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Synthesis of spiroannulated dihydroisobenzofuranylated monosaccharides

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Abstract—An efficient synthesis of spiroannulated dihydroisobenzofurans is achieved using easily accessible carbohydrate-derived furanyl propargyl ethers via an $AuCl_3$ promoted intramolecular Diels–Alder (IMDA) reaction. The scope of the spiroannulation protocol was demonstrated using a diverse range of pentofuranosyl, hexofuransoyl and hexopyranosyl derived substrates in order to synthesize spiroannulated dihydroisobenzofurans. The reaction is high yielding, moisture tolerant, fast and uses only a catalytic amount of $AuCl_3$.

PKCα belonging to the protein kinase C family of enzymes (PKC) plays a dominant role in intracellular signal transduction of a variety of cellular events such as proliferation, differentiation and apoptosis.[1] Benzofuran **1** and dihydroisobenzofuran **2** possess a broad spectrum of biological activity and a recent protein docking study by Sodeoka revealed that chiral isobenzofuranone derivative **3** binds to PKCα.[2] We envisaged that introduction of a spirocyclic moiety would enhance the biological activity of the PKCα inhibitor as the spirocyclic moiety occurs in many natural products and its presence has been shown to inhibit many important proteins in the cellular context because of the increased conformational rigidity.[3] Pioneering contributions from various groups resulted in the development of spirocyclization strategies exploiting ring closing metathesis[4] for the synthesis of spiro compounds comprising peptides, carbohydrates and barbituric acids as their core templates.[5] We recently found that utilization of the Pauson–Khand reaction results in the intramolecular formation of spiroannulated monosaccharides.[6] As a part of our programme[7] dedicated to the exploration of carbohydrate based diversity oriented synthesis pathways for spirocycles, we investigated the use of Au(III) mediated phenol synthesis[8a] for spiroannulation on carbohydrate scaffolds. Dihydroisobenzofurans can be synthesized from furfuryl propargyl ethers exploiting the alkynophilicity of gold (Fig. 1).[8]

However, to the best of our knowledge, the gold mediated phenol synthesis developed by Hashmi's group[8a] has not been explored to synthesize spiroannulated frameworks so far.[8] We disclose in this letter a methodology towards the synthesis of spirocyclic dihydroisobenzofurans from carbohydrate-derived furfuryl propargyl ethers using a catalytic amount of $AuCl_3$.

To commence our studies, readily available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofurano-3-ulose **4**[6] was converted to the corresponding 3-*C*-(2-methylfuranyl)-D-allose using 5-methylfuryl-2-lithium in THF generated at −40 °C for 1 h in 91% yield.[9] The resulting tertiary hydroxyl group was alkylated using propargyl bromide in the presence of NaH in DMF at 0 °C–rt to afford propargyl ether **5**.[6] With the furfuryl and propargyl ether moieties attached to the carbohydrate template, the

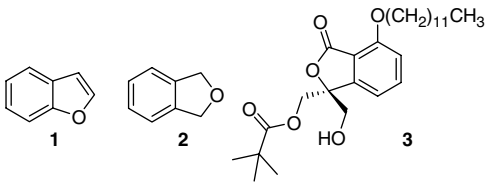

Figure 1. Benzofuran **1**, dihydroisobenzofuran **2** and PKCα inhibitor **3**.

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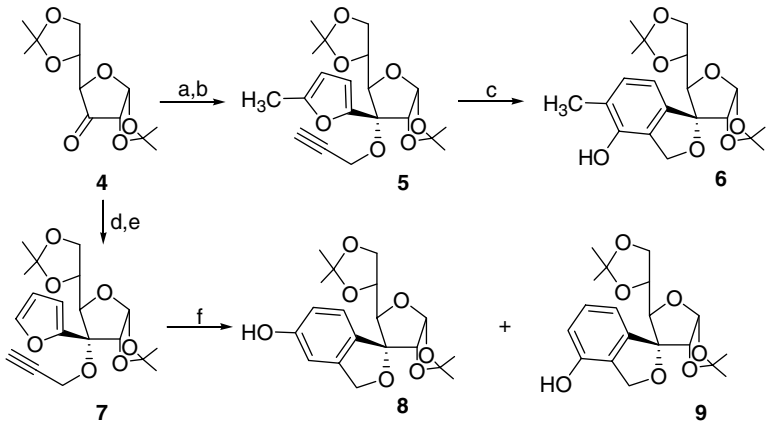
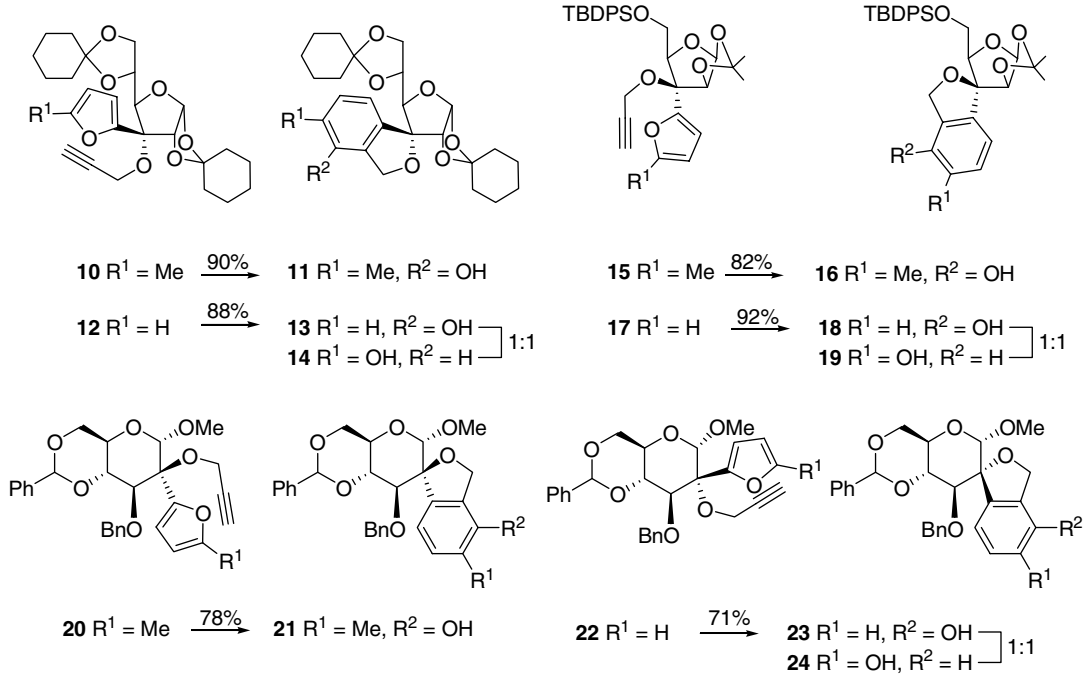
intramolecular Diels–Alder (IMDA) reaction and subsequent C–O bond cleavage was effected[8a] in the presence of a catalytic amount of $AuCl_3$ in acetonitrile for 10 min to afford spiroannulated dihydroisobenzofuran derivative **6** in 93% yield.[10,11] We next performed the current spiroannulation protocol on furfuryl propargyl ether **7** and observed the formation of two regioisomeric spiroannulated derivatives **8** and **9** in a 1:1 ratio, which were easily separated by silica gel column chromatography with a combined yield of 92% (Scheme 1).[12]

It is noteworthy to mention that a large number of compounds can be synthesized exploiting acid sensitive isopropylidene groups. However, with optimized conditions in hand, we decided to explore this spiroannulation protocol on a diverse set of substrates derived from pentofuranosides, hexofuranosides and hexopyranosides. Gratifyingly, we found that sterically demanding substrates **10** and **12** could also be converted into spiroannulated compounds **11**, **13** and **14**.[12] Furthermore, arabinose derived furfuryl propargyl ethers **15** and **17** could be successfully converted to the corresponding spirocycles **16**, **18** and **19** in 82% and 92% yields, respectively. Similarly, glucopyranosides **20** and **22** also underwent IMDA reaction and subsequent C–O bond cleavage to give spiroannulated dihydroisobenzofuran derivatives **21**, **23** and **24** in good yields (Scheme 2).[12]

In summary, we have developed an $AuCl_3$ mediated spirocyclization method that provides access to diverse spiroannulated isobenzofurans, which are otherwise very difficult to synthesize. This reaction proceeds under



Scheme 1. Reagents and conditions: (a) 2-methylfuran, *n*-BuLi, THF, −40 °C, 1 h then **4**, rt, 1 h, 91%; (b) NaH, propargyl bromide, *n*-Bu_4NI, DMF, 2 h, 95%; (c) 3 mol % $AuCl_3$, acetonitrile, 10 min, 93%; (d) furan, *n*-BuLi, THF, −40 °C, 1 h then **4**, rt, 45 min, 78%; (e) NaH, propargyl bromide, *n*-Bu_4NI, DMF, 2 h, 96%; (f) 3 mol % $AuCl_3$, acetonitrile, 10 min, 92%.



Scheme 2. Synthesis of spirocyclic dihydroisobenzofurans.

mild reaction conditions with a catalytic amount of $AuCl_3$ and is moisture tolerant. Further efforts to utilize this pathway towards the synthesis of chiral PKCα inhibitors and diverse ranges of glycosides and nucleosides are currently underway and will be disclosed in due course.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.016.

References and notes

1. (a) Nishizuka, Y. *FASEB J.* **1995**, *9*, 484–496; (b) *Protein Kinase C: Current Topics and Future Perspectives*; Lester, D. S., Epand, R. M., Eds.; Ellis Horwood: New York, 1992.
2. (a) Baba, Y.; Ogoshi, Y.; Hirai, G.; Yanagisawa, T.; Nagamatsu, K.; Mayumi, S.; Hashimoto, Y.; Sodeoka, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2963–2967; (b) Baba, Y.; Mayumi, S.; Hirai, G.; Kawasaki, H.; Ogoshi, Y.; Yanagisawa, T.; Hashimoto, Y.; Sodeoka, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2969–2972.
3. (a) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617–1661; (b) Khasanov, A. B.; Ramirez-Weinhouse, A. B.; Webb, A. R.; Thiruvazhi, M. J. *J. Org. Chem.* **2004**, *69*, 5766–5769; (c) van Hooft, P. A. V.; Leeuwenburgh, M. A.; Overkleeft, H. S.; Van der Marel, G. A.; Van Boeckel, C. A. A.; van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 6061–6064.
4. (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450; (b) Dieters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238; (c) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239–2258.
5. (a) Gurjar, M. K.; Ravindranadh, S. V.; Karmakar, S. *Chem. Commun.* **2001**, 241–242; (b) Kotha, S.; Deb, A. C.; Kumar, R. V. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1039–1043; (c) Holt, D. J.; Barker, W. D.; Jenkins, P. R.; Davies, D. L.; Garratt, S.; Fawcett, J.; Russell, D. R.; Ghosh, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 3298–3300.
6. Hotha, S.; Maurya, S. K.; Gurjar, M. K. *Tetrahedron Lett.* **2005**, *46*, 5329–5332.
7. (a) Hotha, S.; Tripathi, A. *J. Comb. Chem.* **2005**, *7*, 968–976; (b) Hotha, S.; Anegundi, R. I.; Natu, A. A. *Tetrahedron Lett.* **2005**, *46*, 4585–4588; (c) Hotha, S.; Tripathi, A. *Tetrahedron Lett.* **2005**, *46*, 4555–4558; (d) Kashyap, S.; Hotha, S. *Tetrahedron Lett.* **2006**, *47*, 2021–2023.
8. (a) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554; (b) Hashmi, A. S. K.; Ding, L.; Bats, J. W.; Fischer, P.; Frey, W. *Chem. Eur. J.* **2003**, *9*, 4339–4345; (c) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458–7459; (d) Arcade, A.; Bianchi, G.; Marinelli, F. *Synthesis* **2004**, 610–618; (e) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164–11165; (f) Hashmi, A. S. K.; Sinha, P. *Adv. Synth. Catal.* **2004**, *346*, 432–438; (g) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350–5352; (h) Nieto-Oberhuber, C.; Munoz, M. P.; Bunuel, E.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402–2406; (i) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962–6963; (j) Yao, X.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 6884–6885; (k) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 5964–5965; (l) Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669–3671.
9. Sharma, G. V. M.; Reddy, V. G.; Krishna, P. R.; Sankar, A. R.; Kunwar, A. C. *Tetrahedron* **2002**, *58*, 3801–3812.
10. Spiroannulation procedure: To a solution of compound **5** (150 mg, 0.4 mmol) in 5 mL of anhydrous acetonitrile was added $AuCl_3$ (3.6 mg, 3 mol %) in 1 mL of acetonitrile under an argon atmosphere and the resulting mixture stirred at room temperature for 10 min. The reaction mixture was concentrated in vacuo and purified by silica gel column chromatography using 1:4 ethyl acetate and light petroleum as the mobile phase to yield compound **6** as a pale yellow syrup (140 mg, 93%).
11. Compound characterization data:
Compound **5**: $[\alpha]_D$ +59.3 (*c* 1.15, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.29, 1.39, 1.41, 1.63 (4s, 12H), 2.30 (d, 3H, $J = 0.63$ Hz), 2.43 (t, 1H, $J = 2.40$ Hz), 3.32 (dd, 2H, $J = 1.15$, 6.07 Hz), 4.18 (dq, 2H, $J = 2.45$, 14.65 Hz), 4.22 (m, 1H), 4.45 (d, 1H, $J = 3.00$ Hz), 4.71 (d, 1H, $J = 3.89$ Hz), 5.98 (d, 1H, $J = 3.54$ Hz), 6.01 (m, 1H), 6.29 (d, 1H, $J = 3.16$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.4, 24.8, 26.2, 26.6, 26.7, 26.8, 53.9, 63.5, 74.1, 79.6, 80.6, 82.1, 83.4, 104.6, 106.6, 108.3, 110.6, 113.0, 147.4, 152.9; Anal. Calcd for $C_{20}H_{26}O_7$: C, 63.48; H, 6.93. Found: C, 63.37; H, 7.09. Calcd mass for $C_{20}H_{26}O_7$: 378.42. Found: 401.06 (M+23 for Na).
Compound **6**: $[\alpha]_D$ +13.4 (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.19, 1.36, 1.45, 1.67 (4s, 12H), 2.08 (d, 3H, $J = 2.03$ Hz), 3.71 (m, 2H), 3.98 (dd, 1H, $J = 4.02$, 8.36 Hz), 4.30 (d, 1H, $J = 8.09$ Hz), 4.36 (d, 1H, $J = 3.52$ Hz), 5.19 (d, 2H, $J = 2.18$ Hz), 5.23 (br s, 1H), 5.92 (d, 1H, $J = 3.52$ Hz), 6.56 (d, 1H, $J = 7.52$ Hz), 7.03 (d, 1H, $J = 7.52$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 15.0, 25.5, 26.3, 26.7, 26.9, 67.3, 71.7, 74.1, 79.1, 84.4, 94.1, 103.5, 109.4, 112.9, 113.4, 123.4, 126.6, 130.7, 137.2, 148.6; Anal. Calcd for $C_{20}H_{26}O_7$: C, 63.48; H, 6.93. Found: C, 63.07; H, 6.80. Calcd mass for $C_{20}H_{26}O_7$: 378.42. Found: 401.08 (M+23 for Na).
Compound **7**: $[\alpha]_D$ +69.7 (*c* 1.20, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.28, 1.39, 1.40, 1.64 (4s, 12H), 2.44 (t, 1H, $J = 2.52$ Hz), 3.29 (d, 1H, $J = 1.43$ Hz), 3.33 (d, 1H, $J = 0.77$ Hz), 4.21 (dq, 2H, $J = 2.49$, 14.51 Hz), 4.12 (m, 1H), 4.45 (d, 1H, $J = 3.41$ Hz), 4.74 (d, 1H, $J = 3.80$ Hz), 6.00 (d, 1H, $J = 3.67$ Hz), 6.45 (d, 2H, $J = 1.32$ Hz), 7.47 (t, 1H, $J = 1.40$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.1, 26.4, 26.8, 26.9, 54.3, 63.8, 74.1, 74.2, 79.6, 80.9, 82.0, 83.8, 104.8, 108.5, 109.8, 110.8, 113.3, 143.1, 149.9; Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.63; H, 6.64. Found: C, 62.47; H, 6.78. Calcd mass for $C_{19}H_{24}O_7$: 364.39. Found: 387.06 (M+23 for Na).
Compound **8**: $[\alpha]_D$ +9.1 (*c* 1.40, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.17, 1.36, 1.41, 1.67 (4s, 12H), 3.64 (m, 1H), 3.78 (dd, 1H, $J = 5.85$, 8.40 Hz), 3.94 (dd, 1H, $J = 4.93$, 8.48 Hz), 4.30 (d, 1H, $J = 7.84$ Hz), 4.37 (d, 1H, $J = 3.52$ Hz), 5.12 (m, 2H), 5.94 (d, 1H, $J = 3.57$ Hz), 6.11 (br s, 1H), 6.65–6.74 (m, 2H), 6.92 (d, 1H, $J = 8.53$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.4, 26.3, 26.6, 26.9, 67.2, 73.3, 73.9, 79.3, 84.3, 93.3, 103.5, 108.4,

109.3, 113.4, 114.8, 122.3, 129.0, 142.2, 156.9; Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.63; H, 6.64. Found: C, 62.39; H, 6.67. Calcd mass for $C_{19}H_{24}O_7$: 364.39. Found: 387.06 (M+23 for Na).

Compound **9**: $[\alpha]_D$ +18.6 (*c* 1.40, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.23, 1.36, 1.48, 1.68 (4s, 12H), 3.78–3.95 (m, 2H), 4.06 (m, 1H), 4.33 (d, 1H, $J = 8.29$ Hz), 4.37 (d, 1H, $J = 3.53$ Hz), 5.22 (m, 2H), 5.93 (d, 1H, $J = 3.60$ Hz), 6.30 (d, 1H, $J = 7.62$ Hz), 6.57 (br s, 1H), 6.61 (d, 1H, $J = 7.62$ Hz), 7.03 (t, 1H, $J = 7.62$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.3, 26.3, 26.7, 26.9, 67.5, 71.8, 73.9, 79.0, 84.3, 94.2, 103.5, 107.8, 112.9, 113.5, 114.8, 126.6, 129.2, 139.3, 150.8; Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.63; H, 6.64. Found: C, 62.57; H, 6.89. Calcd mass for $C_{19}H_{24}O_7$: 364.39. Found: 387.06 (M+23 for Na).

12. See Supplementary data for ^1H, ^{13}C and DEPT NMR spectral charts. All products gave satisfactory ^1H, ^{13}C, DEPT NMR and CHNS analysis.