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# SYNTHESIS OF CIGUATOXIN (*2S,5R*)-ABC SEGMENT

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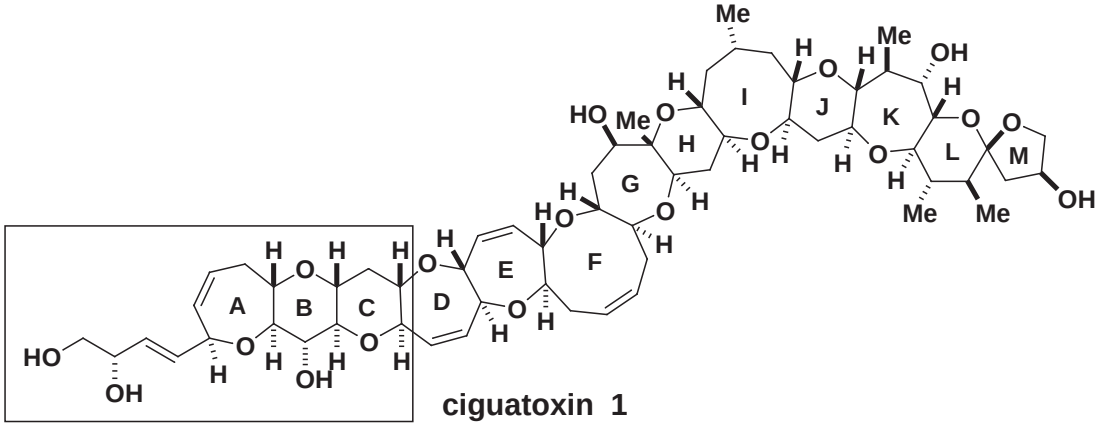
*Abstract- An (2S, 5R)-ABC segment of ciguatoxin has been synthesized based on the previous route for the opposite enantiomer by switching enantiomerism of a pseudosymmetric intermediate. This route has been improved in several steps and ended up with a vinylthioether group for future extension toward the D ring of ciguatoxin molecule.*

## INTRODUCTION

Marine polyether compounds are attracting as the source compounds collecting biological information with unique structures. Ciguatoxin (**1**) is the member of this family, which is produced by certain strains of the benthic dinoflagellate *Gambierdiscus toxicus*.[1] We became interested in the synthesis of (**1**) as one of the most challenging targets regarding to its molecular complexity. Our own efforts to the total synthesis directed toward ciguatoxin, several methodologies have been established as the following; (i) C-glycosidation of an alkynyl group onto hexopyranoses at the C-1 position exclusively in *alpha* orientation[2] and recently other C-glycosidation of pentopyranose lead to exclusively 1,4-*anti* stereochemistry in the product;[3] (ii) epimerization of alkynyl group at C-1 *alpha-axial* into the *beta* orientation *via* biscobalthexacarbonyl complex;[4] (iii) recyclization of the dihydropyranyl ring to medium-sized ether ring with high stereoselectivity;[5] *via* cationic intermediates that are stabilized either by σ–π conjugation with silicon atom or by Nicholas effect[6] with the acetylene biscobalthexacarbonyl complex;[7] (iv) decomplexation of the resulting biscobalthexacarbonylacetylenes under reductive conditions.[8]




**ciguatoxin 1**

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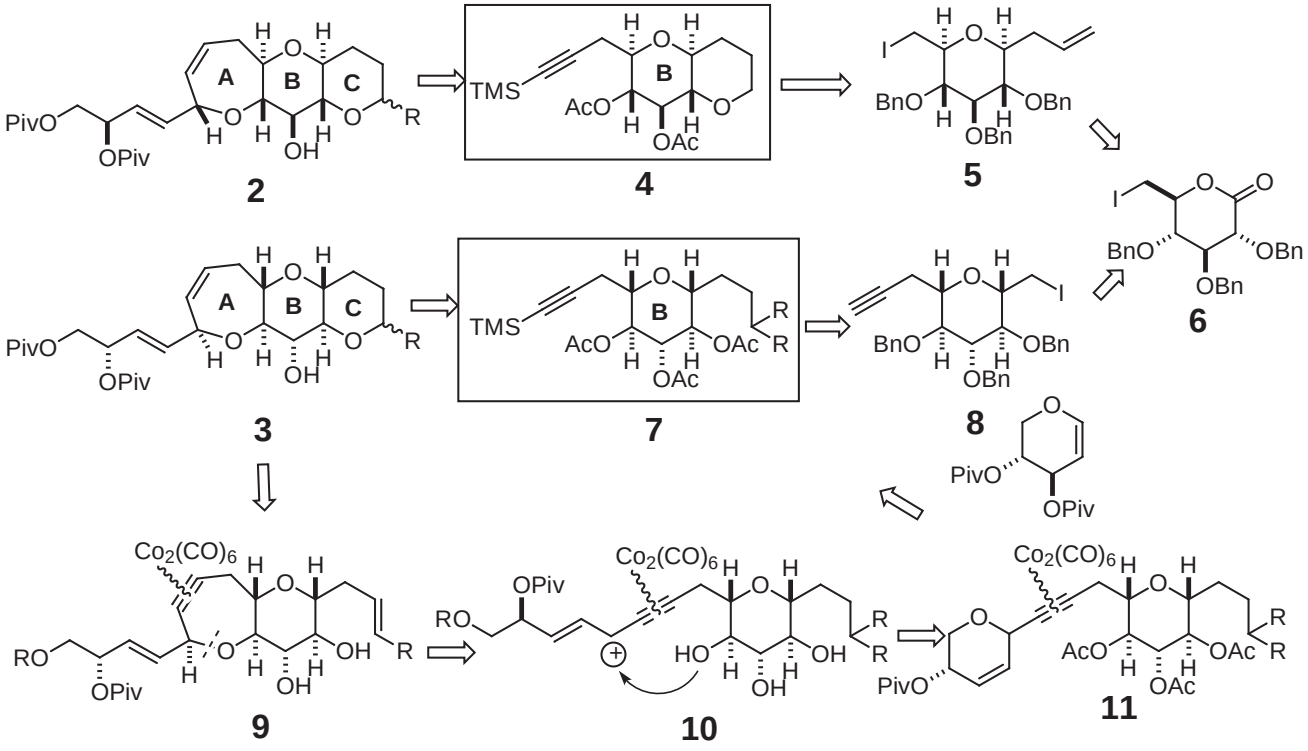
Dedicated to Professor Sho Ito in the occasion of his 77th birthday.

The synthesis of (-)-ABC segments in the opposite enantiomeric form of **1**, namely (*2R,5S*)-ABC segment and (*2S,5S*)-diastereomer has been reported from our laboratory[9] before its absolute configuration was established. However this compound was synthesized *via* the key intermediate which can be applied for switching to either of the enantiomers of the (+)-ABC segment.[10] We present here the synthesis of (+)-ABC segment which proceed *via* the *pseudosymmetric* intermediate with further improvements.

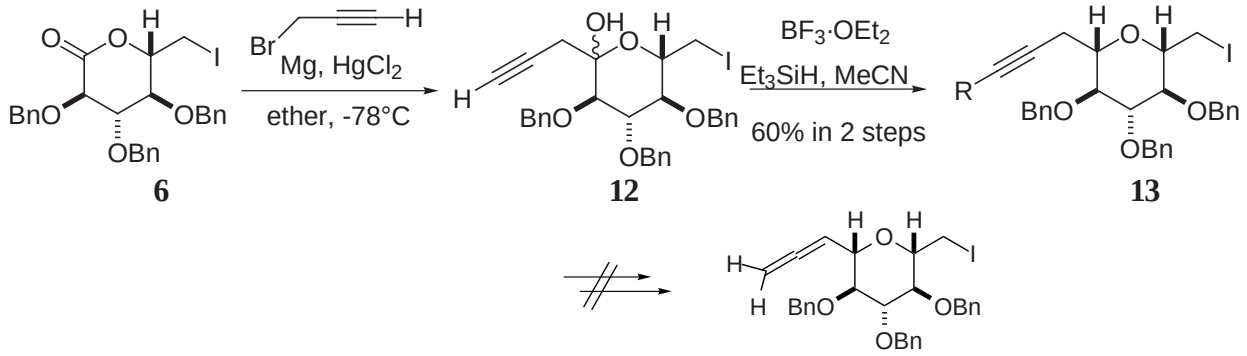



**Scheme 1** Retrosynthetic Analysis to produce the enantiomer from a D-gluconolactone analog

Above synthetic route includes one enantiomer series directing to (*2R,5S)*-ABC **2**, and the other series to (*2S,5R)*-ABC **3**, from the same iode lactone (**6**) with slight modification. Namely, as indicated in **Scheme 1**, the 1-*C*-allyl-6-iodoglucopyranose (**5**) could serve as the key intermediate for a modified approach to the opposite enantiomer (*2S,5R)*-ABC. The synthetic plan was designed to turn over the intermediate (**5**) to provide the *pseudo*-enantiomer related to (**8**) which would be derived from the same starting material (**6**). The retrosynthetic plan of the correct enantiomer (*2S,5R)*-ABC began with the final ring closure which involved the ring C formation step after decobalt-complexation of the oxepene ring A. The oxepene ring A of **9** was retrosynthetically disconnected as indicated in **Scheme 1**, which was designed to cyclize by a cobalt complex known as Nicholas reaction. The triol compound (**10**), precursor for the cyclization, would be derived from ring opening of pivaloylpentopyranose by cobalt complex under acidic condition. In this case, the *cis* allylic cation could equilibrate into more stable *trans* allylic cation that can be attacked by an external nucleophile. Retro C-glycosidation of disaccharide (**11**) lead to D-xylal and silylacetylene (**7**). The latter compound would be derived from chain elongation of the iodo derivative (**6**) in the right hand side and propalgylation of lactone in the left hand side. A substituent R on ring C was introduced in this (+)-ABC enantiomeric synthesis since it might be useful for further elongation toward the D-ring of **1** in later steps.

**RESULTS AND DISCUSSION**

Synthesis of the silylacetylene equivalent (**7**) is shown in the form of **13** in **Scheme 2**. The most remarkable strategy of this synthesis is a direct introduction of the acetylenic group into a lactone carbonyl group. The propargyl metal derivatives were examined to react with the iodolactone (**6**) to provide an intermediate (**12**). From literature reports,[11] propargyl metal can equilibrate to allenyl metal in solution in many cases, and these isomers react differently with carbonyl compounds to provide the different adducts. We became interested to employ a propargyl Grignard reagent[12] since it was reported to react successfully with the alkyl halide substrate to afford acetylene adduct, although this reaction failed to react under the conditions using propalgyllithium.[13] It is of particular interest since the propargyl Grignard reagent is not active to react with the iodo-methyl group. Thus, it was suitable to apply for regioselective introduction of the acetylenic group to lactone (**6**).



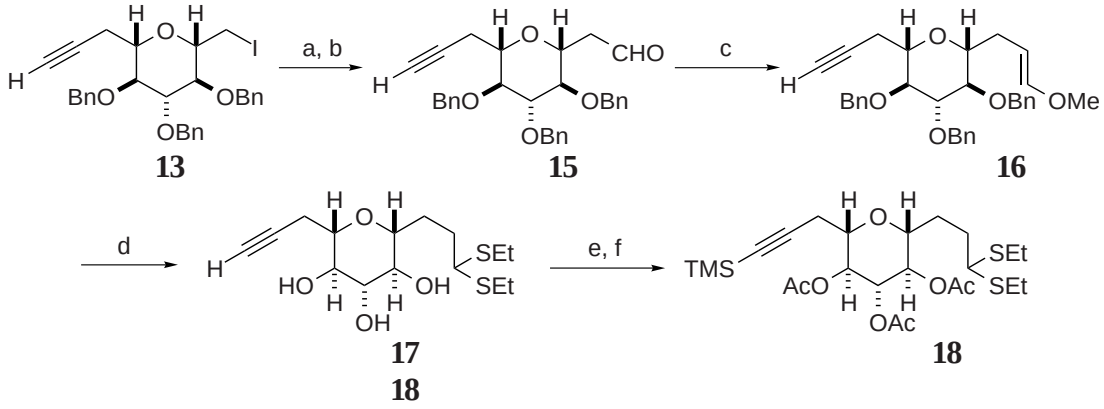

**Scheme 2**

As shown in **Scheme 2**, addition of freshly prepared propargyl Grignard reagent to the lactone (**6**) at -78 °C in ether was followed by stirring for 1.5 h. The resulting product was successively reduced with $Et_3SiH$ and $BF_3 \bullet OEt_2$ in MeCN at -78 °C to obtain the acetylene (**13**) (R = H, 60 % in 2 steps) without the allenic adduct (**14**) (neither allenic signal around δ 210 ppm for $^{13}$C-NMR nor olefinic methylene protons in the $^1$H-NMR were observed). In this regioselective propargylation, the iodide moiety survived at such a low temperature with propargylmagnesium anions, but the propargyllithium reagent afforded an elimination product. Excess Grignard reagent (4.5 equiv.) was used to provide the magnesium acetylide of **12** (R = MgBr) without complication to give exclusively **13** (R= H). Silylation of the terminal acetylene furnished the silylacetylene (**13**) (R = $SiMe_3$) in quantitative yield, it was, however, found that this silyl group was sensitive in the debenzylation condition ($BF_3 \cdot OEt_2$, EtSH) in a later step. So it was designed to introduce the trimethylsilyl group after the debenzylation step.

*Right side chain elongation for ring C*

As a synthetic intermediate for (*5R*)-ABC segment as well as for the total synthesis toward **1**, the functional groups were introduced on a C-ring precursor for future elongation toward the D-ring. The annulation of ring C was created by manipulating the iodo-methyl side chain as shown in **Scheme 3**. The iodide (**13**) was displaced by cyanide and the corresponding nitrile product was then treated with DIBAL-H to convert into the aldehyde (**15**) (90 % overall yield in 2 steps). Wittig reaction of this aldehyde (**15**) gave the vinyl ether

(**16**) as a mixture of *E/Z* olefins (in a ratio of 1.6:1). Debenzylation of this resulting mixture in the presence of ethylmercaptane under Fuji's condition[14] at room temperature effected the vinyl ether moiety and provided a polar triol-thioacetal derivative in one pot reaction. After acetylation and silylation, the product was obtained in the form of **18** (57% overall yield in 3 steps).



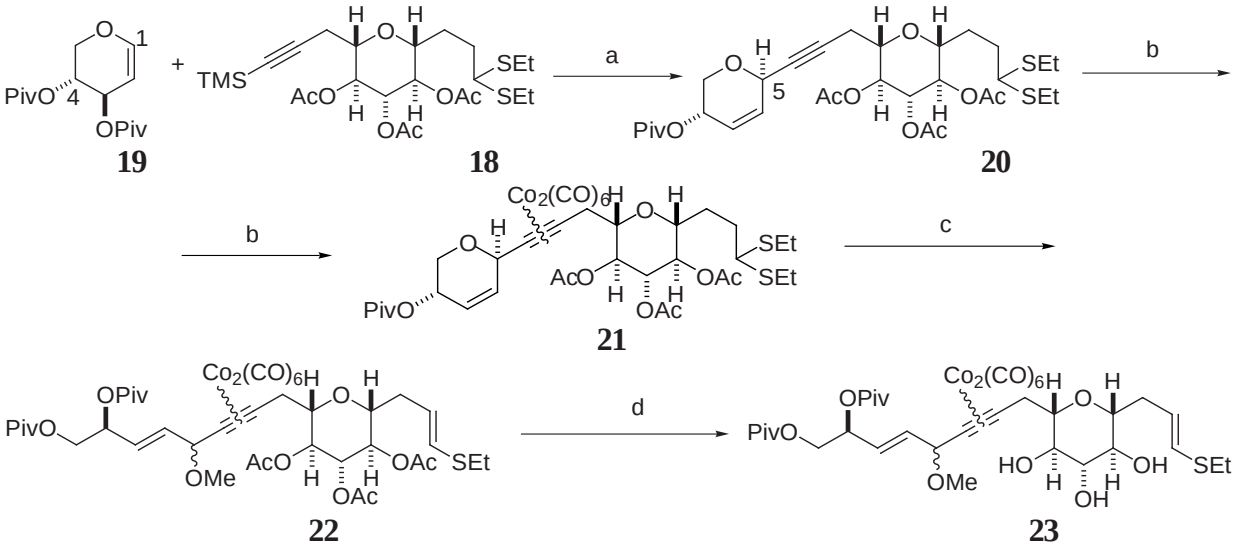

**Scheme 3** Reagents and conditions. a) NaCN in DMSO. b) DIBAL-H, $CH_2Cl_2$ (90 % in 2 steps). c) $[Ph_3PCH_2OMe]^+Cl^-$, *t*-BuLi (68 %). d) $BF_3$•$OEt_2$, EtSH, $CH_2Cl_2$. e) EtMgBr, TMSCl. f) $Ac_2O$, Py, $CH_2Cl_2$ (57 % in 3 steps).

*Left side chain elongation for ring A*

The left side chain elongation was initiated by the C-glycosidation of trimethylsilylacetylene (**18**) to D-xylal (**19**). The pentopyranose ring provides the 4 carbon unit for the dihydroxybutynyl moiety which connect to the ring A of ciguatoxin. At the same time, this crucial step also determined the stereochemistry at the C-2 position of ciguatoxin corresponding to the C-4 position of pentose (**19**) as shown in **Scheme 4**. In addition, this type of C-glycosidation reaction was recently reported from this laboratory to provide a disaccharide in exclusively high stereoselectivity due to 1,4-asymmetric induction. The C-glycosidation reaction was carried out at -20°C in the presence of catalytic amount of $SnCl_4$ in $CH_2Cl_2$ to afford the thioacetal disaccharide product (**20**) in 40 %. The acetylene moiety was converted to its corresponding biscobalthexacarbonyl complex (**21**) in 97 % yield. Opening of the dihydropyran ring of **21** was facilitated by pivalic anhydride in the presence of trifluoromethanesulfonic acid in $CH_2Cl_2$ and the product was isolated after quenching the cation intermediate with methanol to give a mixture of diastereomers (**22**). The acetate was hydrolyzed with potassium carbonate to the corresponding triol (**23**) as the precursor for the ether ring cyclization reaction.

*Ring A cyclization reaction*

For the cyclization of ring A, a variety of acidic conditions were examined with the acetylene biscobalthexacarbonyl (**23**), but not from other precursors such as a deacetylated alcohol from **21**. This is already examined with the opposite enantiomer to result in the opening of the pyranose ring to provide a primary alcohol, to which the pivaloyl group did migrate to give the five membered ring recyclization.[8] So we employed the first opening of the 6-membered ring of **21** into **22**, and then deacetylated to **23**. The results of construction of ring A are summarized in **Table 1** in which 3 products were obtained in the presence of $BF_3$·$OEt_2$ or TfOH as catalyst. In Entry 1, the reactant was treated with $BF_3$·$OEt_2$ at 0°C for 30 min to afford the cyclized product (**24**) (11%) with the recovered starting material (**23**) and isomerized




**Scheme 4** Reagents and conditions. a) $SnCl_4$ in $CH_2Cl_2$ at -20 °C, 1 h (40 %). b) $Co_2(CO)_8$ (97 %). c) $Piv_2O$, TfOH in $CH_2Cl_2$ then MeOH (73 %). d) $K_2CO_3$, MeOH (98 %).

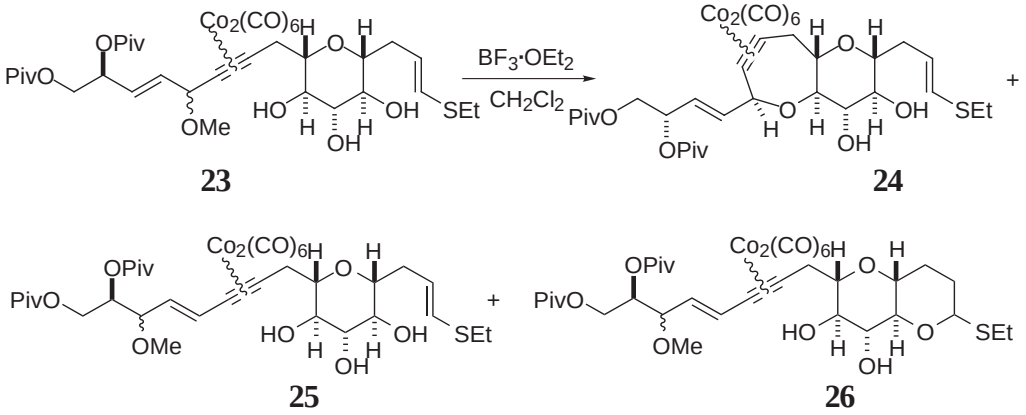


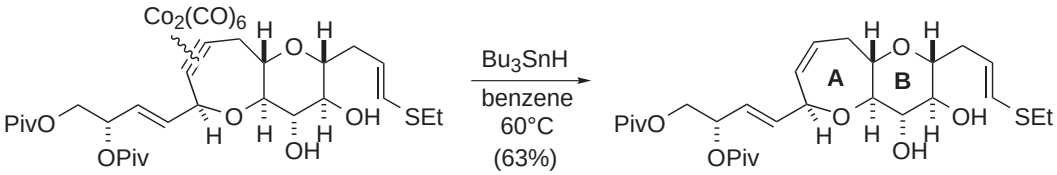

**Table 1 Cyclization reaction of A ring**

| Entry | reagent | temp.(°C) | time | %**24** | %**25** | %**26** | %**23** |
|---|---|---|---|---|---|---|---|
| 1 | $BF_3$·$OEt_2$ | 0 | 30 min | 11 | 10 | 0 | 47 |
| 2 | $BF_3$·$OEt_2$ | 0 | 50 min | 15 | 27 | 0 | 45 |
| 3 | $BF_3$·$OEt_2$ | 10-15 | 40 min | 0 | 30 | 25 | 0 |
| 4 | TfOH | 0 | 25 min | 20 | 0 | 0 | 62 |
| 5 | TfOH | 0 | 2 h | 20 | 33 | 0 | trace |
| 6 | TfOH, MS 4A | 0 | 4 h | 41 | 0 | 0 | 53 |

compound (**25**) (as a more stable product). When the reaction was conducted in the longer reaction time, the yield of A-ring cyclization product (**24**) was not much improved whereas the isomerized compound (**25**) was increased almost 3 times as shown in Entry 2. At higher temperatures (10-15 °C), the cyclized C-ring compound (**26**) was obtained with isomerization of the allyl group without observation of the A-ring product (Entry 3). When TfOH was employed as the acid mediated ring cyclization as shown in Entries 4 and 5. The results are almost similar as $BF_3$·$OEt_2$ in which the isomerization product was increased in the longer

reaction time. To overcome this problem. it was necessary to add MS 4A for trapping methanol after generating the cation intermediate so this methoxy group could not attack back to the cation intermediate and the isomerized cation again. Finally, the A-ring cyclization product was observed in 41% (85% based on recovered triol) as shown in Entry 6.

The oxepene A ring was synthesized by decomplexation through heating **24** with tributyltin hydride in benzene at 60 °C for 2 h to isolate the product (**27**) in 63% yield. This cyclic vinyl ether compound will serve as the ABC-segment precursor for future extension toward the D ring of ciguatoxin molecule.




**24** **27**

We have accomplished a short synthesis of the correct enantiomer of ciguatoxin (*2S,5R)*-ABC segment based on the enantiomeric switching method (21 steps starting from a commercial available D-glucose), involving the propargylation reaction to generate alkynyl adduct with high regioselection. Further studies toward the total synthesis of **1** are now in progress.

## EXPERIMENTAL ***

### (*2R,3R,4S,5R,6R*)-2-Iodomethyl-6-(2-propynyl)-3,4,5-trisbenzyloxytetrahydropyran (13)

To a solution of **6** (20.0 g., 36 mmol) in 200 mL of $Et_2O$ was added a solution of propargylmagnesium bromide (freshly prepare 1.0 M in ether, 150 mL, 150 mmol) at -78°C. After stirring for 1.5 h, the reaction mixture was poured into a solution of cold sat. $NH_4Cl$ and extracted with $Et_2O$ (x3). The combined extracts were washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. The residue was dissolved in 200 mL of MeCN. To this solution were added triethylsilane (23 mL, 144 mmol) and $BF_3{\cdot}OEt_2$ (8 mL, 72 mmol) at -78°C. After stirring for 4.5 h, The reaction mixture was poured into cooled sat. $NaHCO_3$ and extracted with $Et_2O$ (x3). The extracts were washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane / ether = 9 : 1) to give **13** (12.3 g, 60% in 2 steps): mp 92-93 °C; $[\alpha]_D^{27}$ +19.7° (c 1.02, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$), δ 2.05 (1H, t, *J* = 3.0 Hz, H-9), 2.58 (1H, ddd, *J* = 17.5, 5.5, 3.0 Hz, H-7a), 2.69 (1H, dt, *J* = 17.5, 3.0 Hz, H-7b), 3.09 (1H, ddd, *J* = 9.0, 5.5, 3.0 Hz, H-6), 3.36 (1H, dd, *J* = 11.0, 6.0 Hz, H-1a), 3.42 (1H, dd, *J* = 11.0, 2.0 Hz, H-1b), 3.47 (1H, t, *J* =9.0 Hz, H-3), 3.50 (1H, ddd, *J* = 9.0, 6.0, 2.0 Hz, H-2), 3.61 (1H, t, *J* = 9.0 Hz, H-5), 3.76 (1H, t, *J* = 9.0 Hz, H-4), 4.75 (1H, d, *J* = 11.0 Hz, CH*H*Ph), 4.76 (1H, d, *J* = 11.0 Hz, CH*H*Ph), 4.91 (1H, d, *J* = 11.0 Hz, CH*H*Ph), 4.92 (2H, m, $CH_2$Ph) 4.94 (1H, d, *J* = 11.0 Hz, CH*H*Ph); $^{13}$C-NMR (75.4 MHz, $CDCl_3$) δ 7.9, 22.5, 71.3, 76.1, 76.2, 76.4, 77.9, 81.0, 81.3, 82.5, 85.4, 87.2, 128.5, 128.6, 128.8, 129.3, 129.4, 138.4, 138.7, 139.0; IR (KBr) 3292, 3031, 2907, 1497, 1454, 1084, 735, 699 cm$^{-1}$; MS (EI) *m/z* 490 ($M^+$-Bn); Anal. Calcd for $C_{30}H_{31}O_4I$: C, 61.86; H, 5.36 Found: C, 61.89; H, 5.43.

### (*2R,3R,4S,5R,6R*)-2-Formylmethyl-6-(2-propynyl)-3,4,5-trisbenzyloxytetrahydropyran (15)

To a solution of **13** (5.9 g, 0.01 mmol) in DMSO (200 mL), NaCN (1.5 g, 0.03 mmol) was added. After tirring at rt for 1 h, the reaction mixture was heated to 50 °C and stirring was continued for 3 h. After cooling to rt, the reaction mixture was quenched with sat. $NH_4Cl$ and extracted with $Et_2O$ (x3). The combined extracts were washed with $H_2O$ (x2) and brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. The crude product was used in the next step without purification. To a solution of the resulting crude product (5.0 g, 0.01 mmol) in 200 mL of $CH_2Cl_2$ was added a solution of DIBAL ( 0.94 M in hexane, 20

mL, 0.02 mmol) at -78 °C. After stirring for 2 h , to the reaction mixture was added 10% AcOH and extracted with $Et_2O$ (x3). The combined extracts were washed with $H_2O$ (x2), sat. $NaHCO_3$ and brine, dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane / EtOAc = 4 : 1) to give aldehyde (**15**) (4.3 g, 90% in 2 steps): mp 104-106 °C; $[\alpha]_D^{26}$ +11.3° (c 0.53, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$), δ 2.02 (1H, t, *J* = 2.5 Hz, H-9), 2.54 (1H, dd, *J* = 17.0, 5.5 Hz, H-1a), 2.57 (1H, ddd, *J* = 17.0, 7.0, 2.5 Hz, H-7a), 2.63 (1H, dd, *J* = 17.0, 3.5 Hz, H-1b), 2.70 (1H, ddd, *J* = 17.0, 4.5, 2.5 Hz, H-7b), 3.34 (1H, t, *J* = 9.0 Hz, H-5), 3.43 (1H, ddd, *J* = 9.0, 5.0, 3.5 Hz, H-2), 3.60 (1H, t, *J* = 9.0 Hz, H-3), 3.74 (1H, t, *J* = 9.0 Hz, H-4), 3.83 (1H, ddd, *J* = 9.0, 7.0, 4.5 Hz, H-6), 4.60 (1H, d, *J* = 11.0 Hz, CH*H*Ph), 4.74 (1H, d, *J* = 11.0 Hz, CH*H*Ph), 4.90 (2H, d, *J* = 11.5 Hz, CH*H*Ph), 4.91 (2H, d, *J* = 11.5 Hz, CH*H*Ph), 7.20-7.45 (15H, m, *Ph*), 9.70 (1H, s, *CHO*); $^{13}$C-NMR (75.4 MHz, $CDCl_3$) δ 21.7, 45.8, 70.6, 74.4, 75.1, 75.4, 75.6, 76.8, 80.1, 80.6, 81.4, 86.9, 127.7, 127.8, 127.9, 128.1, 128.1, 128.6, 128.6, 137.6, 137.9, 138.3, 200.46; IR (KBr) 3288, 3031, 2910, 1728, 1497, 1456, 1092, 741, 698 cm$^{-1}$; MS (EI) *m/z* 484 ($M^+$), 394 ($M^+$-Bn); Anal. Calcd for $C_{31}H_{32}O_5$: C, 76.84; H, 6.66 Found: C, 76.84; H, 6.77.

**(*2R,3R,4S,5R,6R*)-2-(3-Methoxy-2-propenyl)-6-(2-propynyl)-3,4,5-trisbenzyloxytetrahydropyran (16)**

Methoxymethyltriphenylphosphonium chloride (6.86 g, 20 mmol) was dried *in vacuo* at 140 °C for 2 h and then THF (120 mL) was added. To this suspension under argon atmosphere at -78 °C was added a solution of *t*-BuLi (7.0 mL, 1.8 M in pentane) in a dropwise manner. After stirring for 30 min, to the bright red methoxymethylenetriphenylphosphorane solution was added a solution of **15** (3.6 g, 7.43 mmol) in THF (40 mL). After stirring for 2 h, it was warmed to rt. The stirring was continued at rt for 20 min, then the reaction mixture was poured into ice-water and extracted with $Et_2O$ (x3). The combined extracts were washed with $H_2O$ (x2), sat. $NH_4Cl$ and brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane / EtOAc = 4 : 1) to give vinyl ether (**16**) (2.1 g, 55%) as an oil: $[\alpha]_D^{26}$ +0.72° (c 0.79, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$), δ 2.01 (1H, t, *J* = 2.5 Hz, H-11), 2.39-2.71 (4H, m, H-3, H-9), 3.22-3.40 (3H, m, H-4, H-7, H-8), 3.50, 3.57 (3H, s, -O*Me*), 3.55 (1H, t, *J* =9.0 Hz, H-5), 3.70 (1H, t, *J* = 9.0 Hz, H-6), 4.49-4.96 (7H, m, 3xC*H*$_2$Ph, H-2 *cis*), 5.24 (1H, dd, *J* = 13.5, 6.5 Hz, H-2 *trans*), 5.97 (1H, dd, *J* = 7.0, 1.0 Hz, H-1 *cis*), 6.31 (1H, d, *J* = 13.5 Hz, H-1 *trans*), 7.22-7.42 (15H, m, *Ph*); IR (KBr) 3293, 3031, 2905, 1654, 1496, 1456, 1089, 938, 736, 698 cm$^{-1}$; MS (EI) *m/z* 411 ($M^+$), 421 ($M^+$-Bn); Anal. Calcd for $C_{33}H_{36}O_5$: C, 77.32; H, 7.08 Found: C, 77.31; H, 7.20.

**(*2R,3R,4S,5R,6R*)-2-(3,3-Bis(ethylthio)propyl)-6-(2-propynyl)tetrahydropyran (17)**

To a solution of **16** (2.09 g, 4.1 mmol) in 80 mL of $CH_2Cl_2$ were added EtSH (4.8 mL, 65 mmol) and $BF_3{\cdot}OEt_2$ (7.2 mL, 57 mmol) at 0 °C. After stirring overnight at rt, the reaction mixture was poured into cooled sat. $NaHCO_3$ and extracted with EtOAc (x3). The combined extracts were washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. The crude product was used in the next step without purification. A small portion of the crude product was purified by silica gel column chromatography to afford **17**: $[\alpha]_D^{27}$ +25.3° (c 0.365, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$), δ 1.27 (6H, t, *J* = 8.0 Hz, 2x-SCH$_2$C*H*$_3$), 1.68-1.78 (2H, m, H-3), 1.83-1.95 (1H, m, H-2a), 2.05 (1H, t, *J* = 2.5 Hz, H-11), 2.06-2.13 (1H, m, H-2b), 2.53 (1H, ddd, *J* = 17.5, 6.0, 2.5 Hz, H-9a), 2.59-2.69 (1H, m, H-9b), 2.61-2.74 (4H, m, 2x-SC*H*$_2$CH$_3$), 3.19-3.28 (1H, m, H-8), 3.28 (1H, t, *J* = 9.0 Hz, H-5), 3.32-3.39 (1H, m, H-4), 3.46 (1H, t, *J* = 9.0 Hz, H-7), 3.49 (1H, t, *J* = 9.0 Hz, H-6), 3.88 (1H, t, *J* = 7.0 Hz, H-1); $^{13}$C-NMR (75.4 MHz, $CDCl_3$) δ 15.2, 23.2, 24.7, 24.9, 32.4, 52.0, 71.1, 73.9, 74.7, 77.6, 79.1, 79.8, 81.4; IR (KBr) 3293 (br), 2966, 2925, 1449, 1084 cm$^{-1}$; MS (EI) *m/z* 273 ($M^+$-SEt); Anal. Calcd for $C_{15}H_{26}O_4S_2$: C, 53.86; H, 7.83 Found: C, 53.79; H, 8.07.

**(*2R,3R,4S,5R,6R*)-2-(3,3-Bis(ethylthio)propyl)-6-(3-trimethylsilyl-2-propynyl)-3,4,5-trisacetoxy-tetrahydropyran (18)**

To a solution of crude **17** in $Et_2O$ (100 mL) were added EtMgBr (20 mL, 3.0 M in $Et_2O$, 60 mmol) and excess amount of TMSCl (23 mL) at 0 °C. After raising the temperature to rt, stirring was continued for 1

day. The reaction mixture was quenched with sat. $NH_4Cl$ and extracted with EtOAc (x3). The combined extracts were washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. The crude product was used in the next step without purification. To a solution of the resulting crude compound (1.7 g) in $CH_2Cl_2$ (15 mL) were successively added $Ac_2O$ (25 mL), pyridine (15 mL) and small amount of DMAP at rt. After stirring overnight, the reaction mixture was quenched with ice-water and extracted with $Et_2O$ (x3). The combined extracts were washed with $H_2O$, brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane / ether = 9 : 1) to obtain **18** as a white solid (1.30 g, 57% in 3 steps): mp 85-87 °C; $[\alpha]_D^{25}$ +0.07° (c 0.95, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$), δ 0.16 (9H, s, *TMS*), 1.25 (6H, t, *J* = 8.0 Hz, 2x-$SCH_2CH_3$), 1.61-1.74 (2H, m, H-3), 1.74 -1.90 (1H, m, H-2a), 2.00 (3H, s, Ac), 2.03 (3H, s, Ac), 2.05 (3H, s, Ac), 2.06-2.16 (1H, m, H-2b), 2.44 (1H, dd, *J* = 17.5, 6.0 Hz, H-9a), 2.51 (1H, dd, *J* = 17.5, 5.0 Hz, H-9b), 2.54-2.74 (4H, m, 2x-$SCH_2CH_3$), 3.38-3.47 (1H, m, H-4), 3.53 (1H, ddd, *J* = 9.5, 6.5, 5.0 Hz, H-8), 3.76 (1H, t, *J* =7.0 Hz, H-1), 4.86 (1H, t, *J* = 9.5 Hz, H-5), 4.91 (1H, t, *J* = 9.5 Hz, H-7), 5.14 (1H, t, *J* = 9.5 Hz, H-6); $^{13}$C-NMR (75.4 MHz, $CDCl_3$), δ 0.1, 14.3, 14.4, 20.6, 20.7, 23.7, 24.2, 29.1, 31.2, 51.1, 72.0, 72.1, 74.3, 75.9, 77.3, 86.7, 101.6, 169.7, 169.8, 170.6; IR (KBr) 2960, 2871, 2179, 1755, 1448, 1374, 1220, 1032, 846 $cm^{-1}$; MS (EI) *m/z* 533 ($M^+$), 472 ($M^+$-SEt); Anal. Calcd for $C_{18}H_{34}O_4S_2Si$; C, 54.11; H, 7.57 Found: C, 54.10; H, 7.59.

**2,2-Dimethyl-propionic acid 6-{3-[3,4,5-triacetoxy-6-(3,3-bisethylsulfanylpropyl)tetrahydro-pyran-2-yl]prop-1-ynyl}-3,6-dihydro-2*H*-pyran-3-yl ester (20)**

To a solution of **18** (0.70g. 1.3 mmol) and tri-*O*-pivaloyl-D-xylal (**19**) (0.79 g, 2.7 mmol) in $CH_2Cl_2$ (20 mL) was added $SnCl_4$ (0.33 mL, 2.86 mmol) at -20 °C. After stirring for 30 min at -20 °C, more tri-*O*-pivaloyl-D-xylal (**19**) (0.16 g, 0.56 mmol) was added. After additional stirring 30 min at -20 °C, the reaction mixture was poured into cooled sat. $NaHCO_3$ and sat. $NaK(CH(OH)COO)_2$ (1:1) and extracted with $Et_2O$ (x3). The combined extracts were washed with $H_2O$, brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (hexane / $Et_2O$ = 2 : 1) to give product (**20**) (0.34 g, 40%) as an oil: $[\alpha]_D^{26}$ +62.8° (c 0.465, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$), δ 1.21 (9H, s, Piv), 1.25 (3H, t, *J* = 8.0 Hz, -$SCH_2CH_3$), 1.26 (3H, t, *J* = 8.0 Hz, -$SCH_2CH_3$), 1.57-1.75 (2H, m, H-14), 1.75 -1.90 (1H, m, H-15a), 2.00 (3H, s, Ac), 2.04 (3H, s, Ac), 2.06 (3H, s, Ac), 2.07-2.15 (1H, m, H-15b), 2.45 (1H, ddd, *J* = 17.5, 7.0, 6.0 Hz, H-8a), 2.50-2.58 (1H, m, H-8b), 2.55-2.72 (4H, m, 2x-$SCH_2CH_3$), 3.39-3.48 (1H, m, H-13), 3.53 (1H, ddd, *J* = 9.5, 6.0, 4.5 Hz, H-9), 3.74-3.82 (1H, m, H-16), 3.79 (1H, dm, *J* = 13.0, H-1a), 4.17 (1H, dd, *J* = 13.0, 3.5 Hz, H-1b), 4.87 (1H, t, *J* = 9.5 Hz, H-12), 4.91-4.93 (1H, m, H-5), 4.94 (1H, t, *J* = 9.5 Hz, H-10), 5.00-5.06 (1H, m, H-2), 5.14 (1H, t, *J* = 9.5 Hz, H-11), 5.91 (1H, dddd, *J* = 10.0, 4.5, 2.0, 1.0 Hz, H-4), 6.04 (1H, ddd, *J* = 10.0, 3.5, 1.0 Hz, H-3); $^{13}$C-NMR (75.4 MHz, $CDCl_3$), δ 14.3, 14.4, 20.5, 20.6, 22.5, 23.6, 24.1, 26.9, 27.0, 28.9, 31.1, 38.6, 50.9, 63.0, 63.6, 64.2, 71.8, 74.2, 75.6, 77.1, 77.9, 81.9, 122.6, 132.0, 169.6, 169.7, 170.5, 178.2; IR (KBr) 2972, 2930, 2873, 1756, 1727, 1245, 1220, 1155, 1089 $cm^{-1}$; MS (EI) *m/z* 642 ($M^+$), 581 ($M^+$-SEt); Anal. Calcd for $C_{31}H_{46}O_{10}S_2$; C, 57.92; H, 7.21 Found: C, 57.93; H, 7.36

**Biscobalthexacarbonyl complex of 2,2-Dimethylpropionic acid 6-{3-[3,4,5-triacetoxy-6-(3,3-bis-ethylsulfanylpropyl)tetrahydropyran-2-yl]prop-1-ynyl}-3,6-dihydro-2*H*-pyran-3-yl ester(21)**

To a solution of **20** (0.24 g, 0.37 mmol) in 15 mL of $CH_2Cl_2$ was added a solution of $Co_2(CO)_8$ (1.0 g, 3.0 mmol) in 15 mL of $CH_2Cl_2$ *via* a canula. After stirring for 1 h at rt, the reaction was concentrated *in vacuo* and purified by silica gel column chromatography (hexane / $Et_2O$ = 1 : 1) to give dark red oil compound (**21**) (0.33 g, 97%) as an oil: $[\alpha]_D^{26}$ -103.6° (c 0.047, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$), δ 1.21 (9H, s, Piv), 1.23 (6H, t, *J* = 7.5 Hz, 2x-$SCH_2CH_3$), 1.42-1.70 (2H, m, H-14), 1.70 -2.00 (2H, m, H-15), 2.01 (3H, s, Ac), 2.05 (3H, s, Ac), 2.07 (3H, s, Ac), 2.48-2.72 (4H, m, 2x-$SCH_2CH_3$), 2.94 (1H, dd, *J* = 16.0, 3.0 Hz, H-8a), 3.00 (1H, dd, *J* = 16.0, 8.0 Hz, H-8b), 3.44-3.52 (1H, m, H-13), 3.56 (1H, ddd, *J* = 9.5, 8.0, 3.0 Hz, H-9), 3.64-3.72 (1H, m, H-1b), 3.68 (1H, t, *J* = 8.0 Hz, H-16), 4.25 (1H, dd, *J* = 11.0, 5.5 Hz, H-1a), 4.96 (1H, t, *J* = 9.5 Hz, H-10), 4.97 (1H, t, *J* = 9.5 Hz, H-12), 5.18 (1H, t, *J* = 9.5 Hz, H-11), 5.24-5.33 (1H, m, H-2), 5.34 (1H, dd, *J* = 4.0, 2.0 Hz, H-5), 5.89 (1H, ddd, *J* = 10.5, 2.0, 1.0 Hz, H-4), 5.96 (1H, ddd, *J* =

10.5, 2.5, 1.5 Hz, H-3); $^{13}$C-NMR (100 MHz, $CDCl_3$), δ 14.13, 14.4, 14.5, 20.7, 23.8, 24.5, 27.1, 28.9, 30.4, 30.9, 31.6, 36.3, 38.8, 51.3, 64.3, 65.5, 70.6, 71.9, 74.0, 74.3, 78.6, 91.5, 97.5, 126.3, 131.5, 169.7, 169.9, 170.4, 178.0, 199.6, 207.0; IR (KBr) 2972, 2933, 2872, 2092, 2050, 2028, 1755, 1368, 1243 $cm^{-1}$; MS (FAB) $C_{37}H_{46}O_{16}Co_2S_2$ *m/z* 929 ($M^+$+H), 844 ($M^+$-3CO), 816 ($M^+$-4CO), 788 ($M^+$-5CO), 760 ($M^+$-6CO)

**Biscobalthexacarbonyl complex of 2,2-Dimethylpropionic acid 2-(2,2-dimethylpropionyloxy)-5-methoxy-8-[3,4,5-triacetoxy-6-(3-ethylsulfanylallyl)tetrahydropyran-2-yl]-oct-3-en-6-ynyl ester (22)**

To a solution of pivalic anhydride (0.2 mL, 1.0 mmol) in 6 mL of $CH_2Cl_2$ was added TfOH (0.05 mL, 0.5 mmol) at -20 °C. After stirring for 30 min at -20 °C, to the reaction mixture was added a solution of cobalt complex (**21**) (0.1 g, 0.1 mmol) in 4 mL of $CH_2Cl_2$. After additional stirring for 25 min at -20 °C, MeOH (0.4 mL) was added to the reaction and the resulting dark red solution was poured into cooled sat. $NaHCO_3$ and extracted with $Et_2O$ (x3). The combined extracts were washed with $H_2O$, brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (hexane / $Et_2O$ = 1 : 1) to give dark red oil product (**22**) (71.8 mg, 73%): $^1$H-NMR (300 MHz, $CDCl_3$), δ 1.18, 1.20, 1.21, 1.23 (total 18H, each s, Piv), 1.26-1.32 (3H, m, -$SCH_2CH_3$), 2.00 (3H, s, Ac), 2.15 (3H, s, Ac), 2.20 (3H, s, Ac), 2.28-2.52 (2H, m, H-3), 2.66 (2H, qd, *J* = 8.0, 1.0 Hz, -$SCH_2CH_3$), 2.89 (2H, m, H-8), 3.40, 3.41 (total 3H, each s, -O*Me*), 3.44-3.66 (2H, m, H-9, H-13), 4.05 (1H, dd, *J* = 12.0, 7.5 Hz, H-1a), 4.32 (1H, dd, *J* = 12.0, 3.5 Hz, H-1b), 4.75 (1H, m, H-5), 4.93 (1H, t, *J* = 9.5 Hz, H-10), 4.94 (1H, t, *J* = 9.5 Hz, H-12), 5.18 (1H, t, *J* = 9.5 Hz, H-11), 5.45-5.62 (2H, m, H-2, H-15), 5.80 (2H, m, H-3, H-4), 5.96 (1H, dd, *J* = 15.0, 4.5 Hz, H-16 *trans*), 6.08 (1H, dd, *J* = 10.0, 7.5 Hz, H-16 *cis*); $^{13}$C-NMR (100 MHz, $CDCl_3$), δ 14.5, 15.4, 20.6, 20.7, 20.8, 26.5, 26.8, 27.1, 27.3, 27.7, 30.9, 35.5, 38.8, 57.1, 64.8, 70.6, 70.7, 71.2, 71.7, 74.4, 74.5, 75.4, 76.5, 78.6, 78.8, 80.9, 81.0, 89.8, 92.5, 93.2, 97.7, 98.0, 121.9, 122.1, 122.2, 126.8, 127.1, 127.2, 127.3, 127.4, 128.4, 128.7, 132.7, 132.8, 169.6, 169.8, 169.9, 170.5, 177.1, 180.0, 199.6, 207.1; IR (KBr) 2975, 2091, 2051, 2027, 1735, 1244, 1144, 1033, 758 $cm^{-1}$; MS (FAB) $C_{41}H_{52}O_{18}SCo_2$ *m/z* 982 ($M^+$), 956 ($M^+$+H-CO), 898 ($M^+$-3CO), 870 ($M^+$-4CO), 842 ($M^+$-5CO), 814 ($M^+$-6CO), 783 ($M^+$-6CO-OMe)

**Biscobalthexacarbonyl complex of 2,2-Dimethylpropionic acid 1-(2,2-dimethyl-propionyloxymethyl)-3-[2-(3-ethylsulfanylallyl)-3,4-dihydroxy-3,4,4a,6,9,9a-hexahydro-2*H*-1,5-dioxabenzocyclohepten-6-yl]allyl ester (24)**

To a solution of **23** (49.0 mg, 0.05 mmol) in 10 mL of degassed MeOH was added $K_2CO_3$ (19.6 mg, 0.14 mmol). After stirring at rt for 3 h, the reaction mixture was poured into cooled sat. $NH_4Cl$ and extracted with EtOAc (x2). The combined extracts were washed with brine, dried over $Na_2SO_4$, concentrated, and purified by silica gel column chromatography (hexane / EtOAc = 3 : 7) to give dark red triol compound (42 mg, quantitative). To a solution of the resulting triol (5.7 mg, 6.6 μmol) in degassed 13 mL. of $CH_2Cl_2$ were added molecular sieve (4 A, ca. 50 mg) and a solution of TfOH (0.1 M in $CCl_2FCClF_2$, 0.2 mL) at 0 °C. After stirring at 0 °C for 4 h, the reaction mixture was poured into cooled sat. $NaHCO_3$ and extracted with EtOAc (x3). The combined extracts were washed with $H_2O$, brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (hexane / EtOAc = 2 : 1) to give product (**24**) (2.2 mg, 41% (70% based on recovered starting material)) and recovered starting material triol (3.0 mg, 53%): $[\alpha]_D^{25}$ +110.5° (c 0.038, $CHCl_3$) $^1$H-NMR (400 MHz, $CDCl_3$), δ 1. 17, 1.20 (each 9H, each s, Piv), 1.29 (3H, t, *J* = 7.5 Hz,-$SCH_2CH_3$), 2.40 (1H, m, H-14a), 2.62 (1H, m, H-14b), 2.68 (2H, q, *J* = 7.5 Hz, -$SCH_2CH_3$), 2.88 (1H, dd, *J* = 16.0, 10.0 Hz, H-8a), 2.99 (1H, br s, -O*H*), 3.05 (1H, br s, -*OH*), 3.33 (1H, t, *J* = 9.0 Hz, H-10), 3.30-3.35 (1H, m, H-13), 3.40 (1H, t, *J* = 9.0 Hz, H-12), 3.41 (1H, td, *J* = 9.0, 4.0 Hz, H-9), 3.58 (1H, dd, *J* = 16.0, 4.5 Hz, H-8b), 3.60 (1H, t, *J* = 9.0 Hz, H-11), 4.09 (1H, dd, *J* = 11.5, 5.0 Hz, H-1a), 4.28 (1H, dd, *J* = 11.5, 3.5 Hz, H-1b), 5.04 (1H, d, *J* = 4.7 Hz, H-5), 5.56 (1H, m, H-2), 5.69 (1H, m, H-15), 5.86 (1H, dd, *J* = 16.0, 5.0 Hz, H-3), 5.94 (1H, dd, *J* = 16.0, 4.7 Hz, H-4), 6.06 (1H, dd, *J* = 4.5, 9.5 Hz, H-16); IR (KBr) 3503 (br), 2930, 2093, 2055, 2027, 1735, 1457, 1281,

1147 $cm^{-1}$; MS (FAB) $C_{34}H_{42}O_{14}Co_2S$ *m/z* 826 ($M^+$+H), 798 ($M^+$+H-CO), 770 ($M^+$+H-2CO), 741 ($M^+$-3CO), 713 ($M^+$-4CO), 685 ($M^+$-5CO), 657 ($M^+$-6CO)

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