.0; 71.4; 71.0; 51.6; 47.6; 36.4; 26.9; 18.7; 14.9; MS (C.I.): $[MH]^{+\bullet}=393$ (100%); $[MH-C_2H_4]^{+\bullet}=365$ (95%).
5. Compound **6a**: yellow amorphous solid; ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm), *J* (Hz): 9.08 (s, 1H), 8.26 (s, 1H), 8.20 (d, $^3J=8.4$, 1H), 8.14 (d, $^3J=8.3$, 1H), 7.85 (s, 1H), 7.75 (ddd, $^3J^3J'=7.0$, $^4J=1.3$, 1H), 7.58 (ddd, $^3J^3J'=7.0$, $^4J=1.1$, 1H), 5.48 (q, $^3J=6.5$, 1H), 4.38 (m, 4H), 3.90 (s, 3H), 1.68 (d, $^3J=6.5$, 3H), 1.53 (t, $^3J=7.0$, 1H), 1.28 (t, $^3J=7.1$, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm): 167.0;

165.3; 161.7; 159.7; 157.5; 156.6; 149.2; 143.1; 135.2; 130.7; 130.1; 127.1; 125.7; 123.0; 122.5; 116.7; 106.7; 73.8; 72.3; 52.4; 51.6; 20.5; 15.8; IR ($\bar{\nu}$ cm^{-1}): 1718, 1599, 1561, 1377, 1119; MS (CI): $[MH]^{+\bullet}=449$.

6. Compound **7**: orange amorphous solid; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm), J (Hz): 10.13 (s, 1H), 9.06 (s, 1H), 8.32 (dd, $^3J=8.3$; $^4J=0.8$, 1H), 8.03 (d, $^3J=8.0$, 1H), 7.81 (s+ddd, $^3J^3J'=8.4$; $^4J=1.3$, 1H), 7.60 (ddd, $^3J^3J'=8.1$, $^4J=1.0$, 1H), 5.27 (qd, $^3J=6.5$; $^3J=1.1$, 1H), 5.01 (q, $^3J=7.0$, 2H), 1.69 (d, $^3J=6.5$, 3H), 1.54 (t, $^3J=7.0$, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 190.0; 166.9; 163.9; 159.7; 153.3; 150.9; 148.6; 141.4; 134.0; 129.8; 128.5; 125.1; 123.4; 122.8; 122.6; 105.7; 104.6; 101.5; 73.3; 71.7; 19.5; 15.4; IR ($\bar{\nu}$ cm^{-1}): 1752, 1696, 1656, 1628, 1572, 1378; MS (CI): $[MH]^{+\bullet}=389$.