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Synthesis of (±)-camptothecin using a [3+2] nitrone cycloaddition to construct the CDE ring moiety

Jurong Yu,* Jeffrey DePue and David Kronenthal

Department of Process Research and Development, Bristol-Myers Squibb, Pharmaceutical Research Institute, One Squibb Drive, New Brunswick, NJ 08903-0191, USA

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Abstract—A novel synthesis to camptothecin is described. A Friedlander condensation of *o*-aminobenzaldehye **2** with tricylclic ketone **3** affords camptothecin after further elaboration. Tricyclic ketone **3** is prepared via a route employing a [3+2] nitrone cycloaddition and an intramolecular Knoevenagel condensation.

Camptothecin is an alkaloid with a novel ring system, which was first isolated from *Camptotheca acuminata* by Wall et al. in 1966.[1] For a number of years, it attracted much attention because of its significant cytotoxic activity against a range of tumor cell lines.[2] Recently, camptothecin and related compounds have returned to the forefront of experimental cancer treatment.[3] We became interested in developing a new synthesis of camptothecin that would allow for the facile incorporation of a variety of substituents on the A and B rings. Herein, we report a new synthesis of (±)-camptothecin involving a novel construction of the CDE ring precursor **3** via a [3+2] nitrone cycloaddition and an intramolecular Knoevenagel condensation (Scheme 1).

Our synthesis of camptothecin took the 'classical' Friedlander condensation approach, wherein the AB ring was created by the condensation of *o*-aminobenzaldehyde **2** with tricyclic ketone **3**.[4] The synthesis of **3** was based on the [3+2] cycloaddition of nitrone **4** with allylic alcohol **5**. This approach would allow for a unique assembly of the CDE ring of camptothecin, wherein the stereochemistry present in the α-hydroxyamide moiety in **5** would be preserved, and this, in turn, would result in the construction of camptothecin with the proper stereochemistry at C-20. Further elaboration of the cycloaddition adducts, including an intramolecular Knoevenagel condensation, would provide an efficient synthesis of **3** (see Scheme 3).

Nitrone **4** was prepared from tetronic acid **6** (Scheme 2). Protection of **6** followed by reduction with $LiAlH_4$ afforded diol **7**. The latter was converted to the corresponding bis-mesylate, which was then treated with hydroxylamine hydrochloride in triethylamine to give hydroxylamine **8**. Regioselective oxidation of **8** by mercury(II) oxide at 0 °C exclusively afforded the desired nitrone **4**.[5,6]

The [3+2] cycloaddition of nitrone **4** with racemic **5** proceeded regioselectively to produce a 1:1 mixture of diastereomers **9A** and **9B** (Scheme 3).[7,8] Both **9A** and **9B** were ultimately transformed into **3**. The two newly created asymmetric centers (at C-3 and C-5) were converted into sp^2 carbons, thereby obviating the need to separate the diastereomers. Initially, **9A** and **9B** were separated by silica gel chromatography in order to explore the subsequent steps using the pure diastereomers. After these steps were examined preparative work was carried out on the mixture of diastereomers. The mixture of **9A** and **9B** was treated with zinc in acetic acid to cleave the N–O bond,[9] and the resulting aminoalcohols were then acylated to afford **10** as a diastereomeric mixture. A one-pot conversion of alcohol **10** to lactone **11** was achieved by Swern oxidation, followed

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* Corresponding author. Tel.: +1 732 227 7485; fax: +1 732 227 3938; e-mail: jurong.yu@bms.com

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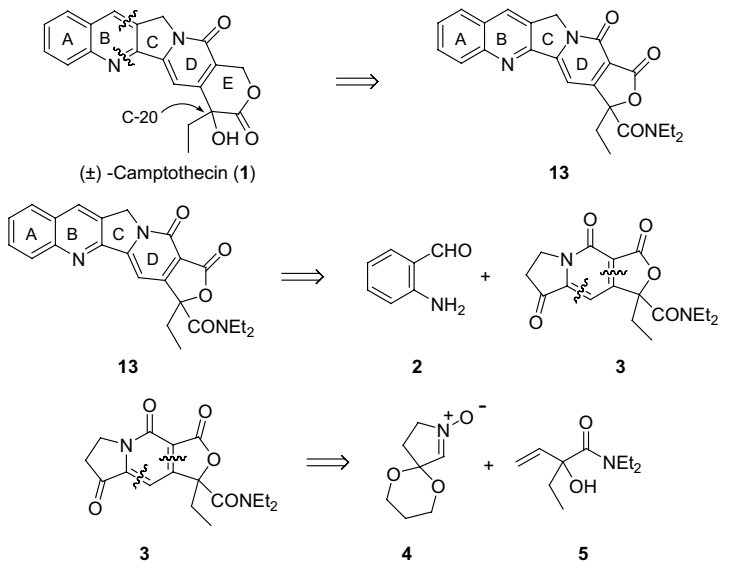
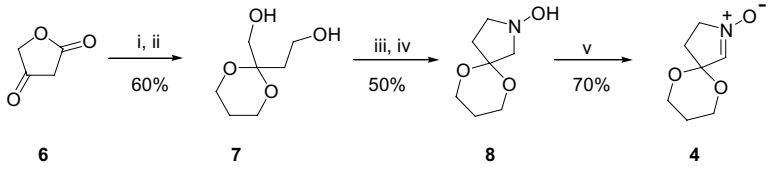
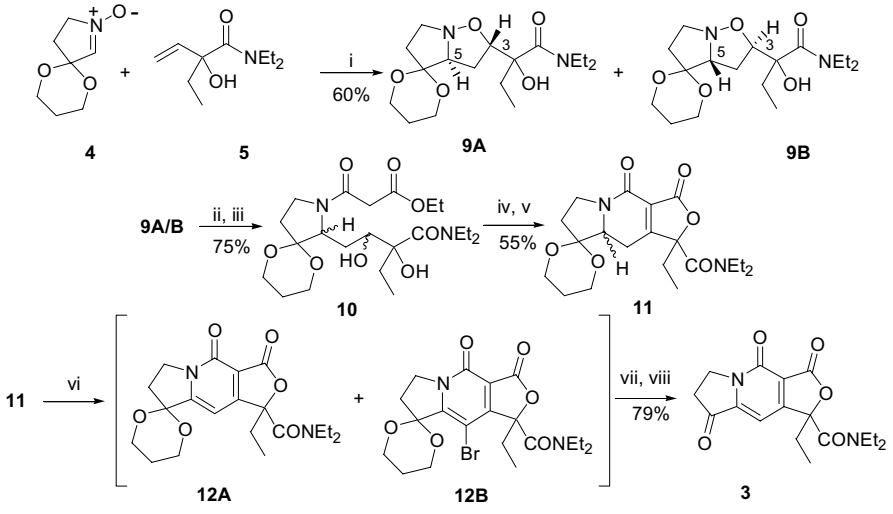


Scheme 1.

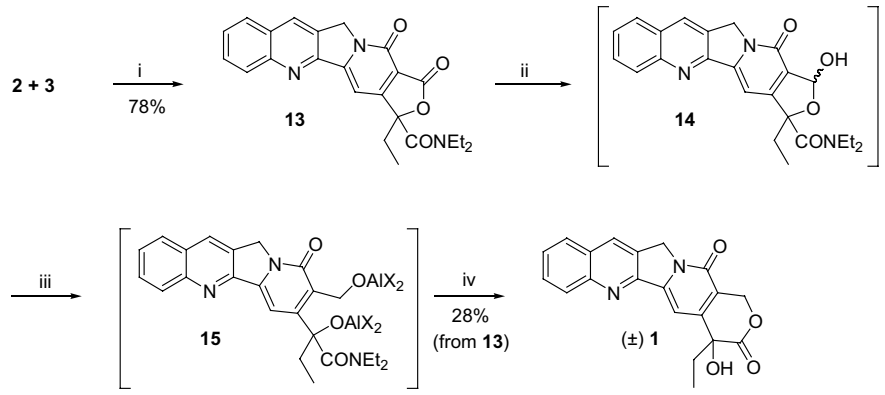


Scheme 2. Reagents and conditions: (i) $HO(CH_2)_3OH$/TsOH, EDC, 120 °C, 5 h; (ii) LAH (1.3 equiv), THF, 0 °C to rt, 3 h; (iii) MsCl/NEt_3, DCM, −45 °C, 3 h; (iv) NH_2OH/NEt_3, 90 °C, 5 h; (v) HgO, DCM, 0 °C, 24 h.



Scheme 3. Reagents and conditions: (i) THF, 80 °C, 24 h; (ii) Zn, HOAc/THF/H_2O (2:1:1), 0 °C, 3 h; (iii) (a) $EtO_2CCH_2CO_2H$/EDAC, DCM, 25 °C, 3 h, (b) K_2CO_3/EtOH, 25 °C, 3 h; (iv) $(COCl)_2$/DMSO/NEt_3, DCM, −78 °C to 25 °C, 2 h; (v) KOBu^t/EtOH, 25 °C, 1 h; (vi) KHMDS/NBS, −78 °C to 25 °C, 3 h; (vii) Bu_3SnH/AIBN, THF, 65 °C, 17 h; (viii) TFA/H_2O (4:1), 25 °C, 3 h.

by intramolecular Knoevenagel condensation.[10] Bromination/dehydrobromination using 2 equiv of KHMDS and NBS converted compound **11** to a 1:1 mixture of the pyridone **12A** and the over-brominated derivative



Scheme 4. Reagents and conditions: (i) PhMe, 25 °C, 1 h; 80 °C, 15 h; (ii) (a) Dibal-H (7.5 equiv), −78 °C, 1 h; (b) HOAc (10 equiv), 25 °C, 1 h; (iii) Dibal-H (10 equiv), 50 °C, 3 h; (iv) 1 N HCl, 85 °C, 15 h.

12B.[11] Treatment of this mixture with Bu_3SnH/AIBN left compound **12A** undisturbed and reduced **12B** to **12A**. Ketal hydrolysis then afforded tricyclic ketone **3**.

Friedlander condensation of **2** and **3** generated lactone **13** (Scheme 4).[12] Surprisingly, the reduction of **13** proved to be the most difficult step in this synthesis. A number of hydride-reducing agents and different conditions were examined for this transformation.[3a,13] However, most conditions resulted in the overreduction of the quinoline and/or pyridone unit or decarbonylative loss of the amide group, and, in general, mixtures of such compounds were formed.[13b] Eventually, a one-pot conversion of lactone **13** to (±)-camptothecin was developed. Reduction of **13** with Dibal-H followed by quenching with acetic acid generated lactol **14** in situ (cf. Ref. 4a). Further treatment with additional Dibal-H, generated **15**, which was then cyclized to (±)-camptothecin **1** by exposure to 1 N HCl.[14] The proton NMR, HPLC, and mass spectrum of the isolated, synthetic **1** were identical to those obtained from a commercially available sample of camptothecin.[15]

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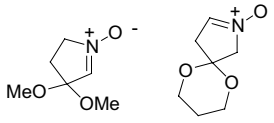

16 **17**

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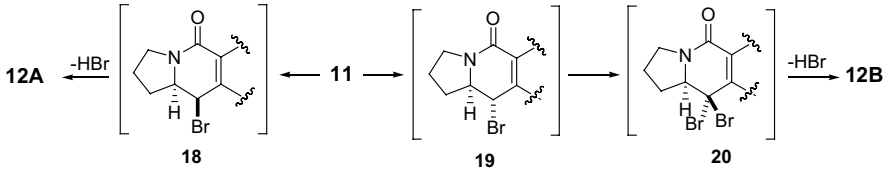

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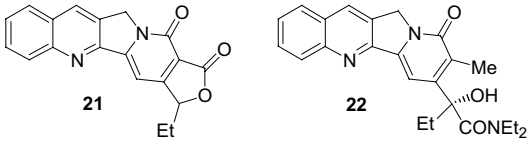
14. The major by-products were **21** and **22** with the combination of these impurities typically comprising greater than 20% of the total reaction mixture.



15. Spectral data for key intermediates: **4**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 3.7–4.1 (m, 6H), 2.44 (m, 2H), 1.9–2.1 (m, 1H), 1.55–1.75 (m, 1H). **12A**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (s, 1H), 3.97–4.25 (m, 6H), 3.88–3.97 (m, 1H), 3.49–3.59 (m, 1H), 3.17–3.28 (m, 1H), 3.06–3.15 (m, 1H), 2.54–2.67 (m, 2H), 2.34–2.45 (m, 1H), 2.17–2.29 (m, 1H), 2.01–2.11 (m, 1H), 1.58–1.64 (m, 1H), 1.21 (t, J = 8 Hz, 3H), 1.14 (t, J = 8 Hz, 3H), 0.88 (t, J = 84 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 7.69, 12.40, 14.78, 25.12, 30.04, 32.17, 42.67, 42.75, 45.60, 61.95, 62.16, 88.51, 98.08, 105.29, 112.41, 155.77, 155.90, 166.18, 166.47, 169.09. **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 4.42–4.55 (m, 1H), 4.37 (t, J = 9 Hz, 2H), 3.92–4.0 (m, 1H), 3.40–3.52 (m, 1H), 3.22–3.32 (m, 1H), 3.12–3.21 (m, 1H), 3.03 (t, J = 9 Hz, 2H), 2.35–2.42 (m, 1H), 1.24 (t, J = 8.5 Hz, 3H), 1.15 (t, J = 8.5 Hz, 3H), 0.87 (t, J = 8.5 Hz, 3H). **13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.24 (d, J = 8 Hz, 1H), 7.95 (d, J = 8 Hz, 1H), 7.90 (s, 1H), 7.85 (t, J = 8 Hz, 1H), 7.70 (t, J = 8 Hz, 1H), 5.38 (d, J = 23.8 Hz, 1H), 5.32 (d, J = 23.8 Hz, 1H), 3.85–4.00 (m, 1H), 3.45–3.55 (m, 1H), 3.25–3.35 (m, 1H), 3.15–3.25 (m, 1H), 2.42–2.52 (m, 1H), 2.17–2.28 (m, 1H), 1.26 (t, J = 9 Hz, 3H), 1.15 (t, J = 9 Hz, 3H), 0.92 (t, J = 9 Hz, 3H).