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# Unexpected fluorous solvent effect on oxidation of 1-thioglycosides†

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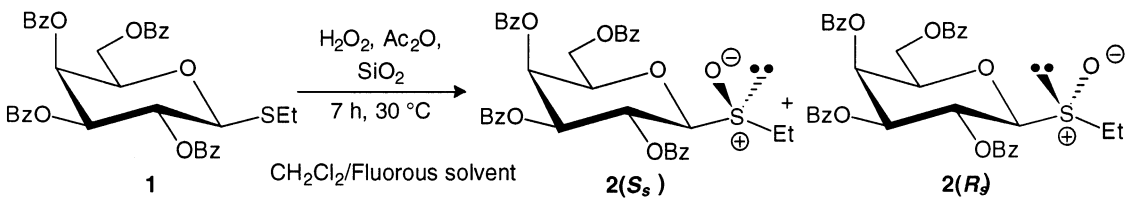
**Abstract**—Oxidation of various 1-thioglycopyrano- and furanosides with $H_2O_2/Ac_2O/SiO_2$ was performed in $CH_2Cl_2$/aprotic perfluorinated solvent mixtures (100:0 to 1:19, v/v). Reactions appeared much faster at a solvent ratio of 1:1 without significant over-oxidation to sulfones and modification of diastereoselectivity. Nevertheless, the nature of both the glycosyl moiety and the protecting group influenced the ($S_S$):($R_S$) product ratio. © 2001 Published by Elsevier Science Ltd.

During the last decade, significant developments have been made in glycochemistry and more especially in the knowledge of glycosylation reaction mechanisms.[1–5] Among the wide variety of glycosyl donors synthetically available, Kahne[6] and Crich[7] independently accumulated considerable data on the glycosylating ability and characterization of sulfinyl glycopyranosides. In this context, we recently observed appreciable differences in reactivity between galactofuranosyl ($R_S$)-sulfoxide and its ($S_S$)-epimer.[8] Parallel to these studies, NMR analysis methods using a chemical shift reagent[9] or not[10] were also developed for the elucidation of the absolute configuration at the anomeric sulfur atom. Nevertheless, little attention was given to the preparation of sulfinyl glycosides.[11]

Recently, the utility of inert and less toxic (per)fluorinated solvents has drawn attention as an alternative media for a variety of reactions.[12] Especially, significant advantages for oxidations in organic synthesis were shown in the preparation of various epoxides[13] or alkyl/aryl sulfoxides[14] from the corresponding olefins and sulfides. For instance, the acid-sensitive isolongifolene[13] was epoxidized under neutral conditions, using $O_2$/pivalaldehyde in perfluoro-2-butyltetrahydrofuran (FC-75) with $Mn(OAc)_3 \cdot 2H_2O$ as catalyst. Unfortunately, this system failed to provide pure sulfoxides from simple sulfides and mixtures of sulfoxides and/or sulfides were obtained, depending on the amount of oxidizing agent. Use of $H_2O_2$ in the protic and acidic hexafluoro-2-propanol (HFIP) was




**Scheme 1.** Oxidation of **1**.

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† Dedicated to Professor Henri Patin on the occasion of his 60th birthday.

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found to be the system of choice, effecting rapid and clean oxidation of various sulfides such as sulfinyl glycosides in the pyranose series.[14] Considering its protic character, HFIP was involved in the oxidation mechanism which led to *S*-racemic sulfoxides.

However, fluorous solvents remain expensive for general synthetic manipulations and large-scale reactions, even if they are classed as recoverable media. As previously reported by us,[8] glycosylation starting from glycosyl sulfoxide could require a specific configuration at the sulfur atom. Finding new large scale synthetic methods to glycopyranosyl sulfoxide synthons, which are also suitable for their more sensitive furanosyl counterparts, is therefore of importance to develop the scope of this reaction.

Considering these precedents, the following report summarizes our preliminary results on the oxidation of thioglycosides using mixtures of chemically inert, non-polar and aprotic perfluorinated solvents and dichloromethane. We were especially interested in studying the influence of these mixtures on (i) the diastereoselectivity and (ii) kinetic aspects of the sulfoxidation reaction.

Reaction of perbenzoylated ethyl 1-thio-β-D-galactopyranoside **1** with peroxyacetic acid, which was prepared in situ in the presence of silica gel,[11] was first carried out in neat dichloromethane (Scheme 1, Table 1).[15] A 1.2:1 diastereomeric mixture of ($S_S$)-**2** and ($R_S$)-**2** was obtained in time-dependent yields [entries 1 (48 h) and 2 (7 h)]. Double $^1$H NMR[9,16] and HPLC[17,18] analysis revealed that both epimers were simultaneously synthesized in a constant ratio slightly in favor of the $S_S$ sulfinyl galactopyranoside ($S_S$)-**2**, regardless of the reaction time. Moreover, neither the diastereoselectivity nor the yield were affected when the oxidation was performed at higher concentration [entry 3 (100 mg/mL versus 25 mg/mL)]. Nevertheless, substituting dichloromethane with at least 50% of perfluorohexane (hexane-F) allowed the reaction to be completed dramatically faster, i.e. 7 h instead of 48 h (entries 4–6). The subsequent result (entry 7) suggested however that increasing yields were not directly connected with a higher proportion of fluorinated co-solvent. This accel-

**Table 1.** Effect of fluorous solvent and $CH_2Cl_2$/fluorous solvent ratio on sulfoxidation of **1** (25 mg/mL) performed for 7 h at 30°C

| Entry | Fluorous solvent | $CH_2Cl_2$/fluorous solvent ratio[a] (v/v) | ($S_S$)-**2**/($R_S$)-**2**[b] | Isolated yield (%) |
|---|---|---|---|---|
| 1[c] | – | – | 1.2:1 | 93 |
| 2 | – | – | 1.2:1 | 55 |
| 3[d] | – | – | 1.2:1 | 54 |
| 4 | Hexane-F | 3:1 | 1.3:1 | 63 |
| 5 | Hexane-F | 1:1 | 1.3:1 | 80 |
| 6 | Hexane-F | 1:3 | 1.3:1 | 76 |
| 7 | Hexane-F | 1:19 | 1.3:1 | 57 |
| 8 | Decalin-F | 3:1 | 1.2:1 | 96 |
| 9 | Decalin-F | 1:1 | 1.2:1 | 97 |
| 10 | Decalin-F | 1:3 | 1.2:1 | 73 |
| 11 | Decalin-F | 1:19 | 1.2:1 | 89 |
| 12 | Toluene-F | 3:1 | 1.5:1 | 95 |
| 13 | Toluene-F | 1:1 | 1.2:1 | 96 |
| 14 | Toluene-F | 1:3 | 1.9:1 | 93 |
| 15 | Toluene-F | 1:19 | 2.3:1 | 91 |

[a] $CH_2Cl_2$/fluorous solvent.
[b] Ratio were determined by $^1$H NMR considering either the integration values of $CH_2CH_3$, $CH_2CH_3$ or those of H-1 from each diastereoisomer.
[c] Oxidation was performed for 48 h.
[d] $C$ = 100 mg/mL.

**Table 2.** Sulfoxidation of **1** at 30°C in $CH_2Cl_2$/fluorous solvent and $CH_2Cl_2$/non-fluorous solvent

| Entry | Fluorous solvent | $CH_2Cl_2$/fluorous solvent ratio[a] (v/v) | ($S_S$)-**2**/($R_S$)-**2**[b] | Isolated yield (%) (reaction time)[c] |
|---|---|---|---|---|
| 1 | – | – | 1.2:1 | 55 (7 h) |
| 2 | Hexane | 1:1 | 1.1:1 | 55 (5 h) |
| 3 | Hexane-F | 1:1 | 1.1:1 | 80 (7 h) |
| 4 | Decaline | 1:1 | 1.2:1 | 50 (4 h) |
| 5 | Decaline-F | 1:1 | 1.2:1 | 97 (7 h) |
| 6 | Toluene | 1:1 | 1.1:1 | 65 (7 h) |
| 7 | Toluene-F | 1:1 | 1.5:1 | 96 (7 h) |

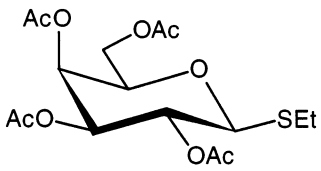
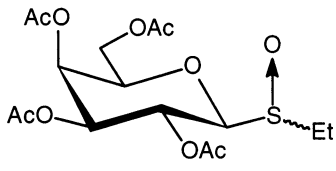
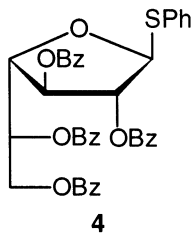
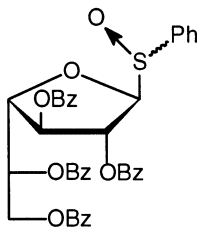
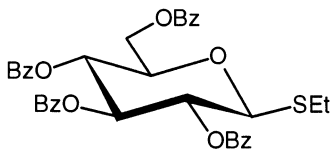
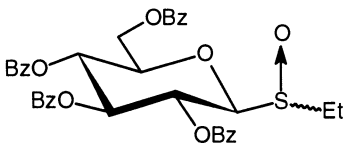
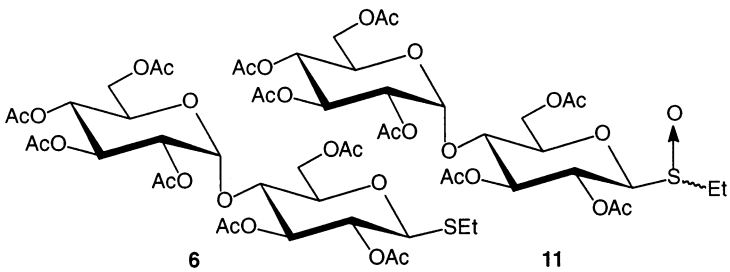
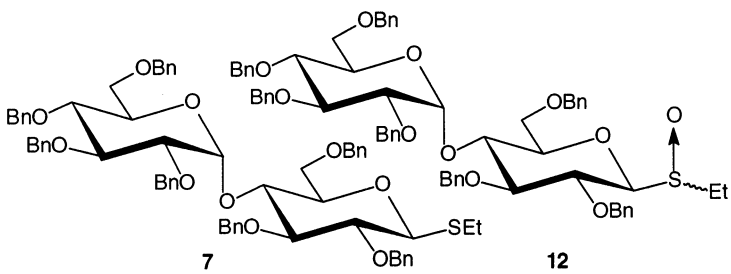
[a] $CH_2Cl_2$/fluorous solvent.
[b] Ratios were determined by $^1$H NMR considering either the integration values of $CH_2CH_3$, $CH_2CH_3$ or those of H-1 from each diastereoisomer.
[c] Reactions were quenched after detection of sulfone.

erating effect on the sulfoxidation kinetics was also observed when decalin-F (entries 8–11) or toluene-F (entries 12–15) were preferred to hexane-F. Finally, it is interesting to note that diastereomeric excesses were similar in all experiments and that the best results were achieved using perfluorodecalin as co-solvent.

Moreover, with this system, we showed that oxidation in $CH_2Cl_2$/fluorous solvent mixtures is faster than in the corresponding $CH_2Cl_2$/non-fluorous solvent mixtures (Table 2). Again, the use of fluorous solvent seems to prevent the formation of sulfones and then sulfoxide **2** was obtained in higher yields (entries 3, 5 and 7). Finally, no significant variation of diastereoselectivity was observed.

The same procedure was further extended to the preparation of sulfoxides **8–12** from thioglycosides **3–7**, respectively, in $CH_2Cl_2$/perfluorodecalin. Once again, the presence of fluorous decalin (Table 3) led to enhanced yields of the oxidized compounds without significant alteration of diastereoselectivity. For

**Table 3.** Oxidation of thioglycosides **3–7** in $CH_2Cl_2$/perfluorodecalin (1:1, v/v) and $CH_2Cl_2$

| Entry | Thioglycoside | Sulfinyl glycoside | $(S_S)/(R_S)$ (reaction time) | Yield (%) |
|---|---|---|---|---|
| 1 |  **3** |  **8** | [a]2.7:1<br>[b]2.6:1<br>(4 h.) | [a]98<br>[b]92 |
| 2 |  **4** |  **9** | [a]1.7:1<br>[b]1.4:1<br>(5 h.) | [a]100<br>[b]76 |
| 3 |  **5** |  **10** | [a]2.0:1<br>[b]1.6:1<br>(6 h.) | [a]78<br>[b]39 |
| 4 |  **6** |  **11** | [a]1.8:1<br>[b]1.8:1<br>(25 h.) | [a]49<br>[b]25 |
| 5 |  **7** |  **12** | [a]0.8:1<br>[b]0.8:1<br>(2.5 h.) | [a]93<br>[b]39 |

[a] $CH_2Cl_2$/perfluorodecalin mixture (1:1, v/v).

[b] $CH_2Cl_2$.

instance, fluorous co-solvent allowed twice as efficient sulfoxidation of maltosyl derivatives (entries 4 and 5) and the sulfinyl furanoside (entry 2) was quantitatively obtained under the same conditions. All these results also showed that diastereoselectivity was heavily dependent on the nature of the protecting groups present on the glycosyl moiety. In fact, shorter reaction times were required when less electron-withdrawing acetyl (versus benzoyl) and benzyl groups were introduced to protect hydroxyl functions. A dramatic effect was observed for the sulfoxidation of the thioglycoside **5** and for the conversion of peracetylated and more interestingly perbenzylated ethyl thiomaltosides **6** and **7**, respectively. Moreover, it is relevant to note that the diastereoselectivity of sulfoxidation was also ensured by (i) the nature of the saccharidic head (D-galactosyl for compounds **1** and **3**, D-glucosyl for **5** and maltosyl for **6** and **7**), and more importantly, (ii) the ring size of the glycosyl entity, i.e. galactopyranosyl for **1** and **3** and galactofuranosyl for **4**.

The sulfinyl sulfur configuration of each ($R_S$)- and ($S_S$)-diastereiosomers **8**–**12** was easily determined on the grounds of signals identified by COSY and heteronuclear $^1H$, $^{13}C$, 2D experiments.[19] As established by Khiar,[10] all ($S_S$)-ethylsulfinyl β-D-glycopyranosides are characterized by a smaller non-equivalence of the diastereotopic protons vicinal to the sulfoxide group than that observed in the ($R_S$)-epimers. For the phenylsulfinyl furanoside **4**, ($S_S$)- and ($R_S$)-isomers were previously discriminated by X-ray analysis,[8] a study from which NMR assignments could be unambiguously established.

The favored oxidation of the unshared pro(*S*) pair can be tentatively rationalized on the basis of the *exo*-anomeric effects and thus favored conformation at equilibrium (Fig. 1).[20] In this conformation, it is assumed that the pro(*R*) pair is sterically less accessible than the pro(*S*) one towards oxidizing reagents. Moreover, a hydrogen bond between peracetic acid and the oxygen atom of the acyl protecting group at the 2-position of thioglycoside could also contribute to the observed diastereoselectivity. The absence of such an interaction could explain the inverted diastereoselectivity between peracetylated ethyl thiomaltoside **6** and its perbenzylated analog **7**.

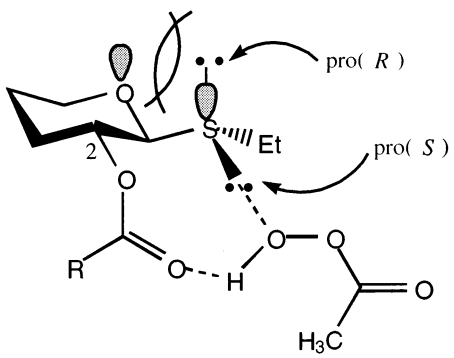



**Figure 1.**

In conclusion, we have reported that perfluorinated co-solvents influence the kinetics but not the diastereoselectivity of the sulfoxidation reactions of various thioglycosides. Unlike HFIP, aprotic perfluorodecalin, hexane and toluene cannot act as participating solvents in the sulfoxidation. Further work is in progress to explain, improve and, finally, to extend the scope of this observation.

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15. Typical procedure: A solution of **1** (100 mg, 0.16 mmol) in a mixture of $CH_2Cl_2$ and fluorous solvent (4 mL, see Table 1) was treated successively at room temperature with silica gel (200 mg/mmol), $Ac_2O$ (15 μL) and 30% aq. $H_2O_2$ (21 μL) After vigorously stirring for 7 h, the reaction mixture was diluted with $CH_2Cl_2$ (20 mL), filtered, washed with aq. sat. $NaHSO_3$, with aq. sat. $NaHCO_3$ and finally with water. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude sulfoxides **2** were purified by flash chromatography (1:1 petroleum ether–EtOAc, v/v).

16. NMR spectra were recorded with an ARX-400 Bruker Spectrometer and assignments using routine COSY and HETCOR experiments. TLC (1:1 petroleum ether–EtOAc): ($S_S$)-**2**: $R_f$=0.3; ($R_S$)-**2**: $R_f$=0.2; $^1$H NMR ($CDCl_3$): ($S_S$)-**2**, $\delta$=8.10–7.20 (m, $C_6H_5$), 6.08 (d, $J_{3,4}$= 3.3 Hz, H-4), 6.01 (t, $J_{1,2}=J_{2,3}$=10.0 Hz, H-2), 5.75 (dd, $J_{6a,6b}$=10.6 Hz, $J_{5,6a}$=5.1 Hz, H-6a), 4.69 (d, H-1), 4.47 (dd, $J_{5,6b}$=6.2 Hz, H-5), 4.43 (dd, H-6b), 3.00–3.15 (m, $CH_2CH_3$), 1.43 (t, $^3J$=7.6 Hz, $CH_2CH_3$); $^1$H NMR ($CDCl_3$): ($R_S$)-**2**, $\delta$=8.21–7.20 (m, $C_6H_5$), 6.30 (t, $J_{1,2}$= $J_{2,3}$=10.1 Hz, H-2), 6.08 (d, $J_{3,4}$=3.3 Hz, H-4), 5.79 (dd, H-3), 4.71 (dd, $J_{6a,6b}$=13.3 Hz, $J_{5,6a}$=9.0 Hz, H-6a), 4.53–4.47 (m, H-5, H-6b), 4.45 (d, H-1), 3.26 (dq, $^2J$= 12.9 Hz, $^3J$=7.6 Hz, $CH_2CH_3$), 2.87 (dq, $^3J$=7.6 Hz, $CH_2CH_3$), 1.34 (t, $CH_2CH_3$).
17. Sulfone as reference was obtained by overoxidation of **1** using a large excess of $H_2O_2/Ac_2O$. Spectroscopic data are in accordance with expected structure. Selected $^1$H NMR data ($CDCl_3$): $\delta$=4.80 (d, 1H, $J_{1,2}$=9.6 Hz, H-1), 3.27–3.11 (m, 2H, $CH_2CH_3$).
18. HPLC conditions: Hypersil BDS C18 column (150×4.6 mm); MeCN/$H_2O$ (60/40); flow rate: 1.0 mL/min; UV detection at 254 nm; for instance, retention factor defined as $k=(t_R-t_R\text{solv})/t_R\text{solv}$: $k$[**1**]=10.62; $k$[($R_S$)-**2**]=3.03; $k$[($S_S$)-**2**]=4.30; $k$[**sulfone**]=5.67.
19. Selected data for sulfoxides **8**–**12**. Compound **8**: $^1$H NMR ($CDCl_3$): $\delta$ (ppm)=5.67 (t, 0.27H, $J_{3,2}=J_{2,1}$=10.0 Hz; H-2$R_S$), 5.46 (d, 1H, $J_{4,3}$=3.3 Hz, H-4$R$,$S_S$), 5.41 (t, 0.73H, $J_{3,2}=J_{2,1}$=10.1 Hz; H-2$S_S$), 5.17 (dd, 0.27H, $J_{3,4}$=3.3 Hz, $J_{3,2}$=10.2 Hz, H-3$R_S$), 5.12 (dd, 0.73H, $J_{3,4}$=3.3 Hz, $J_{3,2}$=10.2 Hz, H-3$S_S$), 4.30 (d, 0.73H, $J_{1,2}$= 10.1 Hz, H-1$S_S$), 4.10 (d, 0.27H, $J_{1,2}$=9.9 Hz, H-1$R_S$), 4.25–4.00 (m, 3H, H-5$R_S$, H-5$S_S$, H-6a$R_S$, H-6a$S_S$, H-6b$R_S$, H-6b$S_S$), 2.72–3.19 (m, 0.27H, $SCH_2R_S$), 2.91 (dq, 1.46H, $SCH_2S_S$), 1.98–2.16 (8s, 12H, 4 $CH_3R$,$S_S$), 1.38 (t, 2.19H, $J$=7.6 Hz, $CH_3S_S$), 1.34 (t, 0.81H, $J$=7.6 Hz, $CH_3R_S$). Compound **9**: $^1$H NMR ($CDCl_3$):$\delta$ (ppm)= 8.12–7.85 (m, 8$H_{arom.}$), 7.70–7.20 (m, 12$H_{arom.}$), 6.27 (t, 0.63H, $J_{1,2}=J_{2,3}$=3.0 Hz, H-2$S_S$), 6.03 (t, 0.37H, $J_{1,2}=J_{2,3}$=2.8 Hz, H-2$R_S$), 5.88 (td, 0.63H, $J_{4,5}=J_{5,6a}$=4,6 Hz, $J_{5,6b}$=6.6 Hz, H-5$S_S$), 5.83 (td, 0.37H, $J_{4,5}=J_{5,6a}$=4.6 Hz, $J_{5,6b}$=6.6 Hz, H-5$R_S$), 5.79 (dd, 0.37H, H-3$R_S$), 5.72 (dd, 0.63H, $J_{3,4}$=4.3, H-3$S_S$), 5.06 (dd, 0.63H, H-4$S_S$), 5.03 (d, 0.63H, H-1$S_S$), 4.88 (d, 0.37H, H-1$R_S$), 4.80 (t, 0.63H, H-4$R_S$), 4.69 (dd, 0.63H, $J_{6a,6b}$=11.7 Hz, H-6a$S_S$), 4.61 (dd, 0.37H, $J_{6a,6b}$=11.2 Hz, H-6a$R_S$), 4.60 (dd, 0.63H, H-6b$S_S$), 4.53 (dd, 0.37H, H-6b$R_S$). Compound **10**: $^1$H NMR ($CDCl_3$):$\delta$ (ppm)=8.03–7.20 (m, 20$H_{arom.}$), 6.01 (t, 0.33H, $J_{1,2}=J_{2,3}$=9.4 Hz, H-2$R_S$), 5.93 (t, 1 H, $J_{1,2}=J_{2,3}$=9.4 Hz, H-2$S_S$), 5.92 (t, 0.33H, $J_{3,4}=J_{4,5}$=9.9 Hz, H-4$R_S$), 5.66 (t, 0.67H, $J_{3,4}=J_{4,5}$=9.6 Hz, H-4$S_S$), 5.64 (t, 0.67H, H-3$S_S$), 5.62 (t, 0.33H, H-3$R_S$), 4.65 (dd, 0.67H, $J_{5,6a}$=3.0 Hz, $J_{6a,6b}$=12.4 Hz, H-6a$S_S$), 4.60 (dd, 0.33H, $J_{5,6a}$=3.0 Hz, $J_{6a,6b}$=10.7 Hz, H-6a$R_S$), 4.63 (d, 0.67H, H-1$S_S$), 4.53 (dd, 0.33H, $J_{5,6b}$=6.6 Hz, H-6b$R_S$), 4.45 (dd, 0.67H, $J_{5,6b}$=4.8 Hz, H-6b$S_S$), 4.43 (d, 0.33H, H-1$R_S$), 4.18–4.22 (m, 1H, H-5$R_S$, H-5$S_S$), 3.25–3.16 (m, 0.67H, $CH_2CH_3R_S$), 3.04–2.95 (m, 1.33H, $CH_2CH_3S_S$), 2.93–2.83 (m, 0.67H, $CH_2CH_3R_S$), 1.29 (t, 2H, $J$=7.6 Hz, $CH_2CH_3S_S$), 1.21 (t, 1H, $J$=7.6 Hz, $CH_2CH_3R_S$). Compound **11**: Selected $^1$H NMR ($CDCl_3$) data: $\delta$ (ppm)= 3.13–3.04 (m, 0.36H, $CH_2CH_3S_S$), 2.90–2.75 (m, 1.64H, $CH_2CH_3S_S$, $CH_2CH_3R_S$), 1.35 (t, 1.92H, $J$=7.6 Hz, $CH_2CH_3S_S$), 1.31 (t, 1.08H, $J$=7.6 Hz, $CH_2CH_3R_S$). **12**: Selected $^1$H NMR ($CDCl_3$) data: $\delta$ (ppm)=5.56 (d, 0.56H, $J_{1,2}$=3.8 Hz, H-1′$R_S$), 5.38 (d, 0.44H, $J_{1,2}$=3.6 Hz, H-1′$S_S$), 3.20–3.11 (m, 056H, $CH_2CH_3R_S$), 2.92–2.70 (m, 1.44H, $CH_2CH_3R_S$, $CH_2CH_3S_S$).
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