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Synthetic studies on bafilomycin A_1: stereoselective synthesis of the C_{12}–C_{17} fragment and its coupling with the C_1–C_{11} subunit

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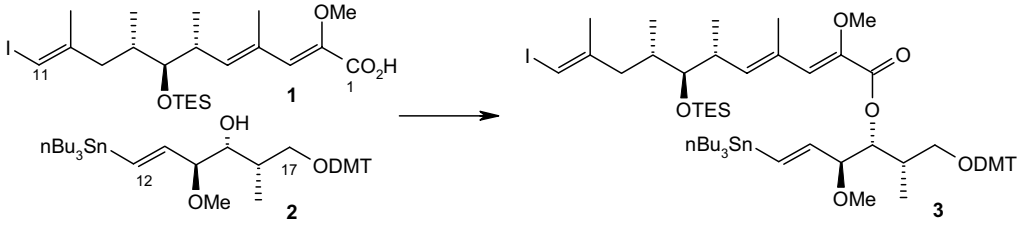
Abstract—Stereoselective addition of (*E*)-1-lithio-2-tributylstannylethylene on a chiral cyclic di-*t*-butylsilyleneketal C_{14}–C_{17} aldehyde afforded the required Felkin–Anh adduct for the synthesis of the C_{12}–C_{17} fragment of bafilomycin A_1, the configuration of which was assigned unambiguously. After appropriate coupling with the enantiopure C_1–C_{11} fragment, the C_{12}–C_{17} subunit obtained here can be used for the study of the 16-membered macrolide formation either by an acyl activation or an intramolecular Stille reaction. Intermolecular esterification of the 15-OH with an acyl activation of the carboxylic acid of the C_1–C_{11} fragment, in modified Yamaguchi's conditions, affords here an intermediate for examining an intramolecular Stille coupling.

In the preceding communication,[1] we described the synthesis of the enantiopure C_1–C_{11} fragment **1** of bafilomycin A_1. We herein report the synthesis of the C_{12}–C_{17} subunit **2** and its structure assignment, and also the preparation of **3** (Scheme 1), in order to examine the formation of the 16-membered macrolactone of bafilomycin A_1 via an intramolecular Stille coupling, which will be discussed in the accompanying communication.[2,3]

1. Synthesis of the C_{12}–C_{17} fragment

In a first approach, we prepared the enantiopure aldehyde **4**,[3] expecting that the OTBS silyl ether, α to the aldehyde, might disfavour the formation of the Cram-chelate adduct with lithio derivatives (or other organometallics) and allow to get the desired stereoisomer stereoselectively.[4] However, the addition of the *E*-lithiovinyltributylstannane **6**, generated in situ from **5**,[5] was found to be almost nonstereoselective in THF/hexane (Scheme 2). The configurations of the two adducts, **7** and **8**, were demonstrated unambiguously by a chemical filiation as discussed further. Modifications of reaction conditions (temperature, excess of **6**, addition of $BF_3{\cdot}Et_2O$ in THF or $LiClO_4$ in Et_2O) were unsatisfactory. Results were not improved with the parent OTES aldehyde **9**. Additions of TMS–C≡C–Li (1.5 equiv, THF, 0 °C, overnight) and *n*-BuLi (1.2 equiv, toluene, −78 °C, 6 h) were also weakly stereoselective with **4**, affording 55/45 and 65/35 mixtures of two diastereoisomers, respectively, moreover in analogous moderate yields.[3] The low stereoselectivity obtained in all those condensations is most likely due to the fact that the two



Scheme 1.

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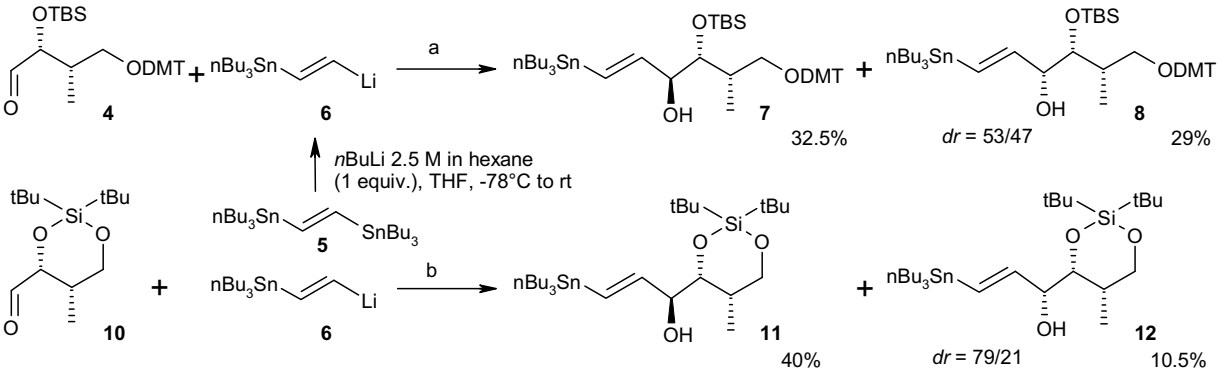
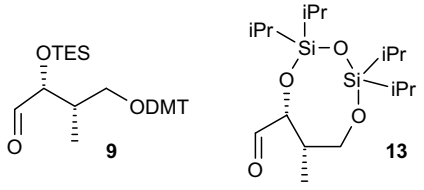


Scheme 2. Reagents and conditions: (a) **6** (1.05 equiv), addition of **4** in THF, −78 °C, 4 h, then MeOH quench at −78 °C; (b) **6** (1.05 equiv), addition of **10** in THF, −78 °C, 7 h, then MeOH quench at −78 °C.

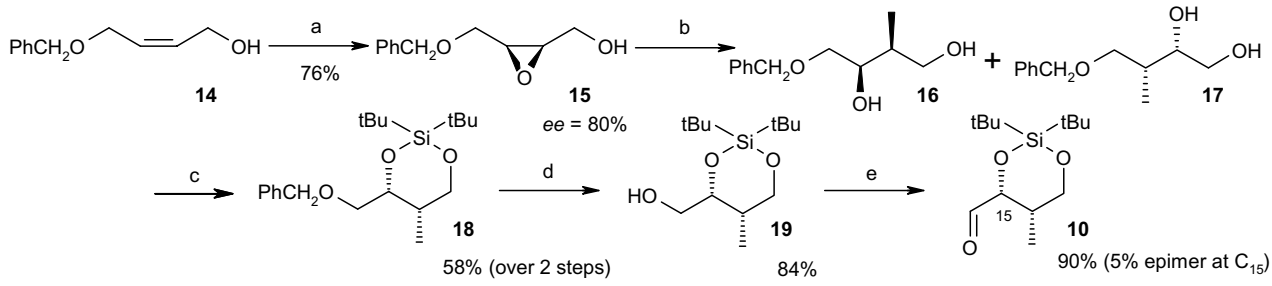
substituents, α to the aldehyde, are large and probably result in a dynamic equilibrium of conformers involved in the reaction; the steric hindrance resulting from these two substituents is also probably responsible of the moderate reactivity of the aldehyde **4**.

We then examined the condensations of **6** with the cyclic di-*t*-butylsilyleneketal aldehyde **10** in order to still have a nonchelating group and also to see if the cyclic ketal might favour a conformation of the aldehyde. In fact the best results were thus obtained with **10** (in a 95/5 ratio with the epimerized aldehyde, see further) in THF since the adducts **11** and **12** were isolated in 40% and 10.5% yield, respectively, in quasi stoichiometric conditions (Scheme 2); a mixture of two other diastereoisomers was also isolated in 6% yield and some pure starting aldehyde **10** was still recovered (13.5%) after chromatography. These results were obtained reproducibly at a 0.2–3.5 mmole scale. The configurations of **11** and **12** were demonstrated by a chemical filiation, as shown further. Yields of adducts **11** and **12** were lower and stereoselection was not significantly improved either with DME (−78 °C, 6 h) or THF/HMPA (9/1) (−78 °C, 4 h); a 50/50 mixture of the two same adducts was obtained with $LiClO_4$ (2 equiv) in Et_2O (−78 °C, 3.5 h).

On the other hand, the aldehyde **13** gave with **6**, at −78 °C, a 50/50 mixture of the corresponding adducts in THF or with $LiClO_4$ (2 equiv) in Pr_2O.[3]



The aldehyde **10** was prepared from commercially available *cis*-4-benzyloxy-2-buten-1-ol **14** (Scheme 3). Sharpless asymmetric epoxidation[6] afforded the epoxy-alcohol **15** in 76% yield with an ee of 80%, determined by ^1H NMR (400 MHz) of the corresponding MTPA esters.[7] We then preferred to open directly the epoxide by Me_2CuLi in Et_2O, even if the reaction afforded a 70/30 mixture of the two regioisomers as in previous related examples,[8] rather than to develop a more lengthy sequence to solve that problem. As the two isomers **16** and **17** were not separable, the most efficient solution was to use the crude mixture for converting them into the corresponding di-*t*-butylsilyleneketals since those corresponding to 1,2-diols are known to be very labile.[9] Thus after aqueous work-up and chromatography over silicagel, the desired ketal **18** was isolated in 58% yield over the two steps from **15**. After hydrogenolysis of the benzyl ether (84% yield), Swern oxidation[10] of the alcohol **19**, using *i*-Pr_2NEt to minimize the epimerization of this sensitive aldehyde, afforded **10** in 90% yield as a 95/5 mixture of epimers at C_{15}, which could not be



Scheme 3. Reagents and conditions: (a) Ti(O-*i*-Pr)$_4$ (1.0 equiv), (−)-DET (1.2 equiv), anhyd CH_2Cl_2, −30 °C, 30 min, then **14**, −30 °C, 1 h, followed by *t*-BuOOH (2.6 M in anhyd CH_2Cl_2, 5 equiv, −30 °C, 4 days); (b) CuI (5 equiv), MeLi 1.6 M in Et_2O (9 equiv) at 0 °C, then −40 °C, **15**, 5 h; (c) crude mixture of **16** and **17** (70/30), 2,6-lutidine (10 equiv), *t*-$Bu_2Si(OTf)_2$ (3.2 equiv), CH_2Cl_2, rt, 3 h; (d) 10% Pd/C (40% in weight), H_2, 95% EtOH, rt, 4 h; (e) oxalyl chloride (1.2 equiv), DMSO (2.4 equiv), CH_2Cl_2, −78 °C, 15 min, then **19**, 30 min, followed by *i*-Pr_2NEt (5.0 equiv), −78 °C to rt, 1 h.

separated. It is worthy to point out that epimerization was observed only on upscaling, after chromatography (heptane/AcOEt 95/5). The configuration of the aldehyde **10** was clearly demonstrated by NMR ($^3J_{15,16} = 4.5$ Hz, compared to $^3J_{15,16} = 11$ Hz for the minor diastereoisomer). The aldehyde **10** is thus obtained in 33% overall yield from **14** (five steps).

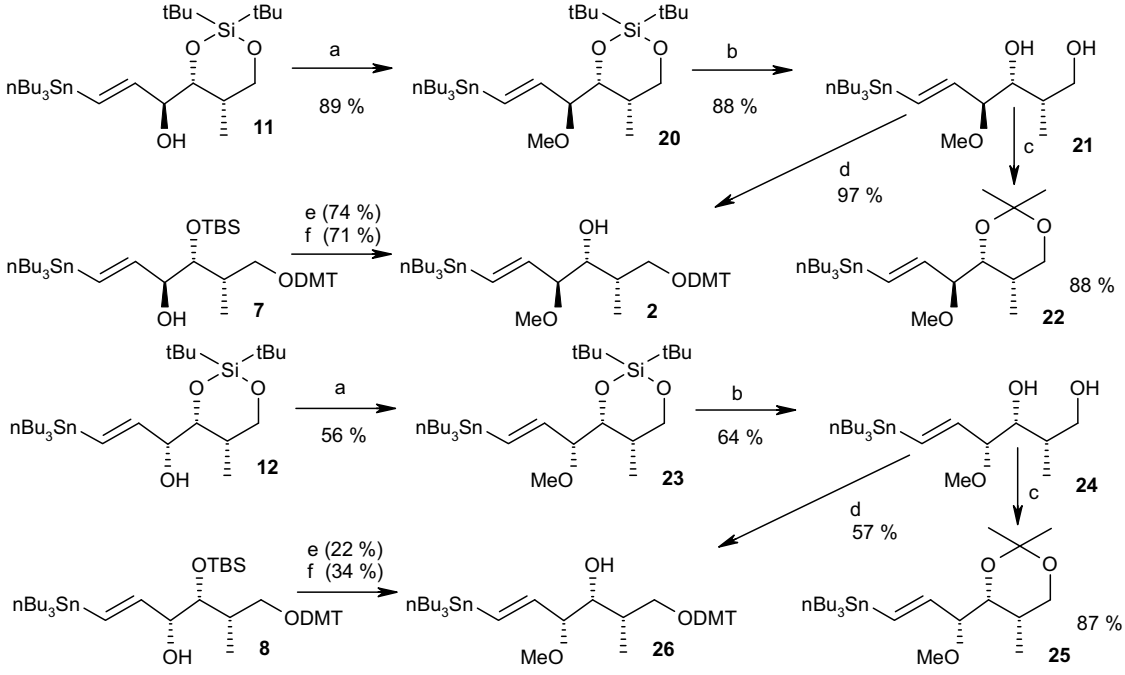
The configurations of the adducts **7**, **8**, **11** and **12**, were determined unambiguously by the chemical filiation between them and **22**, which was an intermediate of the synthesis of bafilomycin A_1 achieved by Toshima et al. (Scheme 4).[11] The NMR spectra of the acetonides **22** and **25** are clearly different in $CDCl_3$ (^1H at 300 MHz, ^{13}C at 50 MHz), and comparison with the data published by Toshima for **22** allows an unambiguous assignment of the structures.[12]

Formation of the methyl ether at C_{14} was quite a difficult problem for avoiding silyl migration, desilylation or destannylation for the adducts **7** and **11**, and showed to be even more difficult for **8** and **12**. The corresponding methyl ethers could however be obtained by reaction of the derived lithium alkoxide, generated in situ, with a large excess of methyl iodide, in THF/HMPA at room temperature. Fortunately, yields were higher with the diastereoisomer required further for the synthesis. Evans and Calter already pointed out the difficulty of the formation of the methyl ether for a related compound with the (*S*) configuration at C_{14}, and gave an other solution to this problem.[13] The di-*t*-butylsilylene ketal could be cleaved with an excess TBAF in THF, at room temperature, with no destannylation, **20** thus affording the diol **21** in 88% yield. The diols **21** and **24** were then converted into the corresponding acetonides **22** and **25** with 2-methoxypropene and PPTS as a catalyst, conditions which were mild enough to avoid protodestannylation. The chemical filiations of **11** with **7**, and of **12** with **8**, were achieved via **2** and **26**, respectively.[3]

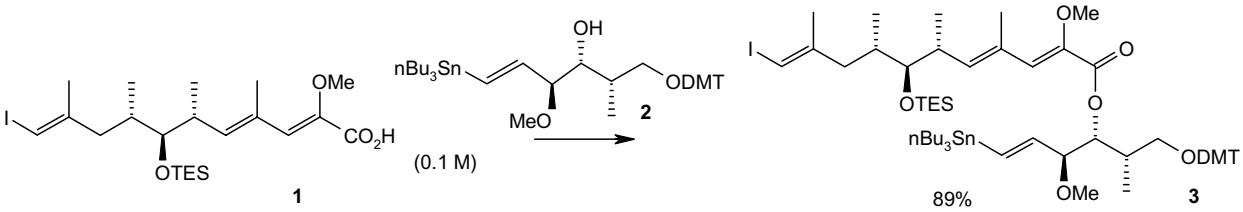
For the synthesis of bafilomycin A_1, the required C_{12}–C_{17} fragment **2** is thus obtained with a 10% overall yield from **14** (ee = 80%, nine steps).

2. Precursor of the macrolide formation (Scheme 5)

The prepared subunits **1** and **2** now allowed us to study the formation of the macrolide either via an acyl activation of their coupling product obtained after an intermolecular Stille coupling, or via an intramolecular Stille reaction of the corresponding ester **3**. For bafilomycin A_1 synthesis, the 16-membered macrolide formation has always been achieved via an acyl activation.[11,13–15] Therefore, instead of an acyl activation and in order to find an alternate solution, we decided to examine the formation of the macrocycle via an intramolecular Stille coupling.[16] Thus, the required enantiopure precursor **3** was obtained in 89% yield by an intermolecular esterification of the enantiopure C_1–C_{11} acid **1** with the chiral C_{12}–C_{17} alcohol **2** (ee = 80%) (1.08 equiv), in the presence of Yamaguchi's chloride,[17] NEt_3 and DMAP, at room temperature, and 11% of the



Scheme 4. Reagents and conditions: (a) *n*-BuLi 1.6 M in hexane (1.2 equiv), MeI (20 equiv), THF, −78 °C to rt, 1 h, then HMPA to get THF/HMPA (10/1), rt, 16 h; (b) TBAF 1 M in THF (5 equiv), rt, 3 days; (c) CH_2=CMe(OMe) (3 equiv), PPTS (0.01 equiv), CH_2Cl_2, rt, 20 h; (d) $DMTBF_4$ (1.8 equiv for **21**, 1.1 equiv for **24**), 2,6-di-*t*-butyl-4-methylpyridine (2.5 equiv for **21**, 1.5 equiv for **24**), MeCN, rt, 4 h; (e) *n*-BuLi 1.6 M in hexane (1.2 equiv), MeI (100 equiv), THF, −78 °C to rt, 1 h, then HMPA to get THF/HMPA (5/1), rt, 16 h; (f) TBAF 1 M in THF (10 equiv), rt, 5 days for **2**, 6 days for **26**.



Scheme 5. Reagents and conditions: **1**, toluene, DMAP (2 equiv), rt, then addition of NEt_3 (4 equiv), followed by 2,4,6-trichlorobenzoyl chloride (2 equiv) and addition of **2** in toluene (1.08 equiv), then rt, 24 h.

alcohol **2** (ee not determined) were reisolated after chromatography (Scheme 5).[18]

Acknowledgements

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12. Compound **11**: pale yellow oil; $[\alpha]_D$ −190 (*c* 0.05, $CHCl_3$); IR (cm^{-1}, $CHCl_3$): 3598 (OH), 1598 (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ/TMS 6.29 (m, 2H, H_{12}, H_{13}), 4.05 (m, 1H, H_{14}), 4.10 (dd, 1H, H_{15}, $J_{15,16}=2.5$, $J_{15,14}=8$), 4.34 (dd, 1H, H_{17a}, $J_{17a,17b}=11$, $J_{17a,16}=3$), 3.92 (dd, 1H, H_{17b}, $J_{17a,17b}=11$, $J_{17b,16}=2$), 1.81 (d, 1H, OH, $J_{OH,14}=4$), 2.01 (m, 1H, H_{16}), 1.48 (m, 6H, $CH_3CH_2CH_2CH_2Sn$), 1.30 (m, 6H, $CH_3CH_2CH_2CH_2Sn$), 1.22 (d, 3H, CH_3, $J_{16,CH_3}=7$), 1.07 (s, 9H, *t*-BuSi), 1.05 (s, 9H, *t*-BuSi), 0.90 (t, 6H, $CH_3CH_2CH_2CH_2Sn$, $J_{CH_2CH_2Sn}=7$), 0.88 (t, 9H, $CH_3CH_2CH_2CH_2Sn$, $J_{CH_3CH_2}=7$); ^{13}C NMR (50.3 MHz, $CDCl_3$): 149.0 (C_{13}), 127.5 (C_{12}), 78.8 (C_{15}), 74.9 (C_{14}), 71.4 (C_{17}), 34.2 (C_{16}), 29.2 and 27.4 ($CH_3CH_2CH_2CH_2Sn$), 28.7 and 27.6 (*t*-BuSi), 23.5 and 20.7 (CqSi), 13.8 ($CH_3CH_2CH_2CH_2Sn$), 11.4 (CH_3), 9.5 ($CH_3CH_2CH_2CH_2Sn$); $C_{27}H_{56}O_3SiSn=575.53$; MS (EI, *m/z*): 575 ($M^+$), 518, 461.
Compound **12**: pale yellow oil; $[\alpha]_D$ +2.0 (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ/TMS 6.41 (d, 1H, H_{12}, $J_{13,12}=19$), 5.88 (dd, 1H, H_{13}, $J_{13,12}=19$, $J_{13,14}=7$), 4.00 (m, 1H, H_{14}), 4.05 (dd, 1H, H_{15}, $J_{15,16}=2.5$, $J_{15,14}=8$), 4.33 (dd, 1H, H_{17a}, $J_{17a,17b}=11$, $J_{17a,16}=3$), 3.89 (dd, 1H, H_{17b}, $J_{17a,17b}=11$, $J_{17b,16}=2$), 2.98 (d, 1H, OH, $J_{OH,14}=1$), 1.78 (m, 1H, H_{16}), 1.47 (m, 6H, $CH_3CH_2CH_2CH_2Sn$), 1.29 (m, 6H, $CH_3CH_2CH_2CH_2Sn$), 1.16 (d, 3H, CH_3, $J_{16,CH_3}=7$), 1.10 (s, 9H, *t*-BuSi), 1.06 (s, 9H, *t*-BuSi), 0.89 (t, 6H, $CH_3CH_2CH_2CH_2Sn$, $J_{CH_2CH_2Sn}=7$), 0.87 (t, 9H, $CH_3CH_2CH_2CH_2Sn$, $J_{CH_3CH_2}=7$); ^{13}C NMR (50.3 MHz, $CDCl_3$): 144.9 (C_{13}), 133.4 (C_{12}), 79.3 (C_{15}), 77.2 (C_{14}), 71.0 (C_{17}), 34.1 (C_{16}), 29.0 and 27.1 ($CH_3CH_2CH_2CH_2Sn$), 28.5 and 27.4 (*t*-BuSi), 23.3 and 20.6 (CqSi), 13.6 ($CH_3CH_2CH_2CH_2Sn$), 11.5 (CH_3), 9.3 (CH_3CH_2-CH_2CH_2Sn); $C_{27}H_{56}O_3SiSn=575.53$; MS (EI, *m/z*): 575 ($M^+$), 518.
Compound **22**: pale yellow oil; IR (cm^{-1}, $CHCl_3$): 1600 (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ/TMS 6.21 (d, 1H, H_{12}, $J_{12,13}=19$), 5.79 (dd, 1H, H_{13}, $J_{12,13}=19$, $J_{13,14}=6$), 4.08 (dd, 1H, H_{17a}, $J_{17a,17b}=11.5$, $J_{17a,16}=3$), 3.82 (dd, 1H, H_{15}, $J_{15,14}=9$, $J_{15,16}=2$), 3.60 (dd, 1H, H_{17b}, $J_{17a,17b}=11.5$, $J_{17b,16}=2$), 3.40 (dd, 1H, H_{14}, $J_{14,15}=9$, $J_{14,13}=6$), 3.28 (s, 3H, OCH_3), 1.77 (m, 1H, H_{16}), 1.37 (s, 3H, CH_{3gem}), 1.35 (s, 3H, CH_{3gem}), 1.48 (m, 6H, $CH_3CH_2CH_2CH_2Sn$), 1.30 (m, 6H, $CH_3CH_2CH_2CH_2Sn$), 1.10 (d, 3H, CH_3, $J_{16,CH_3}=7$), 0.89 (t, 6H, $CH_3CH_2CH_2CH_2Sn$, $J_{CH_2CH_2Sn}=7$), 0.88 (t, 9H, $CH_3CH_2CH_2CH_2Sn$, $J_{CH_3CH_2}=7$); ^{13}C NMR (50.3 MHz, $CDCl_3$): 146.2 (C_{13}), 132.7 (C_{12}), 98.7 (Cq), 83.6 (C_{14}), 73.8 (C_{15}), 67.1 (C_{17}), 56.4 (OCH_3), 30.4 and 29.7 (CH_{3gem}), 29.6 and 27.3 ($CH_3CH_2CH_2CH_2Sn$), 19.0 (C_{16}), 13.8 ($CH_3CH_2CH_2CH_2Sn$), 11.2 (CH_3), 9.6 ($CH_3CH_2CH_2CH_2Sn$); $C_{23}H_{46}O_3Sn=489.32$; MS (EI, *m/z*): 490 (M^+).
Compound **25**: pale yellow oil; IR (cm^{-1}, $CHCl_3$): 1601 (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ/TMS 6.33 (d, 1H, H_{12}, $J_{12,13}=19$), 5.66 (dd, 1H, H_{13}, $J_{12,13}=19$, $J_{13,14}=8.5$), 4.11 (dd, 1H, H_{17a}, $J_{17a,17b}=11.5$, $J_{17a,16}=2.5$), 3.91 (dd, 1H, H_{15}, $J_{15,14}=8.5$, $J_{15,16}=2.5$), 3.55 (dd, 1H, H_{17b}, $J_{17a,17b}=11.5$, $J_{17b,16}=2$), 3.49 (dd, 1H, H_{14}, $J_{14,15}=1$, $J_{14,13}=8.5$), 3.29 (s, 3H, OCH_3), 1.48 (s, 3H, CH_{3gem}), 1.47 (m, 6H, $CH_3CH_2CH_2CH_2Sn$), 1.46 (s, 3H, CH_{3gem}), 1.43

(m, 1H, H_{16}), 1.32 (m, 6H, $CH_3CH_2CH_2CH_2Sn$), 1.07 (d, 3H, CH_3, $J_{16,CH_3}=7$), 0.92 (t, 6H, $CH_3CH_2CH_2CH_2Sn$, $J_{CH_2CH_2Sn}=7$), 0.88 (t, 9H, $CH_3CH_2CH_2CH_2Sn$, $J_{CH_3CH_2}=7$); ^{13}C NMR (50.3 MHz, $CDCl_3$): 143.1 (C_{13}), 136.0 (C_{12}), 99.0 (Cq), 86.8 (C_{14}), 74.0 (C_{15}), 67.2 (C_{17}), 56.4 (OCH_3), 30.4 and 29.9 (CH_{3gem}), 29.2 and 27.2 ($CH_3CH_2CH_2CH_2Sn$), 19.0 (C_{16}), 13.8 ($CH_3CH_2CH_2CH_2Sn$), 10.9 (CH_3), 9.6 ($CH_3CH_2CH_2CH_2Sn$); $C_{23}H_{46}O_3Sn=489.32$; MS (EI, m/z): 490 (M^+).

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18. Compound **3**: pale yellow oil; $[\alpha]_D$ +27 (*c* 0.7, $CHCl_3$); IR (cm^{-1}, $CHCl_3$): 1710 (C=O), 1607 (C=C), 1509 (Ar); ^1H NMR (300 MHz, $CDCl_3$): δ/TMS 7.43 (d, 2H, Ha, $J_{Ha,Hb}=9$), 7.31 (d, 4H, Hd, $J_{Hd,He}=9$), 7.26 (m, 2H, Hb), 7.17 (m, 1H, Hc), 6.81 (d, 4H, He, $J_{Hd,He}=9$), 6.51 (s, 1H, H_3), 5.98 (d, 1H, H_{12}, $J_{13,12}=19$), 5.89 (dq, 1H, H_5, $J_{5,6}=10$, $J_{CH_3,5}=1$), 5.83 (s, 1H, H_{11}), 5.83 (dd, 1H, H_{13}, $J_{13,12}=19$, $J_{13,14}=6$), 5.38 (dd, 1H, H_{15}, $J_{15,14}=6$, $J_{15,16}=6$), 3.77 (s, 6H, OCH_3), 3.50 (m, 1H, H_{14}), 3.49 (s, 3H, CH_3, C_2OCH_3), 3.39 (dd, 1H, H_7, $J_{6,7}=3.5$, $J_{7,8}=5.5$), 3.21 (s, 3H, CH_3, $HC_{14}OCH_3$), 3.03 (dd, 1H, H_{17a}, $J_{17a,17b}=9$, $J_{17a,16}=6$), 2.92 (dd, 1H, H_{17b}, $J_{17a,17b}=9$, $J_{17b,16}=6$), 2.68 (m, 1H, H_6), 2.44 (dd, 1H, H_{9a}, $J_{9a,9b}=13$, $J_{9a,8}=3$), 2.20 (m, 1H, H_{16}), 1.94 (d, 3H, CH_3, $J_{CH_3,5}=1$), 1.92 (m, 1H, H_{9b}), 1.78 (s, 3H, CH_3), 1.72 (m, 1H, H_8), 1.45 (m, 6H, $CH_3CH_2CH_2CH_2Sn$), 1.27 (m, 6H, $CH_3CH_2CH_2CH_2Sn$), 1.04 (d, 3H, CH_3, $J_{16,CH_3}=7$), 0.96 (d, 3H, CH_3, $J_{6,CH_3}=7$), 0.96 (t, 9H, CH_3CH_2Si, $J_{CH_3,CH_2Si}=8$), 0.86 (t, 9H, $CH_3CH_2CH_2CH_2Sn$, $J_{CH_3CH_2}=7$; t, 6H, $CH_3CH_2CH_2CH_2Sn$, $J_{CH_2CH_2Sn}=7$), 0.73 (d, 3H, CH_3, $J_{8,CH_3}=7$), 0.66 (q, 6H, CH_3CH_2Si, $J_{CH_3,CH_2Si}=8$); ^{13}C NMR (50.3 MHz, $CDCl_3$): 164.2 (C_1), 158.1 (C=$COCH_3$), 146.9 (C_{10}), 144.7 (C_{13}), 144.4 and 136.2 (Cq Ar), 142.9 and 135.2 (C_2, C_4), 140.9 (C_5), 130.2 (C_3), 129.3(C_{12}), 129.9, 128.1, 127.5 and 126.4 (CH Ar), 112.8 (C=$COCH_3$), 85.4 (C_{15}), 85.2 (CqO), 80.4 (C_7), 75.4 (C_{11}), 75.0 (C_{14}), 65.7 (C_{17}), 60.0 (C_2OCH_3), 56.1 ($HC_{14}OCH_3$), 54.9 (OCH_3), 42.9 (C_9), 35.8 and 34.7 (C_6, C_8), 28.9 and 27.0 ($CH_3CH_2CH_2CH_2Sn$), 24.5, 18.2, 15.6, 14.5 and 13.5 (CH_3), 13.9 ($CH_3CH_2CH_2CH_2Sn$), 12.6 ($CH_3CH_2CH_2CH_2Sn$), 6.9 (CH_3), 5.3 (CH_2Si); $C_{63}H_{97}IO_8SiSn=1256.15$; MS (FD, m/z): 1256 (M^+), 1199, 1128.