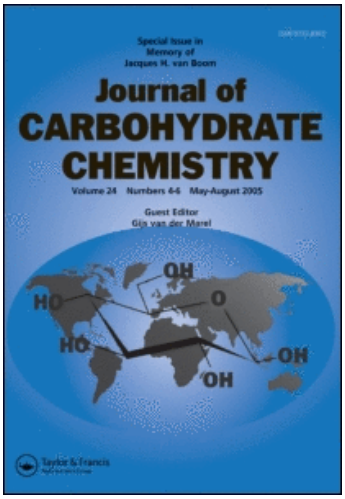

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FREE RADICAL CYCLIZATION OF ACYCLIC SUGAR DITHIOACETALS: AN APPROACH TO MANNOSTATIN A ANALOGUES

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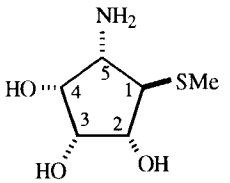
ABSTRACT

The tributyltin hydride + AIBN mediated free radical cyclization of oxime ethers tethered dithioacetals **6** and **12**, obtained from D-ribose or D-glucose, respectively, is reported. The desired carbocycles **7**, **8** and **14** have been obtained in good yield and moderate diastereoselectivity. These products are new mannostatin A analogues.

INTRODUCTION

The intramolecular cyclization of α-sulfenyl radicals is a known method for the synthesis of carbocycles.[1] These reactive species have been obtained from dithioacetals,[2a] 1,3-oxadithiolanes,[2b] 5-oxo-1,3-dithiolanes and α-chlorosulfides[3] by treatment with tributyltin hydride and AIBN.[4] In view of the precedents cited above,[1-4] dithioacetals prepared from sugars are obvious candidates for the preparation of chiral radical precursors for cyclization strategies. The first report of a free radical mediated cyclization of an unsaturated dithioacetal described[5] the photochemical 6-endo ring closure of 2,3,4-tri-*O*-acetyl-5,6-dideoxy-D-*xylo*-hex-5-enose diethyl dithioacetal. We have continued systematic analysis of the cyclization of acyclic intermediates from

carbohydrates for the preparation of inositols,[6] based upon the first tributyltin hydride + AIBN mediated intramolecular cyclization of an unsaturated dithioacetal obtained from D-glucose (1992).[7] In the same year, Roberts and Shoberu reported the 5-exo-trig cyclization of a dithioacetal, obtained from D-allose, leading to an advanced cyclopentanoid for carbocyclic nucleoside synthesis.[8] In 1993, Anaya and coworkers[9] reported the 5-exo-trig cycloisomerization of intermediates derived from protected D-glucosamine dithioacetals; this protocol has been used in a simple and efficient synthesis of methyl carbapenem antibiotics precursors. It is important to point out that in these three reports a high excess of tributyltin hydride (3-6 equiv) and AIBN (2 equiv[8] or catalytic[7,9]) was needed for complete and successful cyclizations; as a result, in some cases, partial[7,9] or total[8] desulfurization was observed.

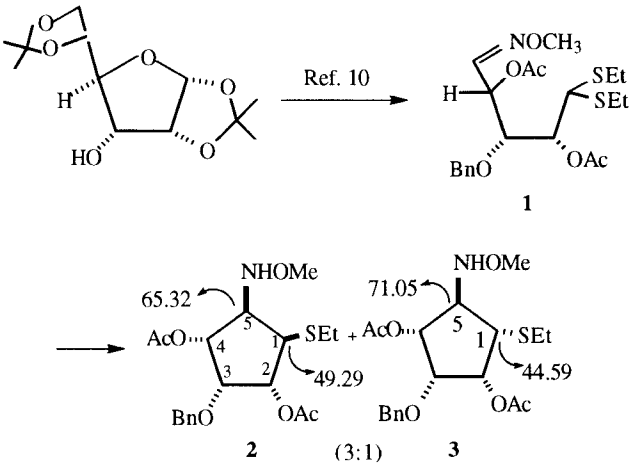


Mannostatin A

Very recently Roberts and coworkers[10] reported the 5-exo free radical cyclization of a dithioacetal tethered oxime ether (**1**), obtained from D-allose (Scheme 1). This cyclization afforded mannostatin A[11] analogues (**2**, **3**; Scheme 1) in good yield and moderate selectivity.

RESULTS AND DISCUSSION

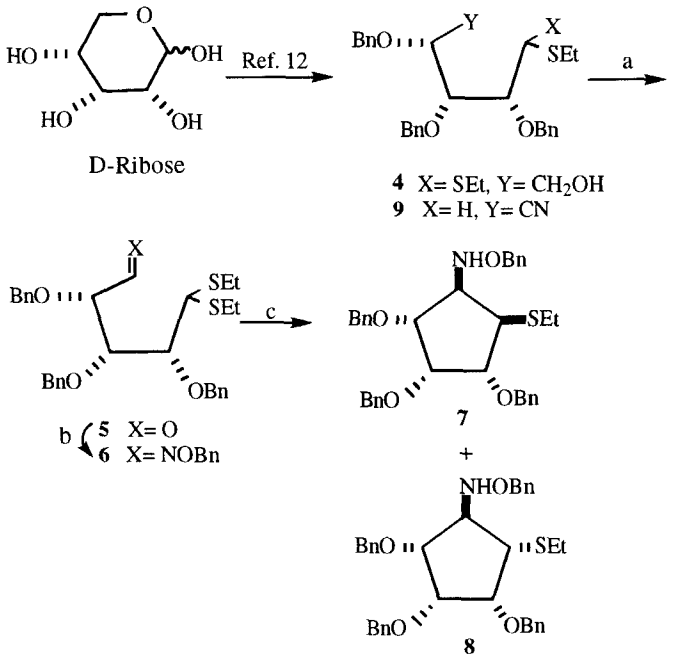
In the above context, we report herein on the results that we obtained in our current project directed to the total synthesis of mannostatin A and analogues. In our strategy, the key step was the 5-exo-trig cyclization of an acyclic intermediate of type **6** (Scheme 2). This compound has been obtained from D-ribose, in six steps following known methodology,[12] as an unseparable mixture of *E* and *Z* isomers (in a 6:1 ratio, respectively, as shown by ^{1}H NMR analysis). The use of this readily available starting material provided us with the correct configurations at C2-C4 in mannostatin A. In our case the use of D-ribose, instead of D-allose,[10] saves some synthetic steps and makes our



Scheme 1

strategy more efficient. It is noteworthy that the strategy reported by Roberts,[10] as well as our approach towards this glycosidase inhibitor, involve, for the first time, a simple free radical cyclization of chiral precursors as the major step. This general approach compares very favorably with other methodologies described in the literature.[11]

Under the typical free radical cyclization conditions (see **Experimental Section**), the tributyltin hydride mediated cyclization of oxime **6** gave the expected carbocycles **7** and **8** (Scheme 2) in 80% yield. Traces of nitrile **9** were also detected in some fractions obtained during the chromatographic purification of compounds **7** and **8**. These products have been isolated as a mixture in a 4:1 ratio, respectively, as shown by ^{1}H NMR analysis. We were unable to chromatographically purify each isomer, but in one of the isolated fractions, compound **7** (~95% purity) was present as the major product with some unseparable, minor impurities of unknown structure. In the ^{13}C NMR spectrum of this mixture we could observe clear signals for C5 (64.40 ppm) and C1 (51.00 ppm). In the other fraction obtained during the chromatography, compounds **7** and **8** appear in a 57:43 ratio, respectively, as determined from the ^{13}C NMR spectrum. This fraction also contained traces of nitrile **9** as confirmed from IR and ^{13}C NMR spectral data: band at 2240 cm^{-1} and signal at 119.05 ppm. Comparison of all the ^{13}C NMR values observed for **7** and **8** with those reported[10] for analogous compounds **2** and **3** obtained in the cyclization of oxime **1** (Scheme 1) confirms that isomers **7** and **8** have the same absolute configuration at the new stereocenters (C5 and C1) as compounds **2** and **3** (Scheme 1). In summary, the tributyltin hydride cyclization of dithioacetal **6**,



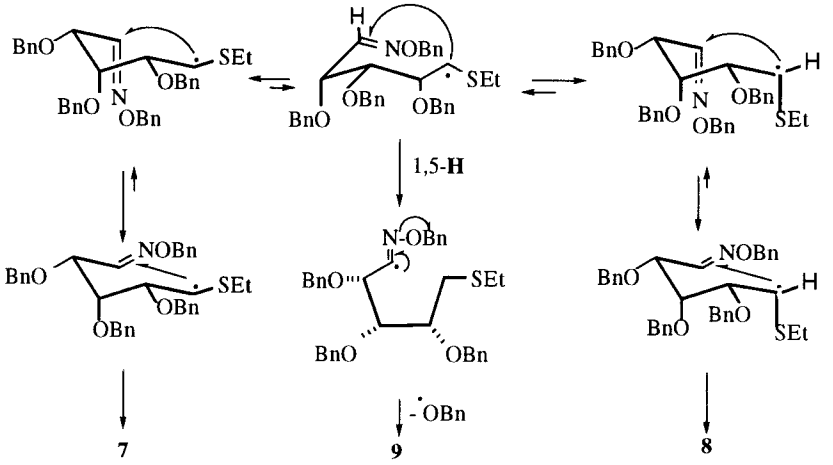
Reagents. a: PCC, methylene chloride, molecular sieves. b: NH_3OBnCl, pyridine, methylene chloride. c: $HSnBu_3$, AIBN, toluene.

Scheme 2

derived from D-ribose in six steps, gives in good yield (80% for the cyclization step) and moderate selectivity (**7**/**8**: 4/1), the expected carbocycles **7**(*cis*) and **8**(*trans*).

Scheme 3 presents a rationale for the stereochemical outcome of the cyclization of precursor **6**. It is assumed that in the transition state of this kinetically controlled 5-exo-trig ring closure, the radical species is in a chair-like conformation, with substituents in preferred pseudo-equatorial positions,[13] that minimizes 1,3-unfavorable steric interactions. As a result, isomer **7** should be more abundant than **8**, as experimentally observed. The formation of minor amounts of nitrile **9** is intriguing. In the absence of any precedent in the literature, its formation could be explained by a reasonable 1,5-hydrogen transfer and elimination of the benzyloxy radical (Scheme 3).

These results encouraged us to test the similar free radical 6-exo intramolecular cyclization with precursor **12** as a route to cyclohexane analogues of mannostatin A. Compound **12** has been obtained from D-glucose *via* the known alcohol **10**,[14] as shown



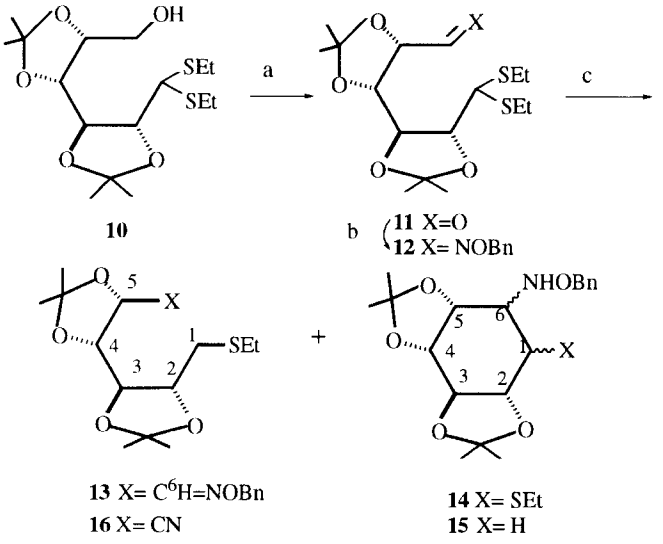
Scheme 3

in Scheme 4. Oxime **12** was obtained as an unseparable mixture of *E* and *Z* isomers (~1:1 ratio).

The free radical cyclization of product **12**, under the same experimental conditions (see **Experimental Section**), gave the reduced product **13**(*Z*) (95% purity due to contamination by some impurities of unknown structure, ~12% yield), **13**(*E*) (11% yield), traces of the totally desulfurized carbocycles **15**, traces of nitrile **16** and the expected carbocycles **14** (56% yield) (Scheme 4). The analysis of the crude reaction mixture by ^{13}C NMR showed that compound **14** was present as four isomers in ~1/1/0.67/1 ratio. As we were unable to isolate in pure form each of the cyclized isomers **14**, and in view of the difficult ^{1}H NMR analysis of these mixtures (see **Experimental Section**), the stereochemistry of these compounds could not be assigned.

The formation of product **13**, absent in the ring closure of product **6**, reflects the known and lower ability of 6-exo-trig cyclizations compared to the 5-exo-trig ones, to give the corresponding carbocycles.[15] This is also reflected by the decrease in the yield of cyclization products (**7**+**8**: 80% from **6**; **14**: 56% from **12**).

These results show that the tributyltin hydride mediated free radical cyclization of unsaturated dithioacetals is an efficient method for the preparation of the corresponding carbocycles, applicable to the synthesis of mannostatin A analogues. Work directed to the total synthesis of this and related glycosidase inhibitors with improved stereochemical control is now in progress and will be described in due course.



Reagents. a: PCC, methylene chloride, molecular sieves. b: NH_3OBnCl, pyridine, methylene chloride. c: $HSnBu_3$, AIBN, toluene.

Scheme 4

EXPERIMENTAL

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

General method for oxidation. To a solution of the alcohol in methylene chloride, sodium acetate (3 equiv), powdered molecular sieves and PCC (2.5 equiv) were successively added. The mixture was stirred at room temperature for 4 h. The mixture was diluted with diethyl ether, filtered over Celite 545 and washed with more ether. The filtrate was concentrated and the residue submitted to flash column chromatography .

General method for oxime ether formation. The corresponding aldehyde was dissolved in methylene chloride and treated with *O*-benzylhydroxylamine hydrochloride (1.2 equiv), pyridine (1.2 equiv) and water (several drops). The reaction mixture was refluxed for 10 h, cooled and the solution was diluted with more methylene chloride, washed with 5% aqueous solution of sodium bicarbonate and then brine. The solution was then dried ($MgSO_4$), concentrated and the residue was submitted to flash column chromatography .

General method for free radical carbocyclization. To a solution of the radical precursor in toluene (0.015 M), under argon, at reflux, a solution of tributyltin hydride (4 equiv) and AIBN (catalytic) in toluene was added slowly *via* syringe pump over 6 h. The reaction mixture was refluxed for another hour, then cooled and concentrated under reduced pressure. The residue was dissolved in diethyl ether, 15% aqueous solution of potassium fluoride was added and the resulting mixture stirred overnight at room temperature. The phases were separated and the organic layer dried, filtered and concentrated. The residue was submitted to flash column chromatography .

(2*R*,3*R*,4*S*)-2,3,4-*O*-Benzyl-1,1-diethylthiolpentanal-*O*-benzyl oxime (6). Following the *General Method* for oxidation and oxime ether formation, starting from alcohol **4**[12] (400 mg, 0.76 mmol), the aldehyde **5** was obtained and used without further purification for the synthesis of oxime **6** following the *General Method.* After chromatography (hexane/ethyl acetate: 95/5) compound **6** (220 mg, 47% overall yield from compound **4**) was obtained as an unseparable mixture of *E* and *Z* isomers (6:1 ratio, respectively): oil; IR (film) υ: 3090, 3060, 3030, 2920, 1495, 1455, 1100 cm^{-1}; ^1H NMR δ (isomer *E*): 7.57 (d, $J_{5,4}$= 8.2 Hz, 1 H, H5), 7.40-7.20 (m, 5 H, aromatic), 5.12 (s, 2 H), 4.96 (d, *J*= 11.2 Hz, 1 H), 4.77 (d, *J*= 10.7 Hz, 1 H), 4.65 (d, *J*= 11.2 Hz, 1 H), 4.56 (d, *J*= 11.8 Hz, 1 H), 4.42 (d, *J*= 11.8 Hz, 1 H) and 4.40 (d, *J*= 10.7 Hz, 1 H) (8 H, 4xOC$H_2C_6H_5$), 4.40 (dd, $J_{4,3}$= 2.1, $J_{5,4}$= 8.2 Hz, 1 H, H4), 4.20 (dd, $J_{3,2}$= 8.2 Hz, 1 H, H3), 4.18 (d, $J_{1,2}$= 2.4 Hz, 1 H, H1), 3.69 (dd, $J_{1,2}$= 2.4 Hz, 1 H, H2), 2.64 (q, *J*= 7.4 Hz, 4 H, 2xSCH_2CH_3), 1.21 (t, *J*= 7.4 Hz, 6 H, 2xSCH_2CH_3); (isomer *Z*): 6.82 (d, $J_{5,4}$= 5.7 Hz, 1 H, H5).

Anal. Calcd for $C_{37}H_{43}NO_4S_2$ (629.72): C, 70.57; H, 6.88; N, 2.22; S, 10.10. Found: C, 70.50; H, 6.76; N, 2.13; S, 10.05.

Compounds 7+8. Following the *General Method* and starting with compound **6** (61 mg, 0.1 mmol), after chromatography (hexane/ethyl acetate: 95/5), the following mixtures of products were obtained (total **7+8**: 44 mg, 80% yield): **7** (16 mg, ~95% purity) and **7+8** (28 mg, 57:43 ratio, respectively). **7**: oil; IR (film) υ: 3090, 3060, 3030, 2920, 1495, 1455, 1350, 1270, 1150-1000 cm^{-1}; ^1H NMR δ 7.50-7.20

(m, 20 H, aromatic), 6.19 (br s, 1 H, N*H*OBn), 4.74 (s, 2 H), 4.66 (s, 2 H), 4.63 (s, 2 H) and 4.57 (s, 2 H) (8 H, 4xOC$H_2C_6H_5$), 4.00-3.50 (m, 4 H, H1-H5), 2.64 (q, *J*= 7.4 Hz, 2 H, SCH_2CH_3), 1.21 (t, *J*= 7.4 Hz, 3 H, SCH_2CH_3); ^{13}C NMR δ 138.83-126.60 (aromatic), 84.17, 79.27 and 75.34 (C2, C3, C4), 75.98, 73.02, 72.52 and 71.87 (4xOC$H_2C_6H_5$), 64.40 (C5), 51.00 (C1), 27.48 (SCH_2CH_3), 15.21 (SCH_2CH_3); MS (70 eV) *m/z* : 462 (2), 402 (1), 310 (2), 294 (2), 253 (5), 220 (3), 207 (33), 181 (7), 107 (6), 91 (100). **7+8**: ^1H NMR δ (signals for the minor isomer **8**) 7.50-7.20 (m, 20 H), 6.11 (br s, 1 H, N*H*OBn), 4.70 (s, 2 H), 4.63 (s, 2 H), 4.60 (s, 2 H) and 4.55 (s, 2 H) (8 H, 4xOC$H_2C_6H_5$), 4.00-3.50 (m, 4 H, H1-H5), 2.64 (q, *J*= 7.4 Hz, 2 H, SCH_2CH_3), 1.21 (t, *J*= 7.4 Hz, 3 H, SCH_2CH_3); ^{13}C NMR δ (signals for the minor isomer **8**) 83.22, 77.70 and 77.54 (C2, C3, C4), 76.24, 73.11, 72.48 and 71.77 (4xOC$H_2C_6H_5$), 68.18 (C5), 46.10 (C1), 26.07 (SCH_2CH_3), 15.00 (SCH_2CH_3).

Anal. Calcd for $C_{35}H_{39}NO_4S$ (569.67): C, 73.79; H, 6.90; S, 5.61; N, 2.46. Found: C, 73.50; H, 6.55; S, 5.42; N, 2.13.

(2*R*,3*S*,4*S*,5*S*)-2,3:4,5-bis-*O*-Isopropylidenedioxy-1,1-diethylthiolhexanal (11). Following the *General Method* alcohol **10**[14] (2.78 g, 7.3 mmol) was transformed into aldehyde **11** (1.2 g, 45% yield; chromatography: hexane/ethyl acetate: 85/15): oil; $[\alpha]_D^{25}$ -80 (*c* 4.6, $CHCl_3$); IR (film) υ: 3600-3100, 2990, 1460, 1380, 1100 cm^{-1}; ^1H NMR δ: 9.60 (d, *J*= 1.5 Hz, 1 H, H6), 4.75 (dd, $J_{4,5}$= 9 Hz, $J_{5,6}$= 1.5 Hz, 1 H, H5), 4.50-4.10 (m, 3 H, H2, H3, H4), 3.90 (d, $J_{1,2}$= 6 Hz, 1 H, H1), 2.70 (q, *J*= 7.3 Hz, 4 H, 2xSCH_2CH3), 1.65 (s, 3 H), 1.45 (s, 9 H), 1.25 (t, *J*= 7.3 Hz, 6 H, 2xSCH2CH_3); MS (70 eV) *m/z* : 364 (M, 3), 305 (4), 303 (3), 277 (3), 245 (6), 228 (12), 171 (29), 145 (23), 135 (74), 129 (12), 115 (12), 71 (100), 59 (37), 43 (63).

Anal. Calcd for $C_{16}H_{28}O_5S_2$ (364.38): C, 52.74; H, 7.75; S, 17.56. Found: C, 52.60; H, 7.42; S, 17.25.

(2*R*,3*S*,4*S*,5*S*)-2,3:4,5-bis-*O*-Isopropylidenedioxy-1,1-diethylthiolhexanal-*O*-benzyl oxime (12). Following the *General Method* aldehyde **11** (950 mg, 2.61 mmol) was converted into oxime **12** (930 mg, 76% yield; chromatography: hexane/ethyl acetate: 95/5). Compound **12** was obtained as an unseparable mixture of *E* and *Z* isomers (~1:1 ratio): oil; IR (film) υ: 3080, 3060, 3020, 2990, 1495, 1450, 1380, 1375, 1250, 1210, 1160, 1100-1000, 900 cm^{-1}; ^1H NMR δ 7.70 (d, *J*= 7.5 Hz, H6, isomer *E*), 7.40-7.20 (m, 5 H, aromatic), 7.15 (d, *J*= 4.5 Hz, H6, isomer *Z*), 5.05, 5.00 (s, s, 2 H, OC$H_2C_6H_5$), 5.10-3.70 (m, 4 H, H1-H5), 2.64 (q, *J*= 7.4 Hz, 4 H, 2xSCH_2CH3), 1.80 (s, 3 H), 1.72 (s, 3 H), 1.50 (s, 6 H), 1.21 (t,

J= 7.4 Hz, 6 H, 2xSCH$_2$CH_3); MS (70 eV) *m/z* : 469 (M, 3), 369 (2), 334 (13), 276 (11), 218 (4), 135 (23), 91 (100), 87 (14), 59 (17), 43 (22).

Anal. Calcd for $C_{23}H_{35}NO_5S_2$ (469.52): C, 58.83; H, 7.51; N, 2.98; S, 13.63. Found: C, 58.60; H, 7.51; N, 3.20; S, 13.25.

Compounds 14. Following the *General Method* and starting with **12** (234 mg, 0.5 mmol), after chromatography (hexane/ethyl acetate: 95/5), the following mixtures of products were isolated: **13**(*Z*) (24 mg, ~95% purity, ~12% yield), **13**(*E*) (almost pure, 11% yield) (22 mg), **14a** and **14b** (69 mg, ~1:1 ratio plus traces of nitrile **16**), **14a**, **14c**, **14b** and **14d** (27 mg, ~1:1:2:5 ratio), **14c** and **14d** (18 mg, ~1.2:1 ratio) [**14** (total): 114 mg; 56 % yield] and isomers **15** (20 mg, ~2:1 ratio, 90% purity due to contamination by tin residues).

13(*Z*): ^{1}H NMR δ 7.03 (d, $J_{5,6}$= 4.1 Hz, 1 H, H6), 5.27 (dd, $J_{5,4}$= 7.5 Hz, 1 H, H5), 3.47 (d, $J_{5,4}$= 7.5 Hz, 1 H, H4). **13** (*E*): ^{1}H NMR δ 7.60 (d, $J_{5,6}$= 7.4 Hz, 1 H, H6), 4.77 (t, $J_{5,4}$= 7.4 Hz, 1 H, H5), 4.33 (dd, $J_{4,3}$= 2.0 Hz, 1 H, H4), 4.20 (m, 1 H, H2), 3.67 (dd, $J_{2,1}$= 7.4 Hz, 1 H, H3).

14a: ^{1}H NMR δ 6.49 (d, J= 2.8 Hz, 1 H, N*H*OBn), 4.76 (s, 2 H, NHOC*H*$_2$C$_6$H$_5$); ^{13}C NMR δ: 47.00 (C1), 67.54 (C6) and **14b**: ^{1}H NMR δ 6.12 (d, J= 2.1 Hz, 1H, N*H*OBn), 4.72 and 4.68 (d, d; J= 10.9 Hz, 2 H, NHOC*H*$_2$C$_6$H$_5$); ^{13}C NMR δ: 41.88 (C1), 60.76 (C6). **14c**: ^{1}H NMR δ 6.33 (d, J= 4.4 Hz, 1 H, N*H*OBn). **14d**: ^{1}H NMR δ: 5.20 (s, 1 H, N*H*OBn). Isomers **14a**, **14c**, **14b** and **14d**: oil; IR (film) υ: 3090, 3060, 3020, 2990, 1495, 1455, 1380, 1375, 1250-1220, 1060 cm^{-1}; MS (70 eV) *m/z* : 409 (M, 1), 394 (1), 302 (5), 290 (8), 244 (7), 117 (13), 91 (100), 59 (10), 43 (11).

Anal. Calcd for $C_{21}H_{31}NO_5S$ (409.47): C, 61.59; H, 7.63; N, 3.42; S, 7.81. Found: C, 61.73; H, 7.70; N, 3.40; S, 7.58.

15: ^{1}H NMR δ 5.79 (d, J= 3.0 Hz, 1 H, N*H*OBn), 4.69 (s, 2 H, NHOC*H*$_2$C$_6$H$_5$), 4.28 (m, 2 H), 3.65 (m, 2 H), 3.40 (m, 1 H, H6), 2.10 (2 H, H1).

Nitrile **16**: IR: band at 2240 cm^{-1}; ^{13}C NMR spectrum: signal at 119.55 ppm (CN).

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