Free-Radical Cyclizations onto Differently Substituted 1,2,3-Triazoles Installed in Sugar Templates

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The synthesis and manipulation of differently substituted 1,2,3-triazoles (**7**−**11** and **12**−**16**) installed in sugar templates gave compounds **29**−**34** and **44**−**50**, after reaction with tributyltin hydride or tris(trimethylsilyl)silane. Following standard procedures compound **44** was transformed into piperidinose derivative **54**. These compounds are chiral, useful building blocks for the synthesis of glycosidase inhibitors of the fused-azole piperidinose type.

Introduction

Several azoles[1−3] fused to furanoses or pyranoses have been identified as good, selective, and potent glycosidase inhibitors (GI).[4] This is the case of compounds **1**, **2**, and nagstatin (**3**) (Figure 1). Several synthetic approaches have been described for the preparation of these aza-sugars and related molecules. Most of these syntheses[5] have relied either on the intramolecular 1,3-dipolar cycloaddition (1,3-DC) of *δ*-azidonitriles[1b] or *δ*-azido-α,*β*-unsaturated esters[2] derived from sugars, by intramolecular S_N2 reaction on tethered azole-triflate sugar derivatives,[6] or from gluconolactams by annulation strategies.[7] Despite these efforts, new synthetic alternatives are sought due to the potential biological activity and therapeutic profile of new target molecules.[4]

In this context, in the last years we have been exploring a new approach for the synthesis of fused-azole piperidinoses, annulated onto furanose templates.[8,9] The basis of this strategy is shown in Scheme 1 and consists of the following: (a) the introduction of an *N*-azole at C3 in an hexofuranose starting material (**A**) and (b) the 5-*exo*-*trig* or the 6-*exo*-*trig* cyclization of a carbon (at C5 or C6)-centered radical species onto an heterocyclic ring system in intermediates (**B**). This process should give new and interesting azaannulated sugars of type **C**. It is expected that further standard synthetic transformations

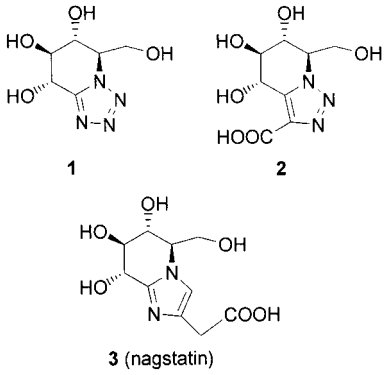
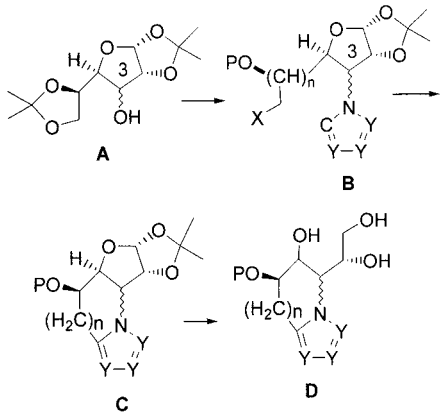


Figure 1. Fused-azole piperidinoses **1**−**3**.

Scheme 1. General Strategy for the Synthesis of Fused Azoles (D) via Free-Radical Cyclization of Intermediate B (P = Protecting Group; X = Leaving Group; Y = N, O, S, CH; *n* = 0, 1)



as hydrolysis of the isopropylidene acetal at carbons C1/C2, followed by 1,2-diol cleavage and hydride reduction, would afford fused-azole pyrrolidinoses or piperidinoses of type (**D**).

The key step in this approach is the free-radical cyclization onto a heterocycle. Examples of this type of cyclization[10] are known in the synthesis of functionalized indoles,[11] imidazoles and benzimidazoles,[12] or pyrroles.[13] However, similar free-radical cyclizations onto triazole ring systems were unprecedented. This fact coupled with

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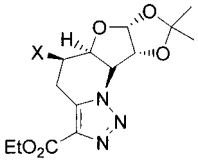
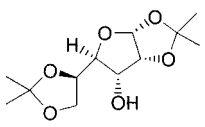
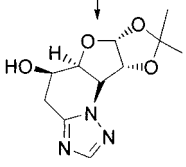
Scheme 2. Synthesis of Fused-Azole Triazole Piperidinoses from 1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranose[8,9]



4 X= OH (46%)
5 X= OAc (57%)



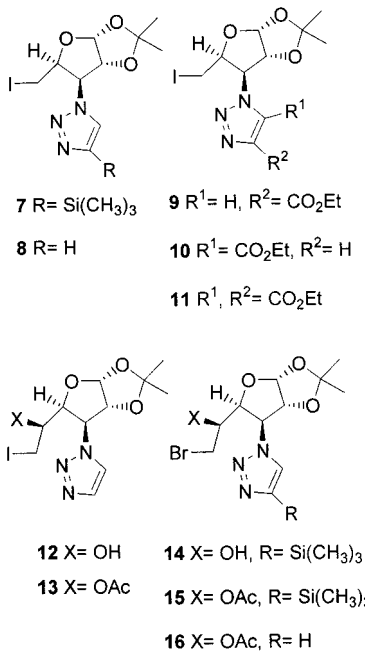
1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose



6 (14%)

the potential biological interest of the resulting molecules prompted us to start a project on the synthesis of fused triazoles on D-glucose templates in the furanose form. Until now, we have explored the *6-exo-trig* free-radical cyclization[14] on radical precursors having difunctionalized 1,2,3-triazoles with alkoxycarbonyl groups at C4 and C5, functionalized with only one alkoxycarbonyl group at C4, or unsubstituted 1,2,4-triazoles. As a result, we have prepared the fused-triazole piperidinoses **4**−**6** from 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose in a short synthetic scheme and in good overall chemical yield, featuring unprecedented carbocyclization protocols (Scheme 2).[8,9]

Continuing with these attempts, and in order to see the scope of the present methodology, we prepared and submitted to free-radical cyclization new radical precursors. These compounds (**7**−**16**) (Figure 2) have been designed in order to explore the 5-*exo-trig* and the 6-*exo-trig* free-radical cyclization onto differently substituted 1,2,3-triazoles. In this paper, we describe the results that we obtained in these transformations.[15]



7 R= $Si(CH_3)_3$
8 R= H
9 R^1= H, R^2= CO_2Et
10 R^1= CO_2Et, R^2= H
11 R^1, R^2= CO_2Et
12 X= OH
13 X= OAc
14 X= OH, R= $Si(CH_3)_3$
15 X= OAc, R= $Si(CH_3)_3$
16 X= OAc, R= H

Figure 2. Radical precursors for 5-*exo-trig* (**7**−**11**) and 6-*exo-trig* (**12**−**16**) cyclizations.

Results and Discussion

A. Synthesis of Fused-Triazole Pyrrolidinoses in Furanose Templates by 5-*Exo-Trig* Free-Radical Cyclization. A1. Synthesis of the Radical Precursors 7−**11.** The synthesis of these precursors was achieved from commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose as shown in Schemes 3 and 4 (see the Supporting Information). Tosylate **17**[16] was submitted to the "one-pot two-step" sodium periodate oxidation plus sodium borohydride reduction to give alcohol **18**, which was transformed into azide **19**. This compound was also prepared from known azide **20**[17] using the same protocol (Scheme 3). All new molecules showed good spectroscopic and analytical data. According to our strategy (Scheme 1), the incorporation of the 1,2,3-triazole ring at C3 was attempted via 1,3-DC of an azide with the selected acetylene.[18]

Using trimethylsilylacetylene, ethyl propiolate, or diethyl acetylenedicarboxylate, compounds **21**−**23**, **24**/**25**, and **26** were obtained from azide **19**, respectively, in good chemical yield (Scheme 3). As expected from the literature[19] and by comparison with the ^{1}H NMR spectroscopic data, the 4-substituted 1,2,3-triazoles were isolated as the major isomers in the reaction with monosubstitued acetylenes. Structural analysis was straightforward as it is well-known that H5 in 4-substituted 1,2,3-triazoles resonates at higher chemical shifts than H4 in 5-substituted 1,2,3-triazoles.[19] In agreement with this, in adduct **24** the signal for H5 appeared at 8.18 ppm, while in product **25** H4 was observed at 8.09 ppm (see the

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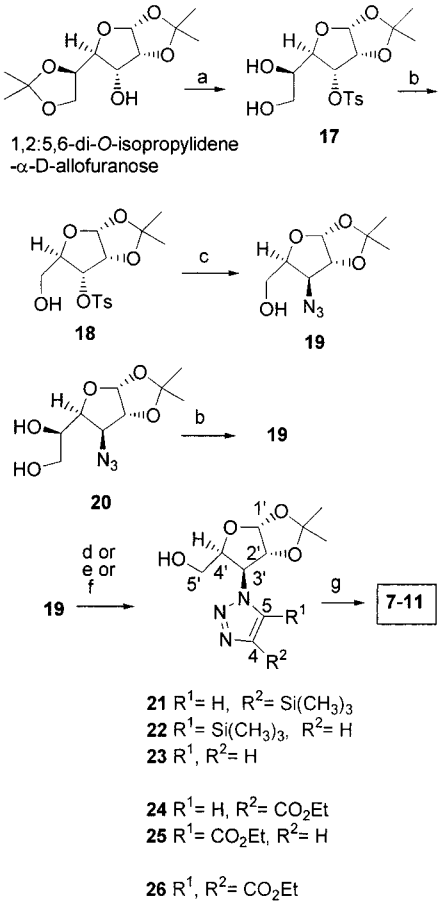
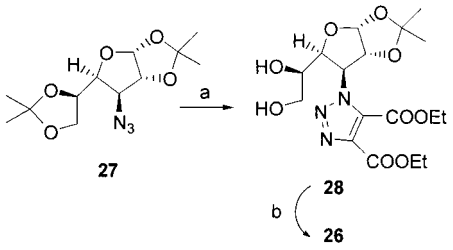
Scheme 3. Synthesis of Precursors 7−11[a]



[a] Reagents: (a) ref 16; (b) (i) $NaIO_4$, (ii) $NaBH_4$ (**17** to **18**, 83%), **20** to **19** [65% (74%)]; (c) NaN_3, DMF (74%); (d) trimethylsilylacetylene, toluene, 110 °C (**21**, 55%; **22**, 4%; **23**, 14%); (e) ethyl propiolate, toluene, 110 °C (**24**, 56%; **25**, 43%); (f) diethyl acetylenedicarboxylate, toluene, 110 °C (**26**, 69%); (g) I_2, Ph_3P, toluene, 110 °C (**7**, 87%; **8**, 62%; **9**, 62%; **10**, 77%; **11**, 89%).

Scheme 4. Synthesis of Intermediate 26 via an Alternative Route[a]



[a] Reagents: (a) ref 23; (b) (i) HIO_4, THF, (ii) $NaBH_4$, EtOH [53% (65%) overall yield from diol **28**].

Supporting Information). Contrary to previous reports,[20] when using trimethylsilyacetylene, in addition to the normal major product **21**, we have also detected the 5-substituted 1,2,3-triazole (**22**) and a third product, which was identified as the unsubstituted substrate **23** (Scheme 3). This compound was obtained from major isomer **21** by desilylation with tetrabutylammonium fluoride. The reasons for this "spontaneous" desilylation are not clear to us, but this is a fact that was previously documented in a related transformation.[21] It is interesting to note that in compound **21** the proton at H5 was observed at 7.53 ppm, while in compound **22**, the 5-substituted 1,2,3-triazole appeared at 7.65 ppm. This is just the reverse trend observed in the series with alkoxycarbonyl groups (see above for products **24** and **25**), and it is probably due to the different electronic properties of the silyl group. Finally, product **26** was also prepared by an alternative route involving compound **28**, readily obtained from azide **27**[22] as described,[23] after periodic acid oxidation followed by sodium borohydride reduction (Scheme 4).

Following with our plan, the final iodination of alcohols (**21** and **23**−**26**) under Garegg's conditions[24] gave the desired radical precursors **7**−**11** (Scheme 3). It is interesting to note that in the ^{13}C NMR spectra of these iodides the chemical shifts for CH_2(C5′)I appear unusually low (around −2.0/−3.0 ppm). This is probably due to the strong shielding effect of the spatially near orientated aromatic 1,2,3-triazole nucleus regarding the methylene group at C5′; this behavior has been previously observed by us in other related molecules in these series.[9]

A2. The Free-Radical Cyclization of Precursors 7−11. With these molecules in hand, the free-radical cyclization was attempted and we obtained the results shown in Scheme 5. Under our experimental conditions, using procedure A (AIBN, $HSnBu_3$) or procedure B (AIBN, $HSnBu_3$, Bu_3SnCl) (see the Experimental Section), the cyclization of substrates **7**, **8**, and **10** afforded the corresponding reduced, uncyclized material. This was evident from simple inspection of the ^1H NMR spectrum, observing that the signals for the group ICH_2(5′) were absent, appearing as a doublet at high field, integrating for three protons instead. In the case of compound **7**, we could also isolate traces of product **30**, the reduced uncyclized desilylated material. The yields of the cyclization products are low, probably due to extensive decomposition or polymerization.

Only in *activated* 1,2,3-triazoles having one ethoxycarbonyl group at C4 (**9**) or two ethoxycarbonyl groups at C4/C5 (**11**) was the 5-*exo-trig* cyclization possible, providing the same adduct **31**, in low yields, along with significant and major quantities of the reduced, uncyclized derivatives **32** or **34**, respectively. Full spectroscopic and analytical data clearly supported this structure; in particular, in the ^1H NMR spectrum of compound **31** (sugar numbering) no aromatic protons were obtained and only one ethoxycarboyl was noticed; in addition, the typical set of signals for the "furanose" ring system was clearly detected. In the ^{13}C NMR/DEPT spectra a signal for a methylene (29.4 ppm) was correlated with the protons at 3.29 and 3.19 ppm in the HMQC experiment. In summary, all these data point out that this compound was the expected pyrrolidinose fused-triazole derivative.

In Scheme 6, we show a possible mechanism for this free-radical ring annulation. The high yield of the reduced uncyclized material (**34**) shows that radical **E** is quite

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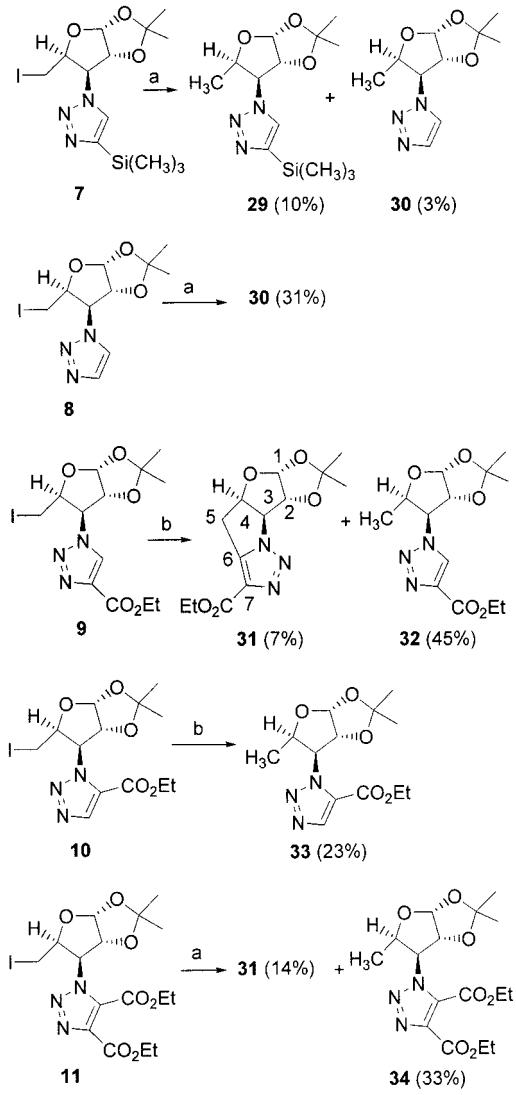
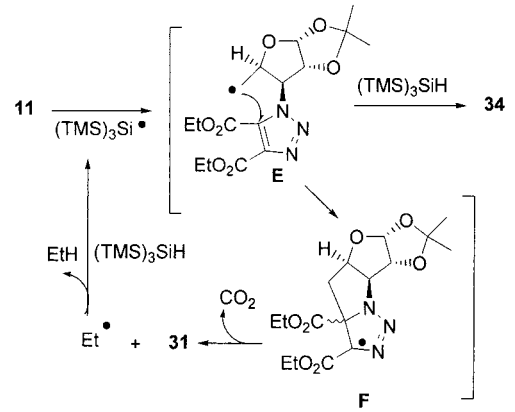
Scheme 5. 5-*Exo-Trig* Free-Radical Cyclization of Precursors 7−11[a]



[a] Reagents: (a) $(TMS)_3SiH$, AlBN (procedure A); (b) $(TMS)_3SiH$, AlBN, Bu_3SnCl (procedure B).

Scheme 6. Mechanism for Free-Radical Cyclization of Precursor 11



reluctant to undergo cyclization. However, this is a possible radical process, and after 5-*exo-trig* cyclization onto carbon C5 of the heterocyclic ring, an allylic radical species **F** results that gives product **31** after ethyl radical formation and carbon dioxide elimination; the ethyl radical captures a proton from $(TMS)_3SiH$, reinitiating the free-radical chain reaction. The final result is the so-called ipso substitution of the ethoxycarbonyl group at C5 in the radical precursor, a well-known process previously described by Bowman and co-workers in 2-substituted (thiophenyl or sulfonyl) benzimidazoles and imidazoles in free-radical mediated intramolecular cyclizations.[12c]

From these results, we can conclude that 5-*exo-trig* cyclizations onto the 1,2,3-triazole nucleus are only possible for very activated heterocyclic ring systems with the substituent at the appropriate position. In these cases, the formation of very strained fused ring assemblies possibly is the reason of the low chemical yields, the major product being the reduced uncyclized material. In the absence of these activating moieties, the ring annulation is absolutely impossible.

B. Synthesis of Fused-Triazole Furanoses by 6-*Exo-Trig* Free-Radical Cyclization. B1. Synthesis of the Radical Precursors 12−16. The synthesis of the radical precursors **12**−**16** has been achieved as shown in Scheme 7 (see the Supporting Information). For precursors **12** and **13**, we chose sugars **20** and **27** as starting materials. Compound **27**[22] (see Scheme 4) afforded adducts **35**−**37** after 1,3-DC reaction with trimethylsilylacetylene. Compound **38** was obtained by acid hydrolysis of intermediate **35** and from diol **20**[17] (see Scheme 3) by reaction with trimethylsilylacetylene. Tosylation of compound **38** afforded derivative **41**, whose S_N2 reaction with sodium iodide gave radical acceptor **12**, which upon acetylation afforded precursor **13**. In the 1,3-DC of compound **20**,[17] besides to adduct **38**, we also isolated compounds **39** and **40**. Compound **40** was synthesized by desilylation of product **38**. Pursuing on with our plan, the 1,3-DC reaction of bromide **42**[8] with trimethylsilylacetylene gave the 4-substituted 1,2,3-triazole **14**, along with minor amounts of other products, probably the 5-substituted isomer and the desilylated derivative, which were not isolated.[20] The acetylated derivative **43** provided adducts **15** and **16** in the 1,3-DC reaction with trimethylsilylacetylene. As in the previous series (see preparation of radical precursors **7**−**11**) major 4-substituted isomers along with minor quantities of the desilylated derivatives were isolated in the 1,3-DC reactions. The full spectroscopic and analytical data coupled to the data from literature and our own previous work confirmed this assignment (Scheme 7).

B2. The Free-Radical Cyclization of Precursors 12−16. In the next free-radical cyclization and having in mind the results of the previous 5-*exo-trig* cyclizations, we observed that the incorporation of additives as Bu_3SnCl (procedure B) (see the Experimental Section)[25] usually gave better yields of the cyclization products and cleaner reactions (Scheme 8). For instance, for compound **12** in the absence of additive (procedure A), compounds **44** and **45** were isolated in in 9% and 29% yields, respectively. This changed dramatically using procedure B, where the yields of the same reaction products (**44** and **45**) were instead 53% and 34%, respectively.

For the analogous acetyl derivative **13**, an unseparable mixture of products **46** and **47** was detected and transformed in mild, basic hydrolysis conditions into products **44** and **45**. Using procedure A, the yields were 39% and 19%, respectively, while changing to procedure B these

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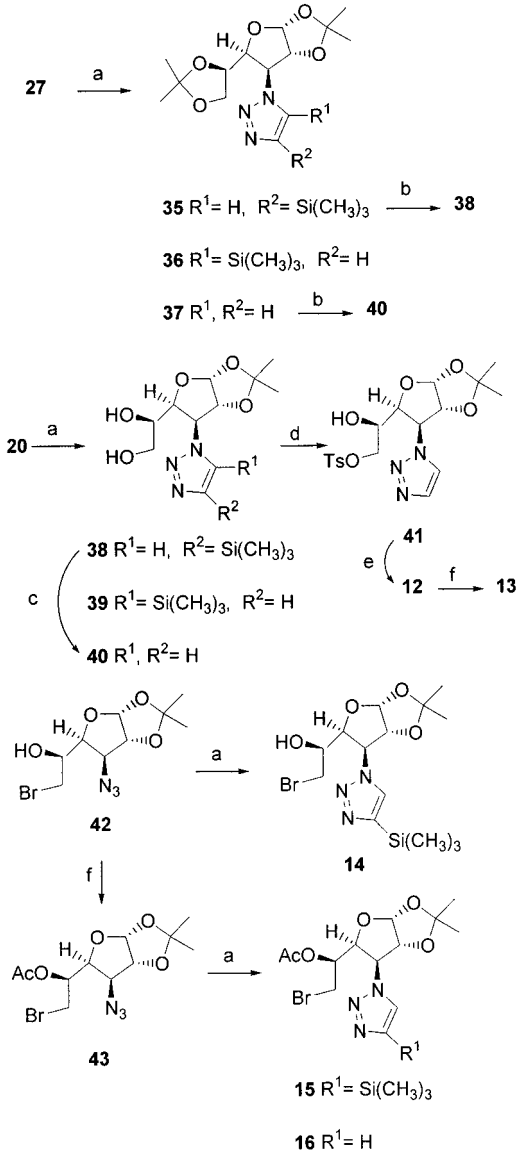
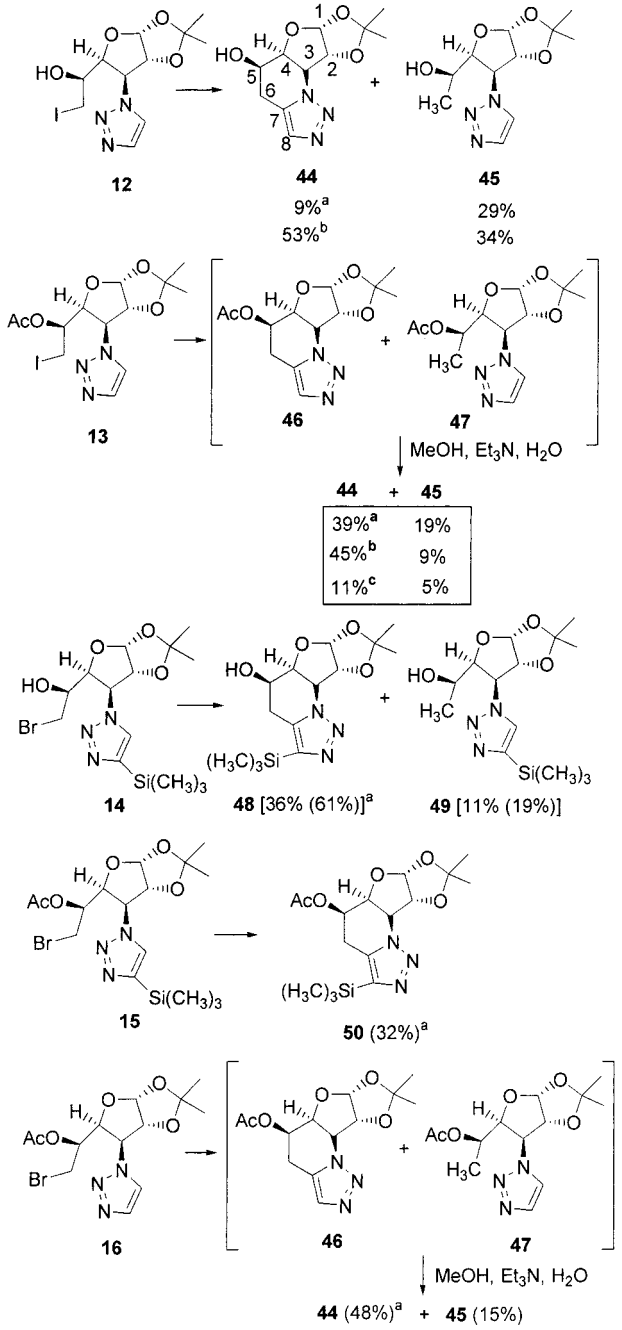
Scheme 7. Synthesis of Precursors 12−16[a]



[a] Reagents: (a) trimethylsilylacetylene, toluene, 110 °C (**35**, 62%; **36**, 5%; **37**, 30%), (**38**, 54%; **39**, 2%; **40**, 43%), (**14**, 69%), (**15**, 59%; **16**, 19%); (b) $AcOH/H_2O$, rt (**38**, 63% from **35**; **40**, 96% from **37**); (c) TBAF, THF, rt (91%); (d) ClTs, py, $(Bu_3Sn)_2O$ (87%); (e) NaI, DMF (84%); (f) Ac_2O, py (**13**, 84%; **43**, 87%).

Scheme 8. 5-*Exo-Trig* Free-Radical Cyclization of Precursors 12−16[a]



[a] Key: (a) procedure A: $(TMS)_3SiH$, AlBN; (b) procedure B: $(TMS)_3SiH$, Bu_3SnCl, AlBN; (c) procedure C: Bu_3SnH, Bu_3SnCl, AlBN.

results were better amounting to 45% and 9%. The power of tris(trimethylsilyl)silane (procedure B) was obvious when we compared it with procedure C (identical, but using $HSnBu_3$ as reducing agent); in this case, products **44** and **45** were isolated in very poor yields of 11% and 5%, respectively.

For the silyl containing precursor **14**, we tested only procedure A. This gave the expected 6-*exo-trig* cyclization product **48** in 36% yield (61% taking into account the recovered starting material) and the reduced, uncyclized derivative **49** in 11% yield (19% taking into account the recovered starting material).

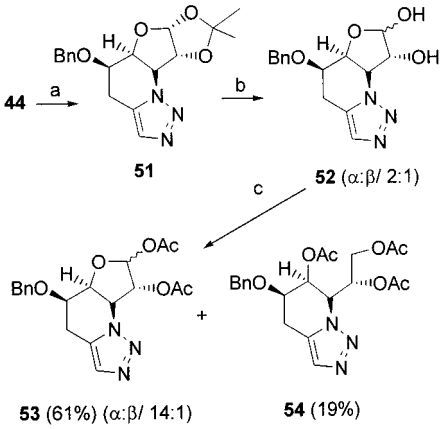
Under the same experimental conditions, precursor **15** afforded compound **50** in a clean but low yieldind reaction (32%).

Finally, for precursor **16**, only procedure A was tested with the same results observed in the cyclization of compound **13** using *procedure B*. This fact shows that in this case the structure of the product overrides other influences due to the reagents used.

In all the cases studied, the ^1H and ^{13}C NMR spectra of the cyclized derivatives, along with complementary $^1H-^1H$ COSY and $^1H-^{13}C$ HMQC experiments confirmed the proposed structure and the chemical shifts or coupling constants assigned to the corresponding protons and carbons.

In summary, from these results, it is clear that the 6-*exo-trig* cyclization onto 1,2,3-triazole ring systems is possible affording moderate yields of the cyclic derivatives, even if no activated substituents have been incorporated in the heterocyclic ring.[9]

Scheme 9[a]



[a] Reagents: (a) NaH, BnBr, THF (80%); (b) TFA/H_2O (60%); (c) (i) $NaBH_4$, MeOH, (ii) Ac_2O, py.

C. Final Transformation of Intermediate 44. With compound **44** in hand, we have performed some experiments in order to evaluate the viability of the strategy shown in Scheme 1 for the synthesis of modified furanose fused systems of type **D**. After some experimentation, it was soon evident that the protection of the hydroxyl group was necessary for a successful approach (see the Experimental Section). Then, we benzylated this group to provide compound **51** (Scheme 9); the acid hydrolysis of this compound afforded lactol **52** as a mixture of anomers at C1 which, without separation, was submitted to reaction with sodium borohydride followed by acetylation. Two products (**53** and **54**) were obtained after workup and chromatography. Compound **53** was the peracetylated derivative of **52**; this means that product **52** was stable as the ring-closed hemi-acetal and therefore stable to the borohydride reduction conditions.Compound **54** was the expected fused 1,2,3-triazole piperidinose, whose structure was established by detailed and extensive spectroscopic analysis.

In summary, we have extended our previous successful results[8,9] on the free-radical cyclization onto 1,2,3-triazole ring systems in sugar templates, analyzing 5-*exo-trig* and 6-*exo-trig* cyclization protocols on conveniently functionalized sugar derivatives having activated or not heterocyclic ring systems. As a result, we observed that the strain associated with the resulting 5-*exo-trig* products is a major impediment for clean and good yielding reactions, a problem that can be partially solved by substituting the ring with alkoxycarbonyl groups as activating moieties for the free radical cyclization. Conversely, the 6-*exo-trig* examples studied revealed that nonsubstituted or silyl containing nucleus are moderately efficient in giving reasonable yields of cyclized derivatives. Finally, we succeeded in designing a simple route to transform these annulated furanoses (**44**)[26] into fused triazole piperidinoses (**54**) of potential biological interest.[27]

(26) Marco-Contelles, J.; Alhambra, C., Martínez-Grau, A. *Synlett* **1998**, 693 (Corrigendum: *Synlett* **1999**, 376).

(27) The glycosidase inhibition of the azole-fused piperidinoses described in this paper has been carried out by Dr. Raynald Demange in Professor Pierre Vogel's laboratory, in Lausanne University (section de Chimie) (Switzerland). These molecules showed a weak activity in a large series of enzymatic assays. The authors would like to thank these colleagues for kindly performing these experiments.

Experimental Section

General Methods. See ref 28.

General Method for Free-Radical Carbocyclization Reactions. Procedure A. To a solution of the radical precursor in toluene (0.02 M) (previously deoxygenated by passing through the solution a current of argon during 20 min) under argon and at reflux was slowly added a solution of $(TMS)_3SiH$ (2.14 equiv) and AIBN (0.1 equiv) in toluene over 11 h via syringe pump. After addition, the reaction was heated at this temperature for 36 h. The mixture was cooled, and the solvent was removed in a vacuum. The residue was submitted to chromatography eluting with hexane/EtOAc mixtures.

Procedure B. As in procedure B but using Bu_3SnCl (1 equiv) as additive.

Procedure C. As in procedure B but using $HSnBu_3$.

General Method for Acid Hydrolysis of 1,2-*O*-Isopropylidene Acetals. The product was cooled at 0 °C and treated with a mixture of trifluoroacetic acid/water (60%).The reaction was warmed at room temperature for 24 h. The solvent was removed and the residue submitted to chromatography eluting with hexane/ethyl acetate mixtures.

General Method for Desilylations. The product was dissolved in dry THF (0.05 M), and the solution was treated at room temperature with a solution of tetrabutylammonium fluoride in THF (1.5 equiv, 1.0 M). After the mixture was refluxed for 3 h, the solvent was removed in a vacuum and the residue was submitted to flash chromatography eluting with hexane/ethyl acetate mixtures.

General Method for Acetylations. The alcohol was treated with a mixture of acetic anhydride/pyridine (v/v, 1/1) at room temperature overnight. The solvent was eliminated in a vacuum, and the residue was submitted to flash chromatography eluting with hexane/ethyl acetate mixtures.

General Method for Basic Hydrolysis of Acetates. The compound was dissolved in a mixture of methanol/water/triethylamine in the usual ratio of (5:1:4 v/v/v). After complete reaction, the solvents were removed, and the residue was submitted to flash chromatography eluting with hexane/ethyl acetate mixtures.

Free-Radical Cyclization of Precursor 7. Following **general procedure A for carbocyclization**, compound **7** (118 mg, 0.28 mmol) afforded products **29** (8 mg, 10%) and **30** (2 mg, 3%), after chromatography (hexane/EtOAc, from 9:1 to 3:2). **29**: mp 140−143 °C; $[\alpha]^{20}_D$ +38 (*c* 0.8, CH_3OH); IR (KBr) ν 2961, 1387, 1250, 1083 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35 (s, 1 H, H5), 6.16 (d, $J_{1',2'}$ = 3.8 Hz, 1 H, H1′), 5.04 (d, $J_{4',3'}$ = 3.8 Hz, 1 H, H3′), 4.88 (d, $J_{1',2'}$ = 3.8 Hz, 1 H, H2′), 4.66 (qd, $J_{4',5'}$ = 6.3 Hz, $J_{4',3'}$ = 3.8 Hz, 1 H, H4′), 1.58, 1.35 [2 s, 2 × 3 H, −OC$(CH_3)_2$O−], 0.91 (d, $J_{4',5'}$ = 6.3 Hz, 3 H, H5′), 0.31 [s, 9 H, $(CH_3)_3$ Si]; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 147.9 (C4), 128.4 (C5), 112.1 [−O*C*$(CH_3)_2$O−], 105.0 (C1′), 84.5 (C2′), 75.1 (C4′), 67.3 (C3′), 26.6, 26.2 [OC(*C*$H_3)_2$O], 13.4 (C5′), −1.1 [$(CH_3)_3$ Si]; MS (70 eV) *m*/*z* 282 (11), 170 (11), 152 (37), 99 (60), 43 (100. **30**: mp 160−163 °C; $[\alpha]^{20}_D$ +56 (*c* 8.9, CH_3OH); IR (KBr) ν 3096, 2988, 1630, 1378, 1220, 1018 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.73 (d, J = 0.9 Hz, 1 H, H5), 7.48 (d, J = 0.9 Hz, 1 H, H4), 6.15 (d, $J_{1',2'}$ = 3.8 Hz, 1 H, H1′), 5.02 (d, $J_{4',3'}$ = 3.8 Hz, 1 H, H3′), 4.91 (d, $J_{1',2'}$ = 3.8 Hz, 1 H, H2′), 4.67 (dq, $J_{4',5'}$ = 6.6 Hz, $J_{4',3'}$ = 3.8 Hz, 1 H, H4′), 1.57, 1.35 [s, s, 2 × 3 H, −OC$(CH_3)_2$O−], 0.90 (d, $J_{4',5'}$ = 6.6 Hz, 3 H, H5′); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 134.0 (C4), 123.3 (C5), 112.2 [−O*C*$(CH_3)_2$O−], 104.9 (C1′), 84.4 (C2′), 75.0 (C4′), 67.6 (C3′), 26.4, 26.1 [OC(*C*$H_3)_2$O, 13.3 (C5′); MS (70 eV) *m*/*z* 226 (12), 181 (27), 123 (100), 99 (70), 41 (79). Anal. Calcd for $C_{10}H_{15}N_3O_3$: C, 53.32; H, 6.71; N, 18.66. Found: C, 53.51; H, 6.78; N, 18.57.

Free-Radical Cyclization of Precursor 8. Following **general procedure A for carbocyclization**, compound **8** (56 mg, 0.16 mmol) afforded product **30** (11 mg, 31%), after chromatography (hexane/EtOAc, from 9:1 to 3:2).

(28) Marco-Contelles, J.; Pozuelo, C.; Jimeno, M. L.; Martínez, L.; Martínez-Grau, A. *J. Org. Chem.* **1992**, *57*, 2625.

Free-Radical Cyclization of Precursor 9. Following **general procedure B for carbocyclization**, compound **9** (100 mg, 0.24 mmol) afforded products **31** (7 mg, 7%) and **32** (31 mg, 45%), after chromatography (from hexane to hexane/EtOAc, 9:1). **31**: mp 139−142 °C; $[\alpha]^{20}_D$ +34 (*c* 5.5, $CHCl_3$); IR (KBr) ν 2984, 1719, 1586, 1375, 1135, 1079, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.83 (d, $J_{1,2}$ = 3.8 Hz, 1 H, H1), 5.54 (t, $J_{4,5B}$ = $J_{4,3}$ = 4.2 Hz, 1 H, H4), 5.28 (d, $J_{1,2}$ = 3.8 Hz, 1 H, H2), 4.97 (d, $J_{4,3}$ = 4.2 Hz, 1 H, H3), 4.37 (q, J = 7.1 Hz, 2 H, $COOCH_2CH_3$), 3.29 (d, $J_{5A,5B}$ = 17.9 Hz, 1 H, H5A), 3.19 (dd, $J_{5A,5B}$ = 17.9 Hz, $J_{4,5B}$ = 4.2 Hz, 1 H, H5B), 1.54, 1.35 [2 s, 2 × 3 H, $-OC(CH_3)_2O-$], 1.37 (q, J = 7.1 Hz, 3 H, $COOCH_2CH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.6 ($COOCH_2CH_3$), 145.2 (C7), 133.7 (C6), 112.9 [$-OC(CH_3)_2O-$], 106.3 (C1), 86.9 (C4), 81.8 (C2), 68.8 (C3), 61.1 ($COOCH_2CH_3$), 29.4 (C5), 26.9, 26.5 [$OC(CH_3)_2O$], 14.3 ($COOCH_2CH_3$); MS (70 eV) *m*/*z* 296 (5), 280 (70), 250 (28), 179 (86), 122 (35), 122 (26), 106 (56), 94 (62), 43 (100). Anal. Calcd for $C_{13}H_{17}N_3O_5$: C, 52.88; H, 5.80; N, 14.23. Found: C, 53.07; H, 5.75; N, 14.12. **32**: mp 196−199 °C; $[\alpha]^{20}_D$ +96 (*c* 3.4, CH_3OH); IR (KBr) ν 3112, 2977, 1727, 1453, 1383, 1127, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.96 (s, 1 H, H5), 6.12 (d, $J_{1',2'}$ = 3.8 Hz, 1 H, H1′), 5.03 (d, $J_{4',3'}$ = 3.7 Hz, 1 H, H3′), 4.86 (d, $J_{1',2'}$ = 3.8 Hz, 1 H, H2′), 4.65 (qd, $J_{4',5'}$ = 6.4 Hz, $J_{4',3'}$ = 3.7 Hz, 1 H, H4′), 4.39 (q, J = 7.1 Hz, 2 H, $COOCH_2CH_3$), 1.55, 1.33 [2 s, 2 × 3 H, $-OC(CH_3)_2O-$], 1.38 (t, J = 7.1 Hz, 3 H, $COOCH_2CH_3$), 0.91 (d, $J_{4',5'}$ = 6.4 Hz, 3 H, H5′); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.5 ($COOCH_2CH_3$), 140.6 (C4), 127.0 (C5), 112.5 [$-OC(CH_3)_2O-$], 104.8 (C1′), 84.3 (C2′), 74.7 (C4′), 68.2 (C3′), 61.5 ($COOCH_2CH_3$), 26.3, 26.0 [$OC(CH_3)_2O$], 14.3 ($COOCH_2CH_3$), 13.2 (C5′); MS (70 eV) *m*/*z* 298 (5), 282 (22), 195 (57), 122 (33), 95 (100), 43 (69). Anal. Calcd for $C_{13}H_{19}N_3O_5$: C, 52.52; H, 6.44; N, 14.13. Found: C, 52.65; H, 6.60; N, 13.99.

Free-Radical Cyclization of Precursor 10. Following **general procedure B for carbocyclization**, compound **10** (100 mg, 0.24 mmol) afforded product **33** (16 mg, 23%), after chromatography (from hexane to hexane/EtOAc, 7:3), and a more polar product whose structure has not been established. **33**: mp 62−64 °C; $[\alpha]^{20}_D$ +153 (*c* 5.0, CH_3OH); IR (KBr) ν 2982, 1727, 1529, 1375, 1066, 1015 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.12 (s, 1 H, H4), 6.21 (d, $J_{1',2'}$ = 3.8 Hz, 1 H, H1′), 5.74 (d, $J_{4',3'}$ = 3.8 Hz, 1 H, H3′), 5.13 (d, $J_{1',2'}$ = 3.8 Hz, 1 H, H2′), 4.72 (qd, $J_{4',5'}$ = 6.4 Hz, $J_{4',3'}$ = 3.8 Hz, 1 H, H4′), 4.38 (q, J = 7.1 Hz, 2 H, $COOCH_2CH_3$), 1.57, 1.35 [2 s, 2 × 3 H, $-OC(CH_3)_2O-$], 1.38 (t, J = 7.1 Hz, 3 H, $COOCH_2CH_3$), 0.81 (d, $J_{4',5'}$ = 6.4 Hz, 3 H, H5′); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 158.5 ($COOCH_2CH_3$), 137.3 (C4), 128.7 (C5), 111.8 [$-OC(CH_3)_2O-$], 105.5 (C1′), 84.4 C2′), 75.6 (C4′), 66.3 (C3′), 61.9 ($COOCH_2CH_3$), 26.6, 26.1 [$OC(CH_3)_2O$], 14.0 ($COOCH_2CH_3$), 13.3 (C5′); MS (70 eV) *m*/*z* 299 (1), 282 (39), 253 (10), 195 (64), 122 (37), 95 (100). Anal. Calcd for $C_{13}H_{19}N_3O_5$: C, 52.52; H, 6.44; N, 14.13. Found: C, 52.43; H, 6.70; N, 13.95.

Free-Radical Cyclization of Precursor 11. Following **general procedure A for carbocyclization**, compound **11** (109 mg, 0.22 mmol) afforded products **31** (9 mg, 14%) and **34** (26 mg, 33%), after chromatography (hexane/EtOAc, from 9:1 to 7:3). **34**: oil; $[\alpha]^{20}_D$ +87 (*c* 9.2, $CHCl_3$); IR (KBr) ν 2985, 1731, 1554, 1374, 1211, 1016 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.20 (d, $J_{1',2'}$ = 3.8 Hz, 1 H, H1′), 5.34 (d, $J_{4',3'}$ = 4.0 Hz, 1 H, H3′), 5.11 (d, $J_{1',2'}$ = 3.8 Hz, 1 H, H2′), 4.71 (qd, $J_{4',5'}$ = 6.3 Hz, $J_{4',3'}$ = 4.0 Hz, 1 H, H4′), 4.43 (q, q, J = 7.3 Hz, 4 H, 2 × $COOCH_2CH_3$), 1.57, 1.36 [2 s, 2 × 3 H, $-OC(CH_3)_2O-$], 1.38 (t, t, J = 7.3 Hz, 6 H, 2 × $COOCH_2CH_3$), 0.87 (d, $J_{4',5'}$ = 6.3 Hz, 3 H, H5′); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.1, 158.5 (2 × $COOCH_2CH_3$), 130.4 (C4), 121.9 (C5), 112.0 [$-OC(CH_3)_2O-$], 105.5 (C1′), 84.4 (C2′), 75.4 (C4′), 67.1 (C3′), 63.1, 62.0 (2 × $COOCH_2CH_3$), 26.6, 26.1 [$OC(CH_3)_2O$], 14.1, 13.8 (2 × $COOCH_2CH_3$), 13.5 (C5′); MS (70 eV) *m*/*z* 370 (3), 354 (26), 324 (12), 267 (35), 214 (41), 194 (100), 167 (50), 139 (17), 122 (40), 99 (66). Anal. Calcd for $C_{16}H_{23}N_3O_7$: C, 52.03; H, 6.28; N, 11.38. Found: C, 52.33; H, 6.40; N, 13.65.

Free-Radical Cyclization of Precursor 12. Following **general procedure A for carbocyclization**, compound **12** (46 mg, 0.12 mmol) afforded products **44** (3 mg, 9%) and **45** (9 mg, 29%). Following **general procedure B for carbocyclization**, compound **12** (96 mg, 0.25 mmol) afforded products **44** (34 mg, 53%) and **45** (22 mg, 34%), after chromatography (from hexane to hexane/EtOAc, 1:4). **44**: oil; $[\alpha]^{20}_D$ +60 (*c* 4.6, $CHCl_3$); IR (KBr) ν 3500−3400, 2920, 1600, 1340, 1225, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40 (s, 1 H, H8), 5.74 (d, $J_{1,2}$ = 3.5 Hz, 1 H, H1), 5.20 (d, $J_{1,2}$ = 3.5 Hz, 1 H, H2), 4.88 (d, $J_{4,3}$ = 3.9 Hz, 1 H, H3), 4.82 (br dd, $J_{4,5}$ = 5.9 Hz, $J_{4,3}$ = 3.9 Hz, 1 H, H4), 4.11 (ddd, $J_{4,5}$ = 5.9 Hz, $J_{6B,5}$ = 15.6 Hz, $J_{6A,5}$ = 10.9 Hz, 1 H, H5), 3.15 (dd, $J_{6A,6B}$ = 15.6 Hz, $J_{6A,5}$ = 10.9 Hz, 1 H, H6A), 2.83 (dd, $J_{6A,6B}$ = 15.6 Hz, $J_{6B,5}$ = 5.6 Hz, 1 H, H6B), 2.29 (br s, 1 H, OH), 1.54, 1.29 [2 s, 2 × 3 H, $-OC(CH_3)_2O-$]; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 132.2 (C7), 130.7 (C8), 112.9 [$-OC(CH_3)_2O-$], 104.9 (C1), 84.5 (C2), 77.3 (C4), 65.7 (C5), 63.2 (C3), 26.6, 26.2 [$OC(CH_3)_2O$], 24.2 (C6); MS (70 eV) *m*/*z* 253 (26), 238 (100), 195 (13), 137 (69), 112 (51), 81 (36). Anal. Calcd for $C_{11}H_{15}N_3O_4$: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.35; H, 6.17; N, 16.40. **45**: mp 153−155 °C; $[\alpha]^{20}_D$ +37 (*c* 7.4, CH_3OH); IR (KBr) ν 3530, 3400−3320, 3040, 2920, 1600, 1365−1355, 1200, 885 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.74 (d, J = 1.0 Hz, 1 H, H5), 7.65 (d, J = 1.0 Hz, 1 H, H4), 6.25 (d, $J_{1',2'}$ = 3.7 Hz, 1 H, H1′), 5.21 (d, $J_{4',3'}$ = 3.6 Hz, 1 H, H3′), 5.09 (d, $J_{1',2'}$ = 3.7 Hz, 1 H, H2′), 4.22 (dd, $J_{4',5'}$ = 9.0 Hz, $J_{4',3'}$ = 3.6 Hz, 1 H, H4′), 2.89 (m, 1 H, H5′), 1.61, 1.38 [2 s, 2 × 3 H, $-OC(CH_3)_2O-$], 1.71 (d, J = 4.5 Hz, 1 H, OH), 1.27 (d, $J_{6',5'}$ = 6.1 Hz, 3 H, H6′); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 133.5 (C4), 124.8 (C5), 112.5 [$-OC(CH_3)_2O-$], 105.9 (C1′), 83.7 (C2′), 83.5 (C4′), 65.5 (C3′), 65.2 (C5′), 26.6, 26.2 [$OC(CH_3)_2O$], 21.2 (C6′); MS (70 eV) *m*/*z* 240 (14), 142 (22), 123 (35), 113 (71), 85 (51), 43 (100). Anal. Calcd for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46. Found: C, 51.89; H, 6.98; N, 16.27.

Transformation of Compound 44. (a) Benzylation of Product 44. To a solution of compound **44** (33 mg, 0.13 mmol) in dry THF (2 mL), under argon and at 0 °C sodium hydride (5.4 mg, 0.13 mmo, 60% dispersion in oil), were added catalytic amounts of tetrabutylammonium iodide and benzyl bromide (18.8 μL, 0.16 mmol, 1.2 equiv). The mixture was warmed at room temperature for 20 h. Then, two drops of acetic acid were added, the crude was filtered over Celite-545, and the cake was washed with methylene chloride. The solvent was evaporated and the residue submitted to chromatography (hexane/ethyl acetate, 3/2) to give product **51** (36 mg, 80%): oil; $[\alpha]^{20}_D$ −49 (*c* 6.2, $CHCl_3$); IR (KBr) ν 2989, 1455, 1375, 1218, 1020, 816 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45 (s, 1 H, H8), 7.37−7.27 (m, 5 H, $-OCH_2C_6H_5$), 5.81 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H1), 5.23 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H2), 4.90 (br s, 1 H, H4), 4.86 (d, $J_{4,3}$ = 3.7 Hz, 1 H, H3), 4.73 (s, 2 H, $-OCH_2C_6H_5$), 3.92 (ddd, $J_{4,5}$ = 3.9 Hz, $J_{6B,5}$ = 5.7 Hz, $J_{6A,5}$ = 10.6 Hz, 1 H, H5), 3.17 (dd, $J_{6A,6B}$ = 15.7 Hz, $J_{6B,5}$ = 5.7 Hz, 1 H, H6B), 3.02 (dd, $J_{6A,6B}$ = 15.7 Hz, $J_{6A,5}$ = 10.6 Hz, 1 H, H6B), 1.59, 1.36 [2 s, 2 × 3 H, $-OC(CH_3)_2O-$]; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.1 (C7), 130.8 (C8), 132.2−127.8 ($-OCH_2C_6H_5$), 112.6 [$-OC(CH_3)_2O-$], 105.1 (C1), 83.9 (C2), 74.8 (C4), 71.4 (C5), 71.3 ($-OCH_2C_6H_5$), 63.5 (C3), 26.6, 26.2 [$OC(CH_3)_2O$], 21.4 (C6); MS (70 eV) *m*/*z* 344 (1), 328 (19), 252 (2), 237 (71), 121 (17), 108 (29), 91 (100). Anal. Calcd for $C_{18}H_{21}N_3O_4$: C, 62.96; H, 6.16; N, 12.24. Found: C, 62.73; H, 6.27; N, 12.55.

(b) Hydrolysis of Acetal 51. Following the **general method for acid hydrolysis of 1,2-*O*-isopropylidene acetals,** compound **51** (92 mg, 0.27 mmol) gave product **52** (73 mg, 89%) isolated as an unseparable mixture of anomers (α/β: 2/1) after chromatography (hexane/ethyl acetate, 1/4): ^1H NMR (CD_3OD, 300 MHz) (major isomer) δ 7.51 (s, 1 H, H8), 7.43−7.28 (m, 5 H, $-OCH_2C_6H_5$), 5.29 (d, $J_{1,2}$ = 4.3 Hz, 1 H, H1), 5.07 (br s, 1 H, H2), 4.98 (br s, 1 H, H3), 4.91 (s, 2 H, $-OCH_2C_6H_5$), 4.68 (dd, $J_{4,5}$ = 3.6 Hz, $J_{4,3}$ = 3.9 Hz, 1 H, H4), 3.95 (ddd, $J_{4,5}$ = 3.6 Hz, $J_{6B,5}$ = 3.7 Hz, $J_{6A,5}$ = 4.9 Hz, 1 H, H5), 3.19 (dd, $J_{6A,6B}$ = 14.9 Hz, $J_{6B,5}$ = 3.7 Hz, 1 H, H6B), 3.05 (dd, $J_{6A,6B}$ = 14.9 Hz, $J_{6A,5}$ = 4.9 Hz, 1 H, H6B); ^{13}C NMR (CD_3OD, 75 MHz) δ 139.3 (C7), 130.8 (C8), 135.1−128.9 ($-OCH_2C_6H_5$), 104.6 (C1), 81.5 (C2), 77.4 (C4), 74.2 (C5), 72.1 ($OCH_2C_6H_5$), 65.5 (C3), 22.3 (C6). Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.43; H, 5.70; N, 13.95.

(c) Sodium Borohydride Reduction + Acetylation of Product 52. Lactol **52** (52 mg, 0.17 mmol) dissolved in ethanol

(3 mL) was treated with a solution of sodium borohydride (6.4 mg, 0.17 mmol, 1 equiv) in ethanol (1 mL). The mixture was stirred at 0 °C for 15 min and warmed at room temperature for 2 h. Sodium borohydride (9.6 mg, 0.25 mmol, 1.5 equiv) was added again and stirred for 4 h more. A saturated aqueous solution of ammonium chloride was added and the ethanol removed. The crude was treated according to the **general method for acetylations**. and the residue was submitted to chromatography (hexane/ethyl acetate, from 2:3 to 1:4) to give product **53** (40 mg, 61%) [isolated as an unseparable mixture of anomers (α/β: 14/1)] and **54** (13 mg, 19%). **53**: oil; $[\alpha]^{20}_D$ +50 (*c* 22.3, $CHCl_3$); IR (KBr) ν 2940, 1755, 1431, 1375, 1238, 1013, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (major isomer) δ 7.44 (s, 1 H, H8), 7.36−7.30 (m, 5 H, $-OCH_2C_6H_5$), 6.50 (d, $J_{1,2}$ = 4.7 Hz, 1 H, H1), 5.54 (dd, $J_{2,3}$ = 5.8 Hz, $J_{1,2}$ = 4.7 Hz, 1 H, H2), 5.24 (dd, $J_{2,3}$ = 5.8 Hz, $J_{3,4}$ = 7.2 Hz, 1 H, H3), 4.86 (dd, $J_{4,5}$ = 3.5 Hz, $J_{4,3}$ = 7.2 Hz, 1 H, H4), 4.66 (s, 2 H, $-OCH_2C_6H_5$), 3.99 (dt, $J_{4,5}$ = 3.5 Hz, $J_{6B,5}$ = 3.5 Hz, $J_{6A,5}$ = 7.1 Hz, 1 H, H5), 3.12 (dd, $J_{6A,6B}$ = 16.2 Hz, $J_{6A,5}$ = 7.1 Hz, 1 H, H6A), 2.85 (dd, $J_{6A,6B}$ = 16.2 Hz, $J_{6B,5}$ = 3.5 Hz, 1 H, H6B), 2.15, 2.09 (2 s, 2 × $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.5, 169.2 (2 × $OCOCH_3$), 137.2 (C7), 131.3 (C8), 131.3−127.8 ($-OCH_2C_6H_5$), 93.9 (C1), 75.6 (C2), 74.1 (C4), 72.2 ($OCH_2C_6H_5$), 71.5 (C5), 59.7 (C3), 21.9 (C6), 21.0, 20.5 (2 × $OCOCH_3$); MS (70 eV) *m*/*z* 359 (3), 344 (1), 328 (25), 299 (17), 268 (31), 211 (12), 91 (100). Anal. Calcd for $C_{19}H_{21}N_3O_5$: C, 61.45; H, 5.70; N, 11.31. Found: C, 61.43; H, 5.70; N, 11.26. **54**: mp 193−195 °C; $[\alpha]^{20}_D$ +14 (*c* 1.4, CH_3OH); IR (KBr) ν 2989, 1754, 1371, 1218, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42 (s, 1 H, H8), 7.38−7.28 (m, 5 H, $-OCH_2C_6H_5$), 5.95 (dt, $J_{1A,2}$ = $J_{1B,2}$ = 3.7 Hz, $J_{2,3}$ = 6.2 Hz, 1 H, H2), 5.88 (m, 1 H, H4), 4.87 (dd, $J_{2,3}$ = 6.0 Hz, $J_{3,4}$ = 3.8 Hz, 1 H, H3), 4.75 and 4.53 (AB system, d, *J* = 11.6 Hz, 2 H, $-OCH_2C_6H_5$), 4.39 (dd, $J_{1A,2}$ = 3.7 Hz, $J_{1A,1B}$ = 12.3 Hz, 1 H, H1A), 4.32 (dd, $J_{1B,2}$ = 3.7 Hz, $J_{1A,1B}$ = 12.3 Hz, 1 H, H1B), 3.90 (dd, $J_{6A,5}$ = 5.9 Hz, $J_{6B,5}$ = 9.6 Hz, 1 H, H5), 3.14 (dd, $J_{6A,6B}$ = 16.4 Hz, $J_{6A,5}$ = 9.6 Hz, 1 H, H6A), 2.99 (dd, $J_{6A,6B}$ = 16.4 Hz, $J_{6B,5}$ = 9.6 Hz, 1 H, H6B), 2.13, 2.09, 2.07 (3 s, 3 × $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.6, 170.2, 169.7 (3 × $OCOCH_3$), 136.9 (C7), 130.8 (C8), 132.2−127.9 ($-OCH_2C_6H_5$), 72.7 (C5), 71.5 ($OCH_2C_6H_5$), 69.7 (C2), 65.9 (C4), 63.2 (C1), 57.8 (C3), 23.0 (C6), 20.9 (3 × $OCOCH_3$); MS (70 eV) *m*/*z* 344 (3), 325 (7), 301 (7), 266 (69), 224 (22), 194 (12), 135 (26), 91 (100). Anal. Calcd for $C_{21}H_{25}N_3O_7$: C, 58.46; H, 5.84; N, 9.74. Found: C, 58.44; H, 5.71; N, 9.95.

Free-Radical Cyclization of Precursor 13. Following **general procedure A for carbocyclization**, compound **13** (71 mg, 0.17 mmol) afforded a crude (**46** + **47**) that was submitted to **basic hydrolysis following the general procedure** to give products **44** (17 mg, 39%) and **45** (8 mg, 19%). Following **general procedure B for carbocyclization**, compound **13** (180 mg, 0.42 mmol) afforded a crude (**46** + **47**) that was submitted to **basic hydrolysis following the general method** to give products **44** (48 mg, 45%) and **45** (9 mg, 9%). Following **general procedure C for carbocyclization**, compound **13** (65 mg, 0.15 mmol) afforded a crude (**46** + **47**) that was submitted to **basic hydrolysis following the general method** to give products **44** (5 mg, 11%) and **45** (2 mg, 5%), after chromatography (hexane/EtOAc, from 2:3 to 1:4).

Following the general method for acetylation, alcohol **44** (11 mg, 0.04 mmol) gave compound **46** (10 mg, 67%). **46**: mp 57−60; $[\alpha]^{20}_D$ −35 (*c* 4.3, CH_3OH); IR (KBr) ν 2940, 1738, 1376, 1231, 1085 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.44 (s, 1 H, H8), 5.78 (d, $J_{1,2}$ = 3.7 Hz, 1 H, H1), 5.23 (m, 2 H, H2, H5), 4.96 (d, $J_{4,3}$ = 3.7 Hz, 1 H, H3), 4.86 (d, $J_{4,3}$ = 3.7 Hz, 1 H, H4), 3.11 (dd, $J_{6A,6B}$ = 15.4 Hz, $J_{6A,5}$ = 5.7 Hz, 1 H, H6A), 3.02 (dd, $J_{6A,6B}$ = 15.4 Hz, $J_{6B,5}$ = 11.4 Hz, 1 H, H6B), 2.12 (s, 3 H, $OCOCH_3$), 1.57, 1.32 [2 s, 2 × 3 H, $-OC(CH_3)_2O-$]; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.2 ($OCOCH_3$), 131.4 (C7), 130.8 (C8), 112.8 [$-OC(CH_3)_2O-$], 105.1 (C1), 83.9 (C2), 74.8 (C4), 66.7 (C5), 63.5 (C3), 26.4, 26.0 [$OC(CH_3)_2O$], 20.9 ($OCOCH_3$), 17.5 (C6); MS (70 eV) *m*/*z* 296 (13), 280 (39), 235 (56), 179 (18), 151 (54), 119 (90), 43 (100). Anal. Calcd for $C_{13}H_{17}N_3O_5$: C, 52.88; H, 5.80; N, 14.23. Found: C, 52.51; H, 5.77; N, 13.89.

Following the general method for acetylation, alcohol **45** (13 mg, 0.05 mmol) gave compound **47** (10 mg, 67%). **47**: IR (KBr) ν 3088, 1737, 1379, 1222, 945 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.75 (d, 1 H, H5), 7.45 (d, 1 H, H4), 5.25 (d, $J_{1',2'}$ = 3.6 Hz, 1 H, H1′), 5.24 (d, $J_{4',3'}$ = 3.7 Hz, 1 H, H3′), 4.91 (d, $J_{1',2'}$ = 3.6 Hz, 1 H, H2′), 4.47 (dd, $J_{4',5'}$ = 8.7 Hz, $J_{4',3'}$ = 3.7 Hz, 1 H, H4′), 4.21 (dd, $J_{4',5'}$ = 8.7 Hz, $J_{5',6'}$ = 6.1 Hz, 1 H, H5′), 2.01 (s, 3 H, $OCOCH_3$), 1.63, 1.39 [2 s, 2 × 3 H, $-OC(CH_3)_2O-$], 1.27 (d, $J_{6',5'}$ = 6.1 Hz, 3 H, H6′); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.0 ($OCOCH_3$), 134.1 (C4), 123.3 (C5), 112.6 [$-OC(CH_3)_2O-$], 105.4 (C1′), 84.3 (C2′), 80.9 (C4′), 67.5 (C3′), 65.5 (C5′), 26.6, 26.1 [$OC(CH_3)_2O$], 20.9 (C6′), 17.6 ($OCOCH_3$); MS (70 eV) *m*/*z* 282 (14), 123 (37), 83 (11), 43 (100). Anal. Calcd for $C_{13}H_{19}N_3O_5$: C, 52.52; H, 6.44; N, 14.13. Found: C, 52.44; H, 6.68; N, 13.95.

Free-Radical Cyclization of Precursor 14. Following **general procedure A for carbocyclization**, compound **14** (72 mg, 0.18 mmol) afforded products **48** [21 mg, 36% (61% taking into account the recovered starting material)] and **49** [7 mg, 11% (19% taking into account the recovered starting material)], after chromatography (from hexane to hexane/EtOAc, 1:4). **48**: 145−147 °C; $[\alpha]^{20}_D$ −31 (*c* 7.7, CH_3OH); IR (KBr) ν 3350, 2940, 1490, 1350, 1225, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.81 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H1), 5.26 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H2), 4.95 (d, $J_{4,3}$ = 3.6 Hz, 1 H, H3), 4.88 (br s, 1 H, H4), 4.18 (m, 1 H, H5), 3.24 (dd, $J_{6A,6B}$ = 15.6 Hz, $J_{6B,5}$ = 5.7 Hz, 1 H, H6B), 2.90 (dd, $J_{6A,6B}$ = 15.6 Hz, $J_{6A,5}$ = 11.0 Hz, 1 H, H6A), 2.69 (br d, *J* = 9.2 Hz, 1 H, OH), 1.60, 1.36 [2 s, 2 × 3 H, $-OC(CH_3)_2O-$], 0.34 [s, 9 H, $(CH_3)_3Si$]; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 141.9 (C8), 137.7 (C7), 112.9 [$-OC(CH_3)_2O-$], 105.0 (C1), 84.7 (C2), 77.3 (C4), 65.9 (C5), 63.1 (C3), 26.6, 26.3 [$OC(CH_3)_2O$], 25.4 (C6), −1.1 [$(CH_3)_3Si$]; MS (70 eV) *m*/*z* 326 (1), 297 (10), 181 (13), 126 (63), 100 (18), 73 (100). Anal. Calcd for $C_{14}H_{23}N_3O_4Si$: C, 51.67; H, 7.12; N, 12.91. Found: C, 51.95; H, 7.40; N, 12.65. **49**: mp 113−115 °C; $[\alpha]^{20}_D$ +41 (*c* 1.8, CH_3OH); IR (KBr) ν 3450, 3020, 2930, 1360, 1220, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52 (s, 1 H, H5), 6.23 (d, $J_{1',2'}$ = 3.7 Hz, 1 H, H1′), 5.24 (d, $J_{4',3'}$ = 3.7 Hz, 1 H, H3′), 5.03 (d, $J_{1',2'}$ = 3.7 Hz, 1 H, H2′), 4.22 (dd, $J_{4',5'}$ = 9.0 Hz, $J_{4',3'}$ = 3.7 Hz, 1 H, H4′), 2.84 (dq, $J_{4',5'}$ = 9.0 Hz, $J_{6',5'}$ = 6.1 Hz, 1 H, H5′), 1.61, 1.38 [s, 2 × 3 H, $-OC(CH_3)_2O-$], 1.27 (d, $J_{6',5'}$ = 6.1 Hz, 3 H, H6′), 0.34 [s, 9H, $(CH_3)_3$ Si]; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 146.0 (C4), 129.6 (C5), 112.4 [$-OC(CH_3)_2O-$], 105.8 (C1′), 83.7 (C3′), 83.6 (C4′), 65.1 (C2′, C5′), 26.6, 26.2 [$OC(CH_3)_2O$], 21.0 (C6′), −1.1 [$(CH_3)_3$ Si]; EM (70 eV) *m*/*z* 312 (13), 283 (5), 184 (32), 142 (40), 98 (51), 73 (100). Anal. Calcd for $C_{14}H_{25}N_3O_4Si$: C, 51.35; H, 7.70; N, 12.83. Found: C, 51.71; H, 7.98; N, 12.57.

Following the general method for desilylation, compound **48** (26 mg, 0.079 mmol) gave compound **44** (20 mg, 99%).

Free-Radical Cyclization of Precursor 15. Following **general procedure A for carbocyclization**, compound **15** (69 mg, 0.15 mmol) afforded product **50** [8 mg, 32% (78% taking into account the recovered starting material)] after chromatography (hexane/EtOAc, from 9:1 to 3:2). **50**: 111−113 °C; $[\alpha]^{20}_D$ +1 (*c* 7.3, CH_3OH); IR (KBr) ν 3040, 2940, 1720, 1460, 1350, 1275, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.79 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H1), 5.25 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H2), 5.23 (ddd, $J_{4,5}$ = 1.9 Hz, $J_{6A,5}$ = 11.3 Hz, Hz, $J_{6B,5}$ = 5.9 Hz, 1 H, H5), 4.96 (d, $J_{4,3}$ = 3.6 Hz, 1 H, H3), 4.87 (m, 1 H, H4), 3.18 (dd, $J_{6A,6B}$ = 15.4 Hz, $J_{6B,5}$ = 5.9 Hz, 1 H, H6B), 3.03 (dd, $J_{6A,6B}$ = 15.4 Hz, $J_{6A,5}$ = 11.3 Hz, 1 H, H6A), 2.17 (s, 3 H, $OCOCH_3$), 1.57, 1.33 [2 s, 2 × 3 H, $-OC(CH_3)_2O-$], 0.32 [s, 9 H, $(CH_3)_3Si$]; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.3 ($OCOCH_3$), 142.2 (C7), 136.8 (C8), 112.8 [-$OC(CH_3)_2O$-], 105.3 (C1), 84.1 (C2), 74.8 (C4), 67.0 (C5), 63.4 (C3), 26.5, 26.1 [$OC(CH_3)_2O$], 21.9 (C6), 21.0 ($OCOCH_3$), −1.1 [$(CH_3)_3Si$]; MS (70 eV) *m*/*z* 368 (4), 307 (88), 279 (13), 189 (11), 163 (29), 114 (45), 43 (100). Anal. Calcd for $C_{16}H_{25}N_3O_5Si$: C, 52.30; H, 6.86; N, 11.43. Found: C, 52.44; H, 6.98; N, 11.29.

Free-Radical Cyclization of Precursor 16. Following **general procedure A for carbocyclization**, compound **16** (34 mg, 0.09 mmol) afforded a crude (**46** + **47**) that was submitted to **basic hydrolysis following the general**

method to give products **44** (11 mg, 48%) and **45** (3.5 mg, 15%), after chromatography (hexane/EtOAc, from 2:3 to 1:4).

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Supporting Information Available: General methods andexperimental procedures for the synthesis of the radical precursors **7**−**16**, with full spectroscopic and analytical data. This material is available free of charge via the Internet at http:/pubs.acs.org.

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