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Synthesis of fused azole-piperidinoses

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Abstract

A new strategy has been reported for the synthesis of fused azole-piperidinoses featuring an unprecedented and very efficient 6-*exo-trig* free radical cyclization onto heterocyclic sugar templates. In this communication we describe our recent and successful results on the synthesis of fused triazole-piperidinoses. These compounds are key intermediates for the synthesis of known or analogues of azole-glycosidase inhibitors, such as nagstatine. Radical precursors (**8**, **10**, **14**) have been prepared by standard methodologies from 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**5**) via triazoles linked at C3, with β-orientation, readily obtained by 1,3-dipolar cycloaddition of sugar azide 6 with diethyl acetylenedicarboxylate or methyl propiolate. The key **6**-*exo-trig* free radical cyclizations proceeded in the usual conditions [tributyltin hydride or tris(trimethylsilyl)silane, AIBN, toluene] yielding the azaannulated sugars **9**, **11** and **15** in good or excellent yields.

Keywords: Azole-piperidinoses; Radical precursors; Cyclizations

1. Introduction

Several tetrazoles (Ermett & Vasella, 1991; Heightman, Vasella, Tsitsanou, Zographos, Skamnaki & Oikonomakos, 1998), triazoles (Krülle et al., 1997) and imidazoles (Aoyama, Naganawa, Suda, Uoptani, Aoyagi & Takeuchi, 1992) fused to furanoses or pyranoses have been identified as selective and potent glycosidase inhibitors (Bols, 1998). This is the case of nagstatin (Aoyama et al., 1992) or other synthetic molecules (Ermett & Vasella, 1991; Krülle et al., 1997) (Fig. 1). Most syntheses of these azasugars have relied either on the intramolecular 1,3-dipolar cycloaddition (1,3-DC) (Gothelf & Jorgensen, 1998) of δ-azidonitriles (Ermett & Vasella, 1991) or δ-azido α,β-unsaturated esters (Krülle et al., 1997) derived from sugars, the intramolecular S_N2 reaction on tethered azole sulfonate sugar derivatives (Frankowski, Deredas, Streith & Tschamber, 1998) or from gluconolactams by annulation of hydrazinecarbaldehyde and aminoacetaldehyde dimethyl acetal (Granier, Gaiser, Hintermann & Vasella, 1997) In spite of these efforts, new synthetic alternatives are sought due to the potential biological activity and therapeutic profile of the new target molecules.

Continuing with our work on the synthesis of glycosidase inhibitors from carbohydrates via free radical cyclization strategies (Marco-Contelles & Alhambra, 1999; Marco-Contelles, Destabel, Gallego, Chiara & Bernabé, 1996), in this paper we report a new and efficient synthetic approach for the preparation of fused azole-piperidinoses, a series of key intermediates for the synthesis of the above cited and related glycosidase inhibitors. The main aspects of this strategy consist in: (a) the introduction of an *N*-azole at C3 in an hexofuranose starting material (**A**) and (b) an unprecedented 6-*exo-trig* cyclization of a radical species at C6 onto an heterocyclic ring system in intermediates (**B**), leading to the azaannulated sugar (Marco-Contelles, Alhambra & Martínez-Grau, 1998) (**C**) (Scheme 1; General strategy for the synthesis o used azole-piperidinoses). It is expected that standard and further synthetic manipulations (hydrolysis of the isopropylidenedioxy at C-1/C2,1,2-diol cleavage and hydride reduction) would afford piperidinoses of type (**D**). In this approach we can modulate the absolute stereochemistry at C3 during the incorporation of the *N*-azole, and differently substituted azole nucleus (X = O, N, S) can be placed at C3 by Mitsunobu reaction and/or S_N2 replacement of good leaving groups (Nair & Nuesca, 1992; Verheggen et al., 1993). In addition, free radical cyclizations onto heterocycles are known (Aldabbagh & Bowman, 1999; Aldabbagh, Bowman & Mann, 1997; Antonio et al., 1994; Curran, Yu & Liu, 1994; Moody & Norton, 1995; Rosa, Lobo, Branco, Prabhakar & Pereira, 1997), but these protocols have seldom been used in sugar templates.

In this paper we report our recent and successful results

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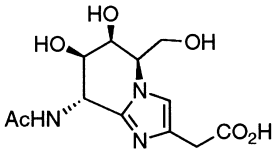


Nagstatin

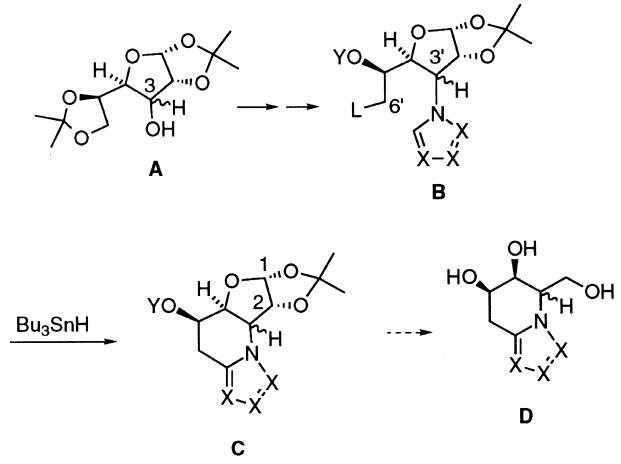
Fig. 1.

on this subject. We have concentrated our efforts in the synthesis and free radical cyclization of triazole derivatives (**8**, **10** and **14**) of type **B** positioned at C3 in β-orientation (Scheme 1).

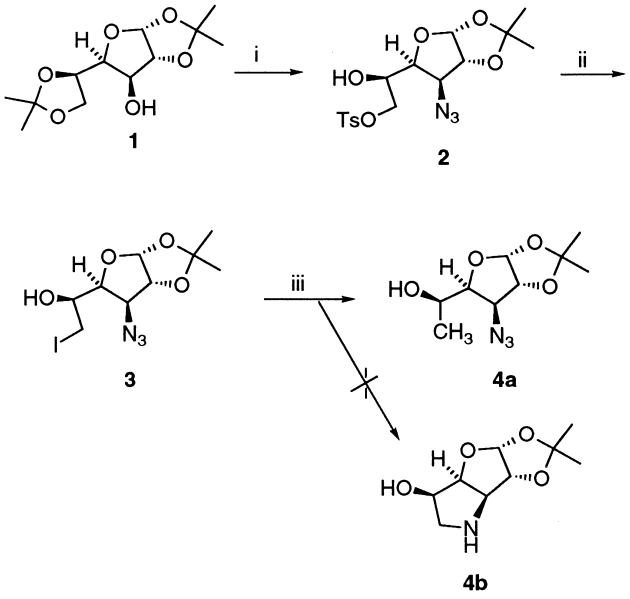
2. Results and discussion

In our preliminary experiments we have directed our attention to the free radical carbocyclization of the 3-azido-3,6-dideoxy-6-iodo derivative (**3**) (Scheme 2; Reagents: i. (a) I_2, PPh_3, imidazole, relux (54%); (b) NaN_3, DMF, 135°C (56%); (c) AcOH, H_2O (7:3) r.t. (95%); (d) TsCl, py, r.t. (59%); (ii) NaI, DMF, 60°C (73%); and (iii): Bu_3SnH, toluene (53%)). This compound has been prepared from commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**) via the known intermediate **2** (Austin, Baird, Fleet, Peach, Smith & Watkin, 1987). The failure in obtaining the pyrrolidine annulated furanose **4b** via free radical mediated cyclization of compound **3** (the only isolated compound was the reduced uncyclized derivative **4a** in 53% yield) moved us to change our strategy according to the general plan shown in Scheme 1.

The radical precursor **8** has been prepared by standard methodologies from commercially available 1,2:5,6-di-*O*-isopropylidene-(α-D-allofuranose (**5**). The 4,5-diethyl carboxylate 1,2,3-triazole was located at C3 by a clean and high yielding 1,3-DC of azide **6** (Austin et al., 1987) with diethyl acetylenedicarboxylate (Scheme 3; Reagents: i.

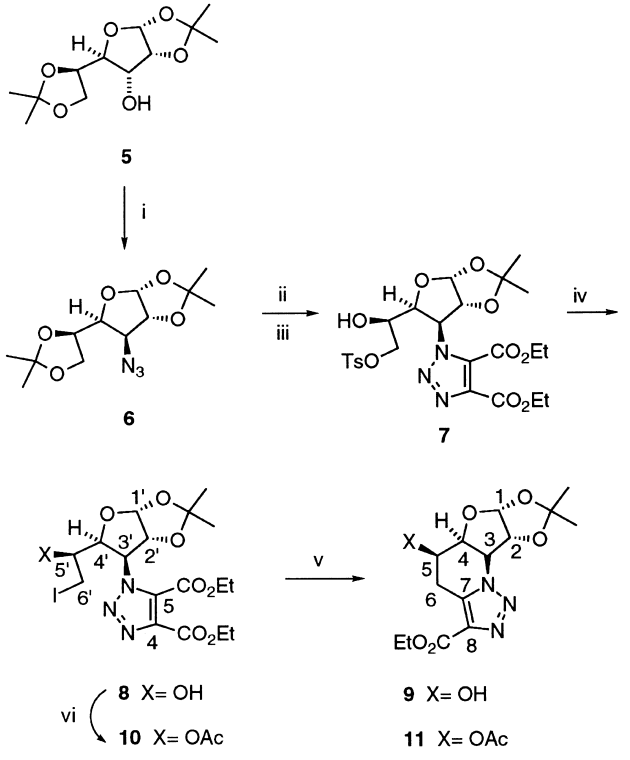


Scheme 1.

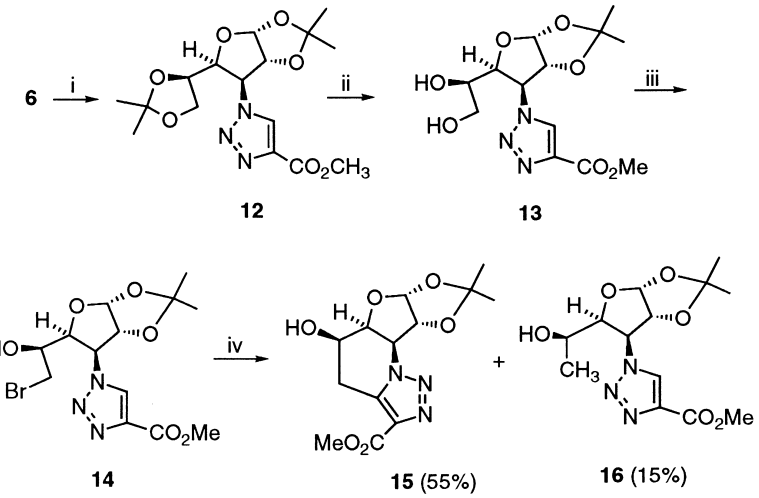


Scheme 2.

(a) TsCl, py, r.t. (95%); (b) NaN_3, DMF, 135°C (95%); ii. Diethyl acetylenedicarboxylate, toluene, 100°C (97%); iii. (a) AcOH, H_2O (7:3), r.t. (97%); (b) TsCl, py (87%); (iv) Nal, DMF (88%); v. (from **8**) $[(CH_3)_3Si]_3SiH$, toluene (0.02 M) (72%); (rom **10**) $[(CH_3)_3Si]_3SiH$, toluene (0.02 M) (94%); vi. Ac_2O, py (93%)). Compound **7** was finally obtained by simple and standard manipulation



Scheme 3.



Scheme 4.

(Marco-Contelles & Alhambra, 1999). Sodium iodide reaction with this intermediate gave the desired radical percursor **8**. Free radical cyclization (Curran, 1988) of compound **8**, in the usual conditions (see Section 3), by using tris(trimethysilyl)silane, gave the fused azole-piperidinose **9** in good yield (54 and 72%, respectively). The analytical and spectroscopic data of this compound clearly supported this structure showing that the 6-*exo-trig* cyclization has occurred into C5, a tetrasubstituted carbon of the 4,5-diethyl dicarboxylate-1,2,3-triazole, with subsequent decarboxylation and aromatization. To the best of our knowledge, this is the first example described in the literature involving a free radical cyclization onto a 1,2,3-triazole heterocyclic system and the first example of a free radical cyclization onto an heterocycle contained in a sugar template (Czernecki, Ayadi & Xie, 1996; Majumdar, Bhattacharjya & Patra, 1997; Xi, Glemarec & Chattopadhyaya, 1993).

Obviously, this result supported our projected strategy for the synthesis of new and different fused azole-piperidinoses. Consequently, the acetylated precursor **10**, submitted to the same experimental conditions, gave the azaannulated sugar **11** in 94% yield (Scheme 3).

The interesting results obtained in the cyclization of intermediates **8** and **10** are noteworthy, and moved us to test an analogous protocol in precursors **14** (Scheme 4; Reagents: i. Methyl propiolate, toluene, 110°C (77%); ii. AcoH/H_2O (99%); iii. CBr_4, PPh_3, dry THF (89%); iv. $[(CH_3)_3Si]_3SiH$, toluene (0.02 M)), having at C3′-β a C4-carbomethoxy substituted *N*-1,2,3-triazole ring. The synthesis of compound **14** has been achieved from azide **6**, after 1,3-DC with methyl propiolate and acid hydrolysis to give product **13** (Marco-Contelles & Alhambra, 1999), followed by bromination, as shown in Scheme 4. The 6-*exo* free radical cyclization proceeded as expected giving the fused triazole **15** in 56% yield. This compound showed spectroscopic data coherent with this structure (see Section 3), very similar to those observed for the analogous adduct **9** (Scheme 3).

The formation of aromatic products (**9**,**11** and **15**) can be explained according to the mechanism advanced by Bowman for the cyclization of radicals derived from 1-(ω-benzeneselenylalkyl)-, 2-(benzenesulfenyl)-benzimidazoles and 2-(*p*-toluenesulfonyl)imidazoles (Aldabbagh et al., 1997). Carbon dioxide and radical ethyl elimination is a strong driving force that accounts for the efficiency of the free radical cyclizations, securing long chain radical reactions.

Work is now in progress to transform the carbocyclic molecules (**9**,**11**,**15**) into the desired target molecules of type **D** (Scheme 1). These transformations will be described in due course.

In summary, a new strategy has been reported for the synthesis of fused azole-piperidinoses featuring an unprecedented and very efficient 6-*exo-trig* free radical cyclization onto triazole nucleus installed at C3, in conveniently functionalized furanose templates.

3. Experimental part

3.1. General methods

Reactions were monitored by TLC using precoated silica gel aluminium plates containing a fluorescent indicator (Merck, 5539). Detection was done by UV (254 nm) followed by charring with sulfuric-acetic acid spray, 1% aqueous potassium permanganate solution or 0.5% phosphomolybdic acid in 95% EtOH. Anhydrous $MgSO_4$ was used to dry organic solutions during workups and the removal of solvents was carried out under vacuum with a rotary evaporator. Flash column chromatography was performed using Kieselgel 60 (230–400 mesh, Merck) and hexane–ethyl acetate mixtures as eluent unless otherwise

stated. Optical rotations were determined with a Perkin–Elmer 257 instrument. ^{1}H and ^{13}C NMR spectra were recorded with a Varian VXR-300S spectrometer, using tetramethylsilane as internal standard.

3.2. General procedure for free radical cyclizations

To a solution of the radical precursor (1 eq.) in toluene (0.02 M), previously purged with argon during 30 min, a solution of tributyltin hydride or tris(trimethylsilyl)silane (1.4 eq.) and AIBN (0.03 eq.) was slowly added at reflux, under argon, via syringe pump in 1 h. After heating for 1 h more, the flask was cooled, the solvent was evaporated and the residue submitted to flash chromatography, eluting with hexane–ethyl acetate mixtures to give the final product.

3-Azido-3,6-dideoxy-6-iodo-1,2-*O*-isopropylidene-α-D-glucofuranose (3). Compound **2** (Austin et al., 1987) (478 mg, 1.2 mmol) was treated with an excess of sodium iodide (2.97 g, 19.8 mmol) in dry dimethylformamide (20 ml) at 80°C (bath temperature) for 1 h. The solvent was removed *in vacuum* and the residue diluted with methylene chloride and washed with brine, dried and evaporated. The crude was submitted to flash chromatography (hexane/ethyl acetate 5%) to give product **3** (294 mg, 73%): oil; $[\alpha]_D^{25}$ − 19 (*c* 1.8, $CHCl_3$); IR (KBr) ν_{max} 3600–3200, 3460, 2110, 2990, 1385–1375, 1340, 1080 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (d, $J_{1,2} = 3.6$ Hz, 1H, H1), 4.64 (d, $J_{1,2} = 3.6$ Hz, 1H, H2), 4.18 (d, $J_{3,4} = 3.2$ Hz, 1H, H3), 4.09 (dd, $J_{3,4} = 3.2$ Hz, $J_{4,5} = 8.8$ Hz, 1H, H4), 3.68 (m, 1H, H5), 3.64 (dd, $J_{6,6'} = 10.9$ Hz, $J_{5,6} = 2.8$ Hz, 1H, H6), 3.42 (dd, $J_{6,6'} = 10.9$ Hz, $J_{5,6'} = 7.1$ Hz, 1H, H6′), 2.34 (d, $J = 5.9$ Hz, 1H, OH), 1.52 and 1.33 [s, s, 3H, 3H, $OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.6 [$OC(CH_3)_2O$], 104.9 (C1), 83.4 (C2), 81.6 (C4), 68.6 (C5), 66.2 (C3), 26.7 and 26.4 [$OC(CH_3)_2O$], 14.6 (C6); MS (70 eV) *m/z* 340 (M^+ − 15, 51), 33 (12), 312 (16), 184 (54), 142 (76), 113 (59), 85 (89), 43 (100). Anal. $C_9H_{14}IN_3O_4$. Calcd: C, 30.44; H, 3.97; N 11.83. Found: C, 30.47; H, 3.71; N 12.01.

Compound 4a. Free radical cyclization of precursor 3 (100 mg, 0.28 mmol) according to the Section 3.2, using tributyltin hydride, gave product **4a** (32 mg, 53%): oil; $[\alpha]_D^{25}$ −22 (*c* 0.42, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (d, $J_{1,2} = 3.7$ Hz, 1H, H1), 4.63 (d, $J_{1,2} = 3.7$ Hz, 1H, H2), 4.09 (d, $J_{3,4} = 3.7$ Hz, 1H, H3), 4.05–3.90 (m, 2H, H4, H5), 2.16 (d, $J = 4.7$ Hz, 1H, OH), 1.52 and 1.33 [s, s, 3H, 3H, $OC(CH_3)_2O$], 1.34 (d, $J = 5.7$ Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) d 112.1 [$OC(CH_3)_2O$], 104.8 (C1), 83.4 (C2), 83.3 (C4), 65.9 (C5), 65.8 (C3), 26.5 and 26.1 [$OC(CH_3)_2O$], 21.2 (C6). Anal. $C_9H_{15}N_3O_4$. Calcd: C, 47.16; H, 6.60; N 18.33. Found: C, 47.27; H, 6.71; N 18.11.

Compound 8. Tosylate 7 (Marco-Contelles & Alhambra, 1999) (170 mg, 0.30 mmol) was treated with an excess of sodium iodide (673 mg, 4.48 mmol) in dry dimethylformamide (8 ml) at 80°C (bath temperature) for 1 h. The solvent was removed *in vacuum* and the residue diluted with methylene chloride and washed with brine, dried and evaporated. The crude was submitted to flash chromatography (hexane/ethyl acetate, 7/3) to give product **8** (99 mg, 63%): oil; $[\alpha]_D^{25}$ +105 (*c* 0.66, $CHCl_3$); IR (KBr) u_{max} 3550–3200, 2950, 1725, 1540, 1430, 1190, 1000 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) d 6.27 (d, $J_{1',2'} = 3.5$ Hz, 1H, H1′), 5.71 (d, $J_{3',4'} = 3.2$ Hz, 1H, H3′), 5.05 (d, $J_{1',2'} = 3.5$ Hz, 1H, H2′), 4.46 (q, $J = 7.1$ Hz, 4H, 2 × $COOCH_2CH_3$), 4.38 (dd, $J_{3',4'} = 3.2$ Hz, $J_{4',5'} = 8.8$ Hz, 1H, H4′), 3.48 (dd, $J_{6'A,6'B} = 10.6$ Hz, $J_{5',6'A} = 2.4$ Hz, 1H, H6′A), 3.36 (dd, $J_{6'A,6'B} = 10.6$ Hz, $J_{5',6'B} = 5.5$ Hz, 1H, H6′B), 2.41 (m, 2H, H5, OH), 1.62 and 1.61 [s, s, 3H, 3H, $OC(CH_3)_2O$], 1.42 (d, $J = 7.1$ Hz, 6H, 2 × $COOCH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) d 159.9 and 158.9 (2 × *C*OOEt), 139.7 (C-4), 131.7 (C-5), 113.0 [$OC(CH_3)_2O$], 106.5 (C1′), 84.5 (C2′), 81.8 (C4′), 67.6 (C5′), 64.7 (C3′), 63.4 and 62.1 (2 × $COOCH_2CH_3$), 27.0 and 26.5 [$OC(CH_3)_2O$], 14.1 (C6), 14.2 and 13.9 (2 × $COOCH_2CH_3$); MS (70 eV) *m/z* 526 (M^+ +1, 27), 510 (M^+ − 15, 40), 480 (21), 398 (21), 398 (21), 354 (74), 214 (100), 113 (52). Anal. $C_{17}H_{24}IN_3O_8$. Calcd: C, 38.87; H, 4.61; N, 8.00. Found: C, 38.67; H, 4.71; N 8.01.

Compound 9. Compound **8** (98 mg, 0.19 mmol) was treated with tris(trimethylsilyl)silane according to the Section 3.1 to give, after flash chromatography (hexane/ethyl acetate, 7/3), compound **9** (44 mg, 72%): mp 154–156°C; $[\alpha]_D^{25}$ − 44 (*c* 0.35, $CHCl_3$); IR (KBr) ν_{max} 3600–3200, 3460, 2990, 2920, 1735, 1380, 1190, 1080 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (d, $J = 3.6$ Hz, 1H, H1), 5.11 (d, $J = 3.6$ Hz, 1H, H2), 4.97 (d, $J = 3.6$ Hz, 1H, H3), 4.89 (br s, 1H, H4), 4.42 (q, $J = 7.1$ Hz, 2H, $COOCH_2CH_3$), 4.20 (m, 1H, H5), 3.69 (dd, $J_{6,6'} = 16.9$ Hz, $J_{5,6} = 5.7$ Hz, 1H, H6), 3.00 (dd, $J_{6,6'} = 16.9$ Hz, $J_{5,6'} = 11.0$ Hz, 1H, H6′), 2.34 (d, $J = 9.6$ Hz, 1H, OH), 1.60 and 1.36 [s, s, 3H, 3H, $OC(CH_3)_2O$], 1.41 (t, $J = 7.1$ Hz, 3H, $COOCH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) d 160.9 ($COOCH_2CH_3$), 137.5 (C8)*, 135.3 (C7)*, 113.1 [$OC(CH_3)_2O$], 104.8 (C1), 84.3 (C2), 76.8 (C4), 65.1 (C3), 63.7 (C5), 61.1 ($COOCH_2CH_3$), 26.5 and 26.2 [$OC(CH_3)_2O$], 25.2 (C6), 14.3 ($COOCH_2CH_3$) (* these values can be interchanged); MS (70 eV) *m/z* 326 (M^+ +1, 27), 310 (M^+ − 15, 100), 280 (17), 250 (8), 209 (24), 184 (21), 152 (15), 107 (24), 85 (18), 59 (28). Anal. $C_{14}H_{19}N_3O_6$. Calcd: C, 51.69; H, 5.89; N 12.92. Found: C, 51.48; H, 5.71; N 13.01.

Compound 10. Compound **8** (190 mg, 0.33 mmol) was treated with acetic anhydride/pyridine (2 ml/2 ml) for 24 h, at rt. After evaporation, co-distilling with toluene, the residue was purified by flash chromatography (hexane/ethyl acetate, 30%) to give acetate **10** (174 mg, 93%): oil; $[\alpha]_D^{25}$ +11 (*c* 0.35, $CHCl_3$); IR (KBr) ν_{max} 2990, 1755, 1735, 1550, 1380, 1220–1210 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (d, $J_{1'}2' = 3.3$ Hz, 1H, H1′), 5.68 (d, $J_{3'}4' = 4.2$ Hz, 1H, H3′), 4.82 (d, $J_{1'}2' = 3.3$ Hz, 1H, H2′), 4.73 (dd, $J_{3',4'} = 4.2$ Hz, $J_{4'}5' = 8.8$ Hz, 1H, H4′), 4.41 (q, $J = 7.1$ Hz, 4H, 2 × $COOCH_2CH_3$), 3.85 (m, 1H, H5′), 3.44 (br s, 2H, 2H6′), 1.99 (s, 3H, $OCOCH_3$), 1.62

and 1.61 [s, s, 3H, 3H, $OC(CH_3)_2O$], 1.40 (t, $J = 7.1$ Hz, 6H, $2 \times COOCH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9 ($OCOCH_3$), 159.8 and 158.3 ($2 \times COOEt$), 140.5 (C-4), 130.3 (C-5), 113.2 [$OC(CH_3)_2O$], 105.9 (C1′), 84.8 (C2′), 79.7 (C4′), 67.4 (C5'), 64.0 (C3′), 63.2 and 62.1 ($2 \times COOCH_2CH_3$), 26.9 and 26.5 [$OC(CH_3)_2O$], 20.8 ($OCOCH_3$), 14.1 and 13.8 ($2 \times COOCH_2CH_3$), 6.9 (C6′); MS (70 eV) *m/z* 552 ($M^+ - 15$, 13), 440 (100), 194 (35). Anal. $C_{19}H_{26}IN_3O_9$. Calcd: C, 40.22; H, 4.62; N. 7.41. Found: C, 40.47; H, 4.73; N, 7.65.

Compound 11. Compound **10** (170 mg, 0.30 mmol) was treated with tris(trimethylsilyl)silane according to the General Method to give, after flash chromatography (hexane/ethyl acetate, 15%), compound 11 (104 mg, 94%): mp 78–80°C; $[\alpha]_D^{25}$ −48 (*c* 0.56, $CHCl_3$); IR (KBr) ν_{max} 2960, 2900, 1735, 1720, 1460, 1360, 1265, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (d, $J = 3.6$ Hz, 1H, H1), 5.29 (m, 1H, H5), 5.26 (d, $J = 3.6$ Hz, 1H, H2), 5.01 (d, $J = 3.6$ Hz, 1H, H3), 4.90–4.87 (br s, 1H, H4), 4.41 (q, $J = 7.1$ Hz, 2H, $COOCH_2CH_3$), 3.65 (dd, $J_{6,6'} = 14.0$ Hz, $J_{5,6} = 4.7$ Hz, 1H, H6), 3.14 (dd, $J_{6,6'} = 14.0$ Hz, $J_{5,6'} = 9.4$ Hz, 1H, H6′), 1.57 and 1.34 [s, s, 3H, 3H, $OC(CH_3)_2O$], 1.39 (t, 3H, $COOCH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) d 170.1 ($OCOCH_3$), 160.8 ($COOCH_2CH_3$), 136.8 (C8)*, 135.6 (C7)*, 113.0 [$OC(CH_3)_2O$], 105.1 (C1), 83.7 (C2), 74.4 (C4), 66.0 (C5), 64.0 (C3), 61.2 ($COOCH_2CH_3$), 26.4 and 26.1 [$OC(CH_3)_2O$], 21.9 (C6), 20.9 ($OCOCH_3$), 14.3 ($COOCH_2CH_3$) (* these values can be interchanged). Anal. $C_{16}H_{21}N_3O_7$. Calcd: C, 52.31; H, 5.76; N, 11.44. Found: C, 52.14; H, 5.72; N 11.31.

Compound 14. Product **13** (Marco-Contelles & Alhambra, 1999) (88 mg, 0.27 mmol) was dissolved in dry THF (4 ml) under argon. Carbon tetrabromide (266 mg, 0.80 mmol) and triphenylphosphine (140 mg, 0.53 mmol) were added and the mixture was stirred at rt for 30 min. The solvent was removed and the residue was submitted to flash chromatography (hexane/ethyl acetate 30%) to give compound **14** (94 mg, 89%): mp 192–195°C; $[\alpha]_D^{25}$ +20 (*c* 0.75, $CHCl_3$); IR (KBr) ν_{max} 3500–3400, 3120, 2960, 2900, 1710, 1430, 1360, 1265, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H, H5), 6.27 (d, $J_{1',2'} = 3.6$ Hz, 1H, H1′), 5.18 (d, $J_{3'}4' = 3.7$ Hz, 1H, H3′), 5.13 (d, $J_{1'}2' = 3.6$ Hz, 1H, H2′), 4.46 (dd, $J_{3'}4' = 3.7$ Hz, $J_{4'}5' = 9.2$ Hz, 1H, H4′), 3.95 (s, 3H, $COOCH_3$), 3.68 (dd, $J_{6'A,6'B} = 10.7$ Hz, $J_{5',6'A} = 2.7$ Hz, 1H, H6′A), 3.57 (dd, $J_{6'A,6'B} = 10.7$ Hz, $J_{5',6'B} = 5.9$ Hz, 1H, H6′B), 2.83 (m, 1H, H5′), 1.59 and 1.39 [s, s, 3H, 3H, $OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8 ($COOCH_3$), 140.2 (C4), 129.5 (C5), 113.1 [$OC(CH_3)_2O$], 106.2 (C1′), 83.4 (C3′), 79.9 (C4′), 67.9 (C5′), 66.1 (C3′), 52.4 ($COOCH_3$), 38.4 (C6′), 26.8 and 26.3 [$OC(CH_3)_2O$]. Anal. $C_{13}H_{18}BrN_3O_7$. Calcd: C, 39.81; H, 4.63; N, 10.71. Found: C, 39.61; H, 4.65; N 10.91.

Free radical cyclization of precursor 14. Compound **14** (84 mg, 0.21 mmol), treated under the standard conditions for free radical cyclization, gave products **15** (34 mg, 55%) and 16 (9 mg, 15%), after purification by flash chromatography (hexane/ ethyl acetate, 30%). **15**: mp 78–80°C; $[\alpha]_D^{25}$ −37 (*c* 0.66, $CHCl_3$); IR (KBr) ν_{max} 3600–3100, 2970, 1710, 1560, 1375, 1190, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (d, $J_{1,2} = 3.5$ Hz, 1H, H1), 5.23 (d, $J_{1,2} = 3.5$ Hz, 1H, H2), 4.96 (d, $J_{3,4} = 3.7$ Hz, 1H, H3), 4.88 (br s, 1H, H4), 4.30–4.23 (m, 1H, H5), 3.92 (s, 3H, $COOCH_3$), 3.65 (dd, $J_{6,6'} = 17.0$ Hz, $J_{5,6} = 2.8$ Hz, 1H, H6), 3.00 (dd, $J_{6,6'} = 17.0$ Hz, $J_{5,6'} = 10.8$ Hz, 1H, H6′), 1.57 and 1.34 [s, s, 3H, 3H, $OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3 ($COOCH_3$), 137.8 (C8)*, 134.9 (C7)*, 112.9 [$OC(CH_3)_2O$], 104.8 (C1), 84.1 (C2), 76.9 (C3), 64.8 (C4), 63.7 (C5), 52.0 ($COOCH_3$), 26.4 and 26.1 [$OC(CH_3)_2O$], 24.9 (C6) (* these values can be interchanged); MS (70 eV) *m/z* 311 (M^+, 1), 296 ($M^+ - 15$, 70), 195 (47), 170 (36), 138 (57), 85 (38), 43 (100). Anal. $C_{13}H_{17}N_3O_6$. Calcd: C, 50.16; H, 5.50; N 13.50. Found: C, 50.28; H, 5.71; N 13.39. 16: mp 143–146°C; $[\alpha]_D^{25}$ −20 (*c* 0.32, $CHCl_3$); IR (KBr) ν_{max} 3600–3200, 3120, 2980, 1720, 1545, 1385, 1250, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H, H5), 6.25 (d, $J_{1,2} = 3.7$ Hz, 1H, H1), 5.19 (d, $J_{1,2} = 3.7$ Hz, 1H, H2), 5.11 (d, $J_{3,4} = 3.7$ Hz, 1H, H3), 4.23 (dd, $J_{3,4} = 3.7$ Hz, $J_{4,5} = 8.9$ Hz, 1H, H4), 3.95 (s, 3H, $COOCH_3$), 2.99–2.85 (m, 1H, H5), 1.60 and 1.38 [s, s, 3H, 3H, $OC(CH_3)_2O$], 1.29 (d, $J = 6.3$ Hz, 3H, CH_3); MS (70 eV) *m/z* 298 ($M^+ - 15$, 10), 181 (18), 168 (20), 122 (36), 95 (100), 85 (54), 43 (96). Anal. $C_{13}H_{19}N_3O_6$. Calcd: C, 49.84; H, 6.11; N 13.41. Found: C, 49.77; H, 6.21; N 13.31.

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