Synthesis of a Malimide Analogue of the Telomerase Inhibitor UCS1025A Using a Dianionic Aldol Strategy

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Abstract: The synthesis of a simplified analogue of UCS1025A via an aldol coupling is described.

Key words: aldol reactions, Diels–Alder reactions, imides, natural products, total synthesis

Telomeres[1] are repetitive hexameric DNA sequences $(TTAGGG)_n$ at the ends of the chromosomes, which protect the chromosomal ends of DNA from being recognized as double-strand DNA breaks. In most somatic cells, telomeres also act as a cellular clock, as they shorten each time a cell divides until a critical length is reached and cell senescence or apoptosis occur. In over 90% of all cancer cells the enzyme telomerase[2] is activated which makes them virtually immortal. During the course of a screening program, Yamashita et al. isolated a new fungal metabolite from *Acremonium* sp. KY4917. Apart from its antimicrobial activity against Gram-positive bacteria, UCS1025A (**1**) was identified to be a novel telomerase inhibitor.[3] UCS1025A possesses a complex pentacyclic framework featuring a contiguous array of eight stereocenters and an unprecedented furopyrrolizidine subunit (Figure 1). Since **1** is one of the first natural product telomerase inhibitors,[4] many research groups[5] have embarked on its synthesis and very recently, Danishefsky[6] and Hoye[7] reported elegant total syntheses. In this communication, we present the synthesis of a malimide analogue (**2**) of UCS1025A.

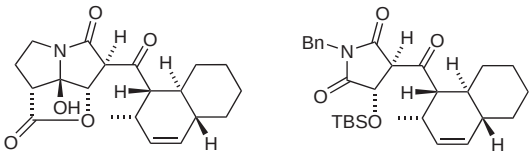
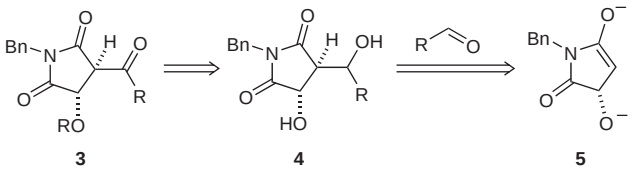


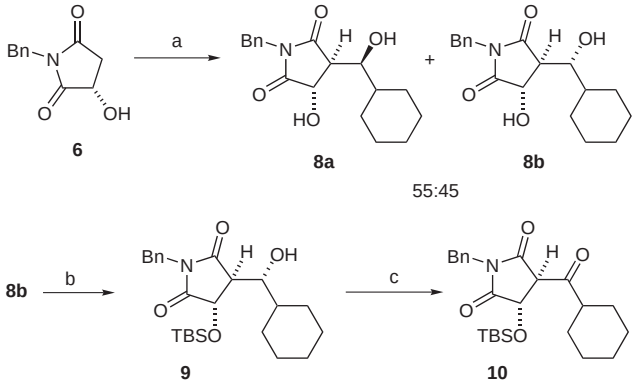
Figure 1 UCS1025A (**1**) and a malimide analogue (**2**)

In our retrosynthetic plan, an aldol scission between the keto group and the pyrrolizidine residue would provide access to UCS1025A and analogues. In fact, Lambert and Danishefsky were not able to couple the decalin fragment with a model pyrrolizidine using an aldol approach because of steric reasons. This strategy is also hampered by the fact that protection of the β-hydroxyl group on the pyrrolizidine is prohibited due to facile β-elimination under basic conditions. We wanted to overcome this problem (Scheme 1) by deprotonation of the free hydroxyl group prior to the enolate formation (to form dianion **5**). From alkylation[8] and aldol reactions[9] of 4-hydroxypyrrolidin-2-ones, it was anticipated that malimide-derived enolates (4-hydroxypyrrolidine-2,5-diones) would be attacked with high facial selectivity as compared to the oxyanion[10] but with low diastereoselectivity with respect to the newly formed hydroxyl group. The selectivity was inconsequential to our strategy, since we oxidized this hydroxyl group later and the keto group was in equilibrium with its enol tautomer.



Scheme 1 Retrosynthetic strategy

We started our synthetic studies toward UCS1025A using imide **6** and cyclohexyl carbaldehyde (**7**) as model substrates (Scheme 2).



Scheme 2 Synthesis of **10**. *Reagents and conditions*: (a) NaHMDS, THF, 0 °C, then –78 °C, cyclohexyl carbaldehyde (**7**), 3.5 h, 56%; (b) TBSCl, imidazole, DMF, r.t., 1 h, 84%; (c) Dess–Martin periodinane, CH_2Cl_2, 0 °C to r.t., 2 h, 82%.

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After some optimization[11] we found that 2.1 equivalents of NaHMDS as base in THF gave rise to the desired products **8a**[12] and **8b** in 56% yield as a 55:45 mixture of diastereomers. For the major isomer **8a** the crystal structure was obtained (Figure 2), and the relative configuration of **8b** was determined by comparison of the NMR spectra.

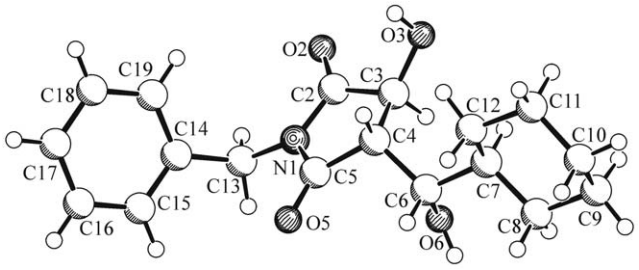
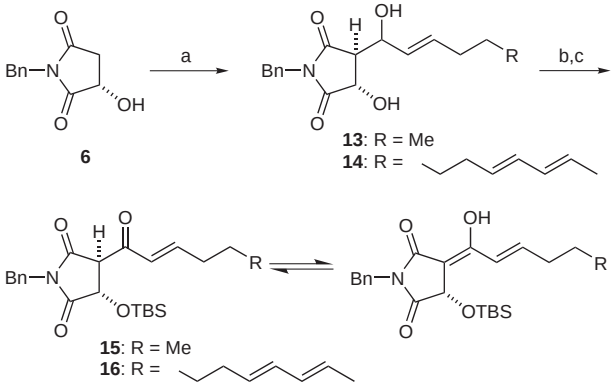


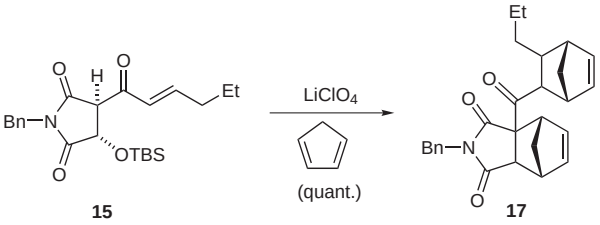
Figure 2 X-ray crystal structure of **8a**

As precedented by the Procter group for a similar substrate,[13] the ring hydroxyl group could be protected selectively over the side-chain hydroxyl (imidazole, TBSCl) giving **9** in 84% yield. A screening of oxidizing agents revealed that pyridinium chlorochromate (PCC), manganese dioxide or employing Swern conditions[14] led to rapid decomposition of the starting material. Using the Dess–Martin periodinane,[15] the reaction proceeded smoothly to give the desired β-ketoimide **10**. When the less bulky aldehydes 2-hexenal and 2,8,10-dodecatrienal were employed in the aldol coupling reaction, the yield could be raised to 65% and 72%, respectively (Scheme 3).



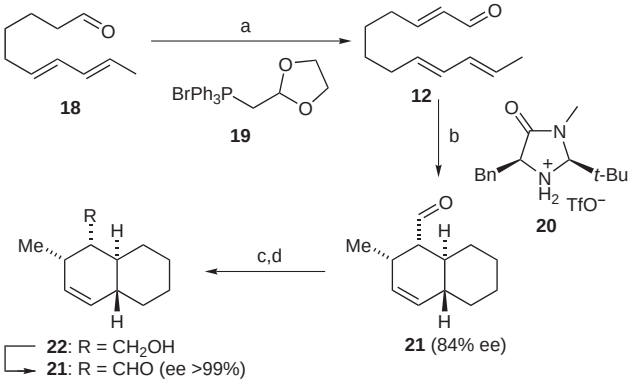
Scheme 3 Synthesis of **15** and **16**. *Reagents and conditions*: (a) NaHMDS, THF, 0 °C, then –78 °C, 2-hexenal (**11**) or 2,8,10-dodecatrienal (**12**), 3.5 h, 65% and 72%, respectively; (b) TBSCl, imidazole, DMF, r.t., 1 h, 77% and 79%; (c) PCC, 4 Å MS, CH_2Cl_2, r.t., 2 h, 76% and 55%.

The aldol products were converted into the corresponding β-ketoimides **15** and **16** as substrates for inter- and intramolecular Diels–Alder reactions. This time PCC was the superior oxidant. Interestingly, both compounds exist as a 1:1 tautomeric mixture as indicated in Scheme 2. Unfortunately, so far all attempts to generate Diels–Alder products (heat, Lewis acids, hexafluoroisopropanol[16]) have led to either decomposition of starting materials or a complex mixture of products.



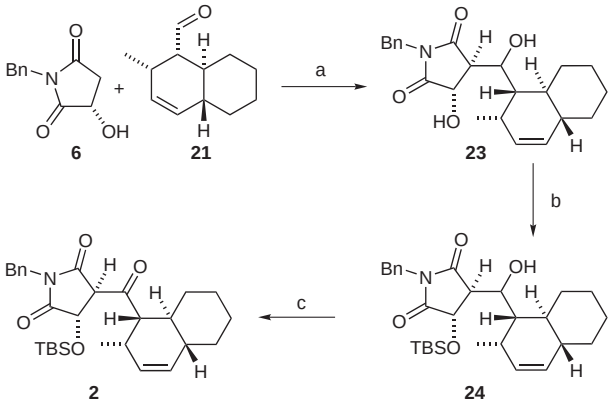
Scheme 4 Synthesis of **17**

One of the reasons behind the decomposition could be the facile β-elimination of TBS-OH giving rise to a highly reactive double dienophile, which was trapped with cyclopentadiene. In fact, the double Diels–Alder adduct **17** was isolated as a 3:1 mixture of diastereomers (Scheme 4).



Scheme 5 Synthesis of **21**. *Reagents and conditions*: (a) *t*-BuOK, **19**, 0 °C, then **15**, 1 h, then 10% aq oxalic acid, r.t., 91% yield; (b) **20** (10 mol%), 0 °C, $MeNO_2$–H_2O (98:2), 48 h, 74%; (c) $NaBH_4$, EtOH, 0 °C, quant., recrystallization (pentane); (d) PCC, 4 Å MS, CH_2Cl_2, r.t., 0.5 h, 95%.

We therefore decided to perform the Diels–Alder reaction prior to the aldol coupling. Aldehyde **18**[17] was treated with the commercially available Wittig reagent **19**, to give the desired trienal **12** in 91% yield (Scheme 5). This compound was subjected to an organocatalytic Diels–Alder reaction using MacMillan's conditions.[18] We could lower the catalyst loading to 10 mol% by choosing nitromethane as the solvent and obtained the Diels–Alder adduct in 74% yield and 84% ee. The ee was raised to >99% by recrystallization of the corresponding alcohol followed by reoxidation to afford the enantiopure aldehyde **21**.[19] This material was coupled to the imide **6** using the previously established conditions to give **23** as a 4:1 mixture of diastereomers. The reaction was more sluggish, confirming the tendency that increasing the size of the electrophile lowers the reaction rate. The product was obtained as a diastereomeric mixture in 55% yield. The major isomer was taken forward to give, after protection and oxidation, the desired analogue **2**[20] of UCS1025A as a mixture of tautomers (Scheme 6).



Scheme 6 Synthesis of **2**. *Reagents and conditions*: (a) NaHMDS, THF, 0 °C, then –78 °C, **21**, 3.5 h, 55%; (b) TBSCl, imidazole, DMF, r.t., 4 h, 77%; (c) PCC, 4 Å MS, CH_2Cl_2, r.t., 2 h, 67%.

In summary, the synthesis of an advanced analogue of UCS1025A has been achieved employing a dianionic aldol approach. Efforts toward UCS1025A as well as structure–activity relationship studies are ongoing and the results will be reported in due course.

Acknowledgment

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References and Notes

(1) Cech, T. R. *Angew. Chem. Int. Ed.* **2000**, *39*, 34.
(2) (a) Greider, C. W.; Blackburn, E. H. *Cell* **1985**, *43*, 405. (b) Jacobs, S. A.; Podell, E. R.; Cech, T. R. *Nat. Struct. Mol. Biol.* **2006**, *12*, 218.
(3) (a) Nakai, R.; Ogawa, H.; Asai, A.; Ando, K.; Agatsuma, T.; Matsumiya, S.; Akinaga, S.; Yamashita, Y.; Mizukami, T. *J. Antibiot.* **2000**, *53*, 294. (b) Agatsuma, T.; Akama, T.; Nara, S.; Matsumiya, S.; Nakai, R.; Ogawa, H.; Otaki, S.; Ikeda, S.-I.; Saitoh, Y.; Kanda, Y. *Org. Lett.* **2002**, *4*, 4387. (c) Nakai, R.; Ishida, H.; Asai, A.; Ogawa, H.; Yamamoto, Y.; Kawasaki, H.; Akinaga, S.; Mizukami, T.; Yamashita, Y. *Chem. Biol.* **2006**, *13*, 183.
(4) Telomestatin: (a) Shinya, K.; Wierzba, K.; Matsuo, K.-I.; Ohtani, T.; Yamada, Y.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1262. (b) Rezler, E. M.; Seenisamy, J.; Bashyam, S.; Kim, M.-Y.; White, E.; Wilson, W. D.; Hurley, L. H. *J. Am. Chem. Soc.* **2005**, *127*, 9439. (c) Doi, T.; Yoshida, M.; Shinya, K.; Takahashi, T. *Org. Lett.* **2006**, *8*, 4165. Dictyodendrins: (d) Warabi, K.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N. *J. Org. Chem.* **2003**, *68*, 2765. (e) Fürstner, A.; Domostoj, M. M.; Scheiper, B. *J. Am. Chem. Soc.* **2006**, *128*, 8087. (f) Axinelloside: Warabi, K.; Hamada, T.; Nakao, Y.; Matsunaga, S.; Hirota, H.; van Soest, R. W. M.; Fusetani, N. *J. Am. Chem. Soc.* **2005**, *127*, 13262.
(5) (a) Snider, B. B.; Neubert, B. J. *J. Org. Chem.* **2004**, *69*, 8952. (b) Dvornikovs, V.; Hoye, T. R. *Abstracts of Papers*, 229th National Meeting of the American Chemical Society, San Diego CA, March 13–17, 2005; American Chemical Society: Washington D.C., **2005**, ORGN 665. (c) Christmann, M. *Abstracts of Papers*, 229th National Meeting of the American Chemical Society, San Diego CA, March 13–17, 2005; American Chemical Society: Washington D.C., **2005**, ORGN 378.
(6) Lambert, T. H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 426.
(7) Hoye, T. R.; Dvornikovs, V. *J. Am. Chem. Soc.* **2006**, *128*, 2550.
(8) (a) Beyersbergen van Henegouwen, W. G.; Hiemstra, H. *J. Org. Chem.* **1997**, *62*, 8862. (b) Washburn, D. G.; Heidebrecht, R. W. Jr.; Martin, S. F. *Org. Lett.* **2003**, *5*, 3523.
(9) Huang, P. Q.; Zheng, X.; Wang, S. L.; Ye, J. L.; Jin, L. R.; Chen, Z. *Tetrahedron: Asymmetry* **1999**, *10*, 3309.
(10) Shieh, H.-M.; Prestwich, D. G. *J. Org. Chem.* **1981**, *46*, 4319.
(11) **Typical Procedure**: THF (4.5 mL) was cooled to 0 °C and NaHMDS (1.02 mL, 2.0 M in THF, 2.05 mmol) was added. To this solution the benzyl-protected (*S*)-3-hydroxy-pyrrolidine-2,5-dione (0.20 g, 0.97 mmol) in THF (3.2 mL) was added dropwise and after complete addition the solution was stirred at 0 °C for an additional 5 min to give a yellowish suspension. The reaction mixture was cooled to –78 °C, cyclohexyl carbaldehyde (0.12 mL, 0.97 mmol) in THF (2.2 mL) was added dropwise and the resulting mixture was stirred at –78 °C for 1 h. The reaction was quenched with sat. NH_4Cl (5 mL) and diluted with Et_2O (30 mL) and CH_2Cl_2 (10 mL). The organic layer was washed with sat. NH_4Cl (2 × 5 mL), dried (Na_2SO_4) and concentrated. Purification by column chromatography (SiO_2; *n*-pentane–Et_2O, 1:1 → 1:3) gave **8a** and **8b** as a mixture of diastereomers in 31% and 25% yields, respectively.
(12) Compound **8a**: mp 135–137 °C; $[\alpha]^{25}_D$ –49.8 (*c* = 1.01, acetone); R_f 0.19 (*n*-pentane–Et_2O, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.27 (m, 5 H), 4.66 (d, *J* = 5.2 Hz, 1 H), 4.61 (d, *J* = 14.6 Hz, 1 H), 4.57 (d, *J* = 14.3 Hz, 1 H), 3.96 (dd, *J* = 2.2, 9.1 Hz, 1 H), 2.93 (dd, *J* = 2.3, 5.1 Hz, 1 H), 2.20 (br s), 1.95 (d, *J* = 12.4 Hz, 1 H), 1.58–1.76 (m, 4 H), 1.44–1.55 (m, 1 H), 1.02–1.26 (m, 3 H), 0.84–0.96 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.8, 176.2, 135.2, 128.7 (2 × C), 128.3 (2 × C), 127.9, 73.2, 67.3, 51.8, 42.7, 41.3, 29.3, 28.8,, 26.3, 25.9, 25.8. IR (KBr): 3462, 2924, 2851, 1696, 1438, 1407, 1356, 1168, 697 cm^{-1}. MS (EI): *m*/*z* (%) = 318 (26), 317 (83) [M$^+$], 299 (23), 234 (77), 205 (74), 204 (36), 127 (17), 106 (26), 96 (25), 95 (31), 92 (23), 91 (100), 73 (26), 71 (18), 56 (30). Anal Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 67.84; H, 7.76; N, 4.26.
(13) Edmonds, D. J.; Muir, K. W.; Procter, D. J. *J. Org. Chem.* **2002**, *68*, 3190.
(14) Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329.
(15) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(16) Lygo, B.; Hirst, D. J. *Synthesis* **2005**, 3257.
(17) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768.
(18) Wilson, R. M.; Jen, W. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 11616.
(19) Hagiwara, H.; Kobayashi, K.; Miya, S. T.; Suzuki, T.; Ando, M.; Okamoto, T.; Kobayashi, M.; Yamamoto, I.; Ohtsubo, S.; Kato, M.; Uda, H. *J. Org. Chem.* **2002**, *67*, 5969.
(20) Compound **2**: colorless oil; R_f 0.38 (pentane–EtOAc, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.51 (s), 7.18 (m), 5.38 (m), 5.22 (d, *J* = 9.9 Hz), 4.76 (s), 4.68 (d, *J* = 4.2 Hz), 4.54 (d, *J* = 14.3 Hz), 4.53 (d, *J* = 14.3 Hz), 4.44 (d, *J* = 14.1 Hz), 4.42 (d, *J* = 14.1 Hz), 3.65 (d, *J* = 4.2 Hz), 2.95 (dd, *J* = 5.4,

11.1 Hz), 2.62 (m), 2.18 (d, *J* = 8.2 Hz), 1.33–1.68 (m), 1.08–1.22 (m), 0.90 (d, *J* = 6.7 Hz, Me), 0.72 (s), 0.71 (s), 0.08 (s), 0.03 (s), 0.01 (s), 0.00 (s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.8, 176.8, 174.7, 174.2, 173.5, 170.1, 135.6, 134.9, 131.4, 130.8, 130.4 (2 × C), 128.7 (2 × C), 128.6 (2 × C), 128.5 (4 × C), 127.9, 127.8, 101.7, 70.1, 68.1, 64.5, 57.4, 46.9, 42.9, 42.5, 42.3, 41.5, 37.3, 36.2, 34.6, 32.8 (2 × C), 30.5, 30.2, 29.8, 26.5, 26.4, 26.3, 26.2, 25.6 (3 × C), 25.4 (3 × C), 18.1, 17.9, 17.5, –3.9, –4.4, –4.9, –5.4. IR ($CHCl_3$): 3674, 3745, 2929, 2856, 2361, 2335, 1709, 1675, 1215, 839, 757 cm^{-1}. MS (EI): *m*/*z* (%) = 438 (100)[M – 57], 363 (11), 214 (7), 91 (46), 75 (42). HRMS: *m*/*z* [M – 57] calcd for $C_{25}H_{32}NO_4Si$: 438.21006; found: 438.21006.