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The lithiation of 2-chloroglucal derivatives

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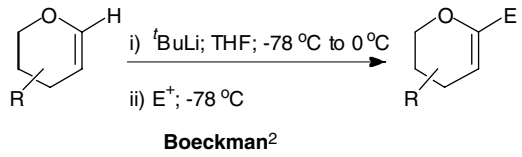
Abstract—Lithiation of 2-chloroglucal derivatives provides ready access to the corresponding 1-lithioglucals which undergo a variety of serve useful intermediates for further elaboration of the carbohydrate nucleus. Removal of the 2-chloro substituent may be affected using a Birch-type reduction.

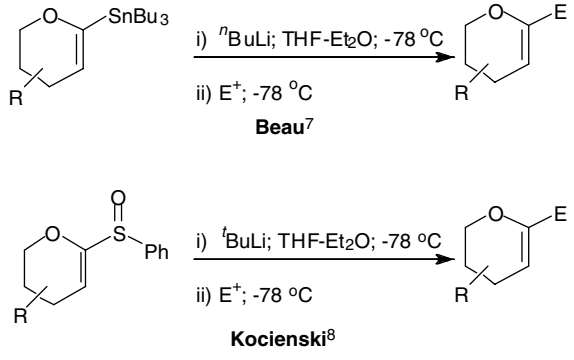
1. Introduction

1,2-Unsaturated sugars which are lithiated at C-1 are useful synthetic intermediates, however their general applicability is hampered by the routes which are currently available for their generation.[1] Whilst Boeckman's[2] lithiation procedure provides, in principle, the most direct route to these intermediates the empirical observation that these reactions may entail the use of a large excess (up to 6 equiv) of *t*-BuLi at temperatures approaching 0 °C is limiting (Scheme 1).

The capricious nature[3] of the direct lithiation of functionalized enol ethers has been amply demonstrated by a number of groups who have, for example, shown that the widely used TBDMS group may suffer competing lithiation α-to silicon[4] whereas benzyl protecting groups are susceptible to competing benzylic lithiation.[5] The successful outcome of the direct lithiation reaction is also heavily dependent upon the substitution pattern within the enol ether: in certain cases lithiation does not proceed at all and it has proven difficult to rationalize the substituent effects.[6] In order to circumvent these problems, the use of vinyl stannanes[7] and sulfoxides[8] have been developed as precursors to the desired lithiated carbohydrates. Unfortunately these stannanes are usually prepared either by the Boeckman lithiation route or via a radical reaction which, in our hands at least, proves difficult to scale-up. The preparation of lithioglycals from the corresponding sulfoxides, via a Durst–Johnson exchange reaction[9] holds much promise and provides a much needed solution to this methodological impasse (Scheme 2).



Scheme 1. Boeckman lithiation.



Scheme 2. Alternative approaches to the preparation of 1-lithioglycals.

Keywords: Glucal; Metalation; Vinyl ether; Glycal; Lithiation; Glycoside.
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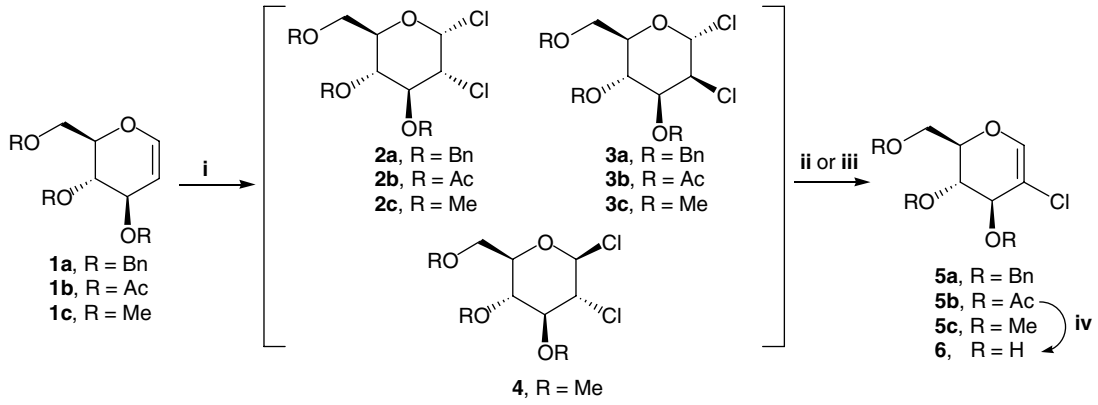
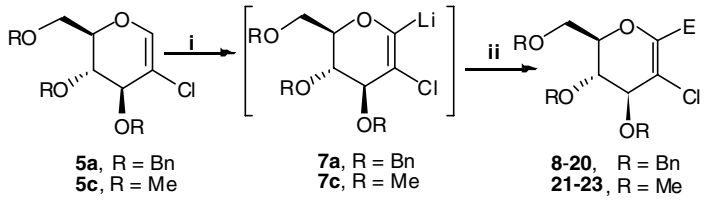


Scheme 3. Reagents and conditions: (i) SO_2Cl_2, 1.02 equiv; Et_2O; 20 °C; (ii) KOBu-*t*, 2 equiv; 20 °C; 80% overall yield; (iii) Et_3N, 1.5 equiv; CH_3CN; 70% overall yield; (iv) Na, cat.; MeOH; 20 °C; 92%.

During the course of a synthetic project we required ready access to lithiated glycals which contained potentially reactive functionality such as benzyl protecting groups. In order to meet our objectives we elected to introduce a temporary activating group at C-2 with the intention that its presence would facilitate proton abstraction at C-1 yet be readily removed at a subsequent stage in the synthetic sequence.[10] A number of reports[11] have shown that the presence of an electronegative chlorine atom has a marked effect upon the kinetic acidity of neighbouring C–H groups and in the context of our own work were mindful of earlier reports from Sclosser et al.[12] and Riobé and co-workers[13] concerning the lithiation of 4-chloro-2,3–dihydrofuran and 5-chloro-3,4-dihydro-2*H*-pyran. Having applied this underlying principle to a variant of the Dötz reaction[14] we decided to investigate the possibility of wider synthetic applications and the results of this initial study provides the basis for this letter. At the outset we required a general synthesis of 2-chloroglucals in order for their lithiation chemistry to be investigated. We have found that these substrates are readily available, on a multi-gram scale in a two step sequence involving the chlorination of glucals **1a**–**c** followed by base-promoted dehydrochlorination. Not wishing to use molecular chlorine in the initial chlorination step we report that the treatment of the glucal derivatives **1a**–**c**, with sulfurylchloride[15] in nonpolar solvents such as dichloromethane or diethyl ether at ambient temperature resulted in the rapid and quantitative conversion to the corresponding 1,2-dichloro sugars. An examination of the ^{1}H NMR spectra of the crude products from these reactions indicated that, in each case, the α-D-*gluco*pyranosyl chlorides[16] (**2a**–**c**) were the major products (^{1}H NMR: H-1 at δ 6.05–6.20 ppm; d, $J_{1,2} \approx 3.5$ Hz) although the product ratio (**2a**:**3a** = 4:1; **2b**:**3b** = 3:1) was dependent upon the nature of the oxygen protecting group. Minor products from these reactions were assigned as the α-D-*manno*pyranosyl chlorides[16] **3a**–**c** (^{1}H NMR: H-1 at δ 6.20–6.28 ppm; d, $J_{1,2} \approx 1$ Hz) and in the case of **1c** the β-D-*gluco*pyranosyl chloride **4** (^{1}H NMR: H-1 at δ 5.15 ppm, d, $J_{1,2} = 9.1$ Hz) was also produced (**2c**:**3c**:**4** = 5:1:2) (Scheme 1). Removal of the solvent used in the first step followed by dissolution of the crude dichlorides derived from **1a** and **1c** in anhydrous ether followed by the addition of potassium *t*-butoxide (2.0 equiv; 20 °C; 3 h) resulted in clean dehyrochlorination affording the chloroglucal derivatives **5a**[17] and **5c** in good overall yields (ca. 80% over two steps). In the case of the dichlorides derived from tri-acetate **1b**, the dehydrochlorination step was best accomplished using triethylamine (1.5 equiv) as a base in refluxing acetonitrile, and afforded glucal **5b**[18] in a 70% overall yield for the two-step sequence. In this particular sequence the minor α-*manno*-isomer **3b**, which was carried through from the chlorination reaction, remained essentially intact during the elimination reaction but could be easily separated from **5b** by column chromatography.[19] Triacetate **5b** is a convenient precursor to protected chloroglucal derivatives as Zemplén deacylation (MeOH; NaOMe, cat.; 20 °C; 2 h; 92%) generated the stable triol **6** which was, for example, permethylated (NaH; MeI; DMF) affording **5c** in 45% isolated yield (Scheme 3).

Having developed an operationally simple route to the preparation of chloroglucals **5a** and **5c** an investigation into their lithiation chemistry was undertaken (Scheme 4). The overall efficiency of the anion generation-trapping sequence was conveniently assayed using the preparation of the chromatographically stable silane **8** as a test reaction. Various bases were screened for the generation of **7a** whilst keeping the reaction conditions constant (THF; −78 °C), Table 1. Whereas the use of LDA was wholly ineffective in the generation of **7a**, the use of *n*-BuLi (1.1 equiv) as base did effect lithiation at C-1 and afforded **8** albeit in a poor overall yield (29%). It is to be noted that simply increasing the quantity of *n*-BuLi used in the lithiation step did not improve the overall efficiency of this sequence. We were more encouraged to observe however that the exposure of **5a** to *s*-BuLi (1.3 equiv) in THF at −78 °C for 40 min resulted in the efficient formation of **7a** which on trapping with TMSCl (1.1 equiv; −78 °C) afforded silane **8** in a 64% isolated yield. The use of 1.3 equiv of base in this reaction appeared optimal. Exchanging *s*-BuLi for *t*-BuLi (1.3 equiv; THF; −78 °C) in this particular example had a detrimental effect on the course of the reaction, resulting in the isolation of **8** in a diminished yield of 39%. Subsequent studies indicated that in most cases the choice of either *s*-BuLi or *t*-BuLi as metallating



Scheme 4. Reagents and conditions: (i) *s*-BuLi or *t*-BuLi, 1.3–1.5 equiv; THF; −78 °C; (ii) 'E^+'; THF; −78 °C.

Table 1. Generation and trapping of vinyl carbanions **7a** and **7c**

Substrate	Metallation conditions[a]	Electrophile	Product (Yield) (%)
5a	LDA (1.1 equiv)	TMS–Cl	**8**, 0
5a	*n*-BuLi (1.1 equiv)	TMS–Cl	**8**, 29
5a	*t*-BuLi (1.3 equiv)	TMS–Cl	**8**, 39
5a	*s*-BuLi (1.3 equiv)	TMS–Cl	**8**, 64
5a	*s*-BuLi (1.3)	$^nBu_3SnCl$	**9**, 67
5a	*s*-BuLi (1.3)	MeI	**10**, 67
5a	*s*-BuLi (1.3)	PhCHO	**11**, 76[b]
5a	*s*-BuLi (1.3)	C_2H_5CHO	**12**, 68[c]
5a	*s*-BuLi (1.3)	*c*-$C_6H_{10}O$	**13**, 57
5a	*s*-BuLi (1.3)	Me_2NCHO	**14**, 54
5a	*s*-BuLi (1.3)	MeOCOCl	**15**, 67
5a	*s*-BuLi (1.3)	$PhSO_2Cl$	**16**, 55
5a	*s*-BuLi (1.3)	NBS	**17**, 42
5a	*s*-BuLi (1.3)	I_2	**18**, 59
5a	*s*-BuLi (1.3)	(1*R*)-(+)-Camphor	**19**, 0[d]
5a	*s*-BuLi (1.3)	4-Cholesten-3-one	**20**, 43[e]
5c	*t*-BuLi (1.5)	c-$C_6H_{10}O$	**21**, 63
5c	*t*-BuLi (1.5)	Ph_2CO	**22**, 48
5c	*t*-BuLi (1.5)	4-Cholesten-3-one	**23**, 61[f]

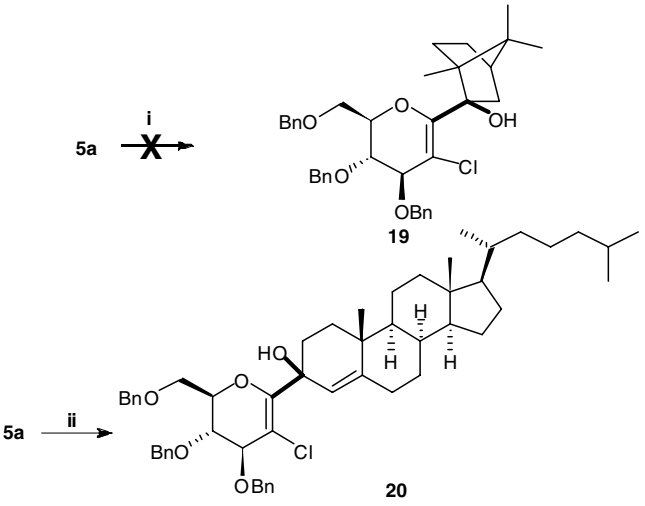
[a] All lithiation reactions were carried out at −78 °C in THF under an atmosphere of argon. The vinyl carbanions **7a** and **7c** were reacted with the appropriate electrophile at −78 °C and allowed to warm up to 0 °C before being quenched with satd. aqueous NH_4Cl.
[b] Isolated as a 2:1 mixture of diastereoisomers.
[c] Isolated as a 1.7:1 mixture of diastereoisomers.
[d] After transmetallation with $CeCl_3$.
[e] Isolated as a 5:1 mixture of diastereoisomers.
[f] Isolated as a single diastereoisomer after column chromatography.

agent in THF at −78 °C has little effect upon product yield and it appears that under these reaction conditions kinetic deprotonation at C-1 is observed rather than at the potentially reactive benzylic/allylic sites.[†]

Subsequent investigations have shown that the alkylation of **7a** proceeds smoothly with a range of electrophiles at temperatures between −78 °C and −20 °C in THF as solvent, Table 1. Reaction with enolizable substrates (cyclohexanone, propanal) is generally observed to proceed in fair overall yields although reaction with (1*R*)-(+)-camphor was wholly unsuccessful, and afforded none of adduct **19**, even after transmetallation with Ce(III) (Scheme 5).[20]

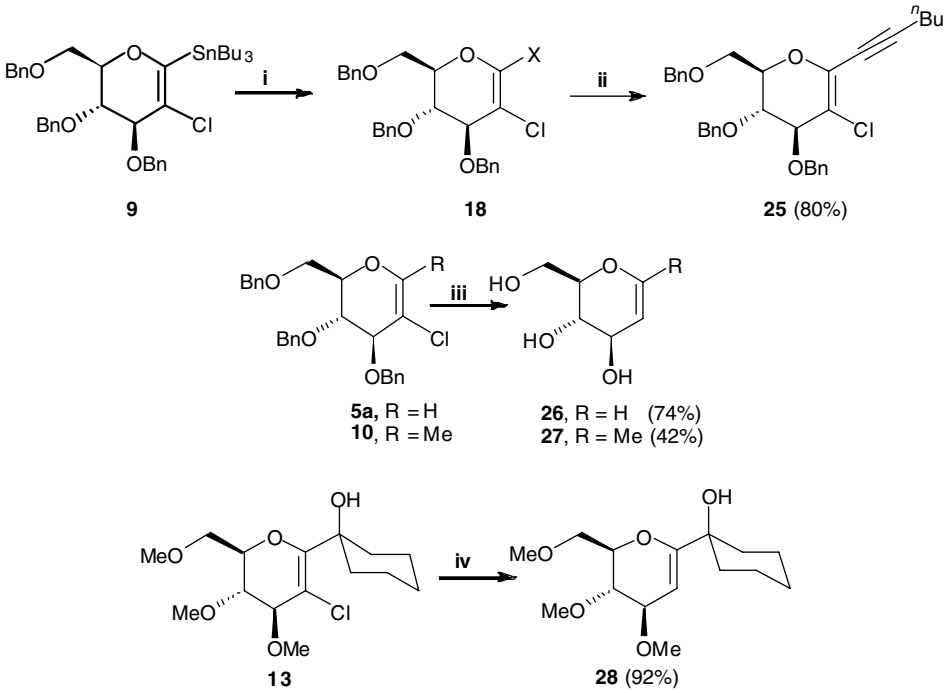
Alkylation with α,β-unsaturated ketones such as 4-cholesten-3-one proceeded in a 1,2-sense, affording adduct **20** in a moderate isolated yield (43%) with reasonable levels of facial selectivity[21] (α:β attack ≈ 5:1). Introduction of a halogen at C-1 is also possible by direct trapping of **6a** with $PhSO_2Cl$,[22] NBS or molecular iodine[23a] (Scheme 4, E = Cl, Br and I, respectively). Alternatively the exposure of stannane **9** to iodine[23b] (1.0 equiv) in CH_2Cl_2 at 20 °C provides a complimentary route to iodide **18**, itself a stable crystalline solid, in an excellent yield (91%). Whereas stannane **9** appears not participate in simple Stille coupling reactions iodide **18** is a suitable partner for such reactions. For example, palladium catalyzed coupling of iodide **18** with stannane **24** [**24**, 1.1 equiv; $Pd(PPh_3)_4$, 2 mol %; toluene; 110 °C] affords alkyne **25** in an excellent isolated yield (80%), Scheme 6. The choice of reaction conditions/partner is pivotal to the outcome of this coupling reaction as the bromide **17** afforded the acetylene **25** in very low yield (8%) under identical conditions whilst attempted coupling of the iodide **18** with 1-hexyne using Alami's conditions[24] was completely ineffective.

Lithiation of glucal **5c** was also observed to occur readily (*t*-BuLi, 1.3–1.5 equiv; THF; −78 °C; 30 min) affording a stable anion which underwent alkylation reactions between −78 °C and −20 °C, Table 1. Although an extensive study of the trapping reactions of anions such as **6a** and **6b** has yet to be carried out, it is clear that this methodology enables access to a range of functionalized 2-chloroglucals and at this stage the question arose as to the removal of the activating 2-chloro-substituent.



Scheme 5. Reagents and conditions: (i) a. *s*-BuLi, 1.3 equiv; THF; −78 °C; b. $CeCl_3$; THF; −78 °C; c. (1*R*)-(+)-camphor, 1.1 equiv; THF; −78 °C to 0 °C and (ii) a. *s*-BuLi, 1.3 equiv; THF; −78 °C; b. 4-cholesten-3-one, 1.1 equiv; −78 °C; c. $NH_4Cl_{(aq)}$; THF; −78 °C; 43%.

[†] The addition of *s*-BuLi or *t*-BuLi to a solution of **5a** in THF at −78 °C generates a red-coloured reaction mixture presumably due to the generation of a low concentration of a highly delocalized anion, most reasonably the result of benzylic deprotonation.



Scheme 6. Reagents and conditions: (i) I_2, 1.0 equiv, CH_2Cl_2; 20 °C; 91%; (ii) *n*-Bu–C≡C–Sn(Bu-*n*)$_3$, **24**, 1.1 equiv; $Pd(PPh_3)_4$, 2 mol %, toluene; 110 °C; 80%; (iii) Na, 12 equiv; EtOH, 12 equiv; $NH_{3(l)}$; −78 °C and (iv) Na, 4 equiv; $NH_{3(l)}$; −33 °C.

Following Schlosser's precedent[12] we elected to effect this transformation using a Birch-type dissolving metal reduction and were delighted to observe, in a model study, that exposure of **5a** to sodium (12 equiv) in liquid ammonia containing ethanol (12 equiv) at −78 °C for 1 h afforded the fully deprotected sugar **26** in 74% yield. Similarly, the 1-methyl derivative **10** underwent global deprotection and dechlorination to **27** in 42% overall yield. Dechlorination of the alcohol **13** also proceeded cleanly, this time at −33 °C (Na, 4 equiv; THF; $NH_{3(liq)}$), affording glucal **28** in a 92% isolated yield, Scheme 6.

In conclusion the methodology described herein demonstrates that readily available 2-chloroglucal derivatives undergo lithiation at C-1 enabling the facile preparation of variety of 2-chloroglucals, which may be of some biological interest in their own right.[18a,25] The acidifying effect of the chlorine substituent is pronounced enough to allow the use of the prototypical, yet base sensitive, benzyl protecting group in such reaction sequences. Furthermore, given the recent advances in the use of vinyl chlorides as 'electrophilic' partners in palladium catalyzed cross-coupling reactions,[26] the synthesis of 1,2-disubstituted glucal derivatives may be considered as a possibility from these intermediates. Finally removal of the temporary activating C-2 chlorine substituent can be readily achieved using Birch-type reductions.

2. Representative experimental procedures

2.1. Preparation of 5a

To a solution of tri-O-benzyl-D-glucal **1a** (7.613 g, 18.3 mmol) in Et_2O (50 mL) at 20 °C under Ar was slowly added sulfuryl chloride (1.5 mL, 18.7 mmol) and the reaction mixture stirred for 10 min. The reaction mixture was sparged with Ar and solid potassium *tert*-butoxide (4.012 g, 35.8 mmol) was added and this mixture was then stirred at 20 °C for 3 h. The solvent was removed in vacuo and the resultant orange oil purified (flash silica, 5% EtOAc/petrol eluent) to afford **5a** as a flaky yellow solid (6.511 g, 79%), mp 31–35 °C, no observable optical rotation. ^{1}H NMR, δ (ppm): (300 MHz, $CDCl_3$) 7.45–7.30 (15H, m, Ar); 6.70 (1H, s, H-1); 4.78–4.62 (4H, m, 2 × CH_2Ar); 4.59 (2H, s, CH_2Ar); 4.33 (1H, m, H-5); 4.14 (1H, d, $J = 4.0$ Hz, H-3); 4.00 (1H, apparent t, $J = 5.0$ Hz, H-4); 3.83 (1H, dd, $J = 10.5$, 6.0 Hz, H-6a); 3.74 (1H, dd, $J = 10.5$, 4.0 Hz, H-6b); ^{13}C NMR, δ (ppm): (75 MHz, $CDCl_3$) 142.5, 137.9, 137.8, 137.6, 128.6, 128.5, 128.0, 127.9, 127.8, 110.0, 76.5, 76.4, 73.8, 73.5, 72.8, 72.5, 67.8. IR, ν_{max} (cm^{-1}): 3064(w), 3031(w), 2906(w), 2867(w), 1649(w), 1496(w), 1454(m), 1364(w), 1207(w), 1179(m), 1098(s), 1072(s), 1028(m), 738(m), 698(s). MS: (CI, NH_3, $C_{27}H_{27}O_4{}^{35}Cl$, ($M^+ = 450$) 468 ($[M+NH_4]^+$, 100%); 360 ($[M-Bn]^+$, 51%); 343 ($[M-OBn]^+$, 44%); MM: (CI, $C_{27}H_{31}NO_4{}^{35}Cl$, $[M+NH_4]^+$) requires 468.1941; found 468.1945.

2.2. Preparation of silane 8

To a solution of 3-chloro-tri-*O*-benzyl-D-glucal **5a** (0.18 g, 0.42 mmol) in dry THF (5 mL) at −78 °C under Ar was added *sec*-butyllithium (0.4 mL, 1.3 M solution in cyclohexane, 0.52 mmol) and the deep red mixture stirred at this temperature for 40 min. Chlorotrimethylsilane (33 μL, 0.43 mmol) was then added and the reaction mixture stirred at −78 °C for a further 20 min before being quenched with saturated $NH_4Cl_{(aq)}$ solu-

tion (5 mL) and was then allowed to warm to room temperature. The solution was diluted with Et_2O (5 mL), then the aqueous phase separated and extracted with Et_2O (5 mL), the organic extracts combined, washed with brine (5 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and the resultant orange oil was purified (flash silica, 5% EtOAc in petrol 40/60 eluent), affording **8** as a clear oil (0.133 g, 64%), $[\alpha]_D = +25.7$ (*c* 0.028, EtOH). ^{1}H NMR, δ (ppm): (300 MHz, $CDCl_3$) 7.45–7.35 (15H, m, Ar); 4.77 (2H, apparent t, $J = 11.5$ Hz, CH_2Ar); 4.69 (2H, apparent t, $J = 11.5$ Hz, CH_2Ar); 4.60 (2H, s, CH_2Ar); 4.20 (1H, d, $J = 5.0$ Hz, H-3); 4.16 (1H, m, H-5); 4.04 (1H, dd, $J = 7.0$, 5.0 Hz, H-4); 3.82 (2H, m, C-6 CH_2); 0.35 (9H, s, 3 $SiMe_3$); ^{13}C NMR, δ (ppm): (75 MHz, $CDCl_3$) 157.8; 138.3, 138.0; 128.5; 128.4; 128.2; 128.0; 127.9; 127.8; 127.6; 127.5; 120.0; 78.6; 76.8; 74.2; 73.5; 73.0; 72.1; 66.3; −1.6; IR, ν_{max} (cm^{-1}): (TF) 3063(w); 3031(w); 2953(w); 2899(w); 2866(w); 1730(w); 1496(w); 1454(m); 1364(w); 1250(m); 1156(m); 1087(s); 1074(s); 1027(m); 846(s); 736(m); 697(s); MS: (CI, NH_3, $C_{30}H_{35}O_4Si^{35}Cl$, MW = 522) 540 ($[M+NH_4]^+$, 56%); 522 (M^+, 9%); 450 ($[M-SiMe_3]^+$, 19%); 415 ($[M-OBn]^+$, 83%); MM: (CI, $C_{30}H_{35}NO_4Si^{35}Cl$, $[M+NH_4]^+$) requires 540.2327; found 540.2327.

Acknowledgements

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