Toward the Synthesis of Reidispongiolide A: An Improved Stereocontrolled Synthesis of the C23-C35 Fragment of Reidispongiolide A

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Abstract: An improved synthesis of the C23-C35 moiety of reidispongiolide A has been completed. An intermolecular Nozaki-Hiyama-Kishi coupling was employed for the union of C23-C30 and C31-C35 fragments. A discussion on the factors influencing the stereochemical outcome of (*E*)-crotylboration reactions of α-methyl-β-alkoxy aldehydes is also presented.

Keywords: Reidispongiolide, antitumoral macrolides, asymmetric synthesis, diastereoselectivity, crotylboration.

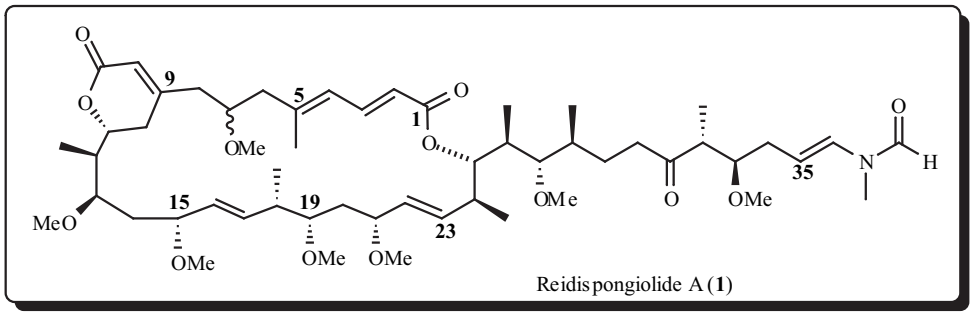
1. INTRODUCTION

We recently reported [1] the stereocontrolled synthesis of **8a,** (Fig. **1**), the C23-C35 portion of the sphinxolide/ reidispongiolide family [2, 3] of antimitotic marine macrolides.

This fragment, besides representing an advanced intermediate for our long-standing, ultimate goal of accomplishing the total synthesis of reidispongiolide A (**1**), proved particularly useful for the stereochemical analysis of the parent natural products. Further elaboration of **8a** to the corresponding polyol fragment [4], allowed the determination of the relative and absolute configuration of all seven stereocentres contained in this moiety, by comparison of its NMR data with the same fragment obtained by chemical degradation of reidispongiolide A (**1**) [5]. Once the problem of the configurational assignment was solved, we moved on to a large-scale preparation of C23-C35 fragment **17** to tackle the total synthesis of **1**.

To this end, we had to address two main problems encountered in our previous synthetic approach. First, the diastereoselectivity attained upon formation of the C27-C28 propionate unit in **6** called for improving. Moreover, an alternative procedure to effect the coupling between the C23-C29 (**6**) and C30-C35 (**7**) units was highly desirable, due to the significant extent of C28 epimerization observed upon scale-up of the Horner-Wadsworth-Emmons coupling protocol, giving rise to a mixture of **8a** and **8b**. In view of the pressing need of an efficient synthetic route to **8**a for pursuing more challenging projects and taking in due account all the above considerations, we set to refine our synthetic approach.

In this paper we report on our study aimed to improving the stereocontrolled synthesis of the C23-C35 fragment (**17)** of reidispongiolide A (**1**) featuring, as key step, a Nozaki-Kishi coupling of the vinyl iodide **14** and the aldehyde **15**



Reidispongiolide A (**1**)

units. This work also provides insights into practical stereochemical issues of the *E*-crotylboronation reaction of α-methyl-β-alkoxy-aldehyde derivatives.

2. RESULTS AND DISCUSSION

Previously [1], we reported that the addition of Brown's $^{d}Ipc_2$B-(*E*)-crotylboronate **3** to the aldehyde **2** gave the adducts **4** and **5** in a 3:7 ratio favoring the undesired product with 3,4 *anti*-4,5-*syn* configuration. This result may appear quite puzzling because Brown's crotylboration has usually been referred to give excellent levels of reagent control in the stereocontrolled addition of allylic groups to aldehydes, with a diastereoselectivity exceeding that displayed by other chiral crotyl reagents [6].

The double asymmetric crotylboronation of α-methyl chiral aldehydes has extensively been studied by Roush and co-workers [7], and it is well established that in tartrate-

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modified *E*-crotylboronation, the preparation of polypropionate substructures with branching methyl groups in a 1,3-*syn* relationship represents a case of mismatched reaction.

However, Roush's group reported that the tartrate-modified (*E*)-crotylboronate reaction on a substrate very similar to the aldehyde **2** proceeded with a satisfactory level of reagent control leading to 73:27 ratio of the expected 3,4 *anti*-4,5 *anti* adduct [7].

In order to investigate the factors influencing the relative extent of reagent and substrate control in the *E*-crotylboronation reactions of α-methyl-β-alkoxy aldehydes, we compared the stereochemical outcome of Roush and Brown asymmetric (*E*)-crotylboronations on aldehydes **2** and **10** [8] differing for the stereochemistry of the β-alkoxy group.

As summarized in Table **1**, the reaction of aldehyde **2** with ^{l}Ipc$_2$-**3** and (*S*,*S*)-**9** produced the Felkin adduct **5** with excellent selectivity, whereas the reactions with ^{d}Ipc$_2$-**3** and (*R*,*R*)-**9**, as expected, gave lower level of diastereoselectivity, favoring in one case the Felkin adduct **5** (entry 2) and in the other the anti-Felkin adduct **4** (entry 3). The question of a divergent stereochemical outcome in crotylation reactions between the chiral aldehyde **2** and the tartrate-ester-modified crotylboronate versus Brown's reagent is quite surprising, even if a case of opposite diastereoselectivity between Roush's and Brown's reagents was recently observed on α-amino aldehyde derivatives [9]. When we tested the same kind of additions on the aldehyde **10,** we observed in all cases that the formation of the Felkin adduct **12** [10] is intrinsically favored. In the latter case, the configurational pattern of the substrate was so relevant in asymmetric induction to override the expected effect of the chiral auxiliary (entries 6 and 7, mismatched cases). Comparison of the results obtained with aldehydes **2** and **10** clearly indicated that, besides the effect arising from the α-methyl group, the β-alkoxy substituent also plays a significant role in influencing the level of diastereoselectivity. In Brown's (*E*)-crotylboronation reaction the favored products display 1,3-*anti* relationship between methyl branching groups (adducts **5** and **12**) whereas the tartrate-modified protocol yield predominately products with a 4,6-*anti* relationship between alkoxy substituents (adducts **4** and **11**) [11].

Turning back to our newly proposed synthesis, the good diastereoselectivity and the satisfactory yield exhibited in the *E*-crotylboronation reaction of aldehyde **2** with (*R*,*R*)-**9**-tartrate-modified reagent prompted us to select these experimental conditions to prepare the homoallylic alcohol **4**. Initially, **4** was then elaborated to aldehyde **6** following our previously reported two-step sequence [1]. However, when aldehyde **6** was subjected to HWE coupling with the ketophosphonate **7** in a large scale, regrettably we observed the formation of the undesired isomeric enone **8b** along with the expected enone **8a.** The latter compounds displayed very similar NMR spectra, with slight differences for the resonances of C27-C30 nuclei, suggesting that a C-28 epimerization (the stereocenter the α-carbon) had occurred. This hypothesis was confirmed by the preparation of an authentic sample of the C-28 epimeric enone. For this purpose, aldehyde **13,** obtained through Evans aldol homologation of aldehyde **2,** was subjected to the HWE coupling with ketophosphonate **7** to afford a single enone product, whose NMR data were superimposable to **8b** [12] (Scheme **1**).

After observing that many attempts of circumventing the above problem by varying experimental conditions for the HWE coupling (such as the base used or the choice of protecting groups at C-23, C-25 and C-35 positions) failed, we decided to turn our attention to alternative protocols.

An attractive alternative route for the formation of the C30-C31 carbon-carbon bond was a Nozaki-Hiyama-Kishi coupling [13, 14], due to its well-known chemoselectivity,

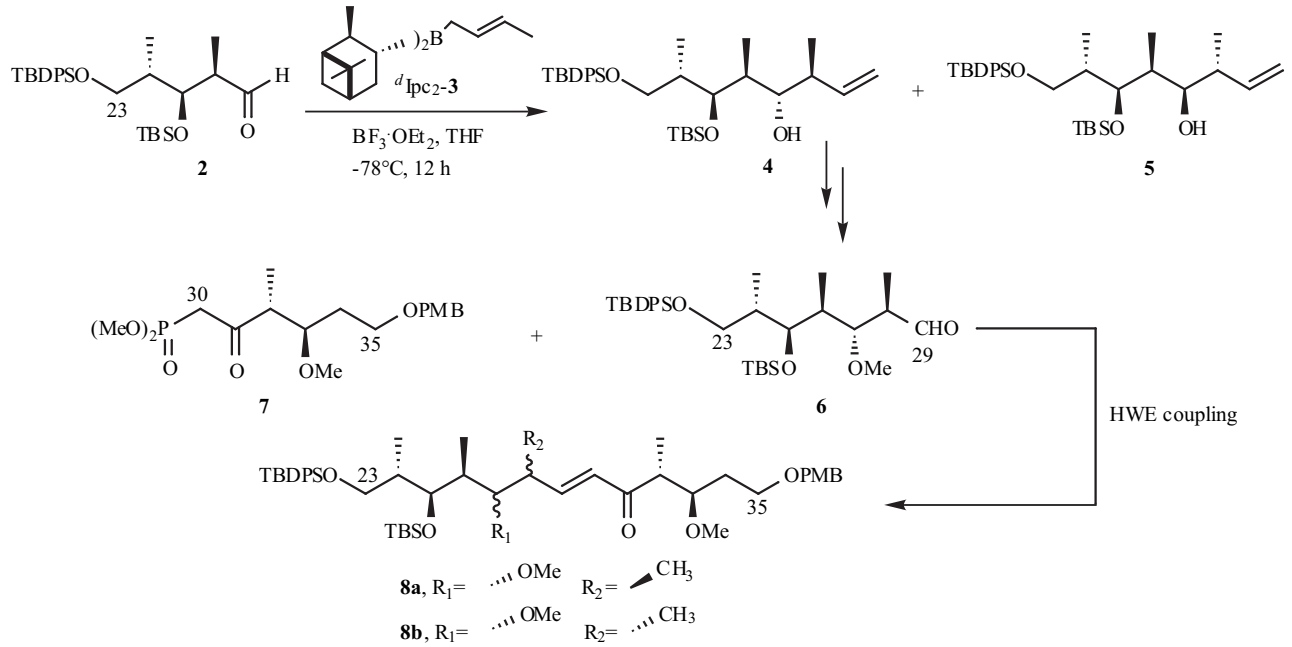
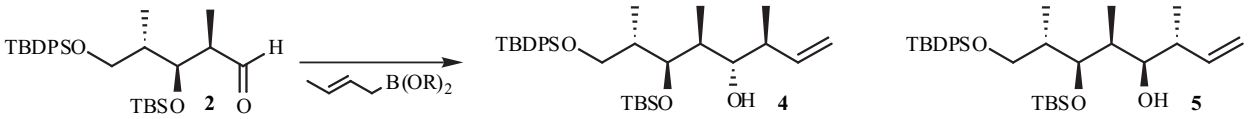
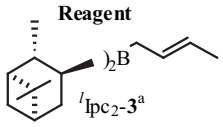
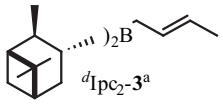
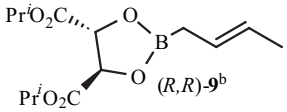
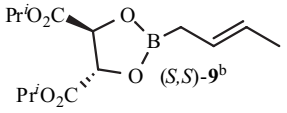
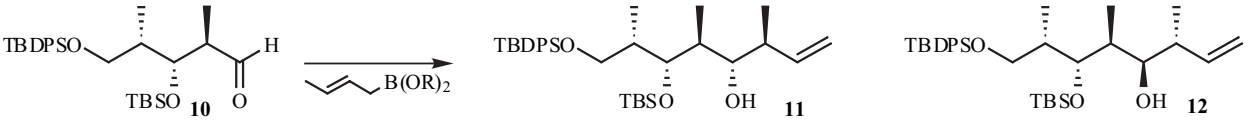


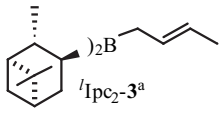
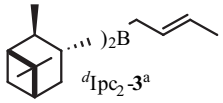
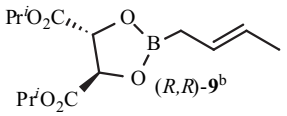
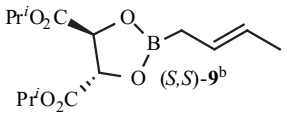
Fig. (1). Summary synthesis of reidispongiolide A precursor **8a**.

Table 1. Diastereoselectivity Data for the E-Crotylboronation Reactions of Chiral Aldehydes 2 and 10



Entry	Regent	Yield	4: 5[c,d]
1	Reagent  ^{l}Ipc$_2$-**3**[a]	75%	2: 98
2	 ^{d}Ipc$_2$-**3**[a]	70%	30: 70
3	 (*R,R*)-**9**[b]	85%	90: 70
4	 (*S,S*)-**9**[b]	70%	2: 98

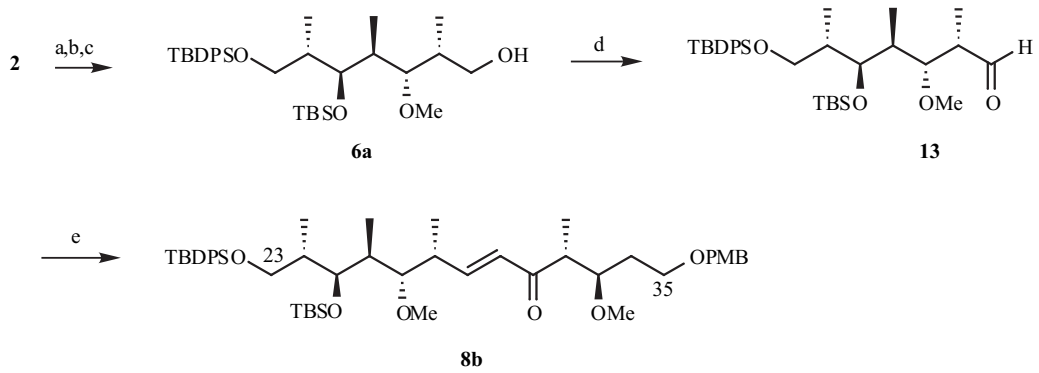


Entry	Reagent	Yield	11: 12[c,d]
5	 ^{l}Ipc$_2$-**3**[a]	72%	2: 98
6	 ^{d}Ipc$_2$-**3**[a]	45%	15: 85
7	 (*R,R*)-**9**[b]	52%	2: 98
8	 (*S,S*)-**9**[b]	78%	2: 98

[a]$BF_3{\cdot}OEt_2$, THF, -78°C, 12 h, then NaOH/H_2O_2.
[b]Toluene, 4 Å mol. sieves, -78 °C, 18 h, $NaBH_4$/absolute EtOH, then NaOH
[c]Diastereomer ratios **4**:**5** and **11**:**12** were determined by HPLC (column: Macherey-Nagel Nucleosil 100-5, flow 1.5 mL/min, hexane:ethyl acetate 997:3 for compounds **4** (t_R= 10.8 min) and **5** (t_R= 10.8 min), hexane:ethyl acetate 995:5 for compounds **11** (t_R= 13.6 min) and **12** (t_R= 12.8 min).
[d]The relative stereochemistry of the 4, 6-diol unit in products **4**-**5** and **11**-**12** was determined on the basis of ^{13}C-NMR acetonide analysis as previous described (ref. 1).

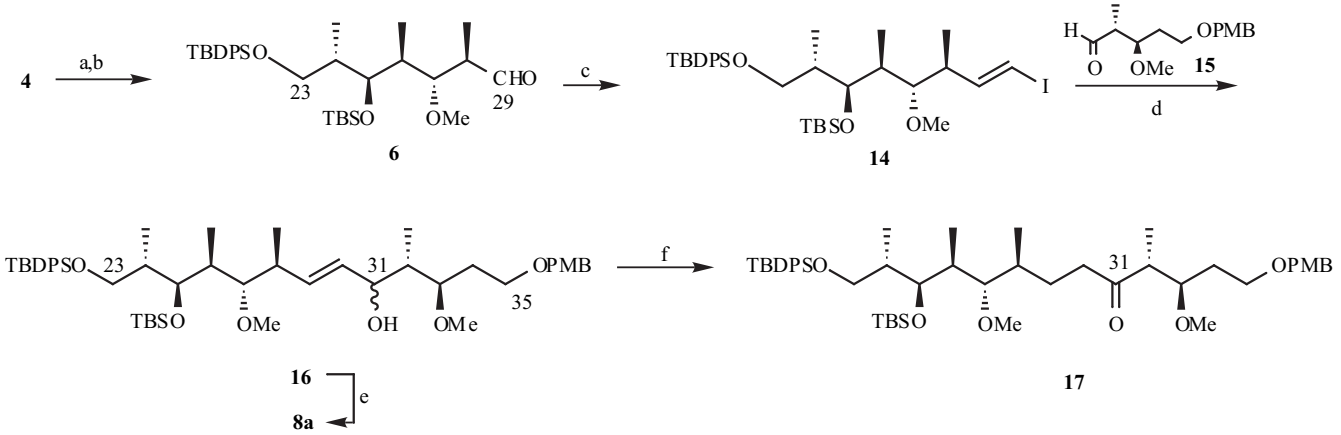
and mild character making such process compatible with a wide range of functionalities [15].

To this end, aldehyde **6** was subjected to Takai olefination [16] to afford the *E*-vinyl iodide **14** in 86% yield



Reagents and conditions: (a) Bu_2BOTf, *S*-4-benzyl-3-propionyl-oxazolidinone, -78°C, 1 h, then **2**, -78°C → -10°C, 2 h, 88%; (b) MeOTf, di-*t*-Bu-Pyr, CH_2Cl_2, 77%; (c) $LiBH_4$, MeOH, rt, 2h, 75%; (d) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78°C → 0°C, 98%; (e) activated $Ba(OH)_2$ 30 min., then **7**, r.t., wet THF, 77%.

Scheme 1.



Reagents and conditions: (a) MeOTf, di-*t*-Bu-Pyr, CH_2Cl_2, 87%; (b) OsO_4, NMO acetone/H_2O 3:1, then H_5IO_6, 97%; (c) $CrCl_2$, CHI_3, THF:dioxane 6:1, 18 h, 86%; (d) $CrCl_2$/$NiCl_2$ (0.1%), DMSO:THF 5:1, 20 min, then **15**, overnight 74%; (e) Pt(C), H_2, ethanol r.t; (f) Dess Martin periodinane, CH_2Cl_2, r.t.

Scheme 2.

(Scheme **2**). Intermolecular Ni/Cr coupling of vinyl iodide **14** with aldehyde **15** provided the allylic alcohol **16** in 74% yield as a 1:1 mixture of diastereomers. Catalytic hydrogenation of C29-C30 double bond, followed by Dess-Martin oxidation of C31 hydroxyl group gave rise to the targeted C23-C35 portion **17** [17] of reidispongiolide A.

3. CONCLUSION

In conclusion, an efficient, improved synthetic route accessing the open-chain C23-C35 portion of reidispongiolide A (**1**) is reported. This work is preliminary to further studies, presently underway in our laboratory, directed towards the total synthesis of members of the reidispongiolide/sphixolide family of actin-binding marine macrolides.

ACKNOWLEDGEMENTS

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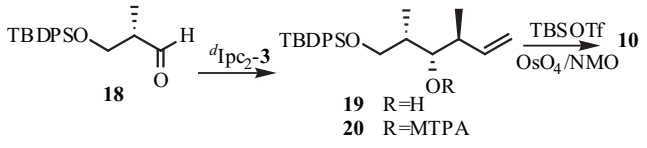
[8] Aldehyde **10** was prepared from (2*S*)-3-hydroxy-2-methyl-propanal **18** following the synthetic scheme.



The diasteromeric purity (< 98%) of homoallylic alcohol **19** was estimated by NMR spectra and the configuration was assigned by NMR Mosher analysis. NMR data (500 MHz, $CDCl_3$) and specific rotation (chloroform) for compound **19**: ^{1}H NMR δ (ppm): 1.01 (6H, d, J= 6.8 Hz, CH_3-2 and CH_3-4); 1.13 (9H, s, tBu-Si); 1.89 (1H, m, H-2); 2.34 (1H, m, H-4); 3.65 (1H, dd, J= 2.1, 8.1 Hz, H-3); 3.78 (2H, d, J= 5.1 Hz, H-1); 5.13 (1H, s, H-6a); 5.13 (1H, d, J= 8.1 Hz, H-6b);5.88 (1H, m, H-5); 7.45 (6H, m, Ph); 7.74 (4H, m, Ph); ^{13}C NMR: δ (ppm) 9.6, 16.7, 19.2, 26.8, 36.6, 41.7, 68.2, 76.1, 115.0, 127.6 (4C), 129.6 (2C), 133.1, 133.3, 135.5 (2C), 135.6 (2C), 141.7; $[\alpha]^{24}_D$ +3.3° (*c* 10.8, $CHCl_3$).

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[10] ^{1}H NMR data (500 MHz, $CDCl_3$) and specific rotation (chloroform) for compound **12**: δ (ppm): -0.03 (3H, s, CH_3-Si); 0.01 (3H, s, CH_3-Si); 0.79 (3H, d, J= 6.6 Hz, CH_3); 0.89 (9H, s, tBu-Si); 0.95 (3H, d, J= 7.3 Hz, CH_3); 0.97 (3H, d, J= 7.0 Hz, CH_3); 1.07 (9H, s, tBu-Si); 1.72 (1H, m); 1.96 (1H, m); 2.23 (1H, m); 3.49 (1H, dd, J=6.2, 9.9 Hz); 3.59 (2H, m); 3.93 (1H, t, J=3.93 Hz); 5.06 (1H, d, J= 6.9 Hz,); 5.09 (1H, d, J= 15.4 Hz); 5.80 (1H, m); 7.39 (6H, m, Ph); 7.67 (4H, m, Ph); $[\alpha]_D$ = +4.2° (*c* 0.9, $CHCl_3$).

[11] ^{1}H NMR data (500 MHz, $CDCl_3$) for compound **11** (analyzed as a mixture with **12**): δ (ppm): 0.03 (3H, s, C**308**82 (3H, d, J= 6.9 Hz, CH_3); 0.88 (9H, s, tBu-Si); 0.86 (3H, overlapped, CH_3); 0.89 (3H, overlapped, CH_3); 1.07 (9H, s, tBu-Si); 1.76 (1H, m); 1.88 (1H, m); 2.12 (1H, m); 3.36 (1H, dd, J=6.2, 9.8 Hz); 3.45 (2H, m); 3.99 (1H, dd, J=5.1, 2.02 Hz); 5.01 (1H, d, J= 11.0 Hz,); 5.07 (1H, d, J= 6.2 Hz); 5.90 (1H, m); 7.39 (6H, m, Ph); 7.67 (4H, m, Ph).

[12] ^{1}H NMR data (500 MHz, $CDCl_3$) for compound **8b**: ^{1}H NMR δ (ppm): -0.05 (3H, s, CH_3-Si); 0.03 (3H, s, CH_3-Si); 0.77 (3H, d, J= 7.3 Hz, CH_3), 0.83 (9H, s, tBu-Si); 0.91 (3H, d, J= 7.0 Hz, CH_3), 1.04 (3H, d, J= 7.0 Hz, CH_3); 1.05 (3H, d, overlapped CH_3), 1.06 (9H, s, tBu-Si); 1.68 (1H, m); 1.74 (1H, m); 1.85 (2H, m); 2.57 (1H, m); 3.03 (1H, m); 3.11 (1H, dd, J= 1.8, 9.1 Hz);. 3.28 (6H, s's, OCH_3); 3.41 (1H, dd, J= 6.9, 9.9 Hz); 3.56 (2H, m); 3.65 (1H, m); 3.71 (1H, dd, J= 5.8, 9.9 Hz), 3.80 (3H, s, OCH_3); 3.97 (1H, d, J= 5.5 Hz); 4.42 (2H, m); 6.22 (1H, d, J= 15.6 Hz); 6.88 (2H, d, J = 8.7 Hz), 7.05 (1H, dd, J= 15.6, 6.0 Hz); 7.24 (2H, d, J = 8.7 Hz); 7.40 (6H, m, Ph); 7.65 (4H, m, Ph).

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[17] NMR data (500 MHz, $CDCl_3$) and specific rotation (chloroform) for compound **17**: ^{1}H NMR δ (ppm): -0.06 (3H, s, CH_3-Si); -0.04 (3H, s, CH_3-Si); 0.76 (3H, d, J= 6.6 Hz, CH_3); 0.81 (9H, s, tBu-Si); 0.90 (3H, d, J= 6.9 Hz, CH_3); 0.96 (3H, d, J= 6.6 Hz, CH_3); 0.98 (3H, d, J= 6.9 Hz, CH_3); 1.05 (9H, s, tBu-Si); 1.36 (1H, m); 1.40 (1H, m); 1.65 (2H, m); 1.75 (1H, m); 1.78 (1H, m); 1.82 (1H, m); 2.42 (1H, m); 2.53 (1H, m); 2.75 (1H, t, J= 7.3 Hz); 2.89 (1H, dd, J=2.6, 8.8 Hz); 3.26 (3H, s, OCH_3); 3.39 (3H, s, OCH_3); 3.40 (1H, m); 3.54 (2H, m); 3.59 (1H, dd, J=2.9, 7.7 Hz); 3.72 (1H, dd, J=5.5, 9.9 Hz); 3.80 (3H, s, OCH_3); 3.93 (1H, d, J=5.5 Hz); 4.43 (2H, m); 6.87 (2H, d, J = 8.4 Hz); 7.25 (2H, d, J = 8.4 Hz); 7.35 (6H, m, Ph); 7.67 (4H, m, Ph); ^{13}C NMR: δ ?-3.9, -3.6, 11.7, 12.4, 13.7, 17.6, ?18.5, 19.2, 24.1, 26.0, 26.9, 31.2, 34.3, 38.1, 41.1, 42.6, 49.7, 55.3, 58.0, 60.6, 66.0, 66.4, 72.6, 72.8, 79.9, 88.1, 113.8 (2C), 127.5 (4C), 129.2 (2C), 129.4 (2C), 130.5, 134.0 (2C), 135.7 (4C), 159.1, 213.5; $[\alpha]_D$ = -5.4° (*c* 22.5, $CHCl_3$).