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Mendeleev Commun., 2012, **22**, 252–253
Mendeleev Communications

A new approach to the synthesis of 15-A_{2t}IsoP isoprostane and 14-A_{4t}NeuroP neuroprostane

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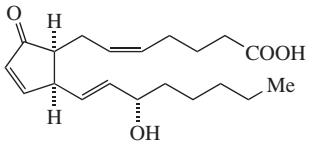
DOI: 10.1016/j.mencom.2012.09.008

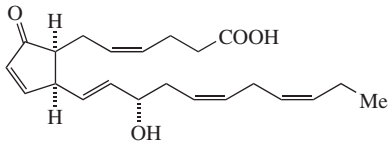
A formal synthesis of the title natural cyclopentanoids was implemented based on intramolecular [3+2] cycloaddition in unsaturated silyl nitronates at the key step.

15-A_{2t}IsoP isoprostane **1** and 14-A_{4t}NeuroP neuroprostane **2** are representatives of natural cyclopentanoids which, unlike prostaglandins, are characterised by a *cis* arrangement of the side chains and are formed *in vivo* as racemates[1] during nonenzymatic free-radical oxidation of arachidonic and docosahexaenoic acids, respectively. For this reason, they attract the attention of researchers as warning agents for the early detection of human diseases associated with oxidative stress, in particular, Alzheimer's disease.[1]



15-A_{2t}IsoP

1

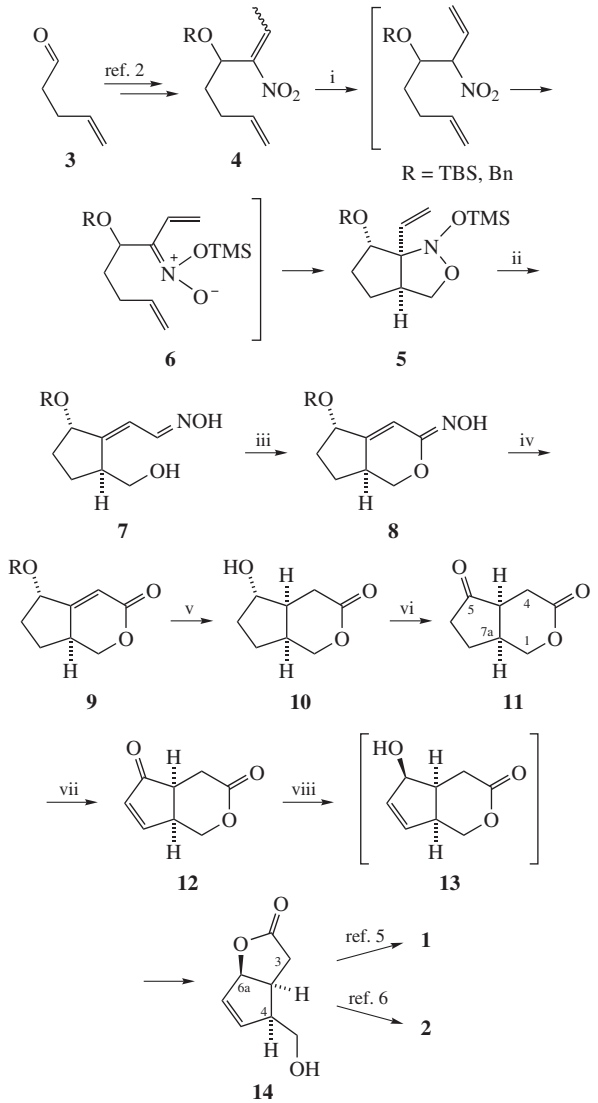


14-A_{4t}NeuroP

2

In this work we used our ongoing methodology[2] to approach compounds **1** and **2** that are hard to obtain from natural sources. This method is based on the stereoselective pentaannelation of acyclic δ-nitro olefins by intramolecular dipolar [3+2]-cycloaddition in the corresponding silyl nitronates (Scheme 1). In fact, silylation of nitro dienes **4** accessible from unsaturated aldehyde **3** in both cases results in stereoselective formation of the corresponding isoxazolidines **5**, whose obvious precursors are the unsaturated silyl nitronates **6** generated *in situ*.[2] Using the known techniques,[2] cyclopentaisoxazolidines **5** were converted *via* the corresponding intermediate hydroximino derivatives **7**, **8** to unsaturated lactones **9**. Catalytic hydrogenation of the latter† occurred stereoselectively to give cyclopentavalerolactone **10**.

Hydroxy lactone **10** was oxidised with PCC and the resulting ketone **11** was α,β-dehydrogenated with a mixture of IBX and NMO (*cf.* ref. 3). Chemoselective reduction of enone **12** was attained with the $NaBH_4$–$CeCl_3$ system. This process apparently gives unstable hydroxy lactone **13**, which undergoes intramolecular translactonisation during standard treatment of the reaction mixture to afford another isomeric lactone **14**.[4,‡] The latter was previously used to obtain 15-A_{2t}IsoP isoprostane **1**[5] and 14-A_{4t}NeuroP neuroprostane **2**.[6]



Scheme 1 *Reagents and conditions*: i, HMDS, Et_3N; ii, KF or NH_4F, MeOH; iii, NCS, Et_3N, $CHCl_3$; iv, IBX, DMF, THF; v, HCl, MeOH (for **9**, R = TBS), H_2, 10% Pd/C, EtOH; vi, PCC–Al_2O_3, CH_2Cl_2, 20 °C, 95%; vii, IBX, NMO, DMF, 20 °C, 64%; viii, $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 81%.

† Lactone **9** (R = TBS) was subjected to preliminary desilylation[2(b)] since its hydrogenation is less stereoselective.[2(a)] Hydrogenation of lactone **9** (R = Bn) is accompanied by debenzylation.

Thus, the reaction sequence we performed is a formal total synthesis of these natural compounds. It should also be noted that this approach can obviously be extended to syntheses of some other iso- and neuroprostanes.

The study was supported by the Russian Foundation for Basic Research (grant no. 10-03-00089).

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Received: 11th March 2012; Com. 12/3894

‡ *(4a*S*,7a*S*)-Hexahydrocyclopenta[c]pyran-3,5-dione* **11**. A suspension containing PCC (0.8 g, 3.55 mmol) and Al_2O_3 ('Neutral according to Brockman', 1.5 g) premixed and ground in a mortar, and hydroxy lactone **10**[5] (0.33 g, 2.11 mmol) in CH_2Cl_2 (10 ml), were stirred for 8 h at 20 °C. The reaction mixture was then diluted with Bu^{t}OMe and transferred in a column packed with SiO_2 stabilised with Bu^{t}OMe. Elution with EtOAc gave 0.31 g (95%) of keto lactone **11** as colourless crystals, mp 54–56 °C (Bu^{t}OMe). IR ($CHCl_3$, ν/cm^{-1}): 667, 728, 789, 955, 1065, 1080, 1167, 1208, 1243, 1389, 1412, 1424, 1604, 1747, 2892, 2960, 3021. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 1.72–1.87 (m, 1H, HC^7), 2.15–2.48 (m, 3H, H′C^7, HC^6), 2.61–2.80 (m, 3H, H_2C^4, HC^{7a}), 2.86 (m, 1H, HC^{4a}), 4.06 (dd, 1H, HC^1, *J* 7.33 and 11.62 Hz), 4.34 (dd, 1H, HC^1, *J* 4.45 and 11.62 Hz). ^{13}C NMR (75.03 MHz, $CDCl_3$) δ: 22.52, 28.56 and 36.60 (C^4, C^6, C^7), 33.47 (C^{7a}), 42.30 (C^{4a}), 69.51 (C^1), 170.75 (C^5), 216.78 (C^3). HRMS (ESI), *m*/*z*: 155.0699 $[M+H]^+$ (calc. for $C_8H_{10}O_3$: 155.0703), 177.0518 $[M+Na]^+$ (calc. for $C_8H_9O_3Na$: 177.0522).

*(4a*S*,7a*S*)-1,4,4a,7a-Tetrahydrocyclopenta[c]pyran-3,5-dione* **12**. A mixture of IBX (616 mg, 2.2 mmol) and NMO (297 mg, 2.2 mmol) in DMF (1.5 ml) was stirred for 20 min at 20 °C, then keto lactone **11** (154 mg, 1 mmol) was added to the resulting homogeneous solution. The reaction mixture was stirred for 20 h at 20 °C, then diluted with Bu^{t}OMe and filtered through a short pad of SiO_2 with final washing with EtOAc. The combined eluates were concentrated *in vacuo* and the residue was chromatographed on SiO_2. Elution with EtOAc gave 98 mg (64%) of compound **12** as colourless crystals, mp 114–116 °C (Bu^{t}OMe). IR (KBr, ν/cm^{-1}): 590, 649, 788, 925, 990, 1042, 1069, 1131, 1204, 1237, 1388, 1420, 1584, 1697, 1739, 2929–3129. ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 2.78–2.96 (m, 3H, H_2C^4, HC^{4a}), 3.45 (m, 1H, HC^{7a}), 4.29 (dd, 1H, HC^1, *J* 4.0 and 11.9 Hz), 4.48 (dd, 1H, H′C^1, *J* 4.5 and 11.9 Hz), 6.39 (dd, 1H, HC^6, *J* 2.1 and 5.8 Hz), 7.62 (dd, 1H, HC^7, *J* 2.6 and 5.8 Hz). ^{13}C NMR (50.03 MHz, $CDCl_3$) δ: 30.83 (C^4), 40.41 and 40.47 (C^{4a}, C^{7a}), 66.90 (C^1), 136.52 (C^6), 162.42 (C^7), 170.05 (C^5), 207.59 (C^3). HRMS (ESI), *m*/*z*: 153.0550 $[M+H]^+$ (calc. for $C_8H_8O_3$: 153.0546), 175.0358 $[M+Na]^+$ (calc. for $C_8H_7O_3Na$: 175.0366).

*(3a*S*,4*S*,6a*S*)-4-Hydroxymethyl-3,3a,4,6a-tetrahydrocyclopenta-[b]furan-2-one* **14**. $NaBH_4$ (23 mg, 0.6 mmol) was added to a solution of keto lactone **12** (61 mg, 0.4 mmol) and $CeCl_3 \cdot 7H_2O$ (164 mg, 0.44 mmol) in MeOH (4 ml) with stirring at 0 °C under argon. After 30 min, the reaction mixture was treated with 1 N HCl (0.4 ml), then concentrated *in vacuo* and extracted with EtOAc. The extract was dried with Na_2SO_4 and concentrated *in vacuo*; the residue was chromatographed on SiO_2. Elution with EtOAc gave 50 mg (81%) of hydroxy lactone **14** as a colourless oil, R_f 0.1 (Silufol, EtOAc). ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 2.03 (br. s, 1H, OH), 2.60–2.71 (m, 2H, H_2C^3), 3.07 (m, 1H, HC^4), 3.24 (m, 1H, HC^{3a}), 3.67 (dd, 1H, C*H*OH, *J* 6.4 and 11.0 Hz), 3.78 (dd, 1H, C*H′*OH, *J* 4.8 and 11.0 Hz), 5.46 (dd, 1H, HC^{6a}, *J* 1.3 and 7.4 Hz), 6.05 (br. s, 2H, HC^5, HC^6). ^{13}C NMR (50.03 MHz, $CDCl_3$) δ: 29.85, 37.89, 49.00, 61.63, 88.90, 129.98, 138.37, 177.93 (*cf.* ref. 4).