Synthesis of an unsymmetrical bis-lexitropsin-1,2,9,9a–tetrahydrocyclopropa[*c*]benzo[*e*]indol-4-one (CBI) conjugate

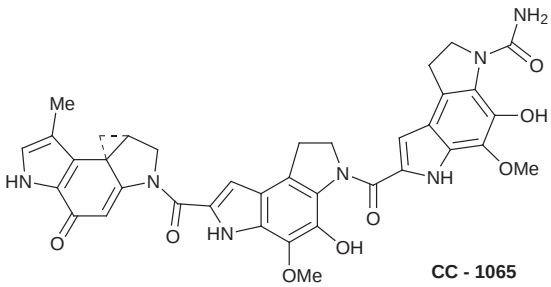
Guofeng Jia, Hirokazu Iida and J. William Lown*

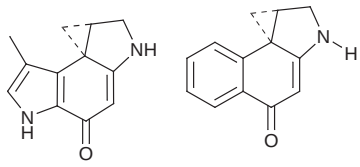
Department of Chemistry, University of Alberta, Edmonton, AB, Canada T6G 2G2.
E-mail: annabella.wiseman@ualberta.ca

Received (in Corvallis, OR, USA) 8th October 1998, Accepted 23rd November 1998

A practical synthesis of a novel bis-functionalized precursor of 1,2,9,9a-tetrahydrocyclopropa[*c*]benzo[*e*]indol-4-one (CBI) is described; the first unsymmetrical bis-lexitropsin–CBI precursor conjugate was thereby synthesized.

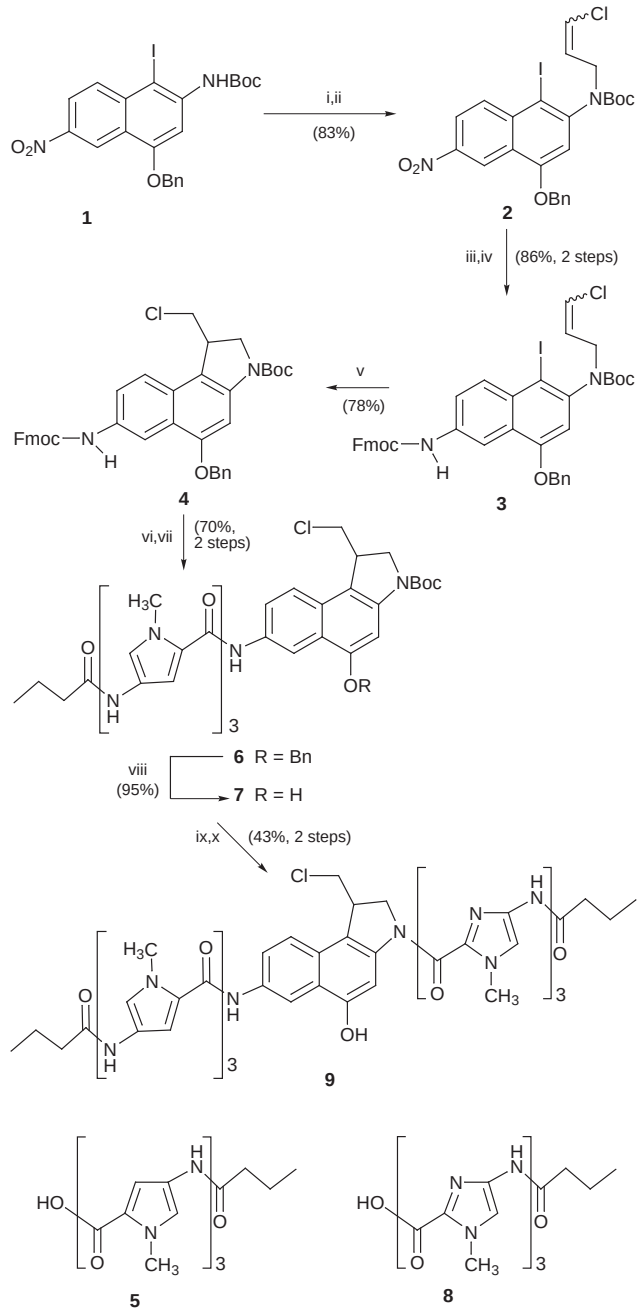
CC-1065, an antitumor antibiotic isolated from the culture of *Streptomyces zelensis*,[1] is one of the most potent cytotoxic agents ever discovered and has a wide spectrum of activity against tumor cells *in vitro* and *in vivo* as well as against microbial organisms.[2] However, CC-1065 cannot be used in humans because it was found that it caused delayed death in experimental animals.[3] In the search for compounds with better antitumor selectivity and DNA sequence specific binding





properties, many CC-1065 analogs have been synthesized in attempts to avoid the undesired side effects while retaining its potency against tumor cells.[4] As a successful example of modification of 1,2,8,8a-tetrahydro-7-methylcyclopropa[*c*]-pyrrolo[3,2-*e*]indol-4-one (CPI), the DNA alkylating moiety of CC-1065, Boger first reported that the simplified moiety, 1,2,9,9a-tetrahydrocyclopropa[*c*]benzo[*e*]indol-4-one (CBI), and its analogs were more stable and more potent than the CPI counterparts.[5]

In our group, attempts have been made to link CPI with lexitropsins, the well-established DNA minor groove binders. It was found that some optimized CPI–lexitropsin conjugates exhibit up to 10000 times higher potency than CC-1065 against KB human cancer cells.[3] Molecular modeling studies predicted that a CBI moiety bearing a lexitropsin carrier on both sides should be more firmly bound to its DNA target sequence and might therefore show enhanced potency. This strategy is designed to exploit binding-driven bonding of the alkylating moiety. We have already reported the synthesis of conjugates of CBI bearing two identical lexitropsins which containing pyrrole units.[6] Studies on lexitropsins or information reading molecules show that replacement of pyrrole units by imidazoles in lexitropsins may cause a change in the base site recognition from AT to GC in minor groove of B-DNA.[7] In order to permit targeting of mixed DNA sequences and to thereby investigate the effects of DNA sequence selective ability, we herein



Scheme 1 *Reagents and conditions*: i, NaH; ii, ClCH=CHCH$_2$Cl, Bu$_4$NI; iii, hydrazine hydrate, FeCl$_3$, C; iv, FmocCl, Et$_3$N; v, Bu$_3$SnH, AIBN; vi, TBAF; vii, **5**; viii, HCO$_2$NH$_4$, Pd/C; ix, HCl; x; **8**.

describe the synthesis of an unsymmetrical bis-lexitropsin–CBI conjugate, which contains two different lexitropsins. In our previous work,[6] the CBI moiety was obtained by an *in situ* primary radical trap with TEMPO. Here, the CBI moiety was synthesized by using a more concise and shorter route which was recently developed by Patel and co-workers.[8]

Deprotonation of carbamate **1**[6] using NaH, followed by alkylation of the resulting anion with 1,3-dichloropropene in the presence of the phase transfer catalyst Bu_4NI gave an mixture of *Z* and *E* isomers of vinyl chloride **2**. Selective reduction of the nitro group of **2** using hydrazine,[9] followed by protection of the amino group, provided **3**, the desired precursor for the intramolecular aryl radical cyclization on to a tethered vinyl chloride.[8] A deoxygenated solution of **3** in dry benzene was heated at reflux for 15 h in the presence of 2 equiv. of Bu_3SnH and a catalytic amount of AIBN to give the fully protected bifunctionalized CBI prodrug form, racemic **4**.† Although not investigated in detail, no reaction occurred when nitro compound **2** was treated under the same conditions as amine **3**.

Detachment[10] of the Fmoc group from **4**, followed by coupling with polypyrrole carboxamide **5**[11] using HOBt and EDCI as the coupling agents[11b,c] afforded the hybrid **6**. Hydrogenolysis[8a] of **6** served to remove the benzyl ether almost quantitatively and provided **7**. Acid-mediated deprotection of **7**, followed by coupling with polyimidazole carboxamide **8**[11] using EDCI provided the final bis-lexitropsin–CBI precursor conjugate **9**‡ in fair yield.

In summary, we have described a synthesis of the bis-functionalized CBI precursor containing two different protective groups and obtained the corresponding unsymmetrical bis-lexitropsin conjugate. Results on the DNA sequence preferences and biological evaluation will be reported in due course.

We are grateful for a research grant (to J. W. L.) from the Natural Sciences and Engineering Research Council of Canada.

Notes and references

† *Selected data* for **4**: δ_H(360 MHz, acetone-d_6) 9.02 (s, NH), 8.38 (s, 1H, C6-H), 7.88–7.30 (m, 16H, Ar-H), 5.30 (s, 2H, $PhCH_2O$), 4.50 (d, 2H, *J* 6.9, CH_2 in Fmoc), 4.30 (t, 1H, *J* 6.9, CH in Fmoc), 4.22–4.05 (m, 3H, C1-H, C2-H), 4.01 (dd, 1H, *J* 3.1, 11.1, C*H*HCl), 3.70 (dd, 1H, *J* 8.4,11.0, CH*H*Cl), 1.58 (s, 9H, Boc-H); Calc. for $C_{40}H_{37}N_2O_5Cl$: C, 72.66; H, 5.64; N, 4.24. Found C, 72.55; H, 5.74; N, 4.20%.

‡ *Selected data* for **9**: δ_H(360 MHz, DMSO-d_6) 10.35 (s, 1H), 10.30 (s, 1H), 10.18 (s, 1H), 9.90 (s, 1H), 9.86 (s, 1H), 9.75 (s, 1H), 9.62 (s,1H), 9.59 (s, 1H), 8.55 (d, 1H, *J* 2.0, C6-H), 7.97 (s, 1H, C4-H), 7.86 (dd, 1H, *J* 2.0, 7.5, C8-H), 7.74 (d, 1H, *J* 7.5, C9-H), 7.64 (s, 1H, Im-H), 7.60 (s, 1H, Im-H), 7.51 (s, 1H, Im-H), 3.31 (d, 1H, *J* 1.5, Py-H), 7.24 (d, 1H, *J* 1.5, Py-H), 7.21 (d, 1H, *J* 1.5, Py-H), 7.16 (d, 1H, *J* 1.5, Py-H), 7.07 (d, 1H, *J* 1.5, Py-H), 6.88 (d, 1H, *J* 1.5, Py-H), 4.7–3.6 (m, 23H, NCH_3, $ClCH_2$, C1-H, C2-H), 2.28 (t, 2H, J 7.3, $COCH_2$), 2.20 (t, 2H, *J* 7.4, $COCH_2$), 1.63–1.53 (m, 4H, $COCH_2CH_2$), 0.91–0.86 (m, 6H, $COCH_2CH_2CH_3$); Calc. for $C_{54}H_{58}N_{17}O_9Cl$: C, 57.15; N, 21.17. Found C, 57.06; N, 20.97%.

1 L. J. Hanka, A. Dietz, S. A. Gerpheide, S. L. Kuentzel and D. G. Martin, *J. Antibiot.*, 1978, **31**, 1211.
2 B. K. Bhuyan, K. A. Newell, S. L. Crampton and D. D. Von Hoff, *Cancer Res.*, 1982, **42**, 3532.
3 H. Iida and J. W. Lown, *Recent Res. Dev. Synth. Org. Chem.*, 1998, **1**, 17 and references cited therein.
4 D. L. Boger and R. S. Coleman, *J. Am. Chem. Soc*, 1988, **110**, 4796; C. H. Lin, D. Sun and L. H. Hurley, *Chem. Res. Toxicol.*, 1991, **4**, 21; M. A. Mitchell, R. C. Kelly, N. A. Wicnienski, N. T. Hatzenbuhler, M. G. Williams, G. L. Petzold, J. L. Slightom and D. R. Siemieniak, *J. Am. Chem. Soc.*, 1991, **113**, 8994; R. C. Kelly, I. Gebhard, N. Wicknienski, P. A. Aristoff, P. D. Johnson and D. G. Martin, *J. Am. Chem. Soc.*, 1987, **109**, 6837; D. L. Boger and D. S. Johnson, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1439.
5 D. L. Boger, T. Ishizaki, R. J. Wysocki, Jr., S. A. Munk, P. A. Kitos and O. Suntornwat, *J. Am. Chem. Soc.*, 1989, **111**, 6461; D. L. Boger and T. Ishizaki, *J. Org. Chem.*, 1990, **55**, 5823; D. L. Boger, W. Yun and B. R. Teegarden, *J. Org. Chem.*, 1992, **57**, 2873; D. L. Boger, P. Mesini and C. M. Tarby, *J. Am. Chem. Soc.*, 1994, **116**, 6461; D. L. Boger and J. A. McKie, *J. Org. Chem.*, 1995, **60**, 1271; P. A. Aristoff and P. D. Johnson, *J. Org. Chem.*, 1992, **57**, 6234; K. J. Drost and M. P. Cava, *J. Org. Chem.*, 1991, **56**, 2240.
6 G. Jia, H. Iida and J. W. Lown, *Heterocycl. Commun.*, 1998, in the press.
7 K. E. Rao and J. W. Lown, *Trends Org. Chem.*, 1992, **3**, 141 and references cited therein.
8 (*a*) V. F. Patel, S. L. Andis, J. K. Enkema, D. A. Johnson, J. H. Kennedy, F. Mohamadi, R. M. Schultz, D. J. Soose and M. M. Spees, *J. Org. Chem.*, 1997, **62**, 8868; (*b*) D. L. Boger, C. W. Boyce, R. M. Garbaccio and M. Searcey, *Tetrahedron Lett.*, 1998, **39**, 2227.
9 D. L. J. Clive, A. G. Angoh and S. M. Bennett, *J. Org. Chem.*, 1987, **52**, 1339.
10 M. Ueki and M. Amemiya, *Tetrahedron Lett.*, 1987, **28**, 6617.
11 (*a*) E. Nishiwaki, S. Tanaka, H. Lee and M. Shibuya, *Heterocycles*, 1988, **27**, 1945; (*b*) L. Huang, J. C. Quada, Jr. and J. W. Lown, *Bioconjugate Chem.*, 1995, **6**, 21; (*c*) R. Zhao, N. H. Al-Said, D. L. Sternbach and J. W. Lown, *J. Med. Chem.*, 1997, **40**, 216.

Communication 8/07884J