Concise synthesis of 22-hydroxyacuminatine, cytotoxic camptothecinoid from *Camptotheca acuminata*, by pyridone benzannulation†

Matej Babjak, Alice Kanazawa,* Regan J. Anderson and Andrew E. Greene

Received 14th November 2005, Accepted 29th November 2005
First published as an Advance Article on the web 14th December 2005
DOI: 10.1039/b516154a

A short, efficient synthesis of 22-hydroxyacuminatine, starting from a readily accessible hydroxy pyridone, is presented; key steps include a Heck coupling with methyl pentadienoate, a flash vacuum pyrolytic cyclization, and a Friedländer condensation.

Camptotheca acuminata contains several closely related cytotoxic lactone alkaloids,[1,2] the best known of which is camptothecin (**1**), isolated by Wall and coworkers in 1966 (Fig. 1).[2] In 1989, Lin and Cordell reported the isolation from this same Chinese tree and the structure elucidation of two new non-lactonic alkaloids, 19-hydroxymappicine (**2**) and 22-hydroxyacuminatine (**3**).[3] The latter camptothecinoid displayed significant cytotoxic activity in the KB and P388 *in vitro* test systems, with ED_{50} values of 0.61 and 1.32 μg mL^{-1}, respectively, and today is still the sole natural product to possess the benz[6,7]indolizino[1,2-*b*]quinolin-11(13*H*)one ring system. These factors and its exceptionally low isolation yield (6 mg from 100 kg of powdered seeds, 0.000006%) combine to make 22-hydroxyacuminatine a particularly interesting synthetic target.[4]

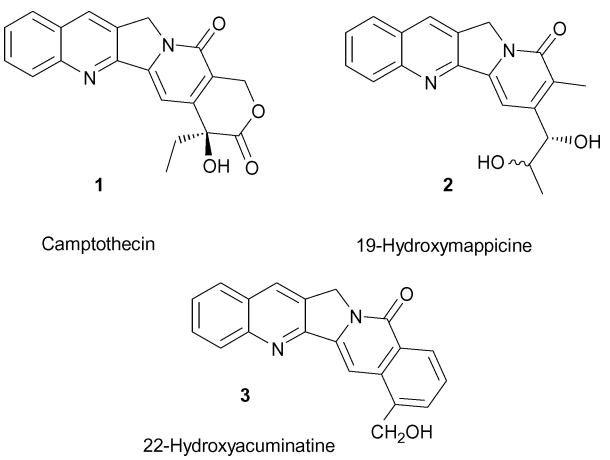
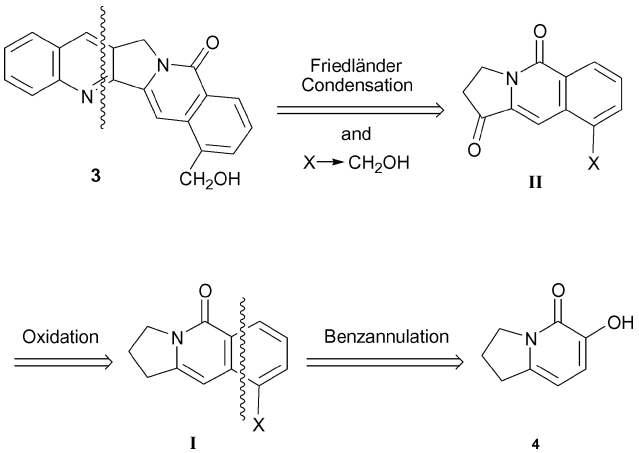


Fig. 1 Camptothecinoids from *Camptotheca acuminata.*

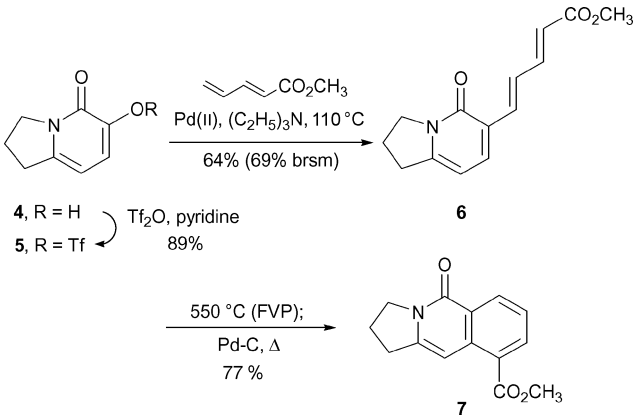
We envisioned its preparation as outlined retrosynthetically in Scheme 1.[5] It seemed likely that the natural product could be accessed from keto pyridone **II** (X = latent CH_2OH) by a Friedländer condensation, an excellent reaction for late-stage analog preparation.[6] Keto pyridone **II** was viewed as arising from



Scheme 1

benzylic-type oxidation of pyridone **I**, which we hoped to form through benzannulation of hydroxy pyridone **4**. Hydroxy pyridone **4** had earlier been prepared by Padwa and coworkers[7] through a clever application of isomünchnone chemistry.[7–10]

Hydroxy pyridone **4** was readily synthesized from 2-pyrrolidinone, as described,[7] and then converted into its triflate derivative **5**[9] (89% yield, Scheme 2). Because of successful Heck reactions that had previously been performed with closely related compounds and methyl acrylate,[7,11] the palladium-mediated coupling of triflate **5** and methyl 2,4-pentadienoate was examined as a possible first step toward benzannulation.[12] After considerable trial and error, conditions were found that provided a 64% yield (69% brsm) of **6**, containing a few percent of the *Z*,*E* isomer. DMF proved to be superior to THF and dichloromethane[13] as solvent in this reaction and bis(triphenylphosphine)palladium(II) dichloride



Scheme 2

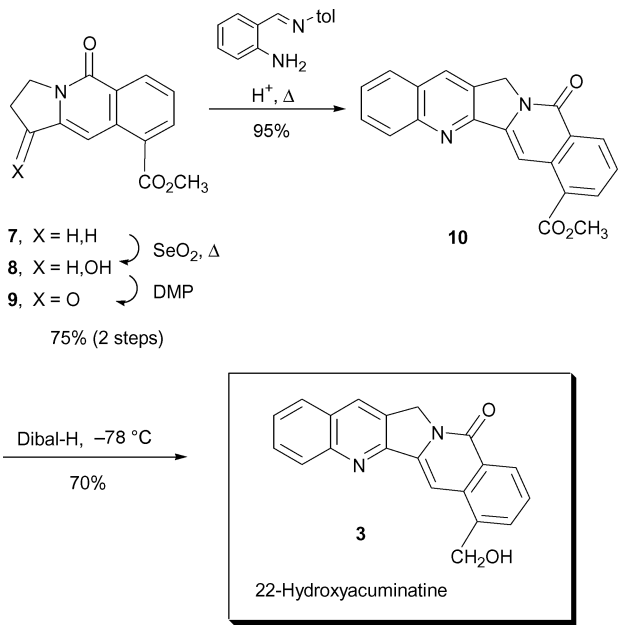
Université Joseph Fourier de Grenoble, Chimie Recherche (LEDSS), 38041, Grenoble, France. E-mail: Alice.Kanazawa@ujf-grenoble.fr; Fax: 33 4 76514494; Tel: 33 4 76514686

† Electronic supplementary information (ESI) available: Complete characterization data for all new compounds. See DOI: 10.1039/b516154a

was found more effective than several other palladium catalysts tested.

Ring closure[14] of **6** was first attempted photochemically (high-pressure mercury lamp, quartz, Corex, or Pyrex filter), but at best only poor yields of cyclized products were obtained. In contrast, under flash vacuum pyrolysis conditions (550 °C, 0.02 torr) cyclization proceeded readily to provide a 3 : 1 mixture of cyclohexadiene isomers and a small amount of the corresponding dehydro derivative **7**. The cyclohexadiene isomers on standing slowly underwent dehydrogenation to yield **7**; however, the crude pyrolysis mixture was more conveniently aromatized by heating for 8 h in toluene in the presence of palladium on carbon,[15] which gave the benzannulated product **7** in 77% yield for the 2 steps.‡ This efficient transformation represents a rare example of pyridone benzannulation.[16]

Benzylic-type oxidation of pyridone **7** was next examined in preparation for the Friedländer condensation (Scheme 3). While IBX,[17] $CrCO_6$–*tert*-C_4H_9OOH,[18] $Rh_2(cap)_4$–*tert*-C_4H_9OOH,[19] and NaHMDS–O_2–$P(OC_2H_5)_3$,[20] failed to yield satisfactory results, SeO_2 in refluxing dioxane[20] smoothly generated the expected alcohol **8**, together with a small amount of the corresponding ketone. The oxidation was completed by treatment of the mixture with the Dess–Martin periodinane (DMP) to afford keto pyridone **9** in 75% overall yield.



Scheme 3

The Friedländer condensation of keto pyridone **9** was next achieved in high yield with an *o*-aminobenzaldehyde surrogate[20] to give ester **10**, which on Dibal-H reduction[21] in dichloromethane produced 22-hydroxyacuminatine. The identity of the synthetic material was confirmed by comparison of its spectroscopic data with the literature values for the natural product.§

In summary, 22-hydroxyacuminatine has been synthesized from readily available hydroxy pyridone **4** through a notably brief and efficient approach (8 steps and 22% overall yield) and in sufficient quantity for more complete biological testing. The flexibility inherent in the approach should permit the preparation of a variety of new analogs for SAR studies.

Acknowledgements

We thank Professor P. Dumy for his interest in our work. Financial support from the Université Joseph Fourier and the CNRS (UMR 5616, FR 2607) is gratefully acknowledged.

Notes and references

‡ Experimental procedure for FVP cyclization–dehydrogenation: A 100-cm^3 flask containing 283 mg (1.16 mmol) of diene **6** was attached to a horizontal pyrolysis column (2 × 55 cm, filled with pyrolysis tubes (1.0 × 0.8 cm) and preheated to 550 °C (Barnstead Thermolyne 21100 oven)), which in turn was connected to a liquid nitrogen-cooled trap. The system was evacuated to 2×10^{-2} torr and the flask was heated, first to 150 °C and then slowly to 200 °C (Büchi Kugelrohr oven), to effect sublimation of the starting material onto the pyrolysis column. Following completion of the sublimation (*ca.* 1 h), the apparatus was allowed to cool to room temperature, the vacuum was broken, and the crude product was isolated with CH_2Cl_2 to give 244 mg of dark brown, viscous oil. This material was dissolved in 10 cm^3 of toluene, 89 mg of 10% Pd–C was added, and the resulting suspension was heated at 160 °C in sealed tube for 8 h. The cooled mixture was then filtered and the filtrate concentrated under reduced pressure to furnish the pure (>95%) benzannulated product **7** as a pale yellow solid (216 mg, 77%). Mp 151–152 °C (ethyl acetate–ether; pale yellow crystals); R_f 0.60 (ethyl acetate); IR (Nujol) 1718, 1652, 1625, 1590, 1429, 1399, 1377 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.22 (tt, J = 7.2, 7.2 Hz, 2 H), 3.15 (t, J = 7.2 Hz, 2 H), 3.95 (s, 3 H), 4.19 (t, J = 7.2 Hz, 2 H), 7.42 (t, J = 7.9 Hz, 1 H), 7.60 (s, 1 H), 8.28 (d, J = 7.9 Hz, 1 H), 8.62 (d, J = 7.9 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.8 (CH_2), 31.7 (CH_2), 48.1 (CH_2), 52.1 (CH_3), 98.1 (CH), 124.4 (CH), 124.9 (C), 125.9 (C), 132.5 (CH), 135.1 (CH), 137.8 (C), 145.8 (C), 161.1 (C), 167.4 (C); MS (DCI, NH_3 + isobutane) m/z 244 (MH^+); HRMS calcd for $C_{14}H_{14}NO_3$: 244.0973. Found: 244.0985 (MH^+).

§ Pale yellow crystals, mp 290–295 °C (dec) [lit.[3] yellow crystals, mp 258–260 °C (dec)]. For spectroscopic data, see the electronic supplementary information.

1 M. E. Wall and M. C. Wani, *J. Org. Chem.*, 1969, **34**, 1364–1367; J. A. Adamovics, J. A. Cina and C. R. Hutchinson, *Phytochemistry*, 1979, **18**, 1085–1086; M. E. Wall, M. C. Wani, S. M. Nataschke and A. W. Nicholas, *J. Med. Chem.*, 1986, **29**, 1553–1555.
2 M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. McPhail and G. A. Sim, *J. Am. Chem. Soc.*, 1966, **88**, 3888–3890.
3 Z.-L. Lin and G. A. Cordell, *Phytochemistry*, 1989, **29**, 1295–1297.
4 For reviews on camptothecin and its derivatives, see: C. J. Thomas, N. J. Rahier and S. M. Hecht, *Bioorg. Med. Chem.*, 2004, **12**, 1585–1604; J. F. Pizzolato and L. B. Saltz, *Lancet*, 2003, **361**, 2235–2242; W. Du, *Tetrahedron*, 2003, **59**, 8649–8687; A. Lansiaux and C. Bailly, *Bull. Cancer*, 2003, **90**, 239–245; *Camptothecins: New Anticancer Agents*, ed. M. Potmesil and H. Pinedo, CRC Press, Boca Raton, 1995; S. Sawada, T. Yokokura and T. Miyasaka, *Curr. Pharm. Des.*, 1995, **1**, 113–132; M. Torck and M. Pinkas, *J. Pharm. Belg.*, 1996, **51**, 200–207; C. R. Hutchinson, *Tetrahedron*, 1981, **37**, 1047–1065.
5 For a recent, totally different approach, see: Z. Ma and D. Y. W. Lee, *Tetrahedron Lett.*, 2004, **45**, 6721–6723.
6 For a review on the Friedländer quinoline synthesis, see: C.-C. Cheng and S. J. Yan, *Org. React.*, 1982, **28**, 37–201.
7 A. Padwa, S. M. Sheehan and C. S. Straub, *J. Org. Chem.*, 1999, **64**, 8648–8659. For previous synthetic applications of **4** in our laboratory, see: G. B. Raolji, S. Garçon, A. E. Greene and A. Kanazawa, *Angew. Chem., Int. Ed.*, 2003, **42**, 5059–5061; R. J. Anderson, A. Kanazawa and A. E. Greene, *Org. Lett.*, 2005, **7**, 2989–2991.
8 D. L. Hertzog, D. J. Austin, W. R. Nadler and A. Padwa, *Tetrahedron Lett.*, 1992, **33**, 4731–4734; A. Padwa, D. L. Hertzog, W. R. Nadler, M. H. Osterhout and A. T. Price, *J. Org. Chem.*, 1994, **59**, 1418–1427; J. P. Marino, Jr., M. H. Osterhout, A. T. Price, M. A. Semones and A. Padwa, *J. Org. Chem.*, 1994, **59**, 5518–5520; A. Padwa, D. L. Hertzog and W. R. Nadler, *J. Org. Chem.*, 1994, **59**, 7072–7084; J. P. Marino, Jr., M. H. Osterhout and A. Padwa, *J. Org. Chem.*, 1995, **60**, 2704–2713; S. M. Sheehan and A. Padwa, *J. Org. Chem.*, 1997, **62**, 438–439.

9 J. M. Harris and A. Padwa, *Org. Lett.*, 2003, **5**, 4195–4197.
10 For reviews on isomünchnone cycloadditions, see: M. C. McMills and D. Wright, in *The Chemistry of Heterocyclic Compounds: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, ed. A. Padwa and W. H. Pearson, John Wiley and Sons, Inc., New York, 2002, pp. 253–314; G. Mehta and S. Muthusamy, *Tetrahedron*, 2002, **58**, 9477–9504; A. Padwa, *Top. Curr. Chem.*, 1997, **189**, 121–158; A. Padwa and M. D. Weingarten, *Chem. Rev.*, 1996, **96**, 223–269; M. H. Osterhout, W. R. Nadler and A. Padwa, *Synthesis*, 1994, 123–141; A. Padwa, *Acc. Chem. Res.*, 1991, **24**, 22–28.
11 R. A. Earl and K. P. C. Vollhardt, *J. Org. Chem.*, 1984, **49**, 4786–4800.
12 Methyl 2,4-pentadienoate is available from Fluka. Surprisingly, it has rarely been used in the Heck reaction. See: W. Fischetti, T. K. Mak, F. G. Stakem, J.-I. Kim, A. L. Rheingold and R. F. Heck, *J. Org. Chem.*, 1983, **48**, 948–955; I. M. Lyapkalo, M. Webel and H.-U. Reißig, *Eur. J. Org. Chem.*, 2001, **58**, 4189–4194.
13 P. M. Wovkulich, K. Shankaran, J. Kiegiel and M. R. Uskokovic, *J. Org. Chem.*, 1993, **58**, 832–839.
14 For an excellent review of electrocyclic processes leading to 1,3-cyclohexadienes, see: W. H. Okamura and A. R. De Lera, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon Press, Oxford, 1991, vol. 5, ch. 6.2.
15 For a similar aromatization, see: M. Noguchi, S. Kakimoto, H. Kawakami and S. Kajigaeshi, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 1355–1362.
16 For photochemical naphthoannulations of benzopyridones, see: V. Arisvaran, M. Ramesh, S. P. Rajendran and P. Shanmugam, *Synthesis*, 1981, 821–823; for a review on the synthesis of isoquinolones, see: M. Álvarez and J. A. Joule, in *Science of Synthesis*, ed. D. Black, Thieme, Stuttgart, 2004, vol. 15, ch. 6.
17 K. C. Nicolaou, T. Montagnon, P. S. Baran and Y. L. Zhong, *J. Am. Chem. Soc.*, 2002, **124**, 2245–2258.
18 A. J. Pearson, Y.-S. Chen, S.-Y. Hsu and T. Ray, *Tetrahedron Lett.*, 1984, **25**, 1235–1238.
19 A. J. Catino, R. E. Forslund and M. P. Doyle, *J. Am. Chem. Soc.*, 2004, **126**, 13622–13623.
20 W. Shen, C. A. Coburn, W. G. Bornmann and S. J. Danishefsky, *J. Org. Chem.*, 1993, **58**, 611–617.
21 For a reduction with $NaBH_4$ of a related molecule, see: T. Naito, E. Kurodo, O. Miyata and I. Ninomiya, *Chem. Pharm. Bull.*, 1991, **39**, 2216–2218.