Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 5989–5991

Total synthesis of 6-deoxyclitoriacetal isolated from *Stemona collinsae* Craib.

Prapas Khorphueng,[a] Jumreang Tummatorn,[a] Amorn Petsom,[a] Richard J. K. Taylor[b] and Sophon Roengsumran[a,*]

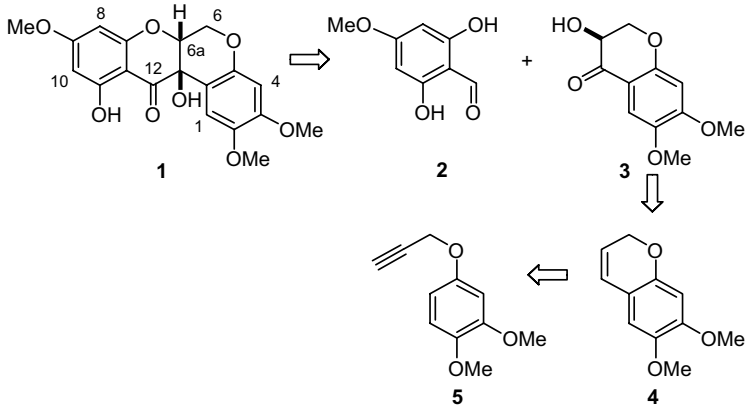
[a]*Research Centre for Bioorganic Chemistry, Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok 10330, Thailand*
[b]*Department of Chemistry, University of York, Heslington, York YO10 5DD, UK*

Received 25 April 2006; revised 10 May 2006; accepted 18 May 2006

Abstract—A total synthesis of the rotenoid, 6-deoxyclitoriacetal, a cytotoxic natural product, was successfully achieved by using platinum-catalysed hydroarylation, Sharpless asymmetric dihydroxylation, regioselective IBX diol oxidation and stereoselective intramolecular keto-aldehyde pinacol coupling as the key steps.

Stemona collinsae Craib. (Stemonaceae) has been used as a traditional Thai medicine with a wide range of applications (liver cancer, skin infections, anti-parasitic agent, etc.).[1] In a previous paper, we reported the isolation and X-ray crystal structure of 6-deoxyclitoriacetal (**1**) from *Stemona collinsae*, and described its potent cytotoxic activity against human breast carcinoma (BT 479), lung carcinoma (CHAGO), hepato-carcinoma (Hep-G2), gastric carcinoma (KATO3) and colon carcinoma (SW620).[2] Moreover, 6-deoxyclitoriacetal obtained from the roots of *Clitoria macrophylla* has been shown to exhibit strong cytotoxic activity against P388 lymphocytic leukaemia cell lines.[3] Since 6-deoxyclitoriacetal (**1**) possesses such strong cytotoxic activity against a variety of cancer cell lines, we initiated a synthetic programme in this area. In this letter, we report the total synthesis of 6-deoxyclitoriacetal (**1**).

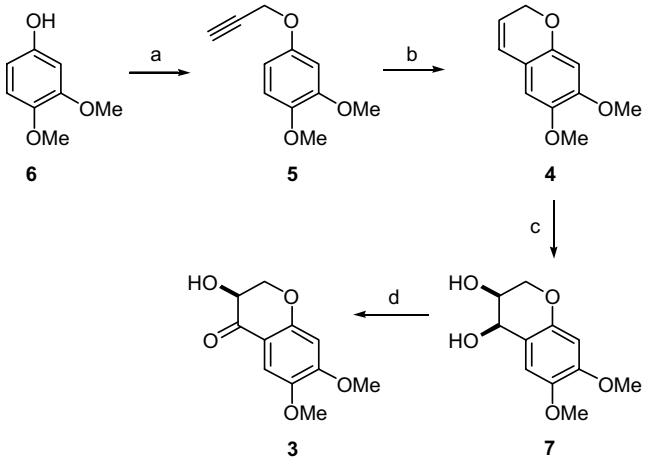
The retrosynthetic approach we adopted for compound **1** is outlined in Scheme 1. The synthetic strategy is based on



Scheme 1. Retrosynthesis of **1**.

Keywords: Rotenoid; Samarium diiodide; Pinacol coupling.
* Corresponding author. Tel.: +66 19173955; fax: +66 22541309; e-mail addresses: prapas@mut.ac.th; mr_big2545@yahoo.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.05.188



Scheme 2. Synthetic route to **3**. Reagents and conditions: (a) Propargyl bromide, K_2CO_3, acetone, KI, rt, quantitative; (b) $PtCl_2$, toluene, 55 °C, 75%; (c) AD-mix-α, *t*-BuOH/H_2O, $MeSO_2NH_2$, 92%; (d) IBX, EtOAc 70 °C, 88%.

the pinacol-type coupling between aldehyde **2** and ketone **3**. We envisaged preparing compound **3** by elaboration of alkene **4**, which we planned to obtain from propargyl aryl ether **5** using hydroarylation methodology.[4]

The synthesis of compound **5** was completed as presented in Scheme 2. The reaction of 3,4-dimethoxyphenol **6** with propargyl bromide and K_2CO_3 in acetone at room temperature gave compound **5**[4a] in quantitative yield. We were delighted to find that cyclisation of compound **5** could be accomplished by platinum-catalysed hydroarylation using $PtCl_2$ in toluene to give the required alkene **4** in reasonable yield (75%). Sharpless asymmetric dihydroxylation was then effected by treatment of alkene **4** with AD-mix-α in *t*-BuOH-H_2O giving diol **7** in 92% yield ($[\alpha]_D$ −12.4 (*c* 0.95, $CHCl_3$)).[5] Regioselective oxidation of diol **7** at the benzylic position with IBX in DMSO[6] provided the desired ketone **3** in 40% yield. However, the yield of this oxidation was significantly improved (88%) by changing the solvent to ethyl acetate.[7]

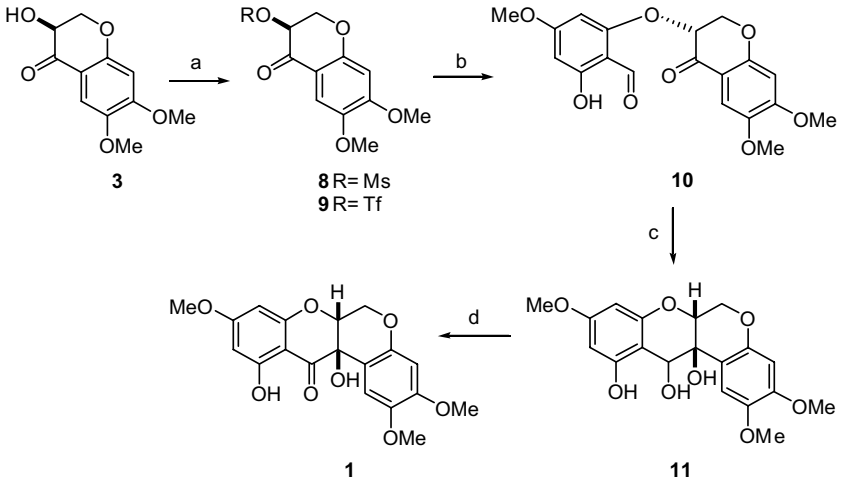
α-Hydroxyketone **3** was next converted into mesylate **8** and triflate **9** in yields of 82% and 88%, respectively, using standard conditions. Coupling of mesylate **8** with the known phenol **2**[8] using 18-crown-6 and K_2CO_3 in CH_3CN generated keto-aldehyde **10** in 67% yield.[9] However, treatment of compound **2** with triflate **9** under the same conditions provided compound **10** in a higher yield of 85%. Treatment of **10** with samarium diiodide in THF/*t*-BuOH at −78 °C provided compound **11** in 65% yield through a stereoselective intra-molecular keto-aldehyde pinacol coupling.[10] Finally, oxidation of **11** with MnO_2 in dichloromethane gave 6-deoxyclitoriacetal (**1**) in 80% yield[11] (Scheme 3).

The synthetic product **1** exhibited ^1H and ^{13}C NMR spectral data (a small doublet at δ 4.67 (d, $J = 2.3$ Hz), assigned to H-6a and an AB quartet at δ 4.33 (dd, $J_1 = 12.3$, $J_2 = 1.6$ Hz, 1H), and δ 4.47 (dd, $J_1 = 12.3$ Hz, $J_2 = 2.3$ Hz, 1H), attributed to H-6), mp (131–132 °C; lit.[3b] mp 130–131 °C) and optical rotation {$[\alpha]_D^{25}$ +219.9 (*c* 1.0, $CHCl_3$), lit.[3b] $[\alpha]_D$ +233 (*c* 0.1, $CHCl_3$)} closely matching those published for the natural product.

In conclusion, the total synthesis of 6-deoxyclitoriacetal **1**, a cytotoxic agent, has been accomplished by utilizing a convergent and efficient strategy which should be suitable for the preparation of novel analogues for biological evaluation.

Acknowledgements

We thank the Thailand Research Fund (RGJ-PhD program to P.K.), the Graduate School and Department of Chemistry, Faculty of Science, Chulalongkorn University, for financial support and also the Ratchadapisaksompote for partial financial support.



Scheme 3. Synthetic route to **1**. Reagents and conditions: (a) MsCl or Tf_2O, CH_2Cl_2, DMAP, Py; R = Ms, 82%; R = Tf, 88%; (b) **2**, K_2CO_3, 18-crown-6, CH_3CN, 67% for **8** and 85% for **9**; (c) SmI_2, THF/*t*-BuOH, −78 °C to rt, 65%; (d) MnO_2, CH_2Cl_2, 80%.

References and notes

1. Shiengthong, D.; Donavanik, T.; Uaprasert, V.; Roengsumran, S.; Massy-Westropp, R. A. *Tetrahedron Lett.* **1974**, 2015–2018.
2. Roengsumran, S.; Khorphueng, P.; Chaichit, N.; Jaiboon-Muangsin, N.; Petsom, A. *Z. Kristallogr. NCS* **2003**, 105–106.
3. (a) Fang, N. B.; Casida, J. E. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 3380–3384; (b) Lin, L. J.; Ruangrungsi, N.; Cordell, G. A.; Shieh, H. L.; Min, Y.; Pezzuto, J. M. *Phytochemistry* **1992**, *31*, 4329–4331; (c) Li, L.; Wang, H. K.; Chang, J. J.; McPhail, A. T.; McPhail, D. R.; Terada, H.; Konoshima, T.; Kokumai, M.; Kozuka, M.; Estes, J. R.; Lee, K. H. *J. Nat. Prod.* **1993**, *56*, 690–698.
4. (a) Pastine, S. J.; Sames, D. *Org. Lett.* **2003**, *5*, 4053–4055; (b) Liu, C.; Han, X.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 3700–3701.
5. Data for compound **7**: mp 98–99 °C; $[\alpha]_D^{25}$ −12.4 (*c* 0.95, $CHCl_3$); IR (chloroform) ν_{max}: 3378, 2938, 1662, 1621, 1541, 1512, 1449, 1403, 1265, 1224, 1200, 1162, 1127, 1057, 938 cm^{-1}; ^1H NMR δ 3.85 (s, 3H), 3.86 (s, 3H), 4.09 (m, 3H), 4.71 (s, 1H), 6.41 (s, 1H), 6.88 (s, 1H); ^{13}C NMR δ 55.9, 56.4, 65.8, 65.9, 66.1, 100.2, 111.8, 113.1, 144.0, 147.9, 150.3; HRMS (ESI-TOF) (M^++Na) *m*/*z* calcd for $C_{11}H_{14}O_5Na$ 249.0739: found 249.0740.
6. Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258.
7. More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001–3003.
8. Lau, C. K.; Belanger, P. C.; Dufresne, C.; Scheigetz, J. *J. Org. Chem.* **1987**, *52*, 1670–1673.
9. (a) Li, K.; Helm, R. F. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2425–2426; (b) Lee, A.-L.; Ley, S. V. *Org. Biomol. Chem.* **2003**, *1*, 3957–3966.
10. (a) Swindell, C. S.; Fan, W. *Tetrahedron Lett.* **1996**, *37*, 2321–2324; (b) Ohmori, K.; Kitamura, M.; Suzuki, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1226–1228.
11. Data for compound **1**: Pale yellow solid, mp 131–132 °C (lit.[3b] mp 130–131 °C); $[\alpha]_D^{25}$ +219.9 (*c* 1.0, $CHCl_3$), {lit.[3b] $[\alpha]_D$ +233 (*c* 0.1, $CHCl_3$)}; IR (chloroform): ν_{max}, 3444, 2939, 2842, 1670, 1610, 1574, 1509, 1461, 1336, 1263, 1206, 1160, 1120, 1044, 1025, 822, 735 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.57 (s, 3H), 3.70 (s, 3H) 3.74 (s, 3H), 4.33 (dd, $J_1 = 12.3$, $J_2 = 1.6$ Hz, 1H), 4.47 (dd, $J_1 = 12.3$ Hz, $J_2 = 2.3$ Hz, 1H), 4.67 (d, $J = 2.3$ Hz, 1H), 6.01 (d, $J = 2.3$ Hz, 1H), 6.06 (d, J= 2.3 Hz, 1H), 6.68 (s, 1H), 6.71 (s, 1H), 11.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.8, 55.9, 56.3, 63.6, 66.9, 75.5, 94.5, 95.6, 100.1, 101.1, 108.2, 109.2, 143.9, 148.3, 151.3, 161.6, 164.3, 169.0, 195.0; HRMS (FAB) *m*/*z* calcd for $C_{19}H_{19}O_8$ (MH^+) 375.1080; found 375.1074.