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Target cum flexibility: synthesis of *C*(3′)-spiroannulated nucleosides

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ABSTRACT

We report a simple strategy for the synthesis of a collection of *C*(3′)-spirodihydroisobenzo-furannulated nucleosides featuring a [2+2+2]-cyclotrimerization as the key reaction. The cyclotrimerization reactions are facile with the unprotected nucleosides having a diyne unit. When both alkynes of the diyne are terminal, the regioselectivity is poor. However, when one of the terminal alkynes is additionally substituted, the cyclotrimerizations are highly diastereoselective. Since the key bicycloannulation is the final step, this strategy provides flexibility in terms of the alkynes and is thus amenable for the synthesis of a focussed small molecule library.

Modification of the sugar backbone in nucleosides is an important therapeutic approach for developing small molecules that control genetic disorders or infections.[1] There are several approaches for the modification of nucleosides.[2–4] The spiroannulation on the sugar backbone is one of the recent approaches for the modified nucleosides.[3,4] Considering the prevalence of the dihydroisobenzofuran structural unit in many of the naturally occurring substances, and drug candidates, our intention has been to spiro-annulate a dihydroisobenzofuran unit on the nucleoside templates.[5] We have recently documented the feasibility of cyclotrimerization of sugar derived diynes and shown that the resultant products can be transformed to the tricyclic and *C*(3′)-spirobenzoisofuran-annulated nucleosides following a sequence of simple chemical transformations. However, in the latter case, the sugar ring was a pentopyranose unit. Also, this strategy is not sufficiently effective as the number of compounds to be accessed is restricted by the limited number of nucleobases available which are introduced at the penultimate step of the synthesis. In addition, it may require additional steps if one intends to place sensitive functional groups on the isobenzofuran ring. This has prompted us to look for an alternative approach which can effectively address the library size and the ease of alteration of the functional groups on the isobenzofuran ring. This has led us into the exploration of the key *C*(3′)-spiroannulation as the final step by means of [2+2+2]-cyclotrimerization of completely free nucleoside-diynes with alkynes.[6–8] Figure 1 provides the salient features of this approach.

The diynes **1–3** have been selected as suitable precursors for the final tricyclic nucleosides. In our earlier investigations, we realized that the peracetylation of *C*(3′)-modified *ribo*-pentose derivatives provide exclusively the corresponding pyranose derivatives.[9] This warrants a suitable protecting group at the *C*(5)–OH which should be stable during the 1,2-*O*-acetonide hydrolysis and at the same

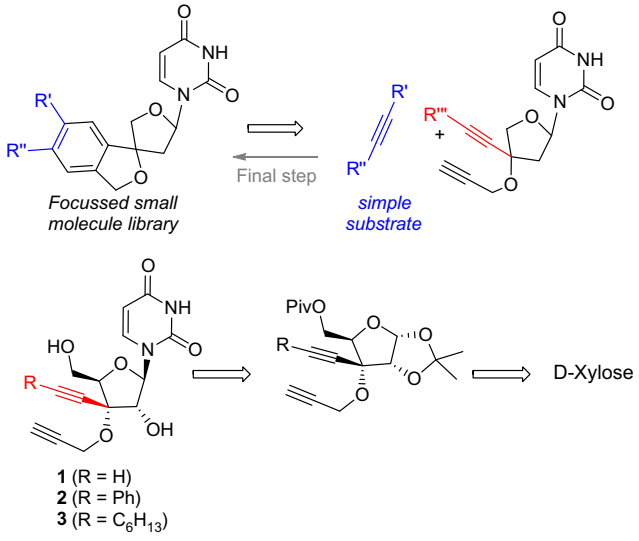

Figure 1. A flexible approach for C(3′)-[2+2+2] approach for spiroannulated nucleosides.

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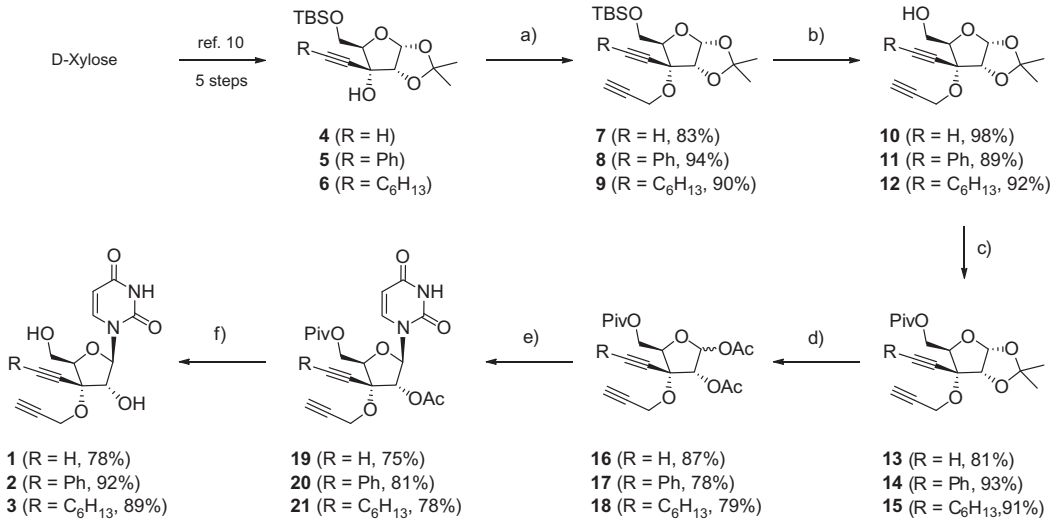
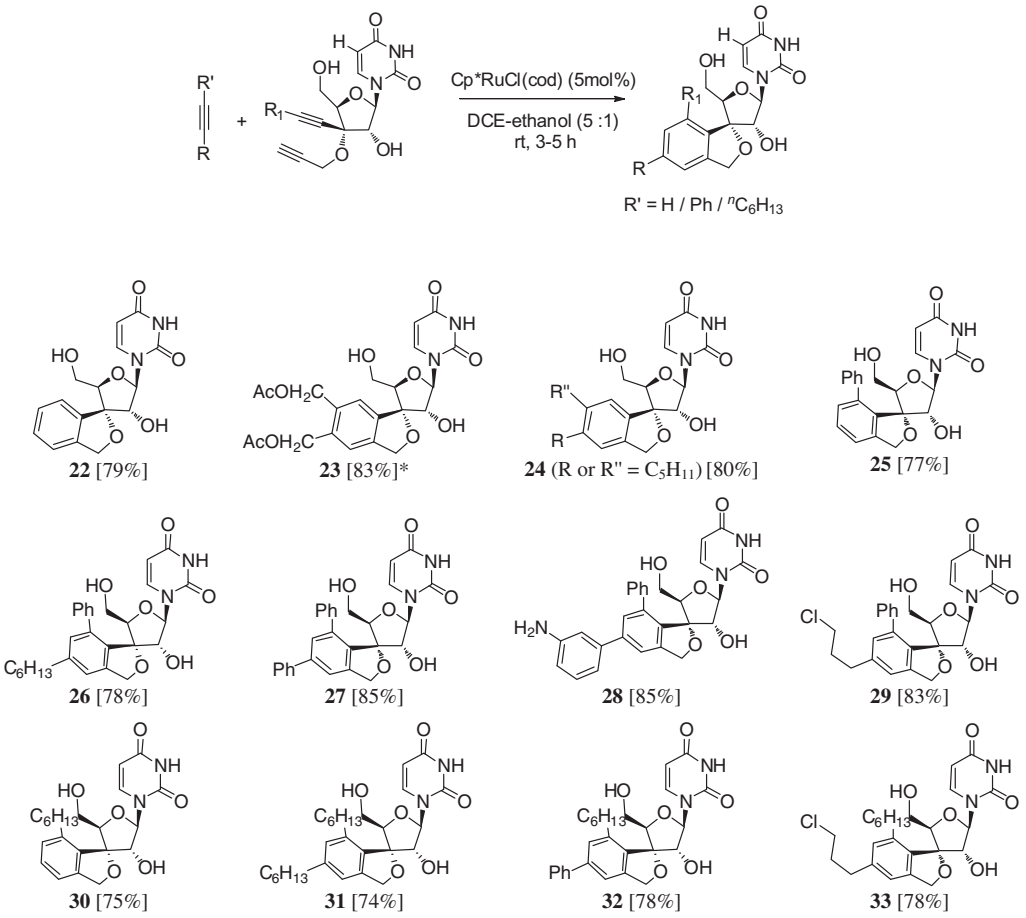


Scheme 1. Reagents and conditions: (a) NaH, Propargyl bromide, THF, 0 °C–rt, 3 h; (b) TBAF, THF, rt, 8 h; (c) PivCl, Et_3N, DMAP, CH_2Cl_2, 0 °C–rt, 6 h; (d) i. 60% AcOH, reflux, 2 h; ii. Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1 h; (e) uracil, N,O-bis(trimethylsilyl)-acetamide (BSA), TMSOTf, CH_3CN, 50 °C, 2 h; (f) NaOMe, MeOH, rt, 20 min.



* Wilkinson catalyst, toluene/ethanol (4:1), 80 °C, 8 h.

Scheme 2. Scope of cyclotrimerization reactions of the diynes **1**–**3**.

time, should be removed during the saponification. A pivaloyl protection at *C*(5)-OH has been opted for in this regard.

Synthesis of the key diynes **1–3** started with the propargylation of the known intermediates **4–6** (Scheme 1).[10] The resulting compounds **7–9** were subjected to the deprotection of the TBS ether using TBAF in THF to afford the alkynols **10–12** respectively. The free hydroxyl group in alkynols **10–12** was protected as pivolate by treatment with pivaloyl chloride and Et_3N. Selective

acetonide hydrolysis of the resulting pivaloates **13–15** followed by peracetylation (Ac_2O/Et_3N) gave a 1:1 anomeric mixture of diacetates **16**–**18,** respectively. The glycosidation of the anomeric mixtures of **16–18** was carried out under modified Vorbrüggen[11] conditions employing uracil as the glycosyl acceptor to afford the protected nucleosides **19–21,** respectively. Subjecting **19–21** to Zemplen's deacetylation afforded the uridines **1–3** having the key diyne unit for the cycloisomerization reactions.

With the fully elaborated diyne frameworks in place, we attempted the cyclotrimerization of diynes **1–3** with symmetric and unsymmetric alkynes (Scheme 2). The trimerization reactions with acetylene proceeded effectively with 5 mol % of Cp*RuCl(cod)[12] (in dichloroethane–ethanol mixture) at rt in a sealed tube to afford the products **22**,[14] **25** and **30,** respectively from the diynes **1–3** (75–79% yield). The diacetate of 2-butyne-1,4-diol, *bis*-(trimethylsilyl)-acetylene and dimethylacetylene dicarboxylate were explored as the representative symmetric disubstituted alkynes for the trimerization reactions. Amongst the three alkynes, the cyclotrimerization of diyne **1** with the diacetate of 2-butyne-1,4-diol was facile with the Wilkinson's catalyst[13] (4:1 toluene-ethanol, 80 °C, 8 h) and yielded **23**. With the other two alkynes, the formation of a complex mixture was observed. The attempted cyclotrimerization of diynes **2** and **3** with any of the above alkynes was found to be unsuccesful at different temperatures and intact diynes **2** or **3** were isolated.

Coming to the terminal alkynes, the cyclotrimerization reaction of diyne **1** with 1-heptyne [using 5 mol % of Cp*RuCl(cod) in dichloroethane, rt] is clean and gave a 1:1 regiomeric mixture **24** in 80% yield. Under similar conditions, the cyclotrimerization of diynes **2** and **3** with 1-octyne as a substrate proceeded smoothly and gave the corresponding nucleosides **26** and **31** in good yields (78% and 74%) and with complete regioselectivity. For example in the ^{1}H NMR spectrum of **31**, the two aromatic protons appeared as singlets at δ 6.85 and 6.95 ppm. The regioselectivity noticed with the trimerization of diynes **2** and **3** endorses them for further exploration in constructing the spiro-nucleosides library. Next the cyclotrimerization reactions with the diynes **2** and **3** were explored employing diverse terminal alkynes such as phenyl acetylene[15] and 1-chloro-4-pentyne and 3-aminophenylacetylene to understand the tolerance for the functional groups such as the alkyl chloride and the amino group. The reactions in general are clean, the regioselectivity was excellent, and products are obtained in good yields (78–83%). The chloro functional group present in the products **29** and **33**, amino group in **28** provide a suitable handle for further diversification.

In conclusion, a simple protocol comprising the [2+2+2]-cyclotrimerisation of the fully deprotected nucleoside diynes as the last step of the process has been developed for a rapid access to *C*(3′)-dihydroisobenzofuran spiroannulated nucleosides. During the synthesis of the penultimate furanose-nucleoside diynes, we have shown that proceeding with ribofuranose intermediates having a pivaloyl protection at *C*(5)-OH is a reliable approach to avoiding unwanted pyranose formation during the hydrolysis and peracetylation.

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Supplementary data

Supplementary data (^{1}H-, ^{13}C- DEPT and MS of selected compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.100.

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14. *General Procedure for compounds **22, 25,** and **30:*** A solution of diyne **1–3** (0.6 mmol) in 1,2-dichloroethane (10 mL) was degassed with dry acetylene for 20 min; then, Cp*RuCl(cod) catalyst (0.03 mmol) was introduced into the mixture. The reaction mixture was sealed with septum and a copper wire and cooled to −78 °C, and acetylene gas was condensed by continuous bubbling for 25 min. and the mixture was stired for 4–6 h at room temperature. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography to afford the cyclotrimerized product. *Spectral data of compound* **22**: Colorless liquid, yield: 78%, $[\alpha]_D^{25}$ +5.7 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) *v*: 3020, 2929, 1698, 1385, 1216, 1046, 929, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, *J* = 6.8 Hz, 3H), 1.24–1.37 (m, 6H), 1.53–1.66 (m, 2H), 2.05 (quint, *J* = 7.3 Hz, 2H), 2.59–2.66 (m, 1H), 2.75 (t, *J* = 7.3 Hz, 3H), 3.43 (dd, *J* = 3.3, 12.1 Hz, 1H), 3.51 (t, *J* = 6.3 Hz, 3H), 3.75 (dd, *J* = 7.5, 12.1 Hz, 1H), 4.33 (dd, *J* = 3.3, 7.3 Hz, 1H), 4.56 (t, *J* = 8.2 Hz, 1H), 5.06 (d, *J* = 12.3 Hz, 1H), 5.13 (d, *J* = 12.3 Hz, 1H), 5.78 (d, *J* = 8.1 Hz, 1H), 5.87 (d, *J* = 8.1 Hz, 1H), 6.88 (s, 1H), 6.98 (s, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 9.40 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 22.6 (t), 29.7 (t), 31.7 (t), 31.9 (t), 32.3 (t), 33.4 (t), 33.8 (t), 44.1 (t), 61.7 (t), 71.9 (t), 76.3 (d), 86.5 (d), 89.0 (d), 92.1 (s), 103.2 (d), 118.9 (d), 129.8 (d), 131.1 (s), 137.7 (s), 140.4 (d), 141.2 (s), 142.1 (s), 150.7 (s), 163.0 (s) ppm; MALDI-TOF: 515.03 (82%, $[M+Na]^+$), 531.00 (100%, $[M+K]^+$).
15. *General Procedure for [2+2+2]-cyclotrimerization:* A solution of diyne (0.6 mmol) with terminal alkyne (0.6 mmol) in dry 1,2-dichloroethane was degassed with dry argon for 20 min. To this, Cp*RuCl(cod) catalyst (0.03 mmol) was added, and the mixture was stirred for 4–6 h at room temperature. The solvent evaporated under reduced pressure. The residue was purified by silica gel chromatography to procure the cyclotrimerization product. *Spectral data of compound* **27**: White solid, yield: 85%, mp: 270–272 °C; $[\alpha]_D^{25}$ +35.0 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) *v*: 3020, 2925, 1694, 1526, 1046, 929, 669 cm^{-1}; ^1H NMR ($CDCl_3$+CD_3OD, 400 MHz): δ 3.29 (dd, *J* = 6.6, 12.1 Hz, 1H), 3.35 (dd, *J* = 4.0, 12.1 Hz, 1H), 4.20 (dd, *J* = 4.2, 6.4 Hz, 1H), 4.47 (d, *J* = 8.2 Hz, 1H), 5.25 (s, 2H), 5.58 (d, *J* = 8.2 Hz, 1H), 6.07 (d, *J* = 8.1 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 7.36–7.51 (m, 10H), 7.60 (dd, *J* = 1.2, 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$+CD_3OD, 100 MHz): δ 61.8 (t), 70.4 (t), 76.4 (d), 85.4 (d), 86.6 (d), 93.1 (s), 102.7 (d), 118.8 (d), 127.0 (3C, d), 127.8 (d), 128.0 (d), 128.3 (d), 128.7 (2C, d), 129.4 (2C, d), 130.0 (s), 130.8 (d), 138.5 (s), 139.5 (s), 139.8 (s), 139.9 (d), 142.0 (s), 142.9 (s), 151.0 (s), 163.7 (s) ppm; MALDI-TOF: 507.02 (70%, $[M+Na]^+$), 522.97 (100%, $[M+K]^+$).