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A free radical approach to the synthesis of the 1,7-dioxaspiro[4,4]nonane ring system from carbohydrate templates

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Abstract—The triphenyltin hydride-mediated free radical cyclization of the radical precursors **1**, **7** and **12** is described. This is a new stereoselective entry into the 1,7 dioxaspiro[4,4]nonane ring system.

In the last 14 years our laboratory has been actively working on free radical cyclization[1] strategies for the synthesis of polyhydroxylated heterocycles and carbocycles (inositols) using readily available precursors derived from carbohydrates.[2]

Continuing with our efforts in this area we herein report the hitherto unexplored triphenyltin-mediated free radical cyclization of radical precursors **1**, **7** and **12** as a new stereoselective entry into the 1,7-dioxaspiro[4,4]nonane **A** ring system (Chart 1). This structural motif is present in a number of natural products, such as prehispanolone[3] (Chart 1), which possesses interesting biological and pharmaceutical properties. Alternative synthetic approaches to compounds containing this key structural unit have been reported.[4]

Our current approach to synthesize the 1,7-dioxaspiro[4,4]nonane ring system relies on the formation of the C3–C4 bond in compounds of type **A** via a 5-*exo*-*trig* free radical cyclization of vinyl radical species obtained by the reaction of triphenyl(or butyl)tin hydride with the acetylene group embodied within the 4-oxa-hept-1-en-6-yne moiety of a radical precursor such as **B** (Chart 1).[5] Structures of type **B** are present in compounds of type **C** which are derived from sugar templates (Chart 1).

For our preliminary studies we selected **1**, which was prepared in two steps from the known and readily available 1,2-*O*-isopropylidene-5-*O*-trityl-α-D-*erythro*-pentofuranos-3-ulose **2**[6] (Chart 3). Thus, **2** was reacted with ethynylmagnesium bromide [THF, 0°C, 12 h

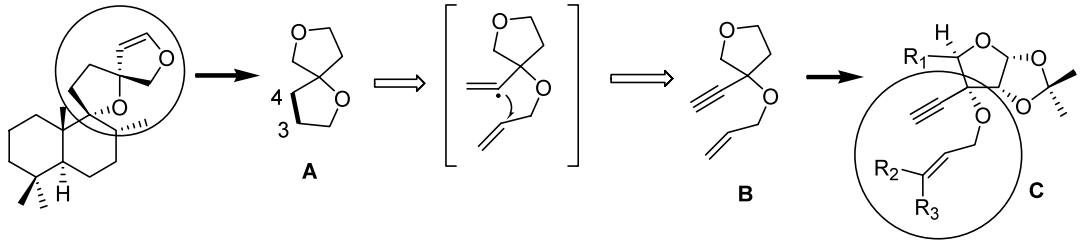

Chart 1.

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(78%)] to give the alcohol **3**[7] (Chart 3), which was subsequently *O*-allylated [allyl bromide, NaH, DMF, 25°C, 14 h (84%)] to give **1**.

With compound **1** in our hands we were able to investigate the aforementioned type of free radical cyclization reaction under standard conditions.[8,9] After the reaction had reached completion, a complex mixture of products was observed. The ^{1}H NMR spectrum of the crude product mixture revealed the presence of three products corresponding to two 5-*exo* and one 6-*endo* compounds, in a 1:1:1 ratio (Chart 2). Careful column chromatography of the mixture resulted in the isolation of the *endo* product **4** (unassigned stereochemistry at the *exo*-double bond), a mixture of **4** and **5** (one of the four possible 5-*exo* resulting products) and the product **6**. Spectroscopic data and detailed NMR analysis[8] of **6** showed it to be a different 5-*exo* product to those of **4** and **5** and to have the (*E*)-stereochemistry at the *exo*-double bond and the (*R*)-absolute configuration at the newly formed stereocenter (C-3′, Chart 2). The ^{1}H NMR spectrum of the mixture of **4** and **5**, showed that, in addition to the signals observed for compound **4**,[8] product **5** (unassigned stereochemistry at the *exo*-double bond, and at C-5′) also showed a diagnostic doublet at $\delta = 0.81$ ($J = 7.0$ Hz, H-5′), a singlet at 5.89 (H-6′) and a doublet at 5.80 ($J = 3.6$ Hz, H-1). In summary, although the total yield for the product mixture was acceptable (50%)[8b] the regioselectivity (the 6-*endo* versus 5-*exo* mode of cyclization) was very poor. Unfortunately, all of our efforts directed towards obtaining destannylated products via the reaction of *n*-BuLi (THF, −78°C)[10] with **6** or the mixture of compounds **4** and **5** gave complex mixtures, which were not fully resolved by column chromatography. However, ^{1}H NMR spectroscopy of the isolated fractions clearly showed, surprisingly, that the reaction with *n*-BuLi gave new tributylstannylated materials[11] resulting from phenyl to butyl interchange, instead of the expected destannylated products. This result prevented unequivocal determination of whether or not the 5-*exo* products **5** and **6** have the same stereochemistry at the *exo*-double bond and the same absolute configuration at the newly formed stereocenter. However, since the ^{1}H NMR spectrum of the mixture of **5** and **6** showed the same chemical shifts for H-6′, but significantly different shifts for C(5′)H_3, it was concluded that they probably have the same stereochemistry at the *exo*-double bond (*E*) but different absolute configurations at C3′ (Chart 2).

The starting material **7**, used in our studies (Chart 2) was obtained by *O*-allylation (50%) of 3-*C*-ethynyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose **8**[12] (Chart 3). The reaction of **7** under standard conditions,[9] was found to reach completion after 32H, to give a mixture of the 6-*endo* **9** and 5-*exo* products **10** and **11** in 61% total yield (Chart 2). The ratio of isomers [(**9** and the pair **10** and **11**; 1:2) (**10** and **11**; 1:3)] in the crude reaction mixture was determined by ^{1}H NMR spectroscopy. Careful column chromatography enabled the isolation of the pure product **9** (unassigned stereochem-

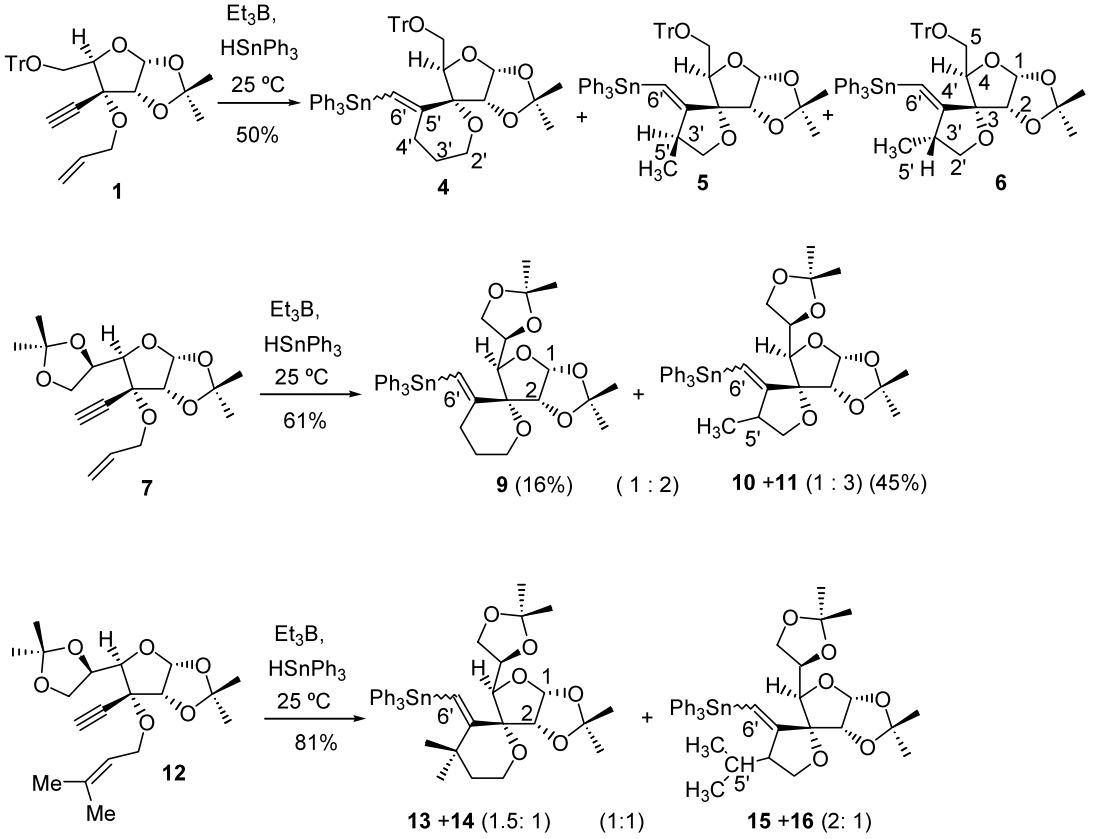

Chart 2. Triphenyltin hydride-mediated free radical cyclization reaction of the precursors **1**, **7** and **12**.

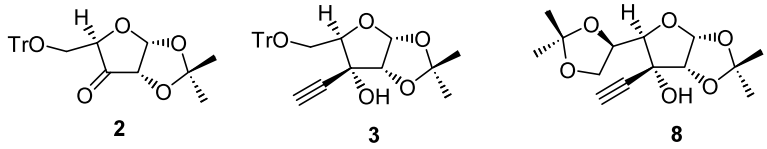

Chart 3.

istry at the exo-double bond), and a mixture of isomers **9**, **10** and **11** in the ratio 1:1.5:2. The ^{1}H NMR spectrum of the isomer **9** showed typical signals at $\delta = 5.71$ (d, $J = 3.8$ Hz, H-1), 5.51 (s, H-6′) and 4.57 (d, $J = 3.8$ Hz, H-2), while in the ^{1}H NMR spectrum of the mixture of **10** and **11** showed the expected doublets for the methyl group at $\delta = 0.91$ ($J = 7$. Hz) and 0.83 ($J =$ 7.2 Hz). As previously described, treatment of the mixture of compounds **9**–**11** with *n*-BuLi afforded a very complex reaction mixture, which was not resolved by chromatography and hence could not be further investigated.[11]

With the aim of minimizing the formation of *endo*-products in the aforementioned cyclizations studies were focused on the use of compound **12** which was obtained in 71% yield (Chart 2) from the intermediate **8** (Chart 3). Compound **12** was chosen on the basis that the presence of two methyl groups in the terminal position of the alkene group would impede formation of the undesired *endo* derivatives. Thus, cyclization of **12** gave a crude mixture which, by ^{1}H NMR spectroscopy, showed the presence of the pair of *endo*-products **13** and **14** in a 1.5:1 ratio and a pair of *exo*-compounds **15** and **16** in a 2:1 ratio; the *endo*- and *exo*-pairs were in the ratio 1:1. The two pairs of cyclized products were isolated by column chromatography in 81% total yield. The pair of *endo*-isomers **13** and **14** was obtained in the ratio of 1.6:1 (39% yield). The ^{1}H NMR spectrum of the mixture showed signals for the major isomer **13** at $\delta = 6.17$ (d, $J = 1.9$ Hz, H-6′), 4.98 ($J = 4.1$ Hz, H-1), 1.39, 1.24, 1.06, 0.99, 0.93, 0.87 (6 s, 6×CH_3), and for the mino isomer **14** $\delta = 6.09$ (d, $J = 2.4$ Hz, H-6′), 4.98 ($J = 4.1$ Hz, H-1). Additional chromatographic fractions were also obtained which possessed a mixture of **13**, **14**, **15** and **16** in the ratio 1:1: 1.3: 3.3 (36% total yield), and a mixture of the three 5-*exo* products **15**, **16** and **17** (6%) in the ratio 2.6: 1.5:1. It is notable that the minor isomer **17** identified in this fraction could not be detected in the ^{1}H NMR spectrum of the crude reaction mixture. The ^{1}H NMR spectrum of the mixture showed signals for the major isomer **15** at $\delta = 5.83$ (d, $J = 1.6$ Hz, H-6′), 5.71 ($J = 3.5$ Hz, H-1), 0.70, 0.26 (2 d, $J = 7$ Hz, CH_3), the isomer **16** at $\delta = 6.00$ (d, $J = 2.0$ Hz, H-6′), 5.66 ($J = 3.4$ Hz, H-1), 0.57, 0.34 (2 d, $J = 6.9$ Hz, CH_3) and minor isomer **17** at $\delta = 6.19$ (br s, H-6′), 5.37 ($J = 4.0$ Hz, H-1).

The stereo- and regiochemical results obtained in this work encouraged us to undertake a computational study of these processes.[13] Thus the cyclization of compound **1** (Chart 4), was modeled, using semiempirical PM3 calculations,[14a] while taking into account the preferred conformers in the transition state for the eight possible structures, the *E*/*Z* stereochemistry at the *exo*-double bond and the *R*/*S* configuration at the newly formed stereocenters, via either chair or boat conformations, to give the 5-*exo* products. In addition, we have performed energy calculations at a DFT level[14b] on these optimized structures in order to obtain more accurate differences in energy between all the possible structures in the transition state. From these results it became clear that the chair were more stable than the boat forms with structures **D1** and **D2** (Chart 5), both

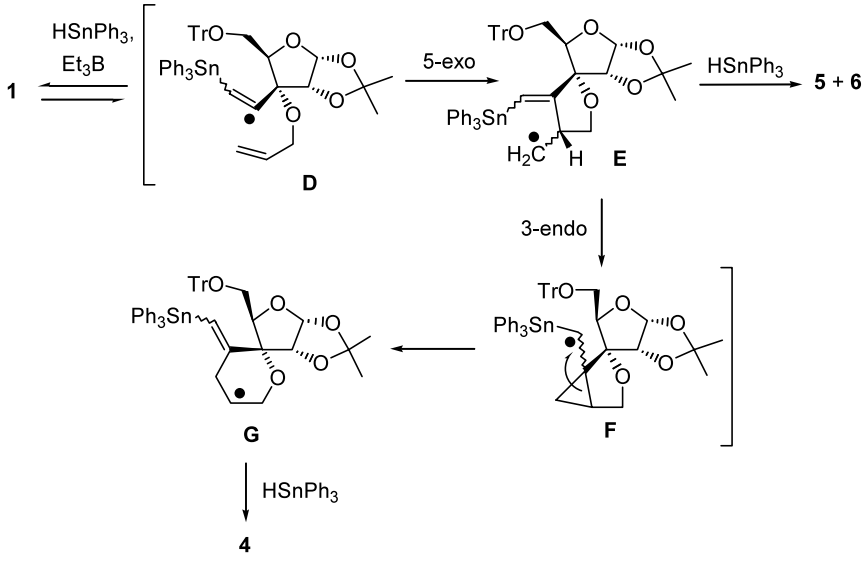

Chart 4. Mechanism for the formation of the products **4**–**6** from the radical precursor **1**.

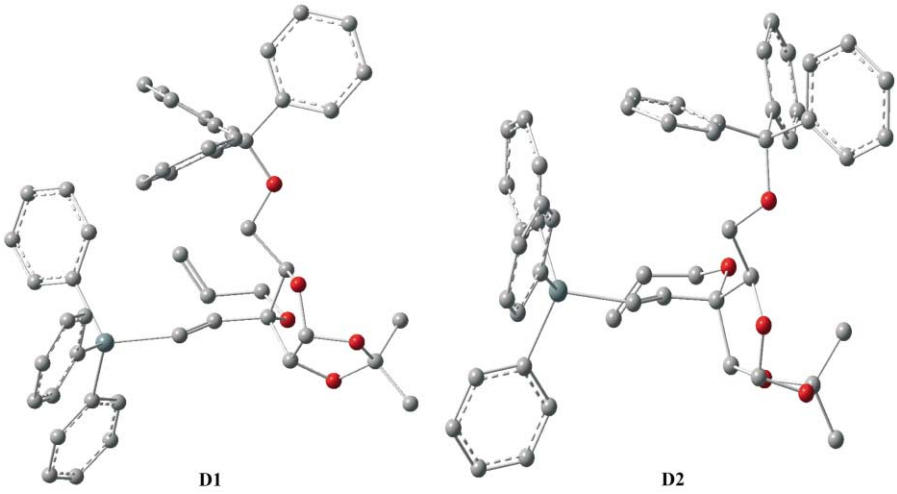

Chart 5. Structures of the **D1** and **D2** conformers in the transition state.

chairs with *E* stereochemistry, being the most stable. Structure **D2** (leading to compound **5**) was only 1.44 kcal/mol ($\Delta E_{DFT+ZPE}$) more stable than **D1** (leading to compound **6**). Structures **D1** (78.52 kcal/mol) and **D2** (79.53 kcal/mol) also showed similar values for the heat formation (H_f, PM3 level).

Regarding the 6-*endo* product, a parallel computational analysis from structure **D1** showed that[15] from the E_{DFT} (a.u.) values, this transition structure presented the highest energy value of all the structures involved in the process (so the formation of **D1** can be assumed as the rate limiting step), and intermediate **G** (–2300.301894) was more stable than intermediate **E** (–2300.292130) (Chart 4), giving an explanation to the large amounts of product **4** observed in the cyclization of precursor **1**.

In summary, the semiempirical PM3 calculations undertaken, strongly support the experimental results, showing that the triphenyltin hydride-mediated free radical cyclization of enynes of type **C** (Chart 1) proceeds to give the corresponding spirocyclic 1,7-dioxaspiro[4,4]nonane ring system **A**, via a 5-*exo* mode of cyclization, in good yield, but with (i) poor diastereoselectively in the formation of new stereocenters outside the furanose template and (ii) significant amounts of the *endo*-products, probably due to the additional strain energy required for the formation of the 5-*exo*-derivatives.

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7. All new compounds showed excellent analytical and spectroscopic data.
8. (a) In a typical experiment, Et_3B (0.13 mL, 0.13 mmol) was added to a solution of compound **1** (130 mg, 0.26 mmol) in toluene (16 mL, 0.016 M), under argon. Thereafter, a solution of $HSnPh_3$ (101.2 mg, 0.28 mmol) in 1.0 mL toluene was added dropwise to the reaction mixture (5 min). The reaction mixture was stirred at 25°C for 70 h. Then, the solvent was removed and the resulting residue dissolved in diethyl ether, treated with a 15% aqueous solution of KF and stirred overnight. The organic phase was separated, dried over Na_2SO_4, filtered,

evaporated and subjected to the flash column chromatography (CH_2Cl_2/hexane, 1:1) to afford the product **4** (10 mg) and fractions containing the pairs **4** and **5** [(1/1), 53.5 mg] and the pairs **5** and **6** (1/2, 44.3 mg) (Total: 107.8 mg; 50% yield). (b) Similarly reaction of **1**, after 2 h and flash column chromatography (CH_2Cl_2/hexane, 1:1) gave **1** (20 mg), **4** (2.3 mg) [^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48–7.09 [m, 15H for $OC(C_6H_5)_3$ and 15H for $3\times SnC_6H_5$, 30H), 5.78 (d, $J=3.6$ Hz, 1H, H-1),], 5.64 (s, 1H, H-6′), 4.40 (d, 1H, H-2), 3.78–3.60 (m, 1H), 3.59–3.42 (m, 1H), 3.40–3.35 (m, 1H), 3.06 (dd, $J=3$, 10 Hz, 1H), 2.15–1.90 (m, 2H, 2H-5′), 1.59 (s, 3H), 1.45 (s, 6H), 1.30 (s, 3H)], a fraction containing the isomeric pair **4** and **5** [(1/1), 68.8 mg] and **6** (35.5 mg) (total: 106.6 mg, 72% yield). [*Selected spectroscopic data for* **6**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48–7.09 [m, 15H for $OC(C_6H_5)_3$ and 15H for $3\times SnC_6H_5$, 30H], 5.90 (s, 1H, H-6′), 5.89 (d, $J=3.6$ Hz, 1H, H-1), 4.44 (d, $J=8.4$, 2.2 Hz, 1H, H-4), 4.26 (d, 1H, H-2), 3.66 (dd, $J=8.6$, 5.6 Hz, 1H, H-2′A), 3.39 (dd, $J=9.8$, 5.5 Hz, 1H, H-5A), 3.33 (dd, $J=8.7$, 1.6 Hz, 1H, H-2′B), 2.83 (dd, $J=10.0$, 2.2 Hz, 1H, H-5B), 2.44 (m, 1H, H-3′), 1.62 (s, 3H), 1.31 (s, 3H), 0.35 (d, $J=7.2$ Hz, 1H, H-5′); ^{13}C NMR (300 MHz, $CDCl_3$) δ 167.4 (C-4′), 144.3–127.3 [$OC(C_6H_5)_3$, $3\times SnC_6H_5$, 18 C], 117.3 (C-6′), 113.9 [$OC(CH_3)_2O$], 105.3 (C-1), 91.3 [$OC(C_6H_5)_3$], 87.4 (C-3), 83.4 (C-2), 79.2 (C-4), 73.8 (C-2′), 65.0 (C-5), 41.5 (C-3′), 27.5, 27.2 [2×C, $OC(CH_3)_2O$], 20.5 (C-5′)].

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14. (a) All structures were optimized and characterized by vibrational analysis with a UHF/PM3 model. At this level, we also determined the ZPE, thermal correction to enthapy and entropy. (b) We performed single-point calculations over the optimized geometries with the UB3LYP hybrid functional, by using the LANL2DZ basis set for Sn, which includes a 46 core electron relativistic ECP, and the 3-21G basis set for the other atoms.
15. Similar conclusions were obtained from structure **D2**.