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A new strategy towards the total synthesis of phenanthridone alkaloids: synthesis of (+)-2,7-dideoxypancratistatin as a model study

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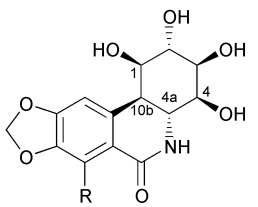
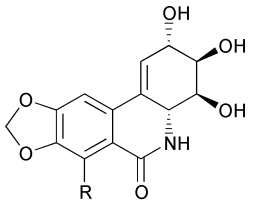
A new strategy towards the synthesis of phenanthridone alkaloids has been reported through the synthesis of (+)-2,7-dideoxypancratistatin from D-(−)-quinic acid employing PET initiated carbocyclization of an electron rich aromatics by silylenol ether as a key step.

The potent cytotoxic and antiviral[1] properties associated with (+)-pancratistatin (**1a**) coupled with its limited availability from natural resources[2] have prompted significant efforts for the total synthesis of this deceptively simple looking molecular structure. Despite commendable efforts expended by numerous research groups over many years for the synthesis of **1a**[3] and its congeners 7-deoxypancratistatin (**1b**),[4] narciclasine (**2a**)[5] and lycoricidine (**2b**),[6] the members of this family of alkaloids remain particularly formidable targets for organic synthesis. The main challenge towards designing any synthetic strategy for **1** lies into the control of the *trans* fused BC-ring junction (4_a,10_b) and with the stereocontrolled installation of continuous hydroxy functionalities located around the perimeter of the C-ring moiety.



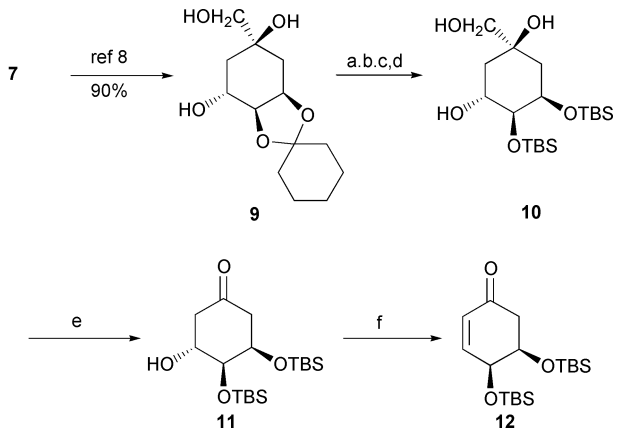
1a: R=OH Pancratistatin
1b: R=H 7-deoxypancratistatin



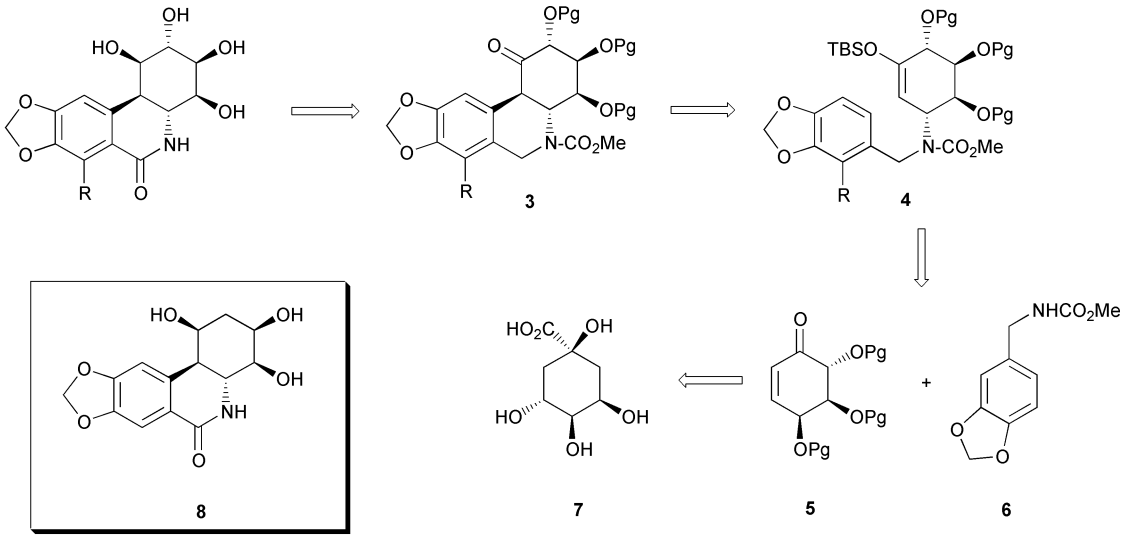
2a: R=OH Narciclasine
2b: R=H Lycoricidine

We viewed a new synthetic approach for **1** through the retrosynthetic route as outlined in Scheme 1. The key features of our synthetic plan involved the utilization of the crucial C–C bond formation step, developed earlier by our group[7] *via* photo induced electron transfer (PET) initiated cyclization of silylenol ether to an electron rich aromatic ring (*ca.* **4** to **3**) and also making use of naturally abundant D-(−)-quinic acid (**7**) as chiral source to build the highly oxygenated C-ring system. This strategy was designed keeping in view the requirement for **1** in significant yield for mapping biological and pharmaceutical profiles. To evaluate the efficacy of the strategy, we have synthesized (+)-2,7-dideoxypancratistatin (**8**) as a model study and report the results in this communication.

The synthesis began with the preparation of **9** from D-(−)-quinic acid (**7**) according to the literature procedure (Scheme 2).[8] To avoid any unforeseen complication in the later part of the synthesis, the cyclohexylidene moiety of **9** was replaced with the corresponding TBS ether **10**. Sodium



Scheme 2 *Reagents and conditions*: a, NaH, BnCl, DMF, 85%; b, HOAc–H_2O, 50 °C, 10 h, 95%; c, TBSCl, ImH, DMAP, DMF, 24 h, 80%; d, H_2–Pd/C, EtOH, quant.; e, $NaIO_4$, EtOH, 95%; f, MsCl, TEA, 0 °C, DCM, 95%.



Scheme 1

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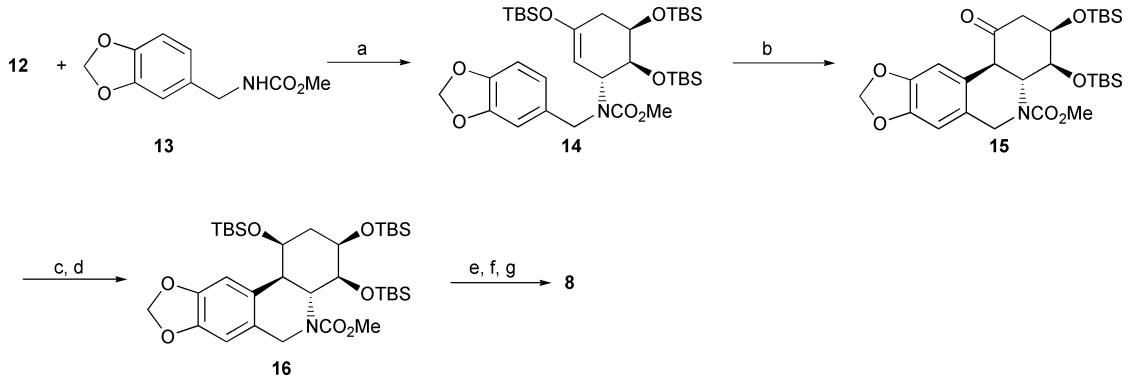

Scheme 3 *Reagents and conditions*: a, n-BuLi, HMPA, THF, −78 °C, TBSCl, 95%; b, hν, DCN, CH_3CN, H_2O, 68%; c, $NaBH_4$, iPrOH; d, TBSCl, ImH, DMAP, DCM, 85% over two steps; e, RuO_2, $NaIO_4$, EtOAc, H_2O, 90%; f, NaOMe, MeOH, reflux; g, TBAF, THF, 90% over two steps.

metaperiodate oxidation of **10** gave **11** in good yield. β-Hydroxy elimination of **11** by treating with MsCl and TEA at 0 °C gave **12** in 95% yield.

Conjugate addition of *N*-lithiated piperonylamine carbamate, prepared by the treatment of **13** with n-BuLi in THF–HMPA at −78 °C followed by trapping the resultant enolate as TBS ether by quenching with TBSCl, afforded **14** in 95% yield (Scheme 3). PET cyclization by irradiating (pyrex filter, >280 nm, 450 W Hanovia medium pressure lamp, 6 h) a mixture of **14** (0.8 g, 1.18 mmol) and 1,4-dicyanonaphthalene (DCN, 0.05 g, 0.028 mmol) in 250 mL of CH_3CN–H_2O (24 : 1) and usual work up and chromatographic purification of the crude photolysate gave cyclized product **15** in 68% yield as a single diastereomer. Compound **15** was fully characterized by spectroscopic methods. Sodium borohydride reduction of **15** followed by the protection of the resultant alcohol moiety as TBS ether gave **16** in 85% yield as a single diastereomer.

The ^{1}H NMR spectrum of **16**[9] showed a characteristic doublet of doublet for H_{10b} at d 2.9 (J = 10.3, 6.3 Hz) confirming the *syn* relationship between H_{10b} and H_1 (J = 6.3 Hz) and *anti* relationship between H_{10b} and H_{4a} (J = 10.3 Hz).

Benzylic oxidation of **16** by utilizing a catalytic amount of RuO_2 and $NaIO_4$,[10] followed by carbamate and silyl deprotection gave **8**, $[\alpha]^{25}_D$ +90.91(c 0.055, MeOH), in overall 23% yield. The final product **8** was also fully characterized by all spectroscopic[11] means.

In conclusion, we have demonstrated a new strategy which could be useful for the synthesis of all of the phenanthridone class of alkaloids utilizing a methodology developed from our group for the key C–C bond formation step. Total syntheses of (+)-pancratistatin and 7-deoxypancratistatin are in progress and will be disclosed appropriately in due course.

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Notes and references

1 (*a*) G. R. Pettit, V. Gaddamidi, D. L. Herald, S. B. Singh, G. M. Gragg and J. M. Schmidt, *J. Nat. Prod.*, 1986, **46**, 995; (*b*) B. Gabrielson, T. P. Monath, J. W. Huggins, J. J. Kirsi, M. Hollingshead, W. M. Shannon and G. R. Pettit, *Natural products as Antiviral Agents*, ed. C. K. Chu, H. G. Cutler, Plenum, New York, 1992, p. 121.

2 G. R. Pettit, G. R. Pettit III, G. Groszek, R. A. Backhaus, D. L. Doubek, R. J. Barr and A. W. Meerow, *J. Nat. Prod.*, 1995, **58**, 756.

3 (*a*) S. Danishefsky and J. Y. Lee, *J. Am. Chem. Soc.*, 1989, **111**, 4829; (*b*) X. Tian, T. Hudlicky and K. Königsberger, *J. Am. Chem. Soc.*, 1995, **117**, 3643; (*c*) B. M. Trost and S. R. Pulley, *J. Am. Chem. Soc.*, 1995, **117**, 10143; (*d*) T. J. Doyle, M. M. Hendrix, D. Van Der Veer, S. Jaanmard and J. Haseltine, *Tetrahedron*, 1997, **53**, 11153; (*e*) P. Magnus and I. K. Sebhat, *J. Am. Chem. Soc.*, 1998, **120**, 5341; (*f*) J. H. Rigby, U. S. M. Maharoof and M. E. Mateo, *J. Am. Chem. Soc.*, 2000, **122**, 6624; (*g*) G. R. Pettit, N. Melody and D. L. Herald, *J. Org. Chem.*, 2001, **66**, 2583.

4 (*a*) H. Paulsen and M. Stubbe, *Liebigs Ann. Chem.*, 1983, 535; (*b*) T. Hudlicky, X. Tian and K. Königsberger, *Synlett*, 1995, 1125; (*c*) G. E. Keck, S. F. McHardy and J. A. Murry, *J. Am. Chem. Soc.*, 1995, **117**, 7289; (*d*) T. Hudlicky, X. Tian, K. Königsberger, R. Maurya, J. Rouden and B. Fan, *J. Am. Chem. Soc.*, 1996, **118**, 10752; (*e*) G. E. Keck, T. T. Wager and S. F. McHardy, *J. Org. Chem.*, 1998, **63**, 9164; (*f*) G. E. Keck, J. A. Murry and S. F. McHardy, *J. Org. Chem.*, 1999, **64**, 4465; (*g*) J. L. Acena, O. Arjona, M. L. Leon and J. Plumet, *Org. Lett.*, 2000, **2**, 3683.

5 (*a*) J. H. Rigby and M. E. Mateo, *J. Am. Chem. Soc.*, 1997, **119**, 12655; (*b*) G. E. Keck, T. T. Wager and J. F. D. Rodriquez, *J. Am. Chem. Soc.*, 1999, **121**, 5176.

6 (*a*) S. Ohta and S. Kimoto, *Tetrahedron Lett.*, 1975, 2279; (*b*) S. Ohta and S. Kimoto, *Chem. Pharm. Bull.*, 1976, **24**, 2969; (*c*) S. Ohta and S. Kimoto, *Chem. Pharm. Bull.*, 1976, **24**, 2977; (*d*) H. Paulsen and M. Stubbe, *Liebigs Ann. Chem.*, 1983, 535; (*e*) S. Ogawa, M. Ohtsuka and N. Chida, *Tetrahedron Lett.*, 1991, **32**, 4525; (*f*) T. Hudlicky and H. R. Olivo, *J. Am. Chem. Soc.*, 1992, **114**, 9694; (*g*) S. F. Martin and H. H. Tso, *Heterocycles*, 1993, **35**, 85; (*h*) S. Ogawa, M. Ohtsuka and N. Chida, *J. Org. Chem.*, 1993, **58**, 4441; (*i*) T. Hudlicky, H. F. Olivo and B. McKibben, *J. Am . Chem. Soc.*, 1994, **116**, 5108.

7 (*a*) G. Pandey, A. Krishna, K. Girija and M. Karthikeyan, *Tetrahedron Lett.*, 1993, **34**, 6631; (*b*) G. Pandey, M. Karthikeyan and A. Murugan, *J. Org. Chem.*, 1998, **63**, 2867.

8 D. Mercier, J. Leboul, J. Cleophax and S. D. Gero, *Carbohyd. Res.*, 1971, **20**, 299.

9 Spectral data for **16**: ^{1}H NMR (200 MHz, $CDCL_3$) d 6.73 (s, 1H), 6.65 (s, 1H), 5.91 (s, 2H), 5.00 (d, J = 15.4 Hz 1H), 3.92 (d, J = 15.4 Hz), 3.72 (m, 7H), 2.95 (dd, J = 10.3, 6.3 Hz, 1H), 2.10 (dd, J = 23.2, 11.7 Hz, 1H), 1.72 (m, 1H), 0.94 (s, 9H), 0.91 (s, 9H), 0.80 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), 0.07 (s, 6H), −0.25 (s, 3H), −0.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) d 156.8, 146.3, 145.9, 131.0, 127.8, 111.0, 106.5, 100.5, 72.2, 70.3, 68.5, 58.1, 52.4, 45.8, 43.9, 36.2, 25.8, 25.6, 18.1, 17.9, 17.6, −4.8, −5.0, −5.1, −5.2, −5.4, −5.9.

10 A. B. Smith III and R. M. Scarborough Jr, *Syn. Commun.*, 1980, **10**, 205.

11 Spectral data for **8**: ^{1}H NMR (200 MHz, CD_3OD) 7.34 (s, 1H), 6.82 (s, 1H), 6.01 (bs, 2H), 3.91 (m, 3H), 3.57 (m, 1H), 2.74 (dd, J = 10.2, 3.9 Hz, 1H), 1.91 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) d 166.3, 150.53, 147.1, 136.7, 121.3, 109.3, 106.3, 101.4, 69, 68.4, 66.4, 55.6, 42.3, 35.7.