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Tetrahedron Letters 45 (2004) 4539–4543
Tetrahedron Letters

Synthetic studies on bafilomycin A_1: first formation of the 16-membered macrolide via an intramolecular Stille reaction

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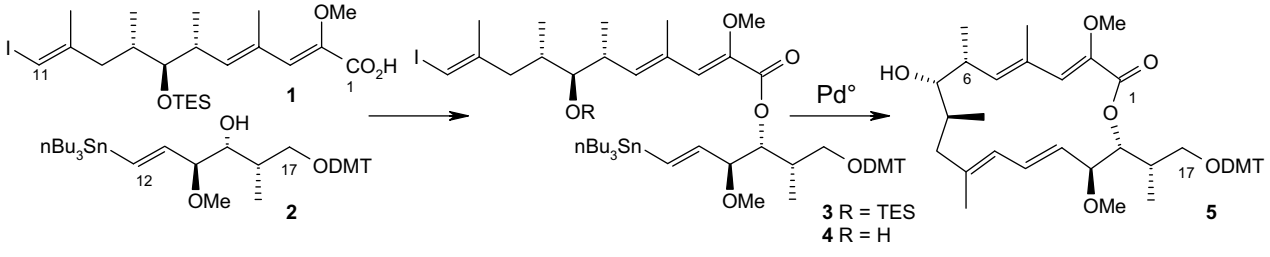
Received 23 March 2004; accepted 7 April 2004

Abstract—The 16-membered macrolide formation of a bafilomycin A_1 synthesis intermediate showed to be very difficult to achieve via an intramolecular Stille reaction. Complex reactions were observed, depending on the nature of the palladium source, ligand, solvent and reaction conditions. Unexpected reactions of the 2-furyl group transfer of trifurylphosphine were observed on the vinylic iodide and (or) the vinylstannane. Best conditions were found with $Pd_2(dba)_3/AsPh_3/i\text{-}Pr_2NEt$ in DMF, at 40 °C, to afford the desired macrocycle in 28% yield (33% corrected), the structure of which was definitely confirmed by chemical filiation.

In the two preceding communications, we described the synthesis of the enantiopure C_1–C_{11} fragment **1** of bafilomycin A_1,[1a] that of the required C_{12}–C_{17} subunit **2** and their intermolecular esterification product **3**.[1b] We herein report our results concerning the formation of the 16-membered macrolactone of bafilomycin A_1, for the first time via an intramolecular Stille coupling, thus obtaining **5** from **4** (Scheme 1).[2] The synthesis of **5** corresponds to a formal one of bafilomycin A_1 via a strategy developed by Evans and Calter for the completion.[3]

At the present time, the 16-membered macrolide formation of bafilomycin A_1 has always been achieved via an acyl activation, first in 55–60% yield by Evans and Calter who used a modification of Yamaguchi's standard procedure,[4] based on the fact that they observed the formation of the symmetric anhydride in the conditions required for the lactonization (dilution, toluene, 100 °C) and therefore used a large excess of 2,4,6-trichlorobenzoyl chloride/NEt_3/DMAP.[3a] Independently, Yonemitsu and co-workers made analogous observations and used a similar procedure in their total synthesis of hygrolidin.[5] Similar procedures have been afterwards employed by Toshima et al.[6] and Roush and co-workers.[7] An acyl activation with (EDC, HCl) in the presence of DMAP was later used by Hanessian et al.[8] The success or failure of macrolactonization via an acyl activation is also highly dependent on the nature of the precursor and its preferred conformation(s).[3–9] Therefore, instead of an acyl activation and in order to study an alternate solution, we decided to examine the



Scheme 1.

Keywords: Macrolides; Intramolecular Stille reaction; Palladium and compounds; Phosphines; Tin and compounds; Solvents and solvent effects.
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doi:10.1016/j.tetlet.2004.04.035

formation of the macrocycle via an intramolecular Stille coupling.[10] 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 C_{12}–C_{17} alcohol **2** (ee = 80%) (1.08 equiv), in the presence of Yamaguchi's chloride,[4] NEt_3 and DMAP, at room temperature.[1b]

1. Attempted intramolecular Stille coupling of 3 (Scheme 2)

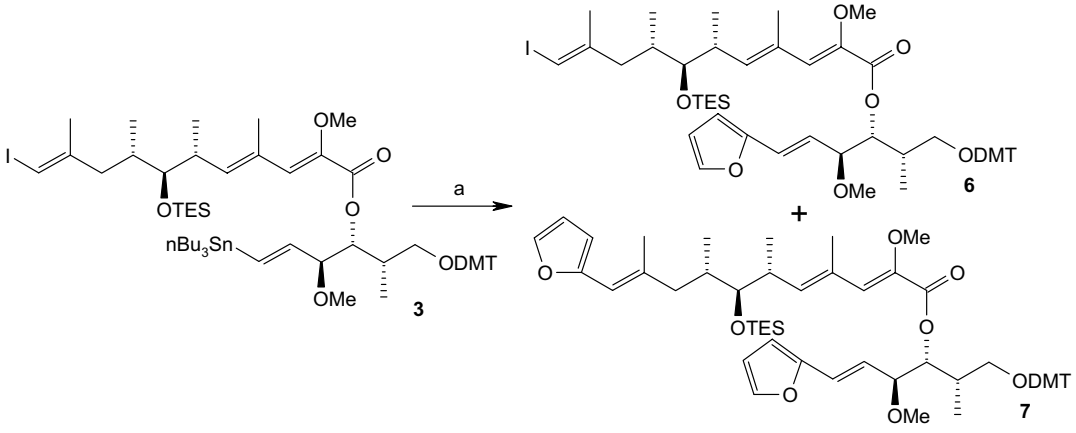
We never could obtain the 16-membered macrolide via an intramolecular Stille coupling of the 7-OTES precursor **3**. Just starting material was recovered with $PdCl_2(MeCN)_2$, in the presence of Ph_3P, in DME at reflux. Very complex reaction mixtures, with some **3** were obtained in other conditions such as {$[Pd(OAc)_2 + 4Ph_3P]$[11] (5–15 mol%), toluene, 65 °C, overnight or in DMF, rt, overnight} or $[Pd(PPh_3)_4$ (10 mol%), toluene, at 80 °C or 110 °C]. Compared to triphenylphosphine, tri-2-furylphosphine (TFP) and triphenylarsine as palladium ligands have been shown to give a large rate increase of the Stille coupling when the transmetalation is the rate-determining step of the catalytic cycle.[12] However, with $[Pd(OAc)_2 + 4TFP]$ (20 mol%), quite surprisingly we only could isolate products resulting from the coupling of **3** with the 2-furyl group from the phosphine, **6** and **7** in 6% and 11% yield, respectively, and some deprotection of the 17-ODMT ether also occurred since we isolated 14% DMTOH (Scheme 2). To our knowledge, such transfers of the 2-furyl group of the phosphine were seldom observed,[13] or even for the phenyl group of triphenylarsine.[13–15] In contrast, the phenyl group transfer of triphenylphosphine as a ligand is sometimes a competitive reaction in palladium-catalyzed reactions (Stille, Heck, Suzuki).[13,15,16] Facile aryl–aryl exchange between an aryl substituted by an electron donating group at the palladium(II) centre and the phenyl groups of triphenylphosphine has been demonstrated by Kong and Chen, the migration from palladium to phosphorus being enhanced with electron donating substituents of the aryl group at the Pd(II) centre and their number.[17]

We then decided to examine the cyclization of the 7-OH derivative **4**, since the nature of the 7-OH protective group has been shown to affect the conformation of the macrolide precursor by Evans and Calter.[3a] Later the free 7-OH was also found to allow the lactonization by Roush and co-workers.[7]

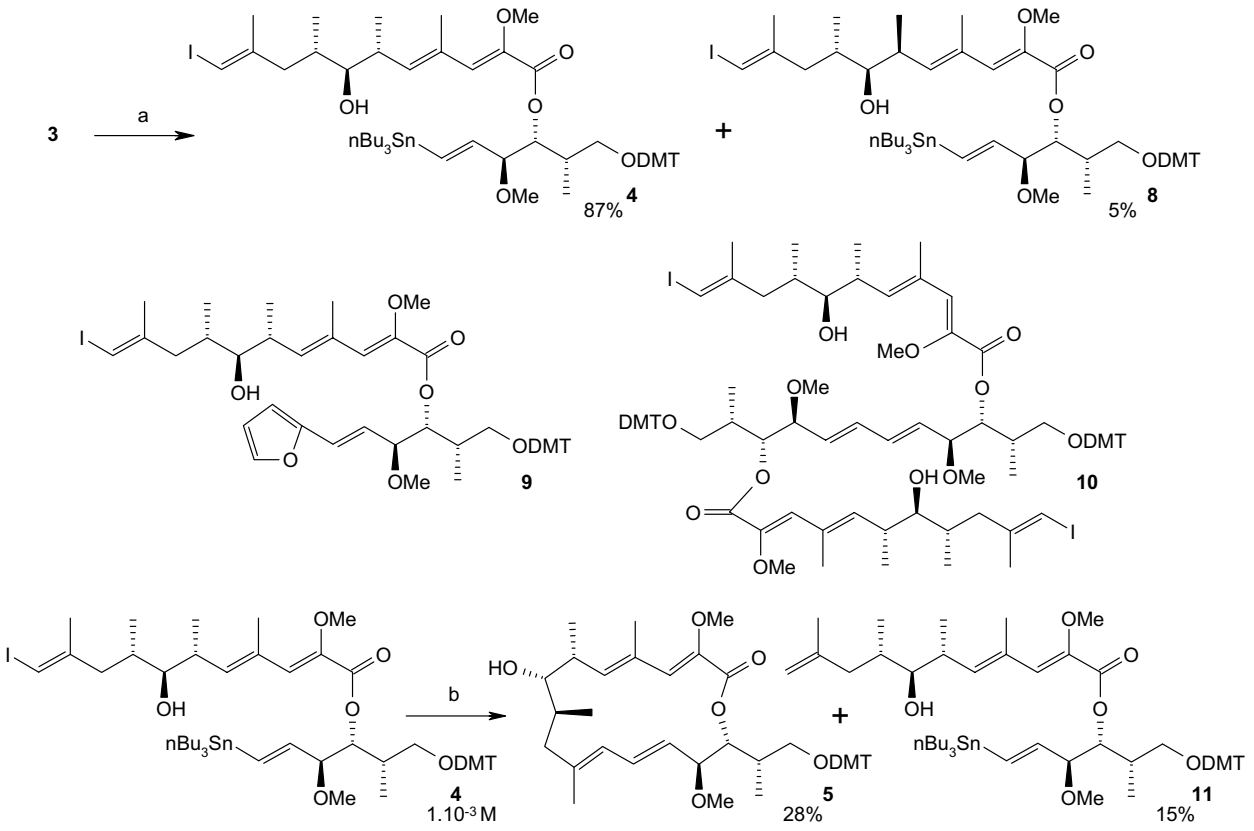
2. Preparation of 4 and intramolecular Stille coupling (Scheme 3)

Hence deprotection with TBAF in THF at rt afforded **4** and the 6-epimer **8**, respectively, in 87% and 5% isolated yields, thus clearly pointing out the high sensitivity of the 6-position to basic conditions.

Attempted cyclizations of **4** with the catalyst produced from $[Pd(OAc)_2 + 4$ TFP] (10–15 mol%), in DME (60 °C, 3 h) or DMF (50 °C, 45 h) gave **9**, which was the only product which could be characterized in 11% and 10% yields, with reisolated starting material (29% and 42%), respectively, for each of reaction conditions. The desired macrolide **5** could only be obtained with $[Pd_2(dba)_3/AsPh_3]$[12] in DMF, in the presence of *i*-Pr_2NEt, at 50 °C, or even at rt (but in a too slow reaction), conditions which minimized deprotection of the DMT ether and destannylation. THF or DME as solvents were unsatisfactory and mixtures of those with DMF (10 equiv), or THF/DMF (1/1), gave inferior results when compared with those obtained in DMF with the same catalytic system. On the other hand, reaction of **4** (0.0005 M) in the presence of $[Pd(OAc)_2 + 4AsPh_3]$ (10 mol%) and *i*-Pr_2NEt (10 equiv), in DMF (50 °C, 3.5 days), just gave 11% of the desired **5**, and **4** was reisolated in 35% yield. $Pd_2(dba)_3$ (10 mol%) with $AsPh_3$ (80 mol%), in otherwise the same conditions, gave after 24 h **5** (23%), recovered **4** (12%) and traces of the homocoupling product **10**. NMP or THF/DMF (1/1) gave inferior results in the same conditions. For comparison also, when associated to $Pd_2(dba)_3$,[11b,18] PPh_3 or P(*p*-$MeOC_6H_4)_3$ gave only traces of **5** after 3.5 and 2 days, respectively, starting material being partly recovered (55% and 33%). Increasing catalyst or substrate concentration in order to try to get faster reactions were



Scheme 2. Reagents and conditions: (a) $Pd(OAc)_2$ (10 mol%), TFP (40 mol%), DME, rt, 2.5 h, then **3** (0.005 M), 60 °C, 11 h, followed by addition of a preformed solution of $Pd(OAc)_2$ (10 mol%) and TFP (40 mol%) in DME, reflux, 7 h.

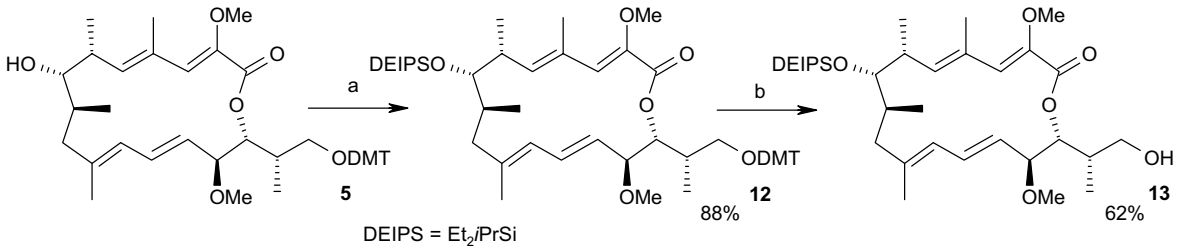


Scheme 3. Reagents and conditions: (a) TBAF 1 M in THF (1.1 equiv), **3** (1 M), rt, 2 h, then addition of TBAF (1.1 equiv), rt, 2 h; (b) $Pd_2(dba)_3$ (10 mol %), $AsPh_3$ (80 mol %), *i*-Pr_2NEt (10 equiv), DMF, rt, then **4** (0.001 M), 40 °C, 30 h.

unsatisfactory; thus **4** (0.005 M) with $Pd_2(dba)_3$ (20 mol %)/$AsPh_3$ (160 mol %)/*i*-Pr_2NEt (10 equiv), in DMF (50 °C, 2.5 h) afforded **5** in only 13% yield and significantly increased **10** (15%). After examination of temperature and dilution effects, the best conditions we found gave the desired macrolide **5** in 28% yield, and the vinylic iodide reduction product **11** (15%) with still some starting material **4** (15%) after chromatography.

More recently, a thorough study of the Stille coupling of phenyl iodide with $CH_2{=}CH{-}SnBu_3$, in DMF, catalyzed by $Pd(dba)_2/AsPh_3$ has shown the complex role of the constituents of the system for the oxidative addition and the transmetalation.[19] It is worth also to mention that when we tried to facilitate the transmetalation step in a different manner, by formation of insoluble $Ph_2PO_2SnBu_3$ as $SnBu_3$ scavenger,[20] the macrolide **5** was obtained in only 10% yield by reaction of **4** (0.0005 M) with $Pd_2(dba)_3$ (10 mol %)/$Ph_2PO_2^-$, $^+NBu_4$ (1.5 equiv)/*i*-Pr_2NEt (10 equiv) in DMF (50 °C, 24 h), with recovered **4** (11%).

Thus, an intramolecular Stille coupling affords the 16-membered ring macrolide of bafilomycin A_1 in a significantly lower yield (28%, 33% corrected yield) than in the related formation of concanolide A, which was obtained in 72% yield in quite comparable conditions by Toshima and co-workers.[21] The same significant difference is observed for macrolactonization via the same acyl activation procedure.[6,21] Examination of the X-rays structures of bafilomycin A_1[22] and concanamycin A[23] show different conformations for the 16- and 18-membered macrolides and that the steric interactions are much more severe for bafilomycin A_1. Consistently, ^1H and ^{13}C NMR studies, and circular dichroism have shown much more conformational flexibility for concanamycin A[24] in solution than for bafilomycin A_1 16-membered lactone ring, that of the latter being very limited in solution and conformation being very similar to that found in the crystal structure.[25] As appearing either from the macrolactonizations by acyl activation or here by the intramolecular coupling, it is probably more difficult to find among the conformations of the macrocycle precursor, which are in dynamic equilibrium, those which allow the formation of the macrolide or of the intermediate palladamacrocycle in the case of bafilomycin than for concanamycin. The problem is still more acute for intramolecular Stille or Suzuki couplings, since dilution is required for avoiding intermolecular reactions, thus slowing down the catalytic process. Indeed here a successful macrocyclization not only requires a good turn-over of the catalyst, that is that the absolute rates of each individual step of the catalytic cycle have to be of the same order of magnitude, but also that those rates have to be compatible with the rates of interconversion between the different conformations of the precursor in order to get those allowing the macrocycle formation.



Scheme 4. Reagents and conditions: (a) DEIPSOTf (6 equiv), *i*-Pr_2NEt (14 equiv), DMF, rt, 3 h; (b) PPTS (1 equiv), MeOH, rt, 4 h.

3. Chemical filiation with Toshima's intermediate (Scheme 4)

In order to get a definite proof of the structure for the macrolide **5**, a chemical filiation was achieved with **13**, intermediate involved in the total synthesis of bafilomycin A_1 of Toshima et al.[6] (Scheme 4). Therefore, formation of the 7-ODEIPS derivative **12** and subsequent DMT ether cleavage afforded the macrolide **13**, which was definitely identical to the previously described compound, as shown by unambiguous comparison of the NMR data.[26]

Acknowledgements

We thank the staff of the Analytical Department of the Research Center at Romainville and also Roussel Uclaf, Hoechst Marion Roussel and the CNRS for a Ph.D. grant to E. Quéron, the Direction des Recherches Chimiques of Roussel Uclaf and HMR for support of this work.

References and notes

1. (a) Quéron, E.; Lett, R. *Tetrahedron Lett.*, **2004**, *45*, preceding paper doi:10.1016/j.tetlet.2004.04.033; (b) Quéron, E.; Lett, R. *Tetrahedron Lett.*, **2004**, *45*, preceding paper doi:10.1016/j.tetlet.2004.04.034.
2. Quéron, E. Ph.D. thesis, Paris VI University, 2000.
3. (a) Calter, M. A. Ph.D. thesis, Harvard University, 1993 (b) Evans, D. A.; Calter, M. A. *Tetrahedron Lett.* **1993**, *34*, 6871–6874.
4. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
5. Makino, K.; Nakajima, N.; Hashimoto, S.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 9077–9080.
6. Toshima, K.; Jyojima, T.; Yamaguchi, H.; Noguchi, Y.; Yoshida, T.; Murase, H.; Nakata, M.; Matsumura, S. *J. Org. Chem.* **1997**, *62*, 3271–3284.
7. (a) Scheidt, K. A.; Tasaka, A.; Bannister, T. D.; Wendt, M. D.; Roush, W. R. *Angew. Chem., Int. Ed.* **1999**, *38*, 1652–1655; (b) Scheidt, K. A.; Bannister, T. D.; Tasaka, A.; Wendt, M. D.; Savall, B. M.; Fegley, G. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 6981–6990.
8. Hanessian, S.; Ma, J.; Wang, W.; Gai, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10200–10206.
9. Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **2002**, *67*, 733–740.
10. Duncton, M. A. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1235–1246.
11. (a) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009–3013; (b) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254–278.
12. (a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595; (b) Farina, V.; Roth, G. P. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI, 1996. Vol. 5, p 1–53.
13. Segelstein, B. E.; Butler, T. W.; Chenard, B. L. *J. Org. Chem.* **1995**, *60*, 12–13.
14. Crisp, G. T.; Glink, P. T. *Tetrahedron* **1994**, *50*, 3213–3234.
15. Morita, D. K.; Stille, J. K.; Norton, J. R. *J. Am. Chem. Soc.* **1995**, *117*, 8576–8581.
16. (a) O'Keefe, D. F.; Dannock, M. C.; Marcuccio, S. M. *Tetrahedron Lett.* **1992**, *33*, 6679–6680; (b) Hunt, A. R.; Stewart, S. K.; Whiting, A. *Tetrahedron Lett.* **1993**, *34*, 3599–3602; (c) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034–5037.
17. Kong, K.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6313–6315.
18. Amatore, C.; Jutand, A. *Coord. Chem. Rev.* **1998**, *178–180*, 511–528.
19. (a) Amatore, C.; Bucaille, A.; Fuxa, A.; Jutand, A.; Meyer, G.; Ndedi Ntepe, A. *Chem. Eur. J.* **2001**, *7*, 2134–2142; (b) Amatore, C.; Bahsoun, A. A.; Jutand, A.; Meyer, G.; Ndedi Ntepe, A.; Ricard, L. *J. Am. Chem. Soc.* **2003**, *125*, 4212–4222.
20. (a) Srogl, J.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 12376–12377; (b) Arimoto, H.; Nishimura, K.; Kuramato, M.; Uemura, D. *Tetrahedron Lett.* **1998**, *39*, 9513–9516; (c) Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935–3948; (d) Toshima, K.; Arita, T.; Kato, K.; Tanaka, D.; Matsumura, S. *Tetrahedron Lett.* **2001**, *42*, 8873–8876.
21. Jyojima, T.; Miyamoto, N.; Katohno, M.; Nakata, M.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **1998**, *39*, 6007–6010.
22. Baker, G. H.; Brown, P. J.; Dorgan, R. J. J.; Everett, J. R.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron Lett.* **1987**, *28*, 5565–5568.
23. (a) Westley, J. W.; Liu, C.-M.; Sello, L. H.; Evans, R. H.; Troupe, N.; Blount, J. F.; Chiu, A. M.; Todaro, L. J.; Miller, P. A. *J. Antibiotics* **1984**, *37*, 1738–1740; (b) Nakai, H.; Matsutani, S. *Acta Cryst.* **1992**, *C48*, 1519–1521.
24. Bindseil, K. U.; Zeeck, A. *Liebigs Ann. Chem.* **1994**, 305–312.
25. (a) Baker, G. H.; Brown, P. J.; Dorgan, R. J. J.; Everett, J. R. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1073–1079; (b) Everett, J. R.; Baker, G. H.; Dorgan, R. J. J. *J. Chem. Soc., Perkin Trans. 2* **1990**, 717–724.
26. Compound **5**: pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ/TMS 7.46 (d, 2H, Ha, $J_{Ha,Hb} = 9$), 7.34 (d, 4H, Hd, $J_{Hd,He} = 9$), 7.29 (m, 2H, Hb), 7.19 (m, 1H, Hc),

6.81 (d, 4H, He, $J_{Hd,He} = 9$), 6.60 (s, 1H, H_3), 6.40 (dd, 1H, H_{12}, $J_{12,13} = 15$, $J_{12,11} = 11$), 5.85 (d, 1H, H_{11}, $J_{11,12} = 11$), 5.77 (dq, 1H, H_5, $J_{5,6} = 7$, $J_{CH_3,5} = 1$), 5.24 (dd, 1H, H_{13}, $J_{13,12} = 15$, $J_{13,14} = 7$), 4.99 (dd, 1H, H_{15}, $J_{15,14} = 6$, $J_{15,16} = 6$), 3.82 (m, 1H, H_{14}), 3.78 (s, 6H, OCH_3), 3.62 (s, 3H, CH_3, C_2OCH_3), 3.39 (m, 1H, H_7), 3.17 (m, 1H, H_{17a}), 3.16 (s, 3H, CH_3, $HC_{14}OCH_3$), 3.01 (dd, 1H, H_{17b}, $J_{17a,17b} = 9$, $J_{17b,16} = 6$), 2.49 (m, 1H, H_6), 2.18 (m, 1H, H_{9a}), 2.16 (m, 1H, H_{16}), 2.02 (br s, 1H, H_{9b}), 1.95 (d, 3H, CH_3, $J_{CH_3,5} = 1$), 1.87 (m, 1H, H_8), 1.74 (s, 3H, CH_3), 1.49 (d, 1H, OH, $J_{OH,7} = 7$), 1.04 (d, 3H, CH_3, $J_{16,CH_3} = 7$), 1.07 (d, 3H, CH_3, $J_{6,CH_3} = 7$), 0.97 (d, 3H, CH_3, $J_{8,CH_3} = 7$); ^{13}C NMR (50.3 MHz, $CDCl_3$): 164.2 (C_1), 158.3 (C═COCH$_3$), 145.0 (C_{10}), 141.8 and 136.4 (Cq Ar), 141.2 and 132.1 (C_2, C_4), 140.8 (C_5), 131.7 (C_3), 131.1 (C_{13}), 130.1, 128.3, 127.7 and 126.6 (CH Ar), 126.0 and 125.2 (C_{11}, C_{12}), 113.0 (C═COCH$_3$), 85.9 (CqO), 82.8 (C_{15}), 81.2 (C_7), 76.7 (C_{14}), 65.4 (C_{17}), 59.8 ($C_2O\mathit{CH}_3$), 55.8 ($HC_{14}O\mathit{CH}_3$), 55.2 (OCH_3), 41.5 (C_9), 38.3, 37.7 and 36.5 (C_6, C_8, C_{16}), 23.2, 18.4, 18.3, 13.8 and 13.6 (CH_3); $C_{45}H_{56}O_8 = 724.39$; HRMS/EI: M^+ calcd: 724.3975, found: 724.3972.

Compound **13**: pale yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ/TMS 6.67 (s, 1H, H_3), 6.47 (dd, 1H, H_{12}, $J_{12,13} = 15$, $J_{11,12} = 11$), 5.92 (d, 1H, H_{11}, $J_{11,12} = 11$), 5.88 (dq, 1H, H_5, $J_{5,6} = 9$, $J_{CH_3,5} = 1$), 5.39 (dd, 1H, H_{13}, $J_{13,12} = 15$, $J_{13,14} = 5$), 5.12 (dd, 1H, H_{15}, $J_{15,14} = 5$, $J_{15,16} = 5$), 3.94 (dd, 1H, H_{14}, $J_{14,13} = 5$, $J_{14,15} = 5$), 3.67 (s, 3H, CH_3, C_2OCH_3), 3.62 (dd, 1H, H_7, $J_{7,6} = 3$, $J_{7,8} = 3$), 3.53 (dd, 1H, H_{17a}, $J_{17a,17b} = 9$, $J_{17a,16} = 6$), 3.37 (dd, 1H, H_{17b}, $J_{17a,17b} = 9$, $J_{17b,16} = 8$), 3.29 (s, 3H, CH_3, $HC_{14}OCH_3$), 3.00 (m, 1H, OH), 2.40–2.55 (m, 2H, H_6, H_{9a}), 2.15 (m, 1H, H_{16}), 1.94 (d, 3H, CH_3, $J_{CH_3,5} = 1$), 1.70–1.85 (m, 2H, H_8, H_{9b}), 1.68 (s, 3H, CH_3), 0.98–1.13 (m, 19H, SiCH(CH$_3$)$_2$, SiCH(CH_3)$_2$, Si(CH$_2\mathit{CH}_3$)$_2$, HC$_8\mathit{CH}_3$, HC$_6\mathit{CH}_3$), 0.90 (d, 3H, CH_3, $J_{16,CH_3} = 7$), 0.64–0.83 (m, 4H, Si(CH_2CH$_3$)$_2$); ^{13}C NMR (50.3 MHz, $CDCl_3$): 165.7 (C_1), 143.7 (C_{10}), 141.2 (C_5), 141.1 and 131.4 (C_2, C_4), 133.3 (C_{13}), 130.8 (C_3), 125.3 and 124.7 (C_{11}, C_{12}), 82.6 (C_{15}), 80.8 (C_7), 77.1 (C_{14}), 64.6 (C_{17}), 60.2 ($C_2O\mathit{CH}_3$), 56.3 ($HC_{14}O\mathit{CH}_3$), 41.5 (C_9), 40.1, 38.0 and 37.7 (C_6, C_8, C_{16}), 24.8, 18.4, 17.8, 13.6 and 11.5 (CH_3), 7.4 (SiCH(CH$_3$)$_2$), 4.8 and 4.3 (Si(CH_2CH$_3$)$_2$).