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Discovery of the tungsten carbonyl-catalyzed *endo*-selective alkynyl alcohol cycloisomerization reaction: applications to stereoselective syntheses of D-olivose, D-olivose disaccharide substructures of landomycin and mithramycin

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Abstract

An account of the discovery of the tungsten carbonyl-catalyzed *endo*-selective cycloisomerization of alkynyl alcohols to dihydropyrans is described. The utility of this new chemical transformation involving tungsten vinylidene catalytic intermediates is demonstrated in stereoselective syntheses of disaccharide substructures **26**–**28** of the landomycin and mithramycin families of anticancer antibiotics.

Keywords: Alkynyl alcohols; Tungsten vinylidenes; Carbohydrate glycals; Disaccharide synthesis

1. Introduction

The interface of organic chemistry with inorganic chemistry has resulted in the invention of many new synthetic methods, which in turn have supported the exploration and application of novel synthetic strategies for constructing many classes of biologically active organic compounds. We recently reported the first examples of a transition-metal catalyzed *endo*-selective cycloisomerization reaction in which 5-hydroxy-1-alkynes are efficiently converted into 3,4-dihydro-2*H*-pyrans [1]. Herein we provide a more detailed account of the discovery of this catalytic transformation which involves the intermediacy of tungsten vinylidene complexes, and a discussion of our most recent applications of this novel transformation in the stereoselective preparation of *arabino*, *arabino*-disaccharide substructures of the anticancer antibiotics landomycin and mithramycin.

2. Results and discussion

2.1. Early work on alkynol cycloisomerization

In late 1992 we discovered that simple homopropargylic alcohols underwent efficient cycloisomerization to 2,3-dihydrofuran products upon catalytic reaction with $(Et_3N)Mo(CO)_5$ [2]. Over the next few years we optimized this reaction for the preparation of variously substituted dihydrofurans including compounds **2** and **6** (Scheme 1), and successfully applied this novel transformation to short syntheses of the biologically active nucleoside compounds d4T **3** [3], cordycepin **4** [3], and puromycin aminonucleoside **7** [4].

Although the molybdenum-catalyzed process was not generally effective for the formation of six-membered ring products from the corresponding acyclic alkynyl alcohols [5], in mid-1995 we observed that six-membered ring products could be formed via a stoichiometric, tungsten-promoted two-step process [6]. The reaction sequence required one to three equivalents of $W(CO)_6$, isolation of the stoichiometric tungsten oxacarbene, and conversion of this oxacarbene intermediate to the endocyclic enol ether by reaction with a tertiary amine base. The yields for this process rarely

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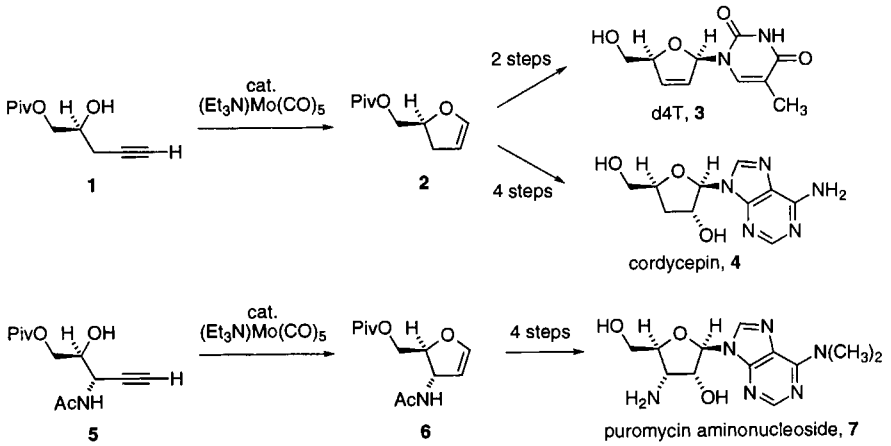


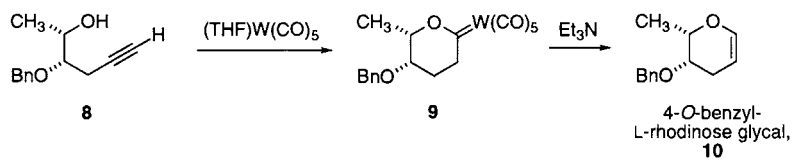
Scheme 1.

exceeded 50%, with the modest overall yield of 32% reported for the two-step conversion of alkynyl alcohol **8** to the moderately functionalized dihydropyran **10** as a representative example [7] (Scheme 2). Pure samples of tungsten oxacarbene intermediates such as **9** could be converted into the corresponding enol ether in nearly quantitative yield, indicating that the first step to form the stoichiometric oxacarbene **9** was the problematic transformation in this synthesis. Our initial attempts to combine base-promoted enol ether formation with the tungsten-promoted alkynyl alcohol cyclization as a single-step cycloisomerization transformation were unsuccessful, as the isolated reagent $(Et_3N)W(CO)_5$ was reported to be inert to simple alkynyl alcohol substrates [8].

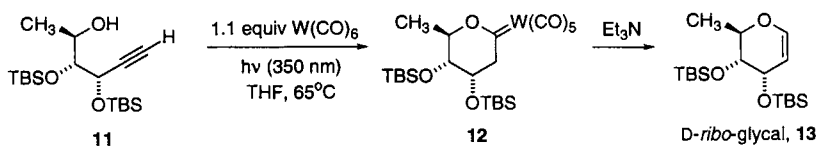
2.2. Discovery of the tungsten-catalyzed cycloisomerization at Emory University

We commenced further explorations in this area with studies of a more highly functionalized substrate **11** in early 1999. Stoichiometric tungsten-promoted cyclization of **11** afforded the tungsten oxacarbene **12**, but the reaction was extremely slow and some starting material **11** was still present after 48 h at room temperature. The tungsten oxacarbene **12** could be observed by ^{1}H-NMR analysis of an aliquot, but was usually not isolated and instead the THF solution of unpurified oxacarbene **12** was directly treated with Et_3N to provide the glycal **13**. We subsequently discovered that the cyclization reaction of **11** to **12** could be pushed to completion by heating the reaction mixture to the reflux point of THF (ca. 65°C). Even better results were obtained when we photolyzed $W(CO)_6$ in the presence of the alkynyl alcohol substrate **11** with heating, and the isolated yields of glycal **13** produced by this stoichiometric tungsten-promoted procedure were consistently in the 40–45% range, with the first step to tungsten oxacarbene **12** judged as the low-yielding operation (Scheme 3).

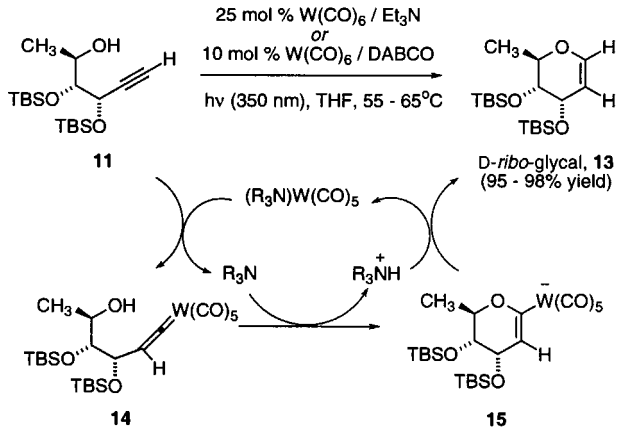
As the alkynyl alcohol substrate **11** and tungsten oxacarbene **12** were observed to be compatible with 350 nm irradiation, we reexplored the idea of a single-step conversion of compound **11** to cycloisomeric product glycal **13** by irradiating $W(CO)_6$ and substrate **11** in the presence of triethylamine, and were gratified to find



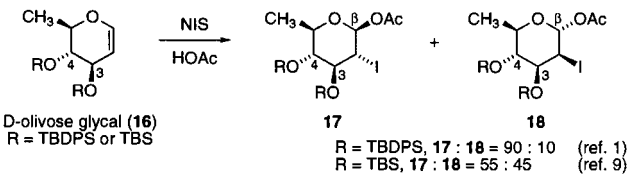
Scheme 2.



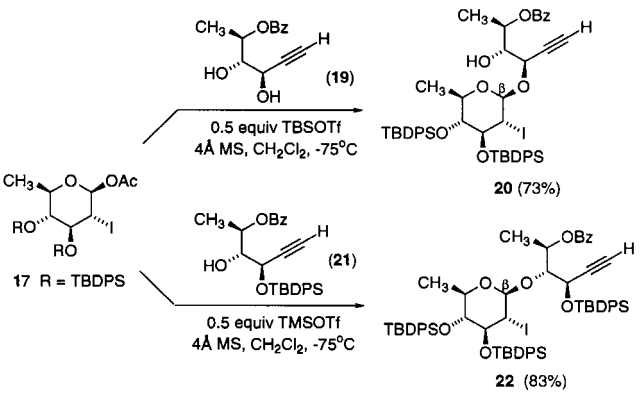
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

that near-quantitative isolated yields of the glycal product **13** were obtained with only 25 mol% of tungsten hexacarbonyl (Scheme 4). Control experiments have demonstrated that continuous irradiation is required in order to effectively regenerate the $(Et_3N)W(CO)_5$ species, which is attributed to be the active catalyst for this cycloisomerization transformation.

This catalytic protocol is perfectly suitable for small-scale operations, but on larger scales, (> 1 mmol) we observe that the observed glycal product is accompanied by partial recovery of starting alkynyl alcohol substrate. We have subsequently explored the use of other tertiary amine co-reagents, and sublimed 1,4-diazabicyclo[2.2.2]octane (DABCO) is currently the base of choice of the cycloisomerization transformation. In reworking the catalytic loading in the presence of excess DABCO, we have observed that as little as 10 mol% of $W(CO)_6$ is sufficient for high-yield cycloisomerization of **11** to **13** within 6 h provided the reaction temperature is maintained above 50°C while under continuous irradiation at 350 nm. $W(CO)_6$ loading below 10 mol% requires significantly longer reaction times and/or result in incomplete conversion of alkynyl alcohol substrate.

The mechanism of the catalytic cycloisomerization transformation probably involves the intermediacy of the tungsten vinylidene **14**, followed by intramolecular nucleophilic addition of the hydroxyl group to provide the carbene anion **15** and protonation to afford the product dihydropyran **13**. Note that this mechanism does not require the neutral oxacarbene **12** as a catalytic intermediate when the reaction is conducted under basic conditions.

2.3. Stereoselective glycosylations and iterative cycloisomerizations in the D-olivose series

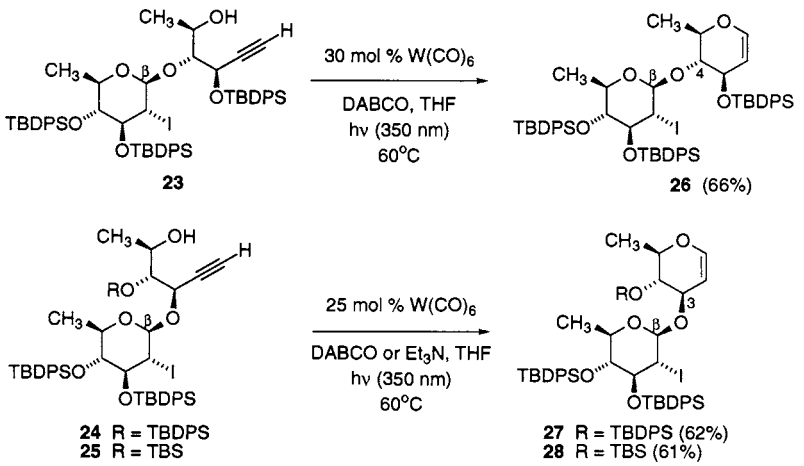
We previously reported that 2,6-dideoxy glycals of *arabino* configuration **16** could be stereoselectively converted into the β-*gluco*-iodoacetate configuration **17** upon reaction with *N*-iodosuccinimide (NIS) and acetic acid, provided that the C3 and C4 oxygen substituents were substituted with sterically bulky protective groups such as *tert*-butyldiphenylsilyl (TBDPS) ethers so that reaction from a $^5H_4$ conformation was preferred [1]. In contrast, the sterically smaller *tert*-butyldimethylsilyl (TBS) ether analog provides a nearly 1:1 mixture of diastereomeric iodoacetates **17** and **18** under identical reaction conditions [9] (Scheme 5).

Recognizing that 3-*O*-linked and 4-*O*-linked D-olivose-β-D-olivose disaccharide substructures are present in the landomycin [10], mithramycin [11], and olivomycin [12] anticancer natural products, we initiated a test of our iterative cycloisomerization/glycosylation strategy [1,7] for oligosaccharide synthesis with these targets in mind. TBSOTf-catalyzed reaction [13] of the iodoacetate **17** (R = TBDPS) [1,10c] with the alkynyl diol **19** [1] afforded regioselective glycosylation of the less hindered propargylic alcohol to provide a single glycoside **20** (Scheme 6). Preparation of the regioisomeric glycoside **22** required monoprotection of the propargylic alcohol of diol **19**. Although the installation of a *tert*-butyldiphenylsilyl protective group did not exhibit the same level of regioselectivity observed in the previously described glycosylation with **19**, the required compound **21** could be obtained as the major silyl ether product in 56% isolated yield. The glycosylation of iodoacetate **17** (R = TBDPS) and the hindered secondary alcohol of **21** proceeded better when the more reactive TMSOTf was used as the glycosylation catalyst, affording **22** as a single isomer.

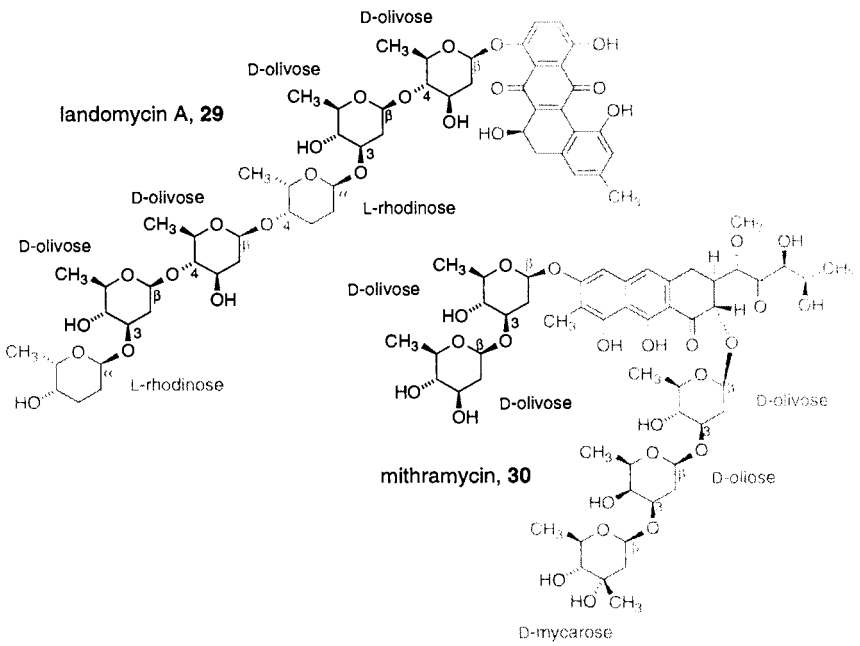
Reductive removal of the benzoyl protective group from **22** afforded the corresponding alkynyl alcohol substrate **23**, which efficiently underwent $W(CO)_6$-catalyzed cycloisomerization to provide the corresponding 4-*O*-linked disaccharide glycal **26** (Scheme 7). Silylation of the free hydroxyl group in glycoside **20** with either TBDPSCl or TBSCl and reductive debenzoylation gave the alkynyl alcohol substrates **24** and **25**, which afforded the regioisomeric 3-*O*-linked disaccharide glycals **27**–**28** upon $W(CO)_6$ catalyzed cycloisomerization. For the preparation of glycals **26** and **27**, we found that the cycloisomerization reaction proceeded much better when DABCO was used instead of triethylamine. Note that the potentially light-sensitive iodide substituents of **23**–**25** are compatible with the continuous photo-irradiation required for $W(CO)_6$ catalyzed cycloisomerization to construct the disaccharide glycals. The β-4-*O*-linked disaccharide glycal **26** corresponds with the configuration of both D-olivose-D-olivose disaccharide substructures of landomycin A, **29** (Scheme 8), and our synthetic β-3-*O*-linked disaccharide glycals **27**–**28** correlate with the D-olivose-*O*-3-D-olivose disaccharide of mithramycin, **30**.

3. Conclusions

These results demonstrate the efficacy of the $W(CO)_6$ catalyzed *endo*-selective alkynyl alcohol cycloisomerization reaction in the synthesis of functionally and stereo-



Scheme 7.



Scheme 8.

chemically complex organic compounds, exemplified by the effective construction of the disaccharide glycals **26**–**28**. Notable features include the compatibility with sensitive functional groups, including glycoside linkages, silyl ethers, and iodide substituents. This method has been applied to the stereoselective synthesis of disaccharide substructures of the landomycin and mithramycin families of antitumor antibiotic natural products. Applications of this methodology to the total synthesis of various families of natural products are in progress.

4. Experimental

4.1. General information

See Ref. [1].

4.2. Cycloisomerization of alkynyl alcohol (*11*) to D-ribo-2,6-dideoxyglycal (*13*)

4.2.1. Procedure A: stoichiometric two-step cycloisomerization

An oven-dried 50 ml Schlenk flask was fitted with a reflux condenser and a magnetic stir bar, under a nitrogen atmosphere, and was charged with tungsten hexacarbonyl (320 mg, 0.91 mmol, dried under vacuum), THF (10 ml), and the alkynyl alcohol **11** (296 mg, 0.827 mmol). The mixture was photolyzed for 5 h at 350 nm (Rayonet photoreactor) without external cooling so that the reaction temperature reached the reflux point (approximately 65°C). The crude oxacarbene–THF solution (yellow color) was cooled to 0°C, freshly distilled Et_3N (1 ml) was added, and the reaction mixture was allowed to warm to room temperature (r.t.) while stirring for 4 h. The reaction mixture was then concentrated in vacuo, and purified by flash chromatography with silica which was pretreated 2.5% v/v with Et_3N, to provide the glycal **13** (118 mg, 40% yield).

A sample of the tungsten oxacarbene intermediate **12** was isolated by silica gel column chromatography (gradient elution, pure pentane to 19:1 pentane–Et_2O) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.82 (app. quintet, $J = 8.8$ Hz, 1H), 3.98 and 3.92 (dd, $J = 26.8$, 6.4 Hz, 1H), 3.70 (app. septet, $J = 2.4$ Hz, 1H), 3.54 and 3.52 (dd, $J = 9.8$, 2.8 Hz, 1H), 3.12 and 3.05 (dd, $J = 26.8$, 4.8 Hz, 1H), 1.60 (d, $J = 8.8$ Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.08 (s, 3H).

4.2.2. Procedure B: catalytic single-step cycloisomerization, with triethylamine

An oven-dried 25 ml Schlenk flask fitted with a reflux condenser and a stir bar, under argon atmosphere, was charged with tungsten hexacarbonyl (37 mg, 0.11 mmol, dried under vacuum) and alkynol substrate **11** (150 mg, 0.42 mmol, azeotropically dried twice from toluene). The mixture was dissolved in freshly distilled dry THF (2 ml) and triethylamine (0.5 ml). The solution was irradiated under argon atmosphere for 5 h at 350 nm (Rayonet photoreactor) without cooling, so that the solvent reflux point was reached. Volatile components were removed under reduced pressure, and the product was purified by silica gel chromatography using an eluent mixture of pentane–triethylamine (99:1) to afford the product glycal **13** (147 mg, 98%).

4.2.3. Procedure C: catalytic single-step cycloisomerization, with DABCO and 10 mol% $W(CO)_6$

The procedure is essentially the same as procedure B (Section 4.2.2) except sublimed DABCO and 10 mol% $W(CO)_6$ were utilized. Thus a mixture of alkynol **11** (716 mg, 2 mmol), $W(CO)_6$ (70 mg, 0.2 mmol, 10 mol%), DABCO (448 mg, 4 mmol), and THF (10 ml) was irradiated under argon for 6 h at a temperature of 50–60°C. The solvent was then removed to give the crude product mixture, which was purified by SiO_2 (pretreated with 2.5% v/v Et_3N) column chromatography (*n*-hexanes eluent) to afford glycal **13** (680 mg, 95%) as a colorless liquid, which solidified to a white solid upon standing. M.p. 38–40°C; $[\alpha]_D^{23}$ +231 ($CHCl_3$, C = 1.66); IR (KBr) 3037, 2957, 2930, 2858, 1642, 1256, 1141, 1127, 1088, 999, 903 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.28 (app. d, $J = 6.0$ Hz, 1H), 4.76 (app. t, $J = 6.0$ Hz, 1H), 4.12 (dq, $J = 8.1$, 3.0 Hz, 1H), 3.98 (dd, $J = 6.0$, 3.2 Hz, 1H), 3.50 (dd, $J = 9.6$, 3.3 Hz, 1H), 1.28 (d, $J = 6.0$ Hz, 1H), 0.91 (s, 9H), 0.88 (9H), 0.08 (s, 6H), 0.063 (s, 3H), 0.06 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 145.0, 102.3, 73.8, 70.5, 64.5, 26.0, 18.2, 18.1, −3.3, −3.6, −4.1, −4.1, −4.6; HRMS (FAB$^+$) Anal. Calc. for $C_{18}H_{38}LiO_3Si_2$ [(M + Li)$^+$] 365.2520. Found 365.2505. Anal. Calc. for $C_{18}H_{38}O_3Si_2$, C, 60.28; H, 10.68. Found C, 60.11; H, 10.53%.

4.3. Preparation of glycoside (*20*)

A mixture of iodoacetate **17** [1] (R = TBDPS, 284 mg, 0.36 mmol, 9:1 mixture of β-**17**: α-**18**), alkynyl diol **19** [1] (84 mg, 0.36 mmol), and 4Å molecular sieves (284 mg) was stirred in dry CH_2Cl_2 (2 ml) for 30 min, and cooled to −75°C. *tert*-Butyldimethylsilyl triflate (41 μl, 0.18 mmol) was added, and the reaction was stirred for 20 min at −75°C. The reaction was quenched with Et_3N (0.2 ml) at low temperature. The cold bath was removed and saturated aqueous $NaHCO_3$ (2 ml) was added. The mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with brine and dried. The solvent was removed under reduced pressure to give a crude product, which was purified by flash silica gel chromatography (gradient elution 19:1–9:1,

n-hexanes–EtOAc) to afford the desired glycoside **20** (251 mg, 73%) as a white flocculent material. IR (neat): 3479, 33054, 3070, 2932, 1721, 1427, 1274, 1110, 1082, 1030, 702 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.06–8.04 (m, 2H), 7.60–7.24 (series of m, 23H), 5.52 (d, $J = 8.4$ Hz, 1H), 5.37 (app. quintet, $J = 6.4$, Hz, 1H), 4.61 (d, $J = 3.6$ Hz, 1H), 4.59 (dd, $J = 6.0$, 2.4 Hz, 1H), 4.00 (app. q, $J = 5.2$ Hz, 3H), 3.82 (d, $J = 8.0$ Hz, 1H), 3.72 (app, q, $J = 6.4$ Hz, 1H), 3.58 (d, $J = 3.2$ Hz, 1H), 2.85 (d, $J = 4.8$ Hz, 1H), 2.85 (d, $J = 4.8$ Hz, 1H), 2.57 (d, $J = 2.0$ Hz, 1H), 1.47 (d, $J = 6.4$ Hz, 1H), 1.03 (s, 9H), 0.96 (s, 9H), 0.64 (d, $J = 6.8$ Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.5, 136.0, 135.9, 135.8, 132.9, 132.8, 132.7, 132.6, 130.5, 129.9, 129.9, 129.8, 129.7, 128.2, 127.8, 127.7, 127.6, 99.9, 80.1, 79.2, 78.4, 76.7, 75.1, 74.3, 70.8, 68.4, 28.0, 27.0, 26.9, 19.5, 19.0, 18.9, 15.5.

4.4. Preparation of alkynyl alcohol (*21*)

Alkynyl diol **19** [1] (234 mg, 1 mmol) and imidazole (170 mg, 2.5 mmol) were dissolved in dry DMF (1 ml), and *tert*-butyldiphenylsilyl chloride (260 μl, 1 mmol) was added. The resulting mixture was stirred at r.t. for 1 h and then quenched with water (2 ml). The reaction mixture was diluted with EtOAc (100 ml), washed with water (20 ml), brine (20 ml), dried over Na_2SO_4, and then concentrated under reduced pressure to give the crude product as a mixture of **21** and the regioisomeric monosilyl ether (69:31 by ^{1}H-NMR) as well as a small amount of bissilyl ether byproduct. The product mixture was separated by silica gel chromatography (gradient elution 19:1–9:1, *n*-hexanes–EtOAc) to afford **21** (265 mg, 56%) as a thick colorless liquid, and the regioisomeric monosilyl ether (140 mg, 30%) as a white solid.

Data for **21**: $[\alpha]_D^{23}$ −21.6 ($CHCl_3$, C, 2.5); IR (neat): 3528, 3302, 3071, 3050, 2932, 1719, 1427, 1275, 1113, 1069, 709 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.97–7.19 (series of m, 15H), 5.29 (app. quintet. $J = 6.4$ Hz, 1H), 4.46 (dd, $J = 3.6$, 1.6 Hz, 1H), 3.90 (app. q, $J = 6.0$ Hz, 1H), 2.70 (dd, $J = 6.4$, 1.2 Hz, 1H), 2.30 (d, $J = 2.4$ Hz, 1H), 1.42 (d, $J = 6.0$ Hz, 3H), 1.09 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.4, 136.1, 135.7, 132.9, 132.6, 131.9, 130.2, 129.9, 129.8, 129.6, 128.2, 127.7, 127.3, 81.6, 76.7, 75.4, 70.6, 63.9, 26.9, 19.3, 15.7. HRMS (FAB^+) Anal. Calc. for $C_{29}H_{32}LiO_4Si$ [$(M + Li)^+$] 479.2230. Found 479.2221. Anal. Calc. for $C_{29}H_{32}O_4Si$, C, 73.69; H, 6.82. Found C, 73.02; H, 6.77%.

Data for the regioisomeric monosilyl ether: M.p. 83–85°C, $[\alpha]_D^{23}$ −30.9 ($CHCl_3$, C, 1.81) IR (neat): 3466, 3304, 3071, 2931, 1715, 1427, 1277, 1111, 708 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.82–7.28 (series of m, 15H), 5.42 (dq, $J = 6.8$, 2.8 Hz, 1H), 4.38 (ddd, $J = 8.0$, 6.4, 2.0 Hz, 1H), 4.02 (dd, $J = 5.6$, 2.8 Hz, 1H), 2.46 (app. q, $J = 2.0$ Hz, 1H), 1.49 (d, $J = 6.4$ Hz, 3H), 1.42 (d, $J = 6.0$ Hz, 1H), 1.13 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.2, 136.1, 135.9, 132.9, 132.8, 132.6, 130.1, 129.9, 129.8, 129.6, 128.2, 127.7, 127.6, 81.8, 77.6, 75.0, 72.2, 63.9, 29.7, 27.1, 19.6, 14.9; HRMS (FAB^+) Anal. Calc. for $C_{29}H_{32}LiO_4Si$ [$(M + Li)^+$] 479.2230. Found 479.2221. Anal. Calc. for $C_{29}H_{32}O_4Si$, C, 73.69; H, 6.82. Found C, 73.47; H, 6.74%.

4.5. Preparation of glycoside (*22*)

A mixture of iodoacetate **17** [1] (R = TBDPS, 200 mg, 0.25 mmol, 9:1 mixture of β-**17**: α-**18**), alkynyl alcohol **21** (120 mg, 0.25 mmol), and 4Å molecular sieves (100 mg) was stirred in dry CH_2Cl_2 (4 ml) for 30 min, and cooled to −75°C. Trimethylsilyl triflate (20 μl, 0.13 mmol) was added, and the reaction was stirred for 1.5 h at −75°C. The reaction was quenched by adding Et_3N (0.2 ml) at low temperature. The cold bath was removed and saturated aqueous $NaHCO_3$ (5 ml) was added. The mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with brine and dried. The solvent was removed under reduced pressure to give crude product, and was purified by flash silica gel chromatography (gradient elution 98:2–19:1, *n*-hexanes–EtOAc) to afford the desired glycoside **22** (0.252 g, 83%) as a white flocculent material. M.p. 50–52°C; $[\alpha]_D^{23}$ +2.5 ($CHCl_3$, C, 1.71); IR (neat): 3307, 3071, 3049, 2931, 2858, 1716, 1427, 1111, 702 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.17–7.19 (series of m, 35H), 5.83 (dq, $J = 7.4$, 2.0 Hz, 1H), 5.09 (d, $J = 7.6$ Hz, 1H), 4.82 (dd, $J = 5.2$, 2.8 Hz, 1H), 4.52 (d, $J = 3.2$ Hz, 1H), 3.85 (d, $J = 7.6$ Hz, 1H), 3.72 (dd, $J = 5.0$, 2.4 Hz, 1H), 3.50 (d, $J = 7.6$ Hz, 1H), 3.31 (app. q, $J = 6.8$ Hz, 1H), 2.36 (d, $J = 2.0$ Hz, 1H), 1.63 (d, $J = 6.8$ Hz, 1H), 1.08 (s, 9H), 0.96 (s, 9H), 0.92 (s, 9H), 0.49 (d, $J = 7.2$ Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.6, 136.1, 136.0, 135.9, 135.9, 135.8, 135.8, 133.2, 133.1, 133.0, 132.9, 132.9, 132.7, 132.6, 130.7, 130.0, 129.9, 129.8, 129.7, 128.2, 127.8, 127.8, 127.7, 127,.6, 127.5, 127.4, 104.7, 82.4, 82.0, 79.5, 79.2, 74.7, 74.3, 70.9, 64.9, 28.1, 27.0, 26.9, 26.9, 19.8, 19.2, 19.0, 18.7, 15.1; HRMS (FAB^+) Anal. Calc. for $C_{67}H_{77}ILiO_7Si_3$ [$(M + Li)^+$] 1107.3920. Found 1107.3933. Anal. Calc. for $C_{67}H_{77}IO_7Si_3$, C, 66.76; H, 6.44. Found C, 67.02; H, 6.70%.

4.6. Preparation of glycosylated alkynyl alcohol substrates *23*–*25*

4.6.1. Preparation of alkynyl alcohol (*23*)

Benzoate **22** (190 mg, 0.16 mmol) was dissolved in dry CH_2Cl_2 (2 ml) and cooled to −70°C. DIBAL-H (1 M solution in CH_2Cl_2, 395 μl, 0.4 mmol) was added at −70°C and the reaction mixture was stirred for 30 min. The reaction mixture was quenched with a −70°C

solution of EtOAc (0.5 ml) and stirred for an additional 30 min at low temperature. The mixture was then poured into a cold solution of 1M aqueous HCl (30 ml). Extractive workup (EtOAc–H_2O) and silica gel chromatography (*n*-hexanes–EtOAc, 19:1) afforded compound **23** (129 mg, 74%). $[\alpha]_D^{23}$ +18.7 ($CHCl_3$, C, 2.11); IR (neat): 3534, 3306, 3071, 3049, 2957, 2932, 2859, 1427, 1110, 1033, 703 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.79–7.23 (series of m, 30H), 5.07 (d, $J = 7.6$ Hz, 1H), 4.98 (app. dd, $J = 5.0$, 2.0 Hz, 1H), 4.48 (d, $J = 3.6$ Hz, 1H), 4.39 (app. q, $J = 6.4$ Hz, 1H), 3.73 (d, $J = 8.0$ Hz, 1H), 3.67 (br, s, 1H), 3.55 (d, $J = 3.2$ Hz, 1H), 3.35–3.30 (m, 2H), 2.39 (d, $J = 1.6$ Hz, 1H), 1.43 (d, $J = 6.0$ Hz, 1H), 1.11 (s, 9H), 1.05 (s, 9H), 0.91 (s, 9H), 0.47 (d, $J = 6.8$ Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 136.1, 135.9, 135.8, 135.7, 133.2, 132.9, 132.9, 132.6, 132.6, 132.1, 130.0, 130.0, 129.8, 129.6, 127.8, 127.8, 127.7, 127.6, 127.5, 104.7, 82.6, 81.6, 79.7, 79.1, 75.1, 74.2, 68.5, 67.5, 67.6, 28.1, 27.1, 26.9, 26.8, 19.9, 19.8, 19.2, 19.0, 18.9; HRMS (FAB^+) Anal. Calc. for $C_{60}H_{73}ILiO_6Si_3$ $[(M + Li)^+]$ 1107.3920. Found 1107.3933. Anal. Calc. for $C_{67}H_{77}IO_7Si_3$, C, 66.76; H, 6.44. Found C, 67.02; H, 6.70%.

4.6.2. Preparation of alkynyl alcohol (*24*)

Glycoside **20** (205 mg, 0.21 mmol) and imidazole (72 mg, 1.1 mmol) were dissolved in dry DMF (2 ml), and *tert*-butyldiphenylsilyl chloride (110 μl, 0.42 mmol) was added. The resulting mixture was stirred for 48 h and then quenched with water (1 ml). The reaction mixture was diluted with EtOAc (100 ml), washed with water (20 ml), brine (20 ml), dried over Na_2SO_4, and then concentrated under reduced pressure to give the crude product. The mixture was purified by silica gel chromatography (gradient elution 98:2–19:1, *n*-hexanes–EtOAc) to afford *O*-TBDPS protected product (212 mg, 83%) as a white solid. M.p. 62–64°C; $[\alpha]_D^{23}$ −6.95 ($CHCl_3$, C, 3.2); IR (neat): 3304, 3071, 2931, 2858, 1717, 1427, 1274, 1111, 1032, 702 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.77–7.19 (series of m, 35H), 5.57 (app. br. d, $J = 8.4$ Hz, 1H), 4.73 (app. d, $J = 2.8$ Hz, 1H), 4.55 (dd, $J = 6.2$, 2.0 Hz, 1H), 4.18 (dd, $J = 6.2$, 2.0 Hz, 1H), 3.88 (d, $J = 8.0$ Hz, 1H), 3.61 (app. q, $J = 6.8$ Hz, 1H), 3.48 (d, $J = 3.6$ Hz, 1H), 2.48 (d, $J = 2.0$ Hz, 1H), 1.58 (d, $J = 6.8$ Hz, 3H), 1.12 (s, 9H), 1.04 (s, 9H), 1.00 (s, 9H), 0.67 (d, $J = 6.4$ Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.6, 136.5, 136.2, 136.1, 136.1, 135.9, 135.9, 135.8, 133.1, 133.0, 132.9, 132.8, 132.7, 132.4, 130.5, 129.8, 129.7, 129.6, 129.4, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.4, 98.9, 79.8, 79.7, 78.9, 77.4, 75.6, 74.4, 72.2, 68.6, 28.2, 27.2, 27.0, 19.6, 19.0, 18.9, 14.9. HRMS (FAB^+) Anal. Calc. for $C_{67}H_{77}ILiO_7Si_3$ $[(M + Li)^+]$ 1211.4182. Found 1211.4207. The benzoate ester of this product was removed by DIBAL-H reduction as described for **23**, to provide compound **24** (192 mg, 100%). M.p. 55–60°C; $[\alpha]_D^{23}$ +27.6 ($CHCl_3$, C, 1.35); IR (neat): 3582, 3306, 3071, 3049, 2931, 1427, 1111, 701 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.76–7.75 (m, 2H), 7.73–7.71 (m, 2H), 7.55–7.53 (m, 2H), 7.49–7.48 (m, 2H), 7.43–7.20 (series of m, 22H), 5.48 (d, $J = 8.4$ Hz, 1H), 4.64 (d, $J = 3.0$ Hz, 1H), 4.55 (dd, $J = 4.2$, 2.4 Hz, 1H), 4.15 (app. q, $J = 6.6$ Hz, 1H), 3.81 (app. sextet, $J = 4.2$ Hz, 1H), 3.78 (d, $J = 8.4$ Hz, 1H), 3.60 (app. q, $J = 6.6$ Hz, 1H), 3.50 (d, $J = 3.0$ Hz, 1H), 2.66 (d, 4.2 Hz, 1H), 2.43 (d, $J = 1.8$ Hz, 1H), 1.25 (br, s, 1H), 1.23 (d, $J = 6.0$ Hz, 3H), 1.10 (s, 9H), 1.00 (s, 9H), 0.97 (s, 9H), 0.69 (d, $J = 7.2$ Hz, 3H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 136.3, 136.0, 135.9, 135.9, 135.8, 133.6, 133.0, 132.9, 132.8, 132.7, 129.9, 129.9, 129.8, 129.7, 129.7, 127.8, 127.7, 127.6, 127.6, 127.5, 98.9, 80.0, 79.9, 76.7, 74.4, 69.4, 69.1, 28.0,.27.2, 27.0, 26.9, 19.6, 19.10, 19.0, 18.9. HRMS (FAB^+) Anal. Calc. for $C_{60}H_{73}ILiO_6Si_3$ $[(M + Li)^+]$ 1107.3920. Found 1107.3866. Anal. Calc. for $C_{60}H_{73}O_6Si_3$ C, 66.75; H, 6.44. Found C, 65.63; H, 6.68%.

4.6.3. Preparation of alkynyl alcohol (*25*)

The procedure for **25** is essentially the same as described for **24** (Section 4.6.2) except *tert*-butyldimethylsilyl chloride was used instead of TBDPSCl. Thus a mixture of **20** (135 mg, 0.14 mmol), imidazole (45 mg, 0.66 mmol), *tert*-butyldimethylsilyl chloride (32 mg, 0.21 mmol), and DMF (2 ml) was stirred for 48 h to give *O*-TBS protected product (141 mg, 94%). IR (neat): 3306, 3071, 3049, 2930, 1719, 1276, 1111, 702 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.07–8.05 (m, 2H), 7.58–7.18 (series of m, 23H), 5.64 (d, $J = 8.4$ Hz, 1H), 5.61 app. sextet, $J = 7.2$, 2.4 Hz, 1H), 4.18 (dd, $J = 7.4$, 2.4 Hz, 1H, 3.92, (d, $J = 8.0$ Hz, 1H), 3.70 (app. q, $J = 7.2$ Hz, 1H), 3.50 (d, $J = 2.8$ Hz, 1H), 1.40 (d, $J = 6.8$ Hz, 1H), 1.04 (s, 9H), 1.00 (s, 9H), 0.93 (s, 9H), 0.68 (d, $J = 6.8$ Hz, 1H), 0.14 (s, 3H), 0.07 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.9, 136.1, 136.0, 135.9, 135.8, 133.1, 133.0, 132.7, 132.7, 130.6, 129.9, 129.8, 129.7, 128.2, 127.8, 127.6, 127.5, 98.8, 79.8, 79.5, 78.6, 75.43, 74.3, 72.4, 68.9, 28.4, 27.1, 27.0, 25.9, 19.6, 19.0, 18.9, 18.3, 14.1, −3.6, −4.8; HRMS (FAB^+) Anal. Calc. for $C_{60}H_{73}ILiO_6Si_3$ $[(M + Li)^+]$ 1087.3869. Found 1087.3821. The benzoate ester of this product was removed by DiBAL-H reduction as described for **23** (Section 4.6.1), to provide compound **25** (114 mg, 89%). IR (neat): 3568, 3480, 3307, 3071, 3049, 2930, 2858, 1471, 1427, 1110, 1084, 1032, 702 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.58–7.19 (series of m, 20H), 5.64 (d, $J = 8.4$ Hz, 1H), 4.72 (d, $J = 3.2$ Hz, 1H), 4.55 (d, $J = 4.0$, 2.0 Hz, 1H), 4.13 (app. quintet, $J = 6.4$ Hz, 1H), 3.88 (d, $J = 8.0$ Hz, 1H), 3.76 (d, $J = 5.6$ Hz, 1H), 3.74 (app. q, $J = 6.0$ Hz, 1H), 3.55 (d, $J = 2.8$ Hz, 1H), 2.52 (d, $J = 2.4$ Hz, 1H), 1.22 (d, $J = 6.4$ Hz, 3H), 1.04 (s, 9H), 0.99 (s, 9H), 0.92 (s, 9H), 0.74 (d, $J = 6.8$ Hz, 3H), 0.16 (s, 3H), 0.13 (s, 3H); ^{13}C-NMR (100

MHz, $CDCl_3$): δ 136.1, 136.0, 135.9, 135.8, 133.1, 132.9, 132.9, 132.6, 129.9, 129.9, 129.8, 127.8, 127.7, 127.7, 127.6, 98.8, 80.0, 79.4, 78.8, 76.8, 76.7, 76.6, 74.4, 69.7, 68.5, 28.3, 27.0, 26.9, 25.9, 19.6, 19.0, 18.9, 18.3, 18.2, −3.8, −4.6; HRMS (FAB^+) Anal. Calc. for $C_{50}H_{69}ILiO_6Si_3$ [$(M + Li)^+$] 983.3607. Found 983.3642.

4.7. Synthesis of disaccharide glycals **26**–**28** via catalytic cycloisomerization of alkynyl alcohols **23**–**25**

4.7.1. Preparation of disaccharide glycal (**26**)

The procedure described for **13** under procedure C (Section 4.2.3) was followed except 25 mol% $W(CO)_6$ loading was used. A mixture of alkynol **23** (70 mg, 64 μmol), $W(CO)_6$ (6 mg, 16 μmol), DABCO (14 mg, 0.12 mmol) and THF (1 ml) was irradiated at 350nm for 5 h. Removal of volatiles and basic silica gel (2.5% v/v SiO_2–Et_3N) chromatography afforded disaccharide **26** (46 mg, 66%) as a white solid. M.p. 46–48°C; $[\alpha]_D^{23}$ +4.8 ($CHCl_3$, C = 2.0); IR (neat): 3070, 3049, 2930, 2858, 1647, 1427, 1110, 1080, 702 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.73–7.17 (series of m, 30H), 6.23 (d, $J = 6.0$ Hz, 1H), 5.35 (d, $J = 7.6$ Hz, 1H), 4.68 (d, $J = 3.2$ Hz, 1H), 4.40 (dd, $J = 3.4$ Hz, 1H), 4.37–4.34 (app. m, 2H), 3.92 (d, $J = 7.6$ Hz, 1H), 3.86 (dd, $J = 3.8$, 3.6 Hz, 1H), 3.65 (app. q, $J = 6.8$ Hz, 1H), 3.52 (d, $J = 3.2$ Hz, 1H), 1.61 (d, $J = 6.8$ Hz, 3H), 1.08 (s, 9H), 1.05 (s, 9H), 0.96 (s, 9H), 0.68 (d, $J = 6.8$ Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 142.8, 136.1, 136.0, 135.9, 135.9, 134.5, 133.7, 133.1, 132.9, 132.8, 132.7, 129.9, 129.8, 129.7, 129.5, 127.7, 127.6, 127.5, 102.2, 101.5, 80.0, 79.6, 79.6, 74.5, 72.1, 65.8, 29.7, 29.6, 27.1, 27.0, 26.9, 19.9, 19.2, 19.0, 18.9, 17.1; HRMS (FAB^+) Anal. Calc. for $C_{60}H_{73}ILiO_6Si_3$ [$(M + Li)^+$] 1107.3920. Found 1107.3945. Anal. Calc. for $C_{67}H_{77}IO_7Si_3$, C, 66.76; H, 6.44. Found C, 67.18; H, 7.28%.

4.7.2. Preparation of disaccharide glycal (**27**)

The procedure described for **26** (Section 4.7.1) was followed. Thus a mixture of alkynol **24** (150 mg, 0.14 mmol), $W(CO)_6$ (12 mg, 34 μmol), DABCO (31 mg, 0.27 mmol) and THF (1.5 ml) was irradiated for 6 h under Ar to provide disaccharide **27** (94 mg, 62%) as a white flocculent solid. M.p. 50–54°C; $[\alpha]_D^{23}$ −11.4 ($CHCl_3$, C, 1.45); IR (neat): 3069, 2932, 1646, 1427, 1108, 702 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.72–7.22 (series of m, 30H), 6.47 (d, $J = 6.4$ Hz, 1H), 5.27 (d, $J = 8.0$ Hz, 1H), 4.93 (dq, $J = 4.8$, 1.6 Hz, 1H), 4.62 (d, $J = 3.2$ Hz, 1H), 4.13 (d, $J = 2.4$, 2.0 Hz, 1H), 3.57 (m, 1H), 1.11 (d, $J = 6.4$ Hz, 3H), 1.08 (s, 9H), 1.05 (s, 9H), 0.97 (s, 9H), 0.66 (d, $J = 7.2$ Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 144.3, 136.1, 136.0, 135.9, 135.9, 135.8, 134.2, 133.6, 133.2, 133.0, 132.9, 132.8, 129.9, 129.8, 129.6, 129.5, 127.7, 127.7, 127.6, 127.5, 101.0, 96.6, 79.5, 79.3, 74.4, 74.4, 74.4, 72.2, 71.9, 29.6, 27.1, 26.9, 19.9, 19.4, 19.0, 18.9, 16.0; HRMS (FAB^+) Anal. Calc. for $C_{60}H_{73}ILiO_6Si_3$ [$(M + Li)^+$] 1107.3920. Found 1107.3893.

4.7.3. Preparation of disaccharide glycal (**28**)

The procedure described for **26** (Section 4.7.1) was followed. Thus a mixture of alkynol **25** (90 mg, 90 μmol), $W(CO)_6$ (9 mg, 23 μmol), Et_3N (0.3 ml) and THF (1.2 ml) was irradiated for 5 h under N_2 to provide disaccharide **28** (51 mg, 61%). $[\alpha]_D^{23}$ −4.7 ($CHCl_3$, C, 1.27); IR (neat): 3070, 3050, 2930, 2858, 1647, 1427, 1111, 1076, 701 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.60–7.19 (series of m, 20H), 6.40 (dd, $J = 6.0$, 0.8 Hz, 1H), 5.29 (d, $J = 8.0$ Hz, 1H), 4.88 (dd, $J = 6.0$, 2.0 Hz, 1H), 4.76 (d, $J = 3.2$ Hz, 1H), 4.2 (dt, $J = 3.2$, 1.6 Hz, 1H), 3.90 (d, $J = 8.0$ Hz, 1H), 3.84 (app. sextet, $J = 6.4$ Hz, 1H), 3.65 (d, $J = 6.8$ Hz, 1H), 3.62 (app. q, $J = 6.8$ Hz, 1H), 3.51 (d, $J = 2.8$ Hz, 1H), 1.34 (d, $J = 6.8$ Hz, 3H), 1.04 (s, 9H), 1.02 (s, 9H), 0.90 (s, 9H), 0.22 (s, 3H), 0.10 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 144.7, 136.1, 136.0, 135.9, 135.8, 133.2, 132.9, 132.7, 129.9, 129.9, 129.8, 129.7, 127.8, 127.7, 127.6, 127.6, 99.7, 98.9, 79.9, 79.3, 75.5, 74.7, 74.4, 73.0, 30.1, 29.1, 27.1, 27.0, 25.0, 19.6, 19.0, 18.8, 18.1, 17.8, −3.2, −4.5; HRMS (FAB^+) Anal. Calc. for $C_{50}H_{69}ILiO_6Si_3$ [$(M + Li)^+$] 983.3607. Found 983.3644. Anal. Calc. $C_{50}H_{69}IO_6Si_3$ C, 61.45; H, 7.12. Found: C, 61.75; H, 7.30%.

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