Preparation of the Three C1-C7, C8-C15, and C16-N22 Fragments of the Hsp90 Inhibitor Herbimycin A

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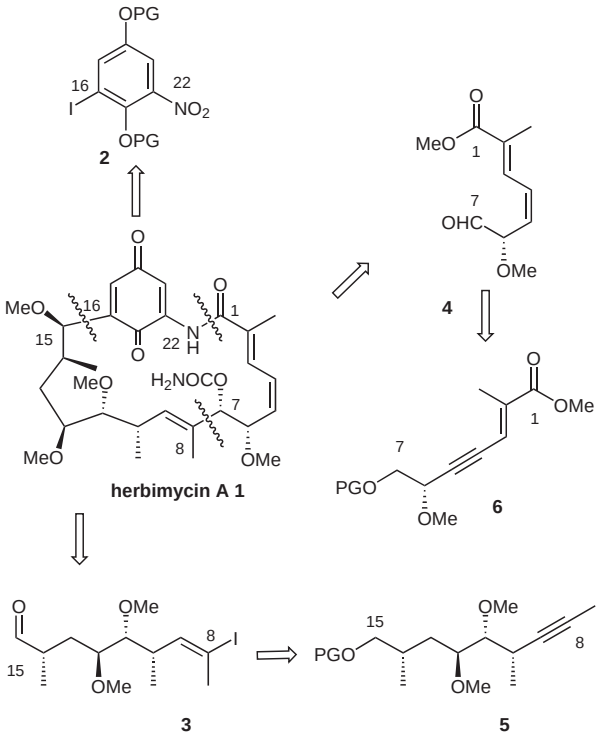
Abstract: The construction of the three C16-N22 **2**, C1-C7 **6** (as **23**) and C8-C15 **5** (as **32**) segments of the Hsp90 inhibitor herbimycin A (**1**) is reported. 1-Iodo-3-nitro-2,5-diphenol compound **2** was obtained in 55% yield for 3 steps from the commercially available diiodo derivative **7**. Reaction between 1,1-dibromo-alkene **22** and vinyltin **17a** using $Pd(PPh_3)_4$ or $Pd(CH_3CN)_2Cl_2$/CuI/diisopropylethylamine, in toluene or DMF at 85 °C, led to enyne **23** in 63% yield (19% overall yield from isopropylidene glyceraldehyde). The synthesis of the C8-C15 sub-unit **32** was performed in 3.4% overall yield for 13 steps, from the commercially available ester **24**, with a Hoppe crotylation as a key step.

Key words: herbimycin A, synthesis, Stille, enyne, 1,1-dibromo-1-alkene, Sharpless oxidation, Hoppe aldehyde allylation

Molecular chaperones such as heat shock protein 90 (Hsp90) assist the folding, maturation and subcellular localization of their client proteins, and target damaged proteins for degradation via the proteasome. Therefore, the inhibition of Hsp90 provides a novel approach toward regulating crucial enzymes involved in the progression of cancer. The benzoquinoid ansamycins, such as herbimycin A and geldanamycin, have recently been identified as inhibitors of the Hsp90 folding process. Consequently, these molecules are getting a lot of attention in the literature.[1]

Herbimycin A (**1**)[2] was isolated from the fermentation broth of *Streptomyces hygroscopicus* strain AM-3672, and exhibits pronounced antitumor and antiangiogenic properties. At this time, only two syntheses of herbimycin A (**1**) have been reported.[3]

Our synthetic plan developed for herbimycin A (**1**) involved the convergent approach depicted in Scheme 1. Our intention was to employ metal-catalyzed coupling reactions to form both the C15-C16 bond between the Northern C16-N22 aromatic fragment **2** and the Southern C8-C15 side chain **3**, and the C7-C8 link between the Eastern C1-C7 dienyl sub-unit **4** and segment **3**. A macrolactamization reaction was programmed for the final cyclization step at N22-C1.



Scheme 1

The present work describes the preparation of C16-N22 diphenol **2**, C1-C7 enyne **6** and C8-C15 alcohol **5** (as precursors of compounds **4** and **3**, respectively).

Northern fragment **2** was prepared in 55% overall yield for 3 steps from the commercially available diiodo compound **7**. Mono-nitration of **7** under classical conditions led to nitro-aldehyde **8** in 80% yield. In order to generate the diphenol derivative **9**, we took advantage of the aldehyde function to perform a Baeyer–Villiger oxidation. This reaction cleanly delivered compound **9** in 80% yield (Scheme 2).

The last step for the preparation of C16-N22 Northern fragment **2** was achieved by methylation of **9** by means of KOH/MeI in DMF at 20 °C for 4 hours, in 85% yield.[4]

For the Eastern fragment **4** synthesis, a Stille Pd(0)-catalyzed coupling reaction was planed between vinyl

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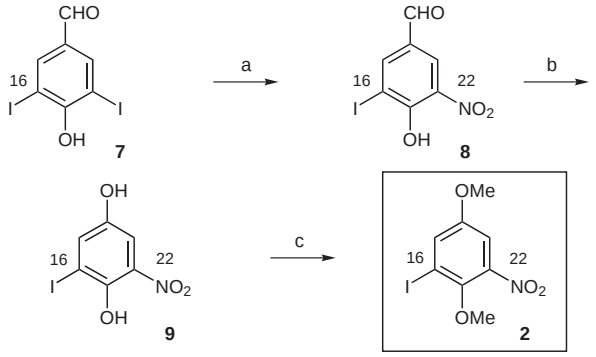
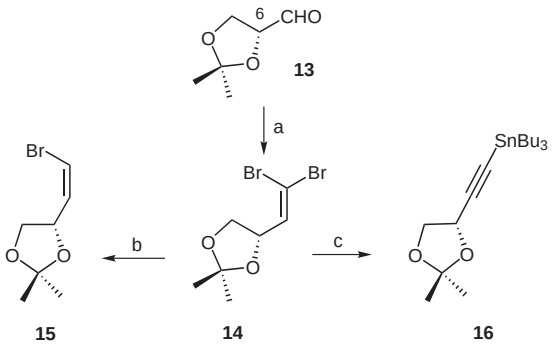


Scheme 2 a) $NaNO_2$ (1 equiv), HOAc 80 °C, 15 h, 80%; b) *m*-CPBA (3 equiv), CH_2Cl_2, 4 °C, 15 h, 80%; c) KOH, MeI, DMF, 20 °C, 4 h, 85%.



Scheme 4 a) Zn (3 equiv), CBr_4 (3 equiv), PPh_3 (3 equiv), CH_2Cl_2, 20 °C 12 h, 65%; b) Bu_3SnH (1.1 equiv), $Pd(PPh_3)_4$, THF, 20 °C, 20 min, 90%; c) *n*-BuLi (3 equiv), –40 °C, 2 h, Bu_3SnCl, 20 °C, 1 h, 95%.

partners **10** and **11** (Scheme 3), or between **10** and acetylenic compound **12**. In this approach, a partial reduction of the resulting enyne **6** is required to reach the desired compound **4**.

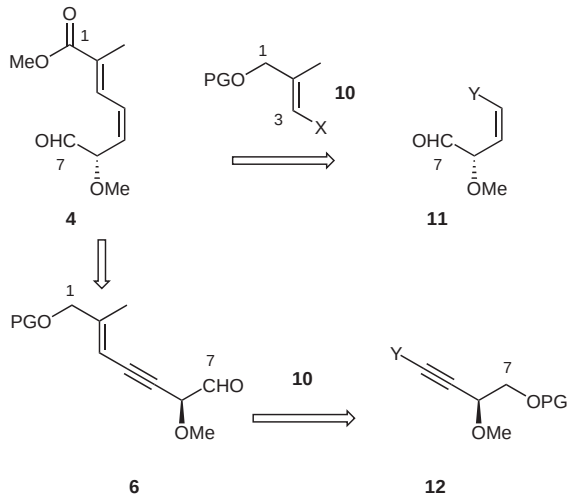
For synthesis of compounds **11** and **12**, isopropylidene glyceraldehyde **13**[5] was selected as an appropriate starting material to introduce the C-6 centre (Scheme 4). Application of the Corey–Fuchs method[6] then led to dibromo alkene **14**, which is a versatile intermediate.[7]

1,1-Dibromo-1-alkene **14** delivered pure (*Z*)-vinyl bromide **15** under Bu_3SnH/Pd(0) conditions, in 90% yield (Scheme 5).[8] Besides, acetylenic compounds **16**[7] (95% yield) was easily obtained by *n*-BuLi treatment of **14**, followed by Bu_3SnCl trap.

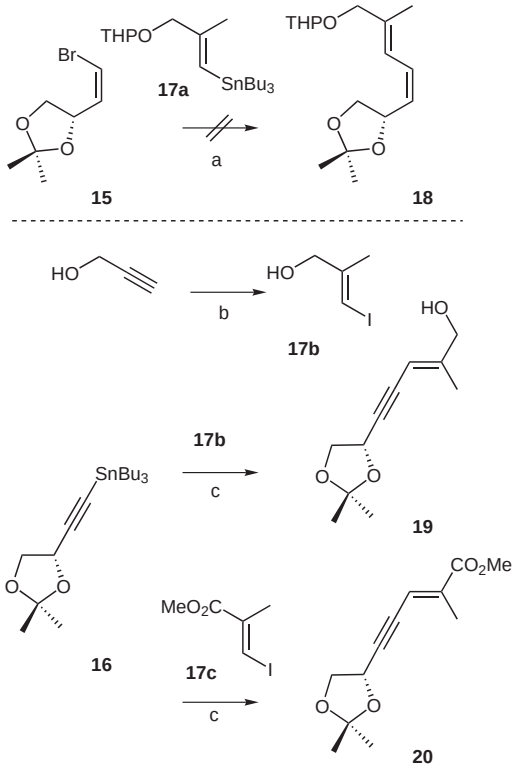
However, we were disappointed to find out that Stille coupling reaction[9] between vinylbromide **15**, vinyliodide **17b** or **17c**[10] and vinyltin **17a**,[11] or tributylstannylalkyne **16** did not lead, in sufficient yields, to expected diene or enyne compounds **18**, **19** or **20**[12] (Scheme 5).

Consequently, we turned to the Shen method.[13] Compound **14** was first transformed in 3 steps via alcohol **21** into the corresponding 1,1-dibromo-alkene derivative **22** in 45% overall yield (Scheme 6).[14] Compounds **22** and **17a** under Shen's conditions [$Pd(PPh_3)_4$ or $Pd(CH_3CN)_2Cl_2$/CuI/diisopropylethylamine, in toluene or DMF at 85 °C] conducted to the expected enyne **23** in 63% yield.[15]

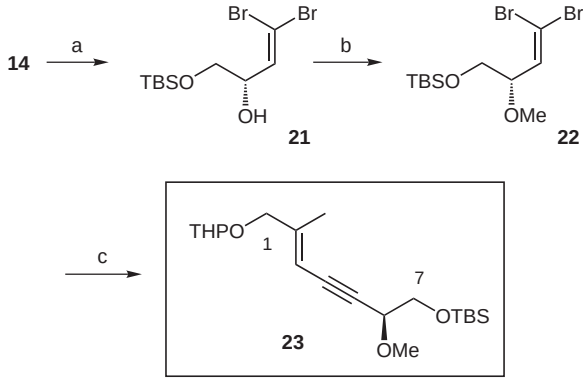
The elaboration of Southern C8-C15 sub-unit **5** started from the commercially available hydroxy-ester **24**; classical transformations gave access, via ester **25**, to the α,β-unsaturated aldehyde **26** in 50% overall yield for 6 steps (Scheme 7).



Scheme 3



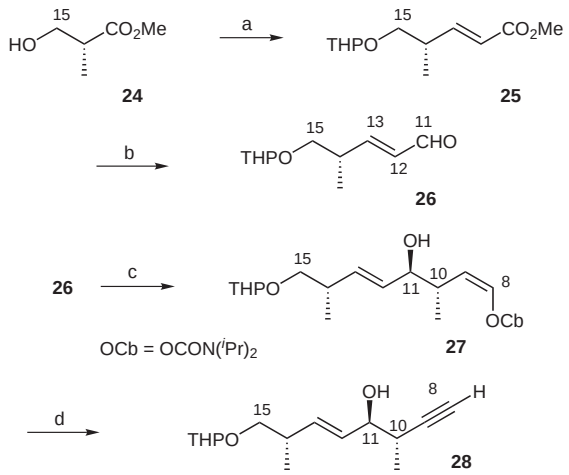
Scheme 5 a) $Pd(PPh_3)_4$ or $Pd(CH_3CN)_2Cl_2$ (15 mol%), CuI (30 mol%), THF, toluene or DMF, 85 °C; b) Cp_2ZrCl_2 (0.25 equiv), $AlMe_3$ (3 equiv), CH_2Cl_2, 20 °C, 24 h, then I_2 (1.2 equiv), 0 °C, 25%; c) **17b** or **17c**, $PdCl(CH_3CN)_2Bn$ (15 mol%), CuI (30 mol%), toluene, 85 °C, 12 h, 30%.



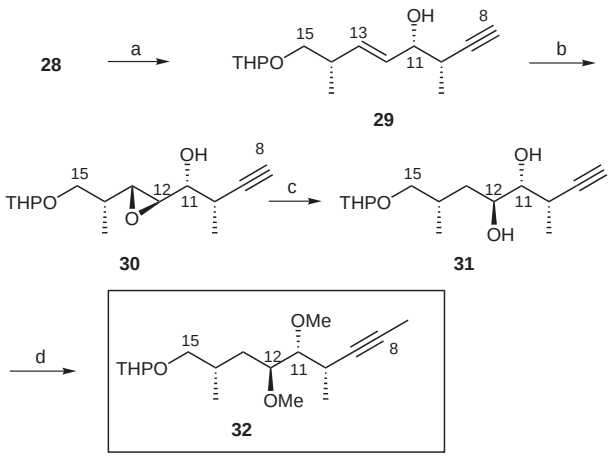
Scheme 6 a) i) Amberlyst 15, MeOH, 20 °C, 12 h, 71%; ii) TBSCl, imidazole, CH_2Cl_2, 20 °C, 10 h, 91%; b) MeI (excess), THF–DMF 8:1, NaH (1.3 equiv), 0 °C, 3 h, 70%; c) **17a**, $Pd(CH_3CN)_2Cl_2$ (15 mol%), CuI (30 mol%), DIPEA (1.5 equiv), DMF, 85 °C, 12 h, 63%.

Elaboration of the C15-C8 skeleton was initiated by an enantioselective Hoppe crotylation[16] of aldehyde **26** to afford the pure vinyl carbamate **27** in 85% yield (100% de, Scheme 7). Further *t*-BuLi (3 equiv) treatment of **27** delivered the expected acetylenic derivative **28** in 70% yield.

Inversion of the C11 center of compound **28** was envisaged under Mitsunobu conditions. As a consequence of the allylic and homopropargylic position of the C11 hydroxyl function, this reaction led to the inverted benzoyl ester in a fair 40% yield when the temperature was kept at –78 °C for 10 minutes. Generation of alcohol **29** was then obtained by $LiAlH_4$ reduction (80% yield, Scheme 8).



Scheme 7 a) i) DHP, APTS, 20 °C, 12 h, 95%; ii) LAH (0.8 equiv)/THF, 0 °C, 3 h, 85%; iii) IBX (2.2 equiv), DMSO, 20 °C, 2 h, quantitative; iv) $(C_6H_5)_3P{=}CHCO_2Me$/toluene, 50 °C, 10 h, 81%; b) i) DIBALH (2.1 equiv)/THF, –78 °C, 1 h, 80%; ii) IBX (2.2 equiv), DMSO, 20 °C, 2 h, 95%; c) (*E*)-crotyl (diisopropyl)carbamate (2.6 equiv), 1.6 M *n*-BuLi in hexane (2.4 equiv), (–)-sparteine (2.3 equiv), –78 °C, 10 min, then –78 °C, 3 h for crystallization. Then Ti(O*i*-Pr)$_4$ (6 equiv), pentane, –50 °C and –78 °C, 30 min for transmetallation, **26** –78 °C, 2 h, 85%; d) *t*-BuLi (3.1 equiv)/Et_2O, –78 °C, 45 min, 70%.



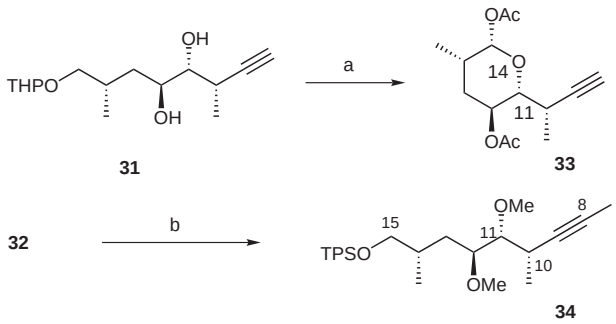
Scheme 8 a) i) DIAD (1.2 equiv), PPh_3 (1.2 equiv), $PhCO_2H$ (1.2 equiv), toluene, –78 °C, 10 min, 40%; ii) $LiAlH_4$, THF, 20 °C, 80%; b) D-(–)-diethyltartarate (1.2 equiv), Ti(O*i*-Pr)$_4$ (1.2 equiv), TBHP (2 equiv), CH_2Cl_2, –25 °C, 15 h, 85%; c) DIBALH (2.1 equiv), THF, 0 °C, 5 h, 60%; d) *n*-BuLi (3.2 equiv), MeI excess, THF, –78 °C to 20 °C, 12 h, 70%.

At this stage, installation of the secondary C12 alcohol function was envisaged in a two steps sequence. Stereoselective matched Sharpless epoxidation[17] of **29** using D-(–)-diethyltartarate gave epoxide **30** in 85% yield as a pure isomer (the corresponding diastereomer was not observed). Reduction of **30** under DIBALH/THF conditions[18] furnished the *anti*-1,2-diol **31** in 60% yield (the corresponding *anti*-1,3-diol was isolated in 9% yield).

Subsequent methylation of **31** was then carried out using 3.2 equivalents of *n*-BuLi and an excess of MeI to furnish dimethoxy derivative **32** in 70% yield.[19]

In this sequence, and in spite of a modest yield for the Mitsunobu reaction, preparation of Southern fragment **32** was achieved in 3.4% overall yield for 13 steps from the commercially available ester **24**.

Structural proof for **31** was obtained by NMR analysis of lactol **33**, prepared in a three-step sequence (Scheme 9); the observed coupling constant $J_{H11\text{-}H12} = 9.8$ Hz, gave confirmation of the C11-C12 *anti* configuration.[20]



Scheme 9 a) i) Amberlyst 15, MeOH, 25 °C, 15 h; ii) IBX (2.2 equiv), DMSO, 0 °C, 1.5 h; iii) Ac_2O, pyridine, 63% yield for 3 steps; b) i) Amberlyst 15, MeOH, 20 °C, 2 h, 75%; ii) TPSCl, imidazole, DMF, 20 °C, 12 h, 85%.

THP ether **32** was also transformed into the TPS derivative **34**[21] which was correlated with the same compound, obtained by another approach based on a sequential Sharpless dihydroxylation–Brown crotylation.[22]

In conclusion, preparation of Northern fragment **2** of herbimycin A **1** was achieved in 55% yield for 3 steps. Synthesis of the Eastern part **23**, precursor of diene fragment **4**, was performed in 19% overall yield for 5 steps from the known glyceraldehyde derivative **13**. Finally, elaboration of the C8-C15 chain **32**, precursor of aldehyde **3**, was accomplished in 3.4% overall yield for 13 steps.

The final synthesis of the Hsp90 inhibitor, herbimycin A (**1**), is under study in our laboratory.

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(4) Compound **2**: ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 2.5 Hz, 1 H), 7.50 (d, *J* = 2.5 Hz, 1 H), 3.85 (s, 3 H, CH_3, OMe), 3.60 (s, 3 H, CH_3, OMe). MS (GC, EI): *m/z* = 309 [M^+].

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(12) Compound **19**: ^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.54 (wide s, 1 H), 4.82 (dd, *J* = 6.4, 6.2 Hz, 1 H), 4.11 (dd, *J* = 7.8, 6.2 Hz, 1 H), 4.04 (s, 2 H), 3.86 (dd, *J* = 7.8, 6.4 Hz, 1 H), 1.81 (s, 3 H, CH_3), 1.57 (s, 1 H, OH), 1.43 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3).

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(14) Compound **22**: ^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.29 (d, *J* = 8.0 Hz, 1 H), 3.93 (m, 1 H), 3.63 (m, 2 H), 3.29 (s, 3 H, CH_3, OCH_3), 0.82 [s, 9 H, 3 CH_3, $SiC(CH_3)_3$], 0.01 [s, 6 H, 2 CH_3, $Si(CH_3)_2$]. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 137.2 (CH), 92.4 (C), 82.2 (CH), 64.4 (CH_2), 57.2 (CH_3, OCH_3), 25.8 [3 CH_3, $SiC(CH_3)_3$], 18.3 [C, $SiC(CH_3)_3$], –4.0, –4.5 [2 CH_3, $Si(CH_3)_2$]. MS (CI, NH_3): *m/z* = 392 [$MH^+ + NH_3$], 375 [MH^+].

(15) Compound **23**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.61 (br s, 1 H), 4.61 (t, *J* = 3.3 Hz, 1 H), 4.19 (d, *J* = 14.4 Hz, 1 H), 4.17 (m, 1 H), 3.94 (d, *J* = 14.4 Hz, 1 H), 3.84 (m, 1 H), 3.79 (dd, *J* = 10.5, 6.5 Hz, 1 H), 3.77 (dd, *J* = 10.5, 5.5 Hz, 1 H), 3.51 (m, 1 H), 3.45 (s, 3 H, CH_3, OCH_3), 1.89 (s, 3 H, CH_3), 1.73–1.58 (m, 6 H, 3 CH_2), 0.82 [s, 9 H, 3 CH_3, $SiC(CH_3)_3$], 0.01 [s, 6 H, 2 CH_3, $Si(CH_3)_2$]. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 148.5 (C), 105.5 (CH), 98.1 (CH), 90.0 (C), 84.2 (C), 73.9 (CH), 70.6 (CH_2), 66.7 (CH_2), 62.5 (CH_2), 57.3 (CH_3, OCH_3), 30.9 (CH_2), 26.4 [3 CH_3, $SiC(CH_3)_3$], 25.8 (CH_2), 19.7 (CH_2), 18.9 [C, $SiC(CH_3)_3$], –4.8, –4.7 [2 CH_3, $Si(CH_3)_2$]. MS (CI, NH_3): *m/z* = 386 [$MH^+ + NH_3$], 369 [MH^+]. IR (CCl_4) 2929, 2856, 2360, 2341, 1578, 1463, 1129, 869 cm^{-1}. Anal. Calcd (%) for $C_{20}H_{36}O_4Si$ (368.58): C, 65.17; H, 9.84. Found: C, 65.35; H, 9.97.

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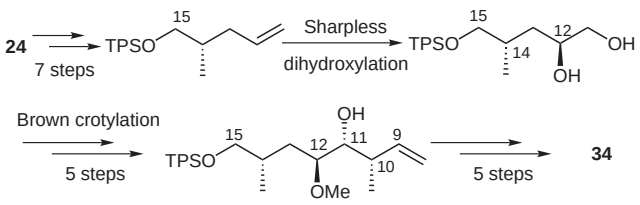
(19) Compound **32**: ^{1}H NMR (270 MHz, $CDCl_3$): δ (two diastereomers) = 4.55 (m, 1 H), 3.87 (m, 1 H), 3.60 (m, 1 H), 3.50 (m, 1 H), 3.39, 3.37 (2 s, 3 H, CH_3, CH_3O), 3.28, 3.26 (2 s, 3 H, CH_3, CH_3O), 3.25 (m, 1 H), 3.20 (m, 1 H), 3.03 (m, 1 H), 2.52 (m, 1 H), 2.03 (m, 1 H), 1.81 (s, 3 H, CH_3), 1.73–1.58 (m, 6 H, 3 CH_2), 1.68 (m, 1 H), 1.32, (m, 1 H), 1.10 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.94 (d, *J* = 6.9 Hz, 3 H, CH_3). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ (two diastereomers) = 98.7, 98.5 (CH), 83.4 (CH), 80.5 (CH), 79.6 (C), 78.5 (C), 72.4, 72.3 (CH_2), 62.4 (CH_2), 61.5, 61.2 (CH_3, CH_3O), 57.9, 57.8 (CH_3, CH_3O), 35.1–34.8 (CH_2), 30.6 (CH_2), 30.4, 30.2 (CH), 29.8 (CH), 25.4, 25.3 (CH_2), 19.3, 19.2 (CH_2), 18.3 (CH_3), 17.8 (CH_3), 3.5 (CH_3). Anal. Calcd for $C_{18}H_{32}O_4$ (312.44): C, 69.19; H, 10.32. Found: C, 69.03; H, 10.56.

(20) Compound **33**: ^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.29 (d, *J* = 5.0 Hz, 1 H), 4.89 (td, *J* = 9.8, 4.3 Hz, 1 H), 3.42 (dd, *J* = 9.8, 2.9 Hz, 1 H), 2.61–2.59 (m, 1 H), 2.34–2.31 (m, 1 H), 2.14–2.04 (m, 9 H, 2 CH_3CO + 2 H), 1.23 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.92 (d, *J* = 6.9 Hz, 3 H, CH_3).

(21) Compound **34**: ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.61–7.58 (m, 4 H, arom.), 7.36–7.31 (m, 6 H, arom.), 3.54 (m, 1 H), 3.42 (m, 1 H), 3.35 (s, 3 H), 3.25 (s, 3 H), 3.15 (m, 1 H), 3.05 (dd, *J* = 7.0, 3.6 Hz, 1 H), 2.55 (m, 1 H), 1.86 (m, 1 H), 1.82 (s, 3 H), 1.64 (m, 1 H), 1.22 (m, 1 H), 1.11 (d, *J* = 7.0 Hz, 3 H), 0.98 [s, 9 H, $SiC(CH_3)_3$], 0.93 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 135.6 (4 CH, arom.), 133.9 (2 C, arom.), 129.4 (2 CH, arom.), 127.5 (4 CH, arom.), 84.0 (CH), 80.2 (CH), 79.8 (C), 78.6 (C), 69.5 (CH_2), 61.2, 57.0 (2 CH_3, 2 CH_3O), 33.2 (CH_2), 30.1 (CH), 28.9 (CH), 26.9 [3 CH_3, $SiC(CH_3)_3$], 19.3 [C, $SiC(CH_3)_3$], 18.5 (CH_3), 16.8 (CH_3), 4.0 (CH_3). Anal. Calcd for $C_{29}H_{42}O_3Si$ (466.73): C, 74.63; H, 9.07. Found: C, 74.86; H, 9.18.

(22) This route used more conventional transformations to reach the desired fragment in a 6% overall yield for 18 steps (Scheme 10). Centonze-Audureau, S.; Porée, F-H.; Betzer, J. F.; Brion, J.-D.; Pancrazi, A.; Ardisson, J. *unpublished results*.



Scheme 10