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Remote 1,5-stereoinduction in boron aldol reactions of methyl ketones: application to the convergent assembly of the 1,3-polyol sequence of (+)-roxaticin

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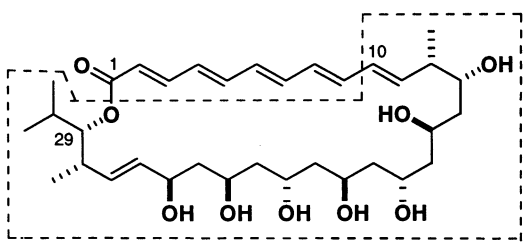
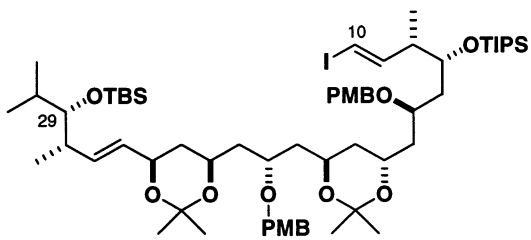
Abstract—By exploiting 1,5-*anti* stereoinduction in the boron aldol coupling of the β-alkoxy methyl ketones **6** and **8** with aldehydes **7** and **9**, the convergent synthesis of **2**, corresponding to the fully protected polyol sequence of the 30-membered macrolide, (+)-roxaticin (**1**), was achieved in an efficient manner (15 steps and 24.0% yield from ketone **15**).

As potent antifungal agents, the polyene macrolides constitute an important class of polyketide metabolites.[1] Their highly oxygenated structures have stimulated synthetic efforts towards the development of general approaches to the asymmetric construction of stereodefined 1,3-polyols.[2] In the case of roxaticin (**1**), a 30-membered macrolide first isolated from a cultured soil streptomycete by Maehr et al. at Roche in 1989,[3] total syntheses have been completed by the Rychnovsky (*ent*-**1**) and Mori groups.[4] By using boron aldol reactions[5] for achieving remote acyclic stereocontrol, we now report an expedient synthesis of the C_{10}–C_{29} subunit **2**, which comprises the full 1,3-polyol sequence of (+)-roxaticin containing all ten stereocentres.

The boron-mediated aldol reaction of chiral ketones is now well established as a powerful tool for polyketide synthesis. However, due to the lower stereoselectivities observed in the aldol reactions of methyl versus ethyl ketones, application to acetate-derived polyketides usually requires reagent control using chiral ligands on boron.[5] A notable exception is the aldol reaction of certain β-alkoxy methyl ketones with aldehydes, as in **3**→**4**→**5** in Scheme 1, which are found to proceed with remarkably high levels of 1,5-*anti* stereoinduction under substrate control.[6,7] Access to stereodefined 1,3,5-triol sequences,[6] as found in the polyene macrolides, can then be realised by suitable reduction (3,5-*syn* or *anti*) of the β-hydroxy ketones **5**.



1: *(+)-Roxaticin*



2: *1,3-Polyol subunit*

Keywords: roxaticin; boron aldol; macrolide; antifungal; remote stereoinduction.

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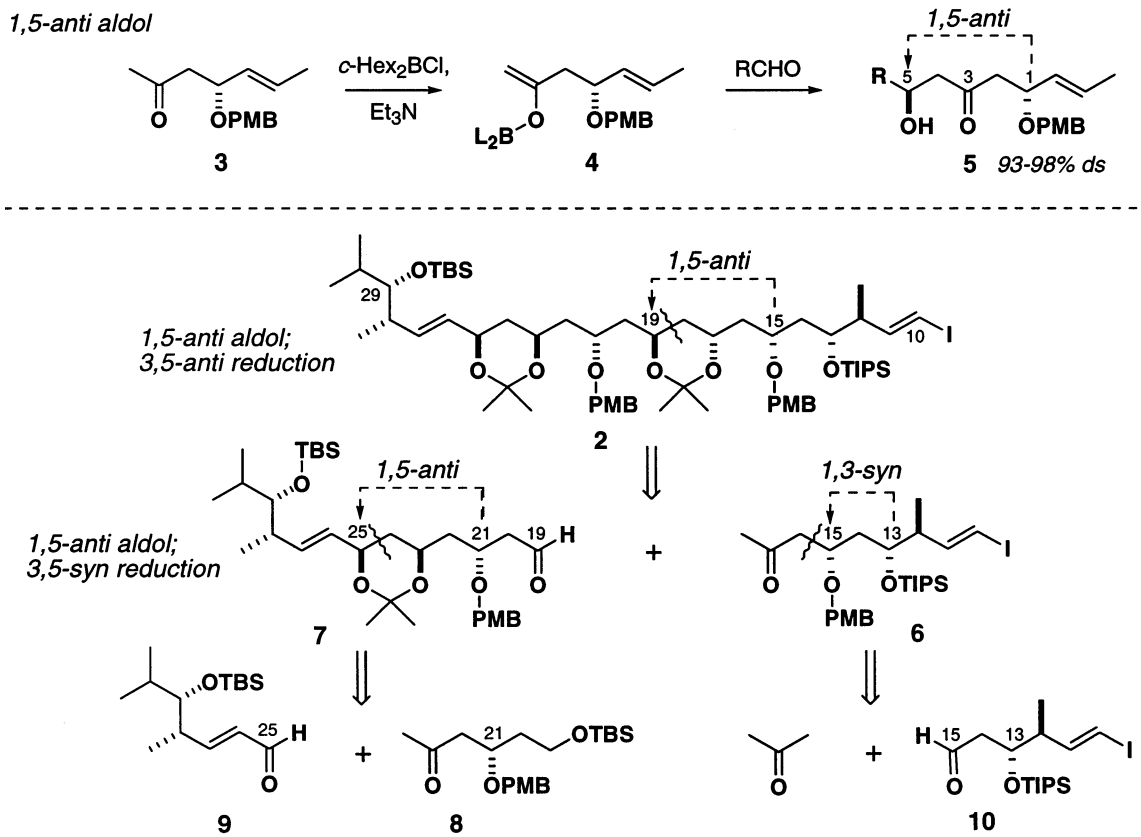
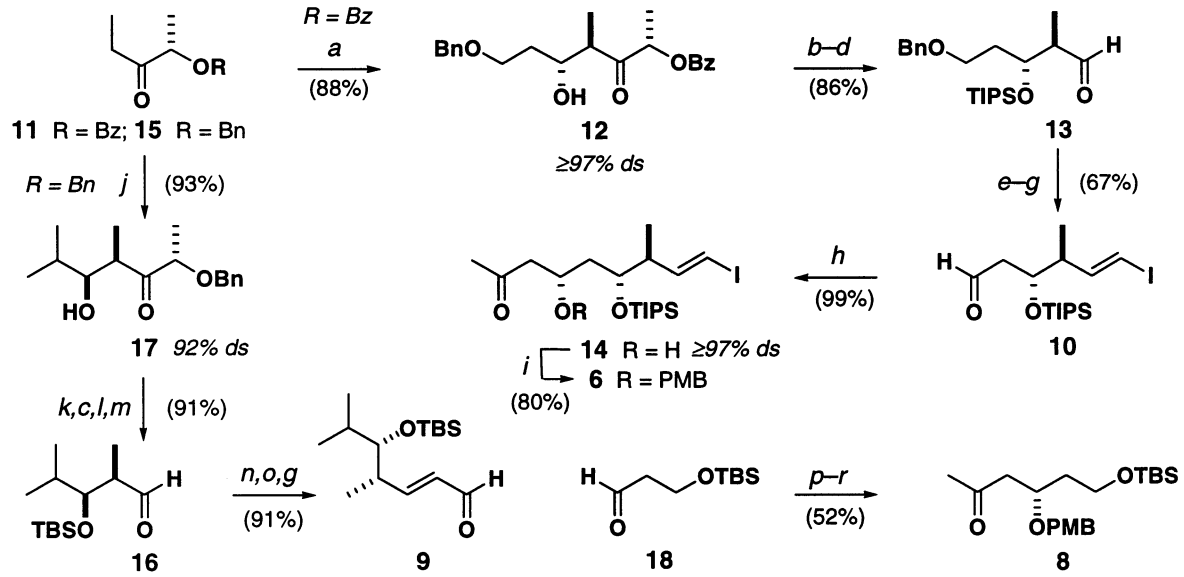
A convergent synthesis of the 1,3-polyol subunit **2** for (+)-roxaticin was planned, following the route outlined in Scheme 1. The pivotal 1,5-*anti* aldol reaction was intended to be used twice, i.e. for the coupling of the simpler fragments **6** with **7** and **8** with **9**. To ensure a useful level of 1,5-stereoinduction, suitable protecting groups, such as PMB (by analogy with **3**), for the C_{15} and C_{21} hydroxyls were incorporated into the methyl ketones **6** and **8**, respectively. Following our synthetic studies on spongistatin, we planned to prepare the methyl ketone **6** using a 1,3-*syn* aldol reaction of acetone with the β-siloxy aldehyde **10**.[6b]

The preparation of the three key subunits **6**, **8** and **9** is outlined in Scheme 2.[8] Following standard conditions,[9a,b] the boron aldol reaction (*c*-Hex_2BCl, Me_2NEt) of the lactate-derived[9b] ketone **11** with 3-(benzyloxy)propanal proceeded with ≥97% ds, giving the *anti* adduct **12** (88%). Protection as a TIPS ether, followed by $LiAlH_4$ reduction and oxidative glycol cleavage with $Pb(OAc)_4$ then gave **13** (86%). Next, the vinyl iodide was introduced (*E*:*Z*=96:4) by Takai olefination[10] using CHI_3 and $CrCl_2$, followed by debenzylation ($BCl_3{\cdot}SMe_2$)[11] and Dess–Martin oxidation to produce aldehyde **10** (67% from **13**). Using (–)-Ipc_2BCl and Et_3N,[12] the aldol addition of acetone to **10** proceeded with ≥97% ds to give 1,3-*syn* adduct **14** (99%). As expected,[6b] the moderate 1,3-stereoinduction from the β-siloxy aldehyde **10** is reinforced here by the chiral boron reagent. Protection as the PMB ether then gave the required C_{10}–C_{18} subunit **6** (80%). The enal **9**, incorporating C_{25}–C_{29}, was obtained using the complementary *syn* aldol chemistry[9a,c] of the ketone **15**, having a benzyl ether in place of the benzoate. Thus, the *syn*-configured aldehyde **16** was readily prepared from the aldol adduct **17**, followed by chain extension[4a] to produce **9** (91%). The final C_{19}–C_{24} subunit, i.e. methyl ketone **8**, was obtained in 95% ee by Brown allyboration of aldehyde **18** using *B*-allylbis(2-isocaranyl)borane,[13] followed by PMB protection and Wacker oxidation of the alkene.

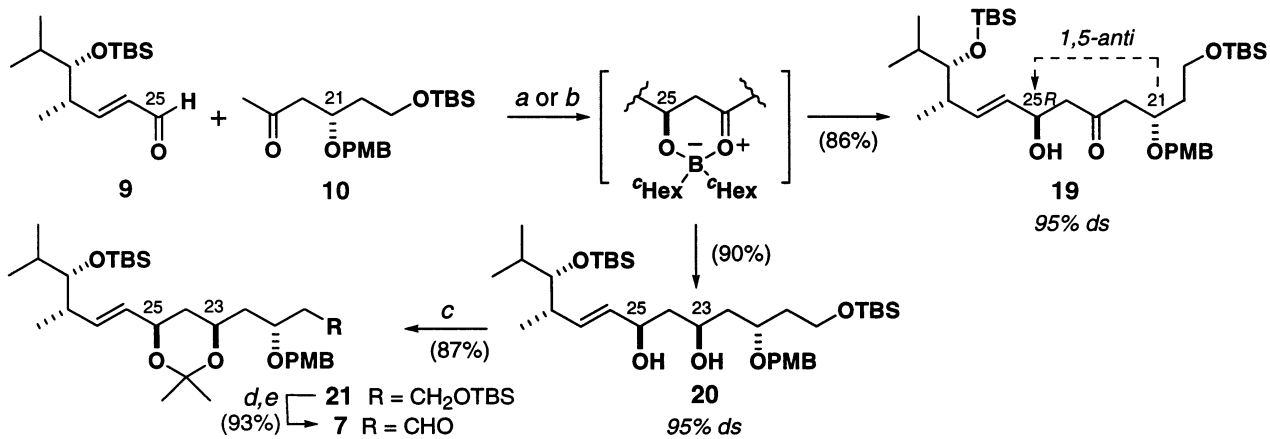
The controlled aldol coupling of the three subunits, followed by suitable manipulation was now addressed. In the first 1,5-*anti* coupling step between equimolar amounts of **8** and **9** (Scheme 3), use of *c*-Hex_2BCl and Et_3N led, after oxidative work-up, to the adduct **19** with 95% ds in 86% yield. By combining this step with an in situ reduction[6a,14] of the intermediate dicyclohexylboron aldolate using $LiBH_4$, the C_{23} and C_{25} stereocentres could be introduced efficiently, generating the 1,3-*syn* diol **20** (95% ds) in 90% yield. The C_{25} configuration was established as (*R*) by ^1H NMR spectroscopy (through use of the advanced Mosher method[15] on the (*R*)- and (*S*)-MTPA esters of **19**), while that at C_{25} was determined in turn by ^{13}C NMR analysis[16] of the acetonide **21**. Selective deprotection of the primary TBS ether in **21** with TBAF was then followed by Swern oxidation to give aldehyde **7** (93%).



Scheme 1. Retrosynthetic analysis based on identification of 1,5-*anti* stereorelationships in **2**.

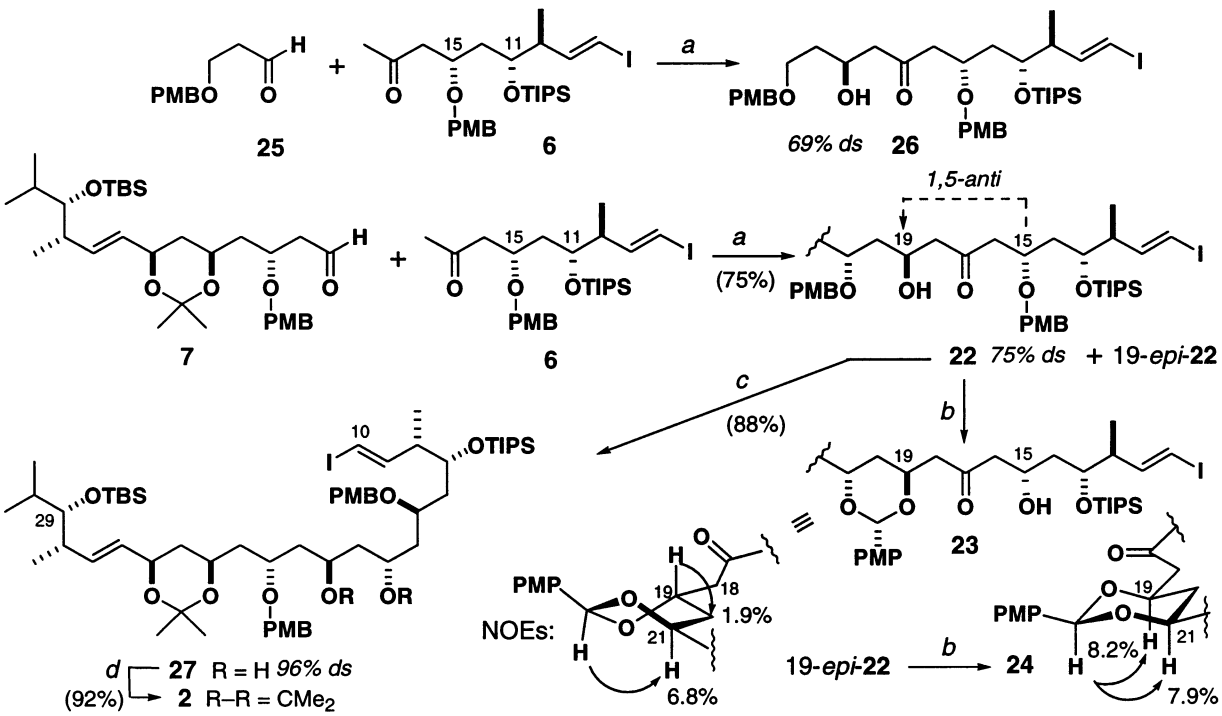


Scheme 2. Reagents and conditions: (a) *c*-Hex_2BCl, Me_2NEt, Et_2O, 0°C, 2 h; $BnOCH_2CH_2CHO$, −78→−20°C, 16 h; H_2O_2, MeOH, pH 7 buffer; (b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78→0°C, 3 h; (c) $LiAlH_4$, −78→0°C, 3 h; (d) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, 0.5 h; (e) CHI_3, $CrCl_2$, THF, dioxane, 8 h; (f) $BCl_3{\cdot}SMe_2$, CH_2Cl_2, 45 min; (g) Dess–Martin periodinane, CH_2Cl_2, 1–3 h; (h) Me_2CO, (−)-Ipc_2BCl, Et_3N, Et_2O, 0°C, 35 min; **10**, −78°C, 1 h; H_2O_2, MeOH, pH 7 buffer; (i) PMB–TCA, cat TfOH, Et_2O, 0°C, 3 h; (j) *c*-Hex_2BCl, Et_3N, Et_2O, −78→0°C, 80 min; *i*-PrCHO, −78→−20°C, 16 h; H_2O_2, MeOH, pH 7 buffer; (k) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78°C, 1 h; (l) H_2, $Pd(OH)_2$/C, EtOAc, 1 h; (m) $NaIO_4$, aq. MeOH, 40 min; (n) $Ph_3P{=}CHCO_2Me$, MeCN, 84°C, 20 h; (o) DIBAL, Et_2O, −78→20°C, 1.5 h; (p) $(2\text{-}^{d}Icr)_2Ballyl$, Et_2O, −78°C, 3 h; H_2O_2, NaOH; (q) PMB–TCA, Ph_3CBF_4,THF, 0°C, 16 h; (r) $PdCl_2$, CuCl, O_2, aq. DMF, 25 h.



Scheme 3. Reagents and conditions: (a) *c*-Hex_2BCl, Et_3N, Et_2O, 0°C, 10 min; **9**, −78→−20°C, 18 h; H_2O_2, MeOH, pH 7 buffer; (b) *c*-Hex_2BCl, Et_3N, Et_2O, 0°C, 10 min; **9**, −78→−20°C, 18 h; $LiBH_4$, 2 h; H_2O_2, MeOH, pH 7 buffer; (c) $(MeO)_2CMe_2$, PPTS, CH_2Cl_2, 16 h; (d) TBAF, THF, 1.5 h; (e) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, 30 min; Et_3N, −78→0°C, 1 h.

In the more challenging, second 1,5-*anti* aldol coupling (Scheme 4), enolisation of ketone **6** with *c*-Hex_2BCl and Et_3N, followed by addition of aldehyde **7**, gave the desired adduct **22** (75% ds), along with 19-*epi*-**22**. After chromatographic separation, the major adduct **22** was isolated in 53% yield. By treatment of each of the aldol products with DDQ, the formation of the corresponding PMP acetals, with concomitant deprotection of the C_{15} PMB ether, was achieved.[17] Subsequent NOE analysis of **23**, along with the 19-*epi* system **24**, enabled the unambiguous assignment of the C_{19} configuration arising from the aldol coupling. In the analogous reaction of methyl ketone **6** with the simple aldehyde **25**, the 1,5-*anti* adduct **26** was obtained in 69% ds, while aldehyde **7** showed low selectivity (61% ds) in reaction with the dicyclohexylboron enolate of acetone. Therefore, we attribute the moderate 75% ds achieved in the formation of **22** (cf. **9**+**10**→**19** in 95% ds) to a reduced level of 1,5-stereoinduction from the ketone component **6** (as opposed to a mismatched coupling situation). This may be a consequence of steric congestion, arising from the bulky C_{11} TIPS ether, adversely affecting the conforma-



Scheme 4. Reagents and conditions: (a) *c*-Hex_2BCl, Et_3N, Et_2O, 0°C, 10 min; **7** or **25**, −78→−20°C, 16 h; H_2O_2, MeOH, pH 7 buffer; (b) DDQ, CH_2Cl_2, pH 7 buffer, 6 h; (*c*) $Me_4NBH(OAc)_3$, MeCN, AcOH, −30→20°C, 18 h; (d) $(MeO)_2CMe_2$, PPTS, CH_2Cl_2, 15 h.

tion of the stereodirecting PMB ether at C_{15}. In comparison, the corresponding lithium and Mukaiyama aldol reactions of **6** with **7** gave much poorer stereoselectivity for **22**.

Finally, a hydroxyl-directed reduction of aldol adduct **22**, employing $Me_4NBH(OAc)_3$,[18] led to the 1,3-*anti* diol **27** with 96% ds, which was transformed into the bis-acetonide **2**[8] in 81% overall yield (allowing confirmation of the stereochemistry by ^{13}C NMR analysis[16]). This contains all ten stereocentres of the 1,3-polyol sequence of (+)-roxaticin, with a vinyl iodide appended at C_{10} for a subsequent Pd-mediated coupling to introduce the polyene unit and close the macrolide ring.

In summary, the asymmetric synthesis of bis-acetonide **2**, corresponding to the fully protected 1,3-polyol sequence for (+)-roxaticin (**1**) and containing all ten stereocentres, has been achieved in 15 steps and high overall yield (24.0%) from ketone **15** (three steps from ethyl (*S*)-lactate[9a]). By exploiting the 1,5-*anti* boron aldol coupling protocol, a convergent synthesis using equimolar amounts of the individual subunits **6**, **8** and **9** was realised. Further studies are underway to explore the generality and origin of these, and other, remote induction effects in boron aldol reactions.[19]

Acknowledgements

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8. All new compounds gave spectroscopic data in agreement with the assigned structures. **2** had: $[\alpha]_D^{20}$ −22.5 (*c* 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (2H, d, J=8.6 Hz, ArH), 7.23 (2H, d, J=8.7 Hz, ArH), 6.88

(2H, d, J=8.6 Hz, ArH), 6.87 (2H, d, J=8.7 Hz, ArH), 6.53 (1H, dd, J=14.5, 8.5 Hz, H_{11}), 5.86 (1H, d, J=14.5 Hz, H_{10}), 5.64 (1H, dd, J=15.6, 8.0 Hz, H_{27}), 5.39 (1H, dd, J=15.6, 6.4 Hz, H_{26}), 4.50 (1H, d, J=10.6 Hz, OCH_AH_BAr), 4.47 (1H, d, J=11.4 Hz, OCH_AH_BAr), 4.46 (1H, d, J=10.6 Hz, OCH_AH_BAr), 4.28–4.34 (1H, m, H_{25}), 4.29 (1H, d, J=11.4 Hz, OCH_AH_BAr), 3.99–4.14 (2H, m, H_{15}, H_{23}), 3.92–3.98 (1H, m, H_{21}), 3.81–3.90 (1H, m, H_{13}), 3.80 (3H, s, OMe), 3.80 (3H, s, OMe), 3.75–3.82 (1H, m, H_{19}), 3.42–3.52 (1H, m, H_{17}), 3.27 (1H, dd, J=4.9, 4.9 Hz, H_{29}), 2.27–2.36 (1H, m, H_{28}), 2.10–2.18 (1H, m, H_{12}), 1.88–1.96 (1H, m, H_{20A}), 1.70–1.80 (2H, m, H_{20B}, H_{30}), 1.25–1.70 (10H, m, H_{14}, H_{16}, H_{18}, H_{22}, H_{24}), 1.46 (3H, s, OC(Me)(Me)O), 1.42 (3H, s, OC(Me)(Me)O), 1.38 (3H, s, OC(Me)(Me)O), 1.36 (3H, s, OC(Me)(Me)O), 1.06 (21H, s, $Si(CHMe_2)_3$), 1.06 (3H, d, *obscured*, C_{12}-Me), 0.98 (3H, d, J=6.8 Hz, C_{28}-Me), 0.91 (9H, s, $SiCMe_3$), 0.88 (3H, d, J=6.9 Hz, C_{30}-Me_A), 0.84 (3H, d, J=6.7 Hz, C_{30}-Me_B), 0.03 (6H, s, $SiMe_2$) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.2, 159.1, 148.1, 136.2, 131.0, 130.8, 129.5, 129.4, 129.2, 113.9, 113.6, 100.2, 98.5, 80.9, 74.9, 72.3, 72.1, 71.9, 71.8, 70.2, 69.8, 65.2, 63.4, 63.3, 55.3 (×2), 44.7, 42.9, 42.3, 40.6 (×2), 40.2, 39.3, 37.7, 31.6, 30.4, 26.2 (×2), 25.2, 20.5, 20.0, 18.4, 18.3, 17.7, 16.6, 15.9, 12.9, −3.5, −3.8 ppm; HRMS (+ESI) calcd for $C_{62}H_{105}O_{10}NaSi_2I$ $[M+Na]^+$ 1215.6183, found 1215.6091.

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