Regio- and Stereoselective Synthesis of 4′-Thiaspiroacetals from Carbohydrates

Alessandra Bartolozzi, Giuseppe Capozzi,* Chiara Falciani, Stefano Menichetti, Cristina Nativi,* and Alessia Paolacci Bacialli

Centro CNR "Chimica dei Composti Eterociclici", Dipartimento di Chimica Organica, Universita' di Firenze, Via Gino Capponi, 9. I-50121 Firenze, Italy

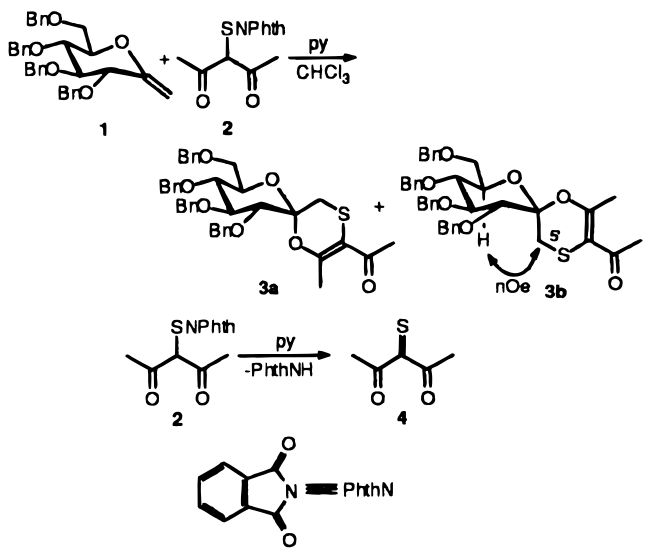
Received March 8, 1999

Introduction

Many biologically active natural products are characterized by a spiroacetal ring system in their structures.[1] Among them there are the structurally simple pheromones[2] or the more complex polyether antibiotics,[3] such as lenoremycin[4] and dianemycin,[5] which contain two spiroacetals substructures. Recently a family of novel spiro-containing macrocyclic lactones, including the altrohyrtins, the spongistatins, and cinachyrolide A, which exhibit an extremely potent cancer cell growth inhibition, have also been isolated.[6]

The relevant role of these compounds has triggered great interest in their total synthesis and particularly in the development of a stereoselective method for the formation of spiro units. The configuration of spiroacetals is generally due to additive steric and anomeric effects, which provide the isomer with the most stable configuration at the spiro carbon. Although the acid-catalyzed cyclization of dihydroxy ketones is still the most used ring-forming process, elegant alternative methods to synthesize stereoselectively spiroacetal skeletons involving radical processes,[7] olefinic cyclizations,[8] or apparent conjugate additions[9] have been reported. Moreover photochemical[10] and alkoxy radical promoted[11] cyclizations were recently applied to obtain spiroacetals from carbohydrates. As a matter of fact, enantiomerically pure O-[10] and C-glycosides[11] were successfully used as starting materials to achieve anomeric spiro derivatives whose stereochemistry depends on the configuration of the anomeric carbon of the corresponding glycosides.[10−12]

Scheme 1



We wish to report here on a versatile synthesis to prepare optically pure thiospiroacetals from easily achievable glycoexoenitols, through an inverse electron demand Diels−Alder reaction with suitable heterodienes. In previous papers, we outlined the versatility of α,α′-dioxothiones[13] and *ortho*-thioquinones[14] as electron-poor dienes that could be trapped by glycals as electron-rich dienophiles to give 1,4-oxathiins. In this paper, different glycoexoenitols were used to cycloadd to α,α′-dioxothiones and *ortho*-thioquinones to form enantiomerically pure spiroacetals. To our knowledge, the method we propose is the first example of sulfur-substituted spiro glycoside synthesis.

Results and Discussion

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-glucohept-1-enitol (**1**), prepared following a known procedure,[15] was reacted with 3-thiophthalimide-2,4-pentandione (**2**)[13] in the presence of pyridine to afford the spiroderivative **3** as a 2.5:1 mixture of stereoisomers. The phthalimido derivative **2** in the presence of a weak base like pyridine underwent proton abstraction to form, after elimination of phthalimide, the reactive heterodiene **4**, which was trapped by the electron-rich dienophile **1**. The diastereomers **3a** and **3b**, formed in 91% overall yield, were completely separated by flash chromatography on silica gel. (Scheme 1).

The cycloaddition was completely regioselective,[13,16] and the ^{1}H NMR analysis of the crude mixture of **3a** and **3b** allowed the assignment of the regiochemistry depicted in Scheme 1 for both isomers [δ CH_2−S 2.65 (**3a**), 3.06

* Tel: +39.055.2757630. Fax: +39.055.2476964. Email: capozzi@chimorg.unifi.it.

(1) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617. (b) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3336.

(2) Francke, W.; Hindorf, G.; Reith, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 862. (b) Kitching, W.; Lewis, J. A.; Fletcher, M. T.; Drew, R. A. I.; Moore, C. J.; Francke, W. *J. Chem. Soc., Chem. Commun.* **1986**, 853.

(3) Davies, H. G.; Green, R. H. *Nat. Prod. Rep.* **1986**, *3*, 87.

(4) Kubota, T.; Hinoh, H.; Mayama, M.; Motokawa, K.; Yasuad, Y. *J. Antibiot.* **1975**, *28*, 931.

(5) Czerwinski, E. W.; Steinrauf, L. K. *Biochem. Biophys. Res. Commun.* **1971**, *45*, 1284.

(6) Claffey, M. M.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 7646. (b) Evans, D. A.; Coleman, P. J.; Dias, L. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2738.

(7) Kalvoda, J.; Heusler, K. *Synthesis* **1971**, 501.

(8) Mehta, G.; Rao, H. S. P.; Reddy, K. R. *J. Chem. Soc., Chem. Commun.* **1987**, 78. (b) Ley, S. V.; Lygo, B. *Tetrahedron Lett.* **1982**, *23*, 4625. (c) Kraus, G. A.; Thurston, J. *Tetrahedron Lett.* **1987**, *28*, 4011.

(9) Danishefsky, S.; Person, W. H. *J. Org. Chem.* **1983**, *48*, 3865. (b) Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1987**, *10*, 1063.

(10) Kozluk, T.; Cottier, L.; Descotes, G. *Tetrahedron* **1981**, *37*, 1875.

(11) Martín, A.; Salazar, J. A.; Suárez, E. *Tetrahedron Lett.* **1995**, *36*, 4489. (b) Martín, A.; Salazar, J. A.; Suárez, E. *J. Org. Chem.* **1996**, *61*, 3999. (c) Dorta, R. L.; Martín, A.; Salazar, J. A.; Suárez, E. *J. Org. Chem.* **1998**, *63*, 2251.

(12) Hough, L.; Richardson, A. C. In *Carbohydrates. Synthetic Methods and Applications in Medicinal Chemistry*; Ogura, H., Hasegawa, A., Suami, T. Eds., VCH: New York, 1992; Chapter 7. (b) Remy, G.; Cottier, L.; Descotes, G. *Can. J. Chem.* **1980**, *58*, 2660.

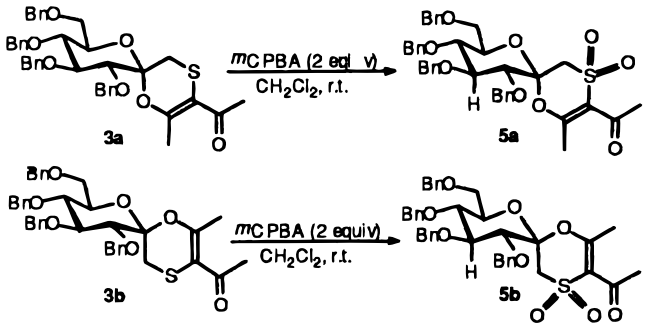
(13) Capozzi, G.; Franck, R. W.; Mattioli, M.; Menichetti, S.; Nativi, C.; Valle, G. *J. Org. Chem.* **1995**, *60*, 6416.

(14) Capozzi, G.; Falciani, C.; Menichetti, S.; Nativi, C. *J. Org. Chem.* **1997**, *62*, 2611.

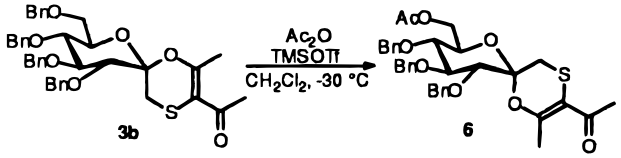
(15) RajanBabu, T. V.; Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458.

10.1021/jo990416z CCC: $18.00
Published on Web 08/03/1999

Scheme 2



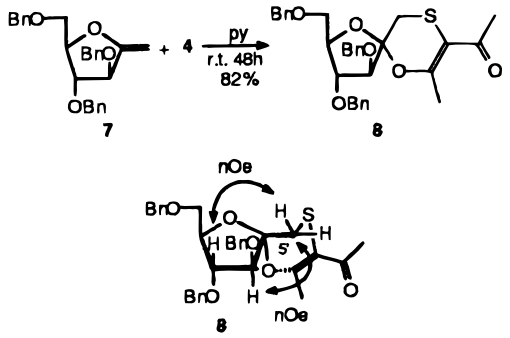
Scheme 3



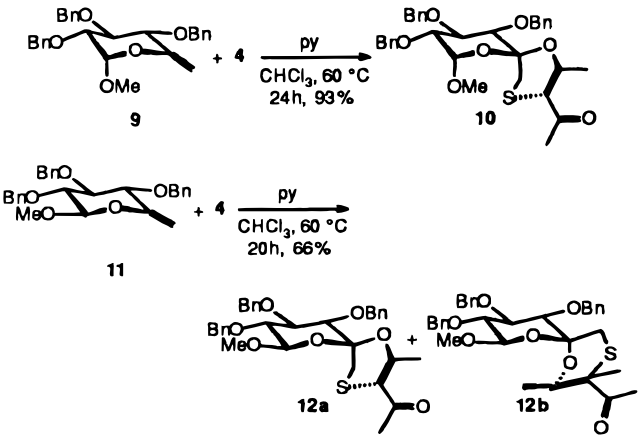
(**3b**)] (see the Experimental Section). Because the structure of **3a** differs from **3b** only in the stereochemistry of C-1, we reasoned that the preferred configuration of the spirocenter might be determined by the anomeric effects and tentatively assigned the structure **3a** (i.e., the structure with two anomeric effects[17]) to the major isomer. This hypothesis was supported by spectroscopic evidences. NOESY experiments of the minor compound (recorded at 500 MHz, see Supporting Information) showed a diagnostic interaction between the C-5′ protons and H-5, proving for this isomer the structure **3b**; this interaction was lacking in the case of the major product (structure **3a**) (Scheme 1). Moreover, we oxidized **3a** and **3b** (*m*CPBA,[13,18] 2 equiv) to the corresponding sulfones **5a** (60%) and **5b** (57%) (Scheme 2). The ^{1}H NMR spectra of the sulfone derived from the minor product showed a clear deshielding for the signal of the H-3 (δ 4.10) with respect to the same signal of the parent sulfide (δ 3.85). This deshielding was not observed in the case of the sulfone derived from the major product, suggesting that the SO_2 group is located far from the H-3 and confirming for the minor product the structure **3b**. The major isomer **3a** was also the thermodynamically more stable product,[16] as indicated by the isomerization in acidic media of **3b** into **6** (Scheme 3). The isomerization accomplished in the presence of acetic anhydride and trimethylsilyltrifluoromethane sulfonate was complete in 2 h at −30 °C and gave **6** in 75% yield. As expected,[19] under these conditions the selective transformation of the benzyl group at C-6 also occurred.

To prepare spiroacetals from furanose exoenitols, diene **4** was reacted with 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-D-arabino-hex-1-enitol (**7**)[15,20] to give, under reaction conditions the same as reported for **3**, spiroacetal **8** in 82% yield as a single isomer (Scheme 4).

Scheme 4



Scheme 5



The complete stereoselectivity of the cycloaddition can be rationalized considering the steric hindrance offered by the substituent at C-3 on exoenitol **7**. As it was shown by molecular mechanics studies using the AM1 force field,[21] the benzyl group on C-2 overlaps the exocyclic double bond and hinders the attack of the heterodiene from the β site of the dienophile.[22] Therefore, in the case of the reaction of **7** with **4** the matching of steric and anomeric effects afforded the thermodynamically more stable α isomer **8** as a single product and in high yield. The NOE between H-2 and the methylene on C-5′, as well as between H-3 and one of the two protons on C-5′, confirmed the stereochemistry that we assigned to **8** (Scheme 4).

A successful extension of this procedure regarded the synthesis of dioxaspiro[5.5]undecane thio derivatives, a new class of spiroacetals with the spirocenter located at C-5. As a matter of fact, glycoexoenitol **9**[23] cycloadded to **4**, giving **10** as a single isomer (Scheme 5). As reported for **1** and **7**, the regiochemistry of the cycloaddition between **9** and **4** was completely selective.[13] Moreover, it was completely stereoselective, suggesting a disfavored approach of the diene toward one of the two faces of the double bond of the dienophile. On the basis of the NMR spectra, we proposed for **10** the stereochemistry indicated in Scheme 5, supposing a favored attack of the diene from

(16) Totally regioselective [4 + 2] cycloadditions of **4** with electron rich dienophiles have been already reported; for examples, see: (a) ref 13 (b) Capozzi, G.; Dios, A.; Franck, R. W.; Geer, A.; Marzabadi, C.; Menichetti, S.; Nativi, C.; Tamarez, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 777.

(17) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauvé, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105.

(18) Capozzi, G.; Fratini, P.; Menichetti, S.; Nativi, C. *Tetrahedron* **1996**, *52*, 12233.

(19) Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. D. *J. Org. Chem.* **1996**, *61*, 1894. (b) Hung, S.-C.; Lin, C.-C.; Wong, C.-H. *Tetrahedron Lett.* **1997**, 5419.

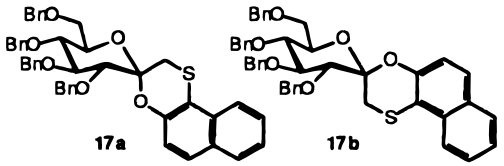
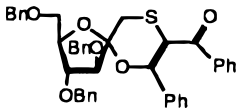
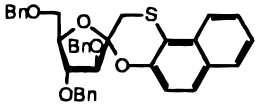
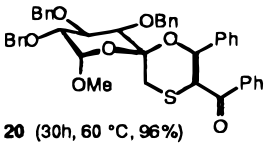
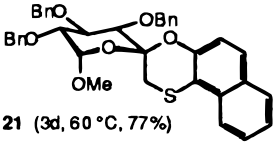
(20) Cipolla, L.; Liguori, L.; Nicotra, F.; Giangiacomo, T.; Vismara, E. *Chem. Commun.* **1996**, 1253.

(21) AM1 semiempirical calculations as implemented in PC Spartan Plus program.

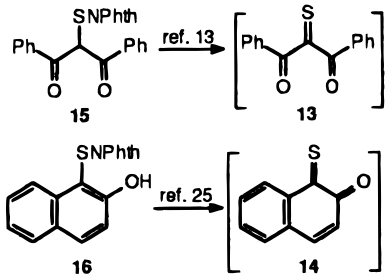
(22) Capozzi, G.; Falciani, C.; Menichetti, S.; Nativi, C.; Raffaelli, B. *Chem. Eur. J.* **1999**, *5*, 1748.

(23) Das, S. K.; Mallet, J.-M.; Sinaÿ, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 493. (b) Sakairi, N.; Kuzuhara, H. *Tetrahedron Lett.* **1982**, *23*, 5327.

Table 1. Reaction of Glycoexoenitols 1, 7, and 9 with Thiones 13 and 14

Entry	Dienophile (HOMO energy, eV)	Diene (LUMO energy, eV)	Cycloadduct (α/β ratio, react. t, T, yield)
1	**1**	**14** (-2.046)	 **17a** **17b** (2.5/1, 3d, 60 °C, 79%)
2	**7** (-9.062)	**13**	 **18** (22h, r.t., 83%)
3	**7**	**14**	 **19** (5d, 60 °C, 65%)
4	**9** (-8.997)	**13**	 **20** (30h, 60 °C, 96%)
5	**9**	**14**	 **21** (3d, 60 °C, 77%)

Scheme 6



the opposite side of the axial methoxyl group. To support this hypothesis, we prepared the β-methyl glycoexoenitol **11**,[23] removing the hindrance offered by the anomeric axial group (Scheme 5). Dienophile **11** was afterward reacted with **4**, affording an inseparable mixture of two stereoisomers, **12a** and **12b**, in a 1:1.2 ratio.[24]

To evaluate the applicability of this new protocol to the synthesis of aromatic spiro carbohydrate-containing derivatives, we performed the cycloadditions of dienophiles **1**, **7**, and **9** with the aromatic α,α′-dioxothione **13** and *ortho*-thioquinone **14**, which were generated in situ as described for **4** from the corresponding phthalimido derivatives **15**[13] and **16**[25] (Scheme 6). Spiroacetals obtained, reaction conditions, and the energy values of the HOMO and LUMO orbitals involved in the reactions[26] are reported in Table 1. The cycloadditions performed with **13** and **14** showed the same regio- and stereoselectivity observed for heterodiene **4**. A single isomer was obtained with **7** and **9** (entry 2−5), and two isomers were produced with **1** (entry 1). Cycloadduct **17a** (entry 1), formed in a 2.5:1 ratio with respect to **17b**, presents the maximum number of anomeric effects. The spirocenter of compounds **18**, **19** and **20**, **21** have the same stereochemistry as depicted for **8** and **10**, respectively. The higher energy of the LUMO of **14** (−2.05 eV) compared to that of **13** (−2.15 eV), determining a higher HOMO−LUMO gap between the dienophiles and the diene involved in the cycloadditions, probably influences the experimental conditions (temperature and reaction time), which are more severe in the case of the *ortho*-thioquinone **14** (entries 3 and 5) with respect to the α,α′-dioxothione **13** (entries 2 and 4).

In conclusion, in this paper several examples of optically pure spiro glycosides were reported. Alkyl and aryl 4′-thiaspiroacetals, with the spirocenter at C-1 or C-5, were prepared in one step from substituted exoenitols and in situ generated heterodienes, with total regio- and remarkable or total stereoselectivity.

Experimental Section

General Method. ^{1}H and ^{13}C NMR spectra were recorded (where not specified) in $CDCl_3$ at 200 and 50 MHz, respectively, using the residual $CHCl_3$ peak at 7.26 ppm for ^{1}H and the central peak of $CDCl_3$ at 77.0 ppm for ^{13}C as reference lines. Only noteworthy IR (cm^{-1}) absorptions are listed. $CHCl_3$, CH_2Cl_2, and THF were dried following standard procedures. All commercial reagents were used without further purifications as obtained from freshly opened containers. Thiophthalimides **2**, **15**, and **16** were prepared as reported elsewhere.[13] Physical and spectroscopic data are as follows.

(24) Calculated by ^{1}H NMR analysis of the crude mixture.
(25) Capozzi, G.; Falciani, C.; Menichetti, S.; Nativi, C. *Gazz. Chim. Ital.* **1996**, *126*, 227.
(26) Oxothiones **13** and **14** and dienophiles **1**, **7**, and **9** were minimized with geometry optimization AM1 calculations.

2,3,4,6-Tetra-*O*-benzyl-1-deoxy-D-glucopyranose-1-spiro-6′-[1′-(5′*H*-2′-methyl-1′,4′-oxathiin-3′-yl)etanone] (3). General Procedure. To a solution of **1** (150 mg, 0.28 mmol) in 4 mL of $CHCl_3$ were added 77.6 mg (0.28 mmol) of **2** and 18 μL (0.22 mmol) of pyridine. The reaction was stirred at room temperature for 4 days diluted with CH_2Cl_2 (10 mL), and washed with NH_4Cl. Drying and concentrating afforded the crude mixture (250 mg) of two stereoisomers in 91% yield (**3a:3b** = 2.5:1, based on ^{1}H NMR). Flash chromatography (petroleum ether:ethyl acetate = 4:1) gave 121 mg of **3a** (R_f = 0.58) and 48 mg of **3b** (R_f = 0.6). (**3a**): $[\alpha]^{25}_D$ +38 (*c* 0.12, CH_2Cl_2). ^{1}H NMR δ 2.29 (s, 3H); 2.33 (s, 3H); 2.65 (AB system J = 12.8 Hz, 2H); 3.53 (d, 1H, J = 9.6 Hz, 1H); 3.67−3.82 (m, 4H); 4.18−4.27 (m, 1H); 4.80−4.97 (m, 8H); 7.16−7.37 (m, 20H). ^{13}C NMR δ 22.3 (q); 25.5 (q); 29.5 (t); 68.4 (t); 72.8, 73.3, 74.9, 75.0 (t, 4C); 75.4, 77.5, 82.9, 83.2 (d, 4C); 97.1 (s); 106.7 (s); 127.61, 127.71, 127.77, 127.87, 127.95, 128.13, 128.33, 128.39, 128.46, 128.52 (d, 20C); 137.7, 137.9, 138.0, 138.2 (s, 4C); 157.24 (s); 195.46 (s). IR (neat) 3030; 2919; 1673; 1536 cm^{-1}. Anal. Calcd for $C_{40}H_{42}O_7S$: C, 72.05; H, 6.35. Found: C, 72.19; H, 6.48 (**3b**): $[\alpha]^{25}_D$ +23 (*c* 0.16, CH_2Cl_2). ^{1}H NMR δ 2.29 (s, 6H); 3.06 (s, 2H); 3.72−3.87 (m, 6H); 4.53−4.83 (m, 8H); 7.16−7.32 (m, 20H). ^{13}C NMR δ 21.8 (q); 29.5 (q); 29.8 (t); 68.0 (t); 73.1, 73.4, 75.2, 75.6 (t, 4C); 75.7, 78.0, 81.7, 83.0 (d, 4C); 95.7 (s); 107.2 (s); 127.6, 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 128.5 (d, 20C); 137.3, 137.8, 138.0, 138.3 (s, 4C); 156.43 (s); 195.7 (s).

2,3,4,6-Tetra-*O*-benzyl-1-deoxy-D-glucopyranose-1-spiro-6′-[1′-(5′*H*-2′-methyl-*S*,*S*-dioxo-1′,4′-oxathiin-3′-yl)etanone] (5a). To a solution of **3a** (25 mg, 0.038 mmol) in 1.5 mL of CH_2Cl_2, cooled to 0 °C, was added dropwise 26 mg (0.084 mmol) of *m*-chloroperbenzoic acid (55%) dissolved in 1.5 mL of CH_2Cl_2. After 0.5 h at 0 °C, the mixture was allowed to reach room temperature. In 24 h the reaction was complete, and the mixture was diluted with 10 mL of CH_2Cl_2 and washed with 10% aqueous $Na_2S_2O_3$, a saturated solution of Na_2CO_3, and water. The organic layer was dried (Na_2SO_4) and concentrated; the crude mixture was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 4:1) to give 17 mg of **5a** (57%) (R_f = 0.35) as yellowish oil. ^{1}H NMR δ 2.37 (s, 3H); 2.57 (s, 3H); 2.91−2.98 (B part of an AB system, J = 13.8 Hz, 1H); 3.37 (d, J = 9.4 Hz, 1H); 3.57−3.64 (A part of an AB system, J = 13.8 Hz, 1H); 3.72−3.89 (m, 4H); 4.12 (at, 1H); 4.59−4.95 (m, 8H); 7.18−7.39 (m, 20H). ^{13}C NMR δ 21.9 (q); 31.8 (q); 53.9 (t); 67.7 (t); 73.7, 75.4, 75.7, 75.9 (t, 4C); 74.8, 77.2, 80.3, 82.1 (d, 4C); 102.2 (s); 120.7 (s); 127.6, 127.7, 127.9, 128.0, 128.1, 128.3, 128.5, 128.8, 128.9 (d, 20C); 136.5, 137.5, 137.9, 138.1 (s, 4C); 166.6 (s); 191.3 (s). IR (neat) 3032; 2931; 1686; 1552; 1309; 1126 cm^{-1}. Anal. Calcd for $C_{40}H_{42}O_9S$: C, 68.75; H, 6.06. Found: C, 68.59; H, 6.33.

2,3,4,6-Tetra-*O*-benzyl-1-deoxy-D-glucopyranose-1-spiro-6′-[1′-(5′*H*-2′-methyl-*S*,*S*-dioxo-1′,4′-oxathiin-3′-yl)etanone] (5b). As reported for **5a**. Flash chromatography on silica gel (petroleum ether:ethyl acetate = 4:1) afforded 14 mg (57%) of **5b** (R_f = 0.38). ^{1}H NMR δ 2.30 (s, 3H); 2.60 (s, 3H); 3.61−3.86 (m, 7H); 4.01 (at, 1H); 4.43−4.81 (m, 8H); 7.11−7.35 (m, 20H). ^{13}C NMR δ 22.2 (q); 31.8 (q); 49.2 (t); 67.3 (t); 73.4, 74.9, 75.0, 75.3 (d, 4C); 74.4, 76.7, 81.9, 82.5 (d, 4C); 103.0 (s); 119.9 (s); 127.8, 127.9, 128.2, 128.2, 128.4, 128.4, 128.5, 128.6 (d, 20C); 137.0, 137.8 (s, 4C); 167.8 (s); 191.1 (s). IR (neat) 3033; 2918; 1684; 1362; 1067 cm^{-1}. Anal. Calcd for $C_{40}H_{42}O_9S$: C, 68.75; H, 6.06. Found: C, 68.50; H, 6.37.

2,3,4-Tri-*O*-benzyl-6-acetyl-1-deoxy-D-glucopyranose-1-spiro-6′-[1′-(5′*H*-2′-methyl-1′,4′-oxathiin-3′-yl)etanone] (6). To a solution of **3b** (20 mg, 0.03 mmol) in 0.5 mL of dry CH_2Cl_2, cooled to −30 °C, were added 144 μL (1.4 mmol) of acetic anhydride and 6 μL (0.03 mmol) of trimethylsilyltrifluoromethane sulfonate. After 2 h at −30 °C, the reaction was complete and was quenched with 1 mL of a saturated solution of $NaHCO_3$. The mixture was allowed to reach room temperature, diluted with CH_2Cl_2 (10 mL), and washed with water. Concentration and column chromatography on silica gel (petroleum ether:ethyl acetate = 5:1) afforded 14 mg (70%) of **6** (R_f = 0.3) as colorless oil. $[\alpha]^{25}_D$ +26 (*c* 0.20, $CHCl_3$). ^{1}H NMR δ 2.00 (s, 3H); 2.31 (s, 3H); 2.33 (s, 3H); 2.65 (AB system, J = 12.8 Hz, 2H); 3.48 (d, J = 9.4 Hz, 1H); 3.63 (dd, J = 8.8, 9.8 Hz, 1H); 3.73−3.81 (m, J = 2.2, 4.8 Hz, 1H); 4.15−4.36 (m, 3H); 4.56−4.98 (m, 6H); 7.30−7.39 (m, 15H). ^{13}C NMR δ 20.7 (q); 21.7 (q); 29.4 (t); 29.6 (q); 62.5 (t); 70.9, 75.2, 75.7 (3t + 1s, 4C); 77.9, 81.8, 82.9 (d, 3C); 95.3 (s); 107.3 (s); 127.4, 127.8, 128.1, 128.2, 128.3, 128.5 (d, 15C); 137.2, 137.3, 138.1 (s, 3C); 156.1 (s); 170.6 (s); 195.6 (s). Anal. Calcd for $C_{35}H_{38}O_8S$: C, 67.94; H, 6.19. Found: C, 67.70; H,6.31.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-D-arabinofuranose-hex-1-enitol (7). A solution of 2,3,5-tri-*O*-benzyl-arabino-1,4-lactone (1.23 g, 2.94 mmol) in 4 mL of dry THF was cooled to −25°C, and then 4 mL (2.65 mmol) of Tebbe's reagent (0.5 M in toluene) was slowly added. The reaction mixture was stirred at −25°C for 30 min, and then it was allowed to reach room temperature. In 2 h the reaction was complete (monitored by TLC) and was then cooled to 0 °C and quenched by the dropwise addition of 2 mL of NaOH (15% aqueous solution). The organic layer was diluted with 10 mL of CH_2Cl_2 and washed twice with NaOH (15% aqueous solution). Drying, concentrating, and flash chromatography on silica gel (petroleum ether:ethyl acetate = 3:1) afforded 1.04 g (85%) of **7** (R_f = 0.76). ^{1}H NMR δ 3.61−3.62 (B part of an ABX system, J = 6.0, 2.2 Hz, 1H); 3.64−3.65 (A part of an ABX system, J = 6.0, 2.2 Hz, 1H); 4.06 (at, 1H); 4.19 (d, J = 1.0 Hz, 1H); 4.39−4.71 (m, 9H); 7.28−7.33 (m, 15H). ^{13}C NMR δ 69.7 (t); 70.7, 71.7, 73.3 (t, 3C); 81.5, 82.0 (d, 2C); 83.5 (d); 85.7 (t); 127.6, 127.7, 127.8, 128.3, 128.4 (d, 15C); 137.4, 137.6, 137.8 (s, 3C); 159.8 (s).

2,3,5-Tri-*O*-benzyl-1-deoxy-D-arabinofuranose-1-spiro-6′-[1′-(5′*H*-2′-methyl-1′,4′-oxathiin-3′-yl)etanone] (8). Compound **7**: 100 mg, 0.24 mmol. After 48 h at room temperature the reaction was complete. Flash chromatography on silica gel (petroleum ether:ethyl acetate = 4:1) afforded 108 mg (82%) of **8** (R_f = 0.53). $[\alpha]^{25}_D$ +32 (*c* 0.06, $CHCl_3$). ^{1}H NMR δ 2.29 (s, 3H); 2.33 (s, 3H); 3.00 (AB system, J = 13.2 Hz, 2H); 3.61−3.62 (B part of an ABX system, J = 5.0, 3.2 Hz, 1H); 3.63−3.64 (A part of an ABX system, J = 5.0, 3.2 Hz, 1H); 4.03 (dd, J = 2.2, 4.8 Hz, 1H); 4.04 (d, J = 2.2 Hz, 1H); 4.42−4.57 (m, 7H); 7.26−7.35 (m, 15H). ^{13}C NMR δ 22.0 (q); 27.4 (q); 29.4 (t); 69.4 (t); 71.8, 72.6, 73.3 (t, 3C); 82.6, 83.0 (d, 2C); 86.5 (d); 105.6 (s); 123.3 (s); 127.46, 127.55, 127.62, 127.70, 127.92, 128.24, 128.30, 128.35 (d, 15C); 137.0, 137.5, 137.8 (s, 3C); 157.5 (s); 195.4 (s). IR (neat) 3030; 2922; 1672; 1554; 1451; 1413; 1244 cm^{-1}. Anal. Calcd for $C_{32}H_{34}O_6S$: C, 70.31; H, 6.27. Found: C, 70.21; H, 6.38.

1-Methyl-2,3,4-tri-*O*-benzyl-5-deoxy-α-D-glucopyranose-5-spiro-6′-[1′-(5′*H*-2′-methyl-1′,4′-oxathiin-3′-yl)etanone] (10). Compound **9**: 20 mg, 0.04 mmol. After 24 h at 60 °C, the reaction was complete. Flash chromatography on silica gel (petroleum ether:ethyl acetate = 3:1) afforded 24 mg (93%) of **10** (R_f = 0.53). ^{1}H NMR δ 2.25 (s, 3H); 2.34 (s, 3H); 3.18 (s, 2H); 3.61 (s, 3H); 3.68 (dd, J = 3.6, 9.2 Hz, 1H, H-2); 3.80 (d, J = 9.4 Hz, 1H, H-4); 3.95 (at, J = 9.4 Hz, 1H, H-3); 4.61−4.92 (m, 7H); 7.25−7.36 (m, 15H). ^{13}C NMR δ 22.0 (q); 29.5 (q); 29.9 (t); 58.8 (q); 73.8, 75.5, 75.7 (t, 3C); 77.7 (d); 78.8 (d); 84.1 (d); 98.8 (s); 100.2 (d, C-1); 106.6 (s); 127.72, 127.89, 127.95, 128.12, 128.20, 128.37, 128.55 (d, 15C); 137.7, 137.8 (s, 3C); 138.3 (s); 156.7 (s). IR (neat) 3030; 2922; 1676; 1562; 1451; 1415; 1246 cm^{-1}. Anal. Calcd for $C_{33}H_{36}O_7S$: C, 68.73; H, 6.29. Found: C, 68.85; H, 6.47.

1-Methyl-2,3,4-tri-*O*-benzyl-5-deoxy-β-D-glucopyranose-5-spiro-6′-[1′-(5′*H*-2′-methyl-1′,4′-oxathiin-3′-yl)etanone] (12). Compound **11**: 26 mg, 0.06 mmol. After 20 h at 60 °C, the reaction was complete (**12a/12b** = 1.2/1 based on ^{1}H NMR of the crude). Flash chromatography on silica gel (petroleum ether:ethyl acetate = 3:1) afforded 22 mg (66% yield) of **12a** + **12b** (R_f = 0.53). ^{1}H NMR δ 2.27−2.40 [m, 6H (**12a**) $2CH_3$; 7H (**12b**) $2CH_3$+ A part of an AB system]; 2.91 [B part of an AB system (**12b**), J = 12.8 Hz, 1H]; 3.02 [as, 2H, (**12a**)]; 3.47 [s, 3H (**12a**), 3H (**12b**)]; 3.47−3.75 (m, 4H); 4.02 [d, 1H (**12a**), J = 8.0 Hz, H-1]; 4.08−4.18 (m, 1H); 4.52 [d, 1H (**12b**) J = 8 Hz, H-1]; 4.60−5.0 (m, 13H); 7.25−7.36 (m, 30H). ^{13}C NMR δ 21.6 (q); 22.2 (q); 27.8 (q); 29.5 (t); 29.5 (q); 30.1 (t); 56.6 (q); 57.2 (q); 73.8, 75.0, 75.5, 76.0 (t, 6C); 80.7, 80.8, 81.1, 82.2, 82.5, 82.6 (d, 6C); 92.0, 96.2 (s, 2C); 101.0, 101.2 (d, 2C); 106.4, 107.3 (s, 2C); 127.7, 127.8, 127.9, 128.0, 128.2, 128.2, 128.4, 128.4, 128.5 (d, 30C); 137.7, 137.9, 138.1, 138.2 (s, 6C); 156.9 (s, 2C); 195.5, 195.8 (s, 2C). Anal. Calcd for $C_{33}H_{36}O_7S$: C, 68.73; H, 6.29. Found: C, 68.50; H, 6.36.

2,3,4,6-Tetra-*O*-benzyl-1-deoxy-D-glucopyranose-1-spiro-6′-(5′*H*-1′-oxa-4′-thia) phenanthrene (17). Compound **1**: 110 mg, 0.20 mmol. After 20 h at 60 °C, the reaction was complete (**17a/17b** = 1.5/1 based on ^{1}H NMR of the crude). Flash

chromatography (petroleum ether:ethyl acetate = 10:1) afforded 82 mg of **17a** (R_f = 0.3) and 53 mg of **17b** (R_f = 0.4) (79% overall yield). **17a**: $[\alpha]^{25}_D$ +63 (*c* 0.06, $CHCl_3$). ^{1}H NMR δ 3.40 (AB system, J = 14.1 Hz, 2H); 3.65−3.91 (m, 5H); 4.04−4.08 (m, 1H); 4.37−4.98 (m, 8H); 7.10−7.96 (m, 26H). ^{13}C NMR δ 29.6 (t); 68.4 (t); 72.9, 73.3, 75.2, 75.8 (t, 4C); 78.4, 83.3 (d, 4C); 96.1 (s); 111.9 (s); 120.2, 122.6, 124.4, 125.9, 126.4, 127.8, 127.9, 128.1, 128.3, 128.5, 128.6, 129.6, 130.7, (d, 26C); 137.9, 138.5 (s, 4C); 147.2 (s). **17b**: $[\alpha]^{25}_D$ −4 (*c* 0.14, $CHCl_3$).^{1}H NMR δ 3.02 (AB system J = 12.6 Hz, 2H); 3.53−3.73 (m, 3H); 3.80−3.95 (m, 2H); 4.35−5.08 (m, 9H); 7.09−7.55 (m, 24H); 7.76−7.96 (m, 2H). ^{13}C NMR δ 28.9 (t); 68.2 (t); 73.2, 75.0, 75.6, 75.8, (t, 4C); 82.2, 83.8 (d, 4C); 93.9 (s); 111.2 (s); 120.3, 122.7, 125.6, 126.3, 127.4, 127.9, 128.0, 128.2, 128.4, 128.5, 128.6, 128.8, 129.7, 131.0 (d, 26C); 137.6, 138.4 (s, 4C); 146.0 (s). IR (neat) 3032; 2933; 1616; 1258 cm^{-1}. Anal. Calcd for $C_{45}H_{42}O_6S$: C, 76.03; H, 5.96. Found: C, 76.30; H, 6.12.

2,3,5-Tri-*O*-benzyl-1-deoxy-D-arabinofuranose-1-spiro-6′-[1′-(5′*H*-2′-phenyl-1′,4′-oxathiin-3′-yl)phenone] (18). Compound **7**: 20 mg, 0.05 mmol. After 22 h at room temperature, the reaction was complete. Flash chromatography on silica gel (petroleum ether:ethyl acetate = 3:1) afforded 27 mg (83%) of **18** (R_f = 0.59).^{1}H NMR δ 3.31 (s, 2H); 3.67−3.75 (B part of an ABX system, J = 10.6, 5.8 Hz, 1H); 3.78−3.86 (A part of an ABX system, J = 10.6, 5.2 Hz, 1H); 4.16 (ad, J = 4.0 Hz, 1H); 4.30 (as, 1H); 4.55−4.73 (m, 7H); 6.85−7.11 (m, 5H); 7.18−7.35 (m, 18H); 7.58 (d, J = 7.0 Hz, 2H). ^{13}C NMR δ 28.7 (t); 70.1 (t); 72.2, 72.7, 73.5 (t, 3C); 83.7, 84.2 (d, 2C); 85.8 (d); 105.8 (s); 109.5 (s); 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.4, 128.5, 128.6, 128.7, 129.0, 129.2, 129.3, 129.5, 129.6, 129.9, 130.5, 131.9, 132.7, 134.3, 134.6 (d, 25C); 132.4, 135.3, 136.9, 137.5, 137.9 (s, 5C); 153.4 (s); 194.7 (s). IR (neat) 3029; 2862; 1635; 1560 cm^{-1}. Anal. Calcd for $C_{42}H_{38}O_6S$: C, 75.20; H, 5.71. Found: C, 74.95; H, 5.42.

2,3,5-Tri-*O*-benzyl-1-deoxy-D-arabinofuranose-1-spiro-6′-(5′*H*-1′-oxa-4′-thia) phenanthrene (19). Compound **7**: 120 mg, 0.29 mmol. After 6 days at 60 °C, the reaction was complete. Flash chromatography on silica gel (petroleum ether:ethyl acetate = 4:1) afforded 110 mg of **19** (65%) (R_f = 0.64).^{1}H NMR δ 3.33 (s, 2H); 3.71 (A part of an ABX system, J = 8.8, 2.6 Hz, 1H); 3.65 (B part of an ABX system, J = 8.8, 2.8 Hz, 1H); 4.17 (dd, J = 2.6, 5.2 Hz, 1H); 4.27 (d, J = 2.6 Hz, 1H); 4.47−4.65 (m, 7H); 7.12 (d, J = 8.8 Hz, 1H); 7.26−7.59 (m, 18H); 7.69 (d, J = 8.4 Hz, 1H); 7.95 (d, J = 8.4 Hz, 1H). ^{13}C NMR δ 27.9 (t); 69.5 (t); 71.8, 72.5, 73.4 (t, 3C); 82.5, 83.3 (d, 2C); 87.3 (d); 103.7 (s); 111.1 (s); 120.11, 122.73, 124.20, 125.86, 126.22, 127.55, 127.62, 127.73, 127.92, 128.19, 128.26, 128.35, 129.42, 129.48, 130.81 (d+s, 22C); 137.3, 137.8, 138.0 (s, 4C); 147.2 (s). IR (neat) 3061; 2925; 1618; 1227 cm^{-1}. Anal. Calcd for $C_{37}H_{34}O_5S$: C, 75.23; H, 5.80. Found: C, 75.19; H, 6.00.

1-Methyl-2,3,4-tri-*O*-benzyl-5-deoxy-*β*-D-glucopyranose-5-spiro-6′-[1′-(5′*H*-2′-phenyl-1′,4′-oxathiin-3′-yl)phenone] (20). Compound **9**: 42 mg, 0.09 mmol. After 30 h at 60 °C, the reaction was complete. Flash chromatography on silica gel (petroleum ether:ethyl acetate = 4:1) afforded 63 mg of **20** (96%) (R_f = 0.48). $[\alpha]^{25}_D$ −24 (*c* 0.19, $CHCl_3$). ^{1}H NMR δ 3.46 (AB system, J = 13.2 Hz, 2H); 3.65 (s, 3H); 3.86 (dd, J = 3.6, 8.4 Hz, 1H); 3.96−4.10 (m, 2H); 4.60−4.93 (m, 7H); 7.00−7.78 (m, 25 H). ^{13}C NMR δ 30.83 (q); 58.88 (t); 73.67, 75.20, 75.49 (d, 3C); 77.80, 78.45, 83.32 (t, 3C); 98.26 (s); 99.94 (s); 109.53 (s); 127.79, 127.83, 127.97, 128.06, 128.15, 128.32, 128.43, 128.59, 129.01, 129.25, 129.54, 132.18 (d, 25C); 134.35, 135.42, 137.68, 137.73, 138.06, 138.40 (s, 5C); 152.48 (s); 194.70 (s). Anal. Calcd for $C_{43}H_{40}O_7S$: C,-73.69; H,5.75. Found: C,73.35; H,5.71.

1-Methyl-2,3,4-tri-*O*-benzyl-5-deoxy-α-D-glucopyranose-5-spiro-6′-[1′-(3′*H*-1′-oxa-4′-thia)phenanthrene] (21). Compound **9**: 30 mg, 0.07 mmol. After 3 days at 60 °C, the reaction was complete. Flash chromatography on silica gel (petroleum ether:ethyl acetate = 4:1) afforded 32 mg of **21** (77%) (R_f = 0.58). $[\alpha]^{25}_D$ +39 (*c* 0.29, CH_2Cl_2). ^{1}H NMR δ 3.52 (AB system, J = 13.6 Hz, 2H); 3.67 (s, 3H); 3.77 (dd, J = 4.0, 7.4 Hz, 1H); 3.94−4.06 (m, 2H); 4.51−4.98 (m, 7H); 7.04 (d, J = 8.8 Hz, 1H); 7.25−7.49 (m, 17H); 7.55 (dd, J = 8.8 Hz, 1H); 7.77 (d, J = 7.4 Hz, 1H); 7.95 (d, J = 8.4 Hz, 1H). ^{13}C NMR δ 29.8 (q); 58.9 (q); 73.7, 75.3, 75.7 (t, 3C); 77.8, 78.9, 84.5 (d, 3C); 97.4 (s); 100.1 (d); 111.3 (s); 119.6, 122.6, 124.4, 125.9, 126.3, 127.68, 127.7, 128.0, 128.1, 128.2, 128.2, 128.3, 128.3, 128.5 (d, 21C) 129.6, 130.0 (s, 2C); 137.8, 137.9, 137.5 (s, 3C); 146.6 (s). Anal. Calcd for $C_{38}H_{36}O_6S$: C, 73.52; H, 5.85. Found: C, 73.90; H, 6.00.

Acknowledgment. This work was supported by MURST "Progetto Nazionale Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni" and by CNR, Italy. We thank Dr. Stefano Roelens for helpful discussion on NMR data.

Supporting Information Available: ^{1}H NMR spectra for componds **3a** (200 MHz) and **3b** (500 MHz) and NOESY spectra for componds **3a** (200 MHz), **3b** (500 MHz), and **8** (200 and 500 MHz). This material is available free of charge via the Internet at http://pubs.acs.org.

JO990416Z