Tetrahedron 66 (2010) 7738–7742

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Large-scale synthesis of 1,1,3,3,6-pentamethyl-1,3-disilaindan-5-ol via a $CoBr_2$/Zn-catalyzed [2+2+2] cycloaddition reaction

Ryo Mizojiri [a,*], Richard Conroy [c], Jürgen Daiss [b], Etsuo Kotani [a], Reinhold Tacke [b,*], David Miller [c], Louise Walsh [c], Tetsuji Kawamoto [a,*]

[a] Pharmaceutical Research Division, Takeda Pharmaceutical Company Ltd., 2-17-85 Jusohonmach, Yodogawa-ku, Osaka 532-8686, Japan
[b] Universität Würzburg, Institut für Anorganische Chemie, Am Hubland, D-97074 Würzburg, Germany
[c] Takeda Cambridge Ltd., 418 Cambridge Science Park, Cambridge CB4 0PA, UK

ARTICLE INFO

Article history:
Received 18 June 2010
Received in revised form 26 July 2010
Accepted 26 July 2010
Available online 1 August 2010

Keywords:
Sila-substituted drug
Gonadotropin releasing hormone receptor antagonist
1,1,3,3,6-Pentamethyl-1,3-disilaindan-5-ol
Cobalt-catalyzed [2+2+2] cycloaddition reaction
Cobalt(II) bromide

ABSTRACT

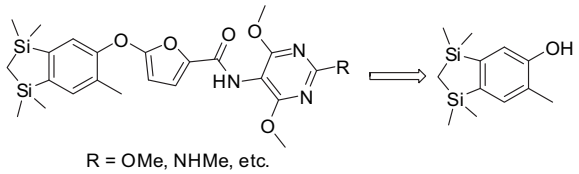
1,1,3,3,6-Pentamethyl-1,3-disilaindan-5-ol (**2**) is a key intermediate in the synthesis of new sila-substituted gonadotropin releasing hormone receptor antagonists, such as **1**. In order to produce sufficient quantities of **1** for pharmacological and toxicological evaluation, an efficient synthesis of **2** has been developed. (1,1,3,3,6-Pentamethyl-1,3-disilaindan-5-yl)methanal (**11**) was synthesized in a one-pot procedure. $CoBr_2$/Zn-catalyzed [2+2+2] cycloaddition of diyne **3** with the commercially available monoalkyne **15** was achieved through a slow addition of **3** and $CoBr_2$ to a mixture of **15** and zinc powder in refluxing acetonitrile, giving rise to 5-(diethoxymethyl)-1,1,3,3,6-pentamethyl-1,3-disilaindane (**14**). In-situ aqueous acidification yielded **11**. Conversion to **2** was then achieved via a Baeyer–Villiger oxidation followed by hydrolysis under basic condition. This novel methodology is useful, not only for the rapid, large-scale synthesis of **2**, but also for the synthesis and development of new sila-substituted drugs derived from **11**.

1. Introduction

Synthesis and evaluation of sila-substituted drugs has attracted considerable attention as a consequence of the unique biological activities, physicochemical properties, and chemical reactivities of sila-drugs when compared with their parent carbon compounds.[1] Tacke and Daiss have synthesized, structurally characterized, and biologically evaluated a large variety of sila-substituted drugs. These include: selective noradrenaline reuptake inhibitors,[2] α-amino acids and peptides as gonadotropin releasing hormone receptor antagonists,[3] muscarinic receptor antagonists,[4] selective σ receptor antagonists,[5] calcium channel antagonists,[6] dopamine receptor antagonists,[7] and histamine H_1 antagonists.[8]

In a continuation of research into the discovery of sila-substituted drugs,[1] 1,3-disilaindanes and 1,4-disila-1,2,3,4-tetrahydronaphthalenes have recently been prepared utilizing cobalt-catalyzed [2+2+2] cycloaddition reactions.[9] These molecular backbones have been used for the synthesis of sila-analogues of RXR-selective retinoid agonists,[10] RAR-selective retinoid agonists,[11] and gonadotropin releasing hormone (GnRH) receptor antagonists.[12]

In order to elucidate the pharmacological properties of 1,3-disilaindanes, such as **1**, as gonadotropin releasing hormone receptor antagonists,[12,13] it was necessary to develop an efficient methodology for the synthesis of the key intermediate 1,1,3,3,6-pentamethyl-1,3-disilaindan-5-ol (**2**) (Scheme 1). However, reports on large-scale syntheses utilizing cobalt-catalyzed [2+2+2] cycloaddition reactions are rare.[14] Herein, we describe an efficient preparation of **2** utilizing a $CoBr_2$/Zn-catalyzed [2+2+2] cycloaddition reaction.



R = OMe, NHMe, etc.

1 **2**

Scheme 1.

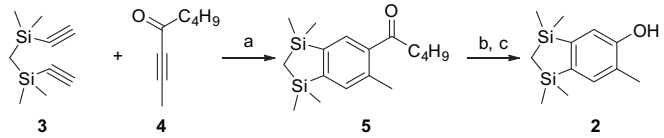
* Corresponding authors. Tel.: +81 6 6300 6836; fax: +81 6 6300 6306 (R.M.); tel.: +49 931 31 85250; fax: +49 931 31 84609 (R.T.); tel.: +81 6 6300 6337; fax: +81 6 6300 6306 (T.K.); e-mail addresses: Mizojiri_Ryo@takeda.co.jp (R. Mizojiri), r.tacke@uni-wuerzburg.de (R. Tacke), Kawamoto_Tetsuji@takeda.co.jp (T. Kawamoto).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.07.068

2. Results and discussion

2.1. General considerations

Initially **2** was synthesized as described by Tacke et al.[12b] (Scheme 2). Compound **2** was obtained from **5** via a Baeyer–Villiger oxidation and subsequent hydrolysis. Compound **5** was in turn prepared in moderate yield from **3** and **4** via a cobalt-catalyzed [2+2+2] cycloaddition reaction utilizing a stoichiometric amount of toxic and pyrophoric dicobaltoctacarbonyl ($Co_2(CO)_8$) in refluxing *p*-xylene.



3 **4** **5** **2**

a) $Co_2(CO)_8$ (1 eq.), *p*-xylene, reflux, 50%; b) CH_3CO_3H, CH_3CO_2H, 65°C, 64%; c) NaOMe, MeOH, rt, 90%

Scheme 2. Initial synthesis of compound **2**.

Generally, the cobalt-mediated [2+2+2] cycloaddition reaction required prolonged reaction times, affording complex mixtures, which were difficult to purify. This lead to the use of impure **5** for the subsequent step. Therefore, for the large-scale synthesis of **2**, a safe and efficient route to 1,3-disilaindanes was required.

Recently, Tacke et al. reported a simple, efficient catalytic system for [2+2+2] cycloaddition reactions, namely cobalt(II) iodide (CoI_2) and zinc powder in acetonitrile. This was used to synthesize 1,3-disilaindanes and 1,4-disila-1,2,3,4-tetrahydronapthalenes.[9a,d,e,10d,e,11b] They demonstrated the preparation of compound **6** from **7b** via conventional oxidation (Scheme 3, method A).[10d] We envisaged that compound **7a** could potentially be used in an analogous fashion as an intermediate in the synthesis of **2**. However, the monoalkyne **9** is not commercially available, so alternative methodologies were considered.

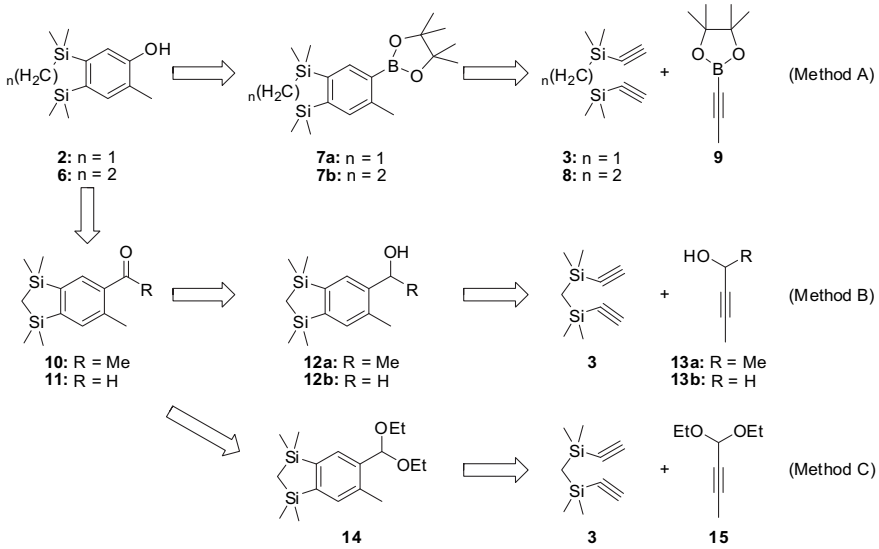
Tacke et al. also reported the synthesis of **10** (by oxidation of **12a** with MnO_2), which is a potential precursor of **2** (Scheme 3, method B).[9e] However, method C (Scheme 3) seemed to be most attractive for the rapid assembly of **2**, as **11** can be obtained from **14** without the need for an oxidation reaction. In addition, this intermediate could be prepared via a cobalt-catalyzed [2+2+2] cycloaddition reaction of **3** and commercially available **15**. Accordingly, we investigated the synthesis of **2** according to method C.

2.2. Synthesis of compound 14 utilizing a cobalt-catalyzed [2+2+2] cycloaddition reaction

To synthesize compound **14**, cobalt-catalyzed [2+2+2] cycloaddition reactions of dialkyne **3** with the commercially available monoalkyne **15** were investigated under various reaction conditions with different catalytic systems (Table 1). To ensure that the reaction mixtures remained safe, a solution of the cobalt catalyst was added dropwise to the mixture of **3**, **15**, and zinc to prevent a violent reflux occurring as a result of the strongly exothermic cycloaddition reaction[9a,14] (in run 8, a mixture of the cobalt catalyst and **3** was added dropwise; in run 11, a ruthenium catalyst was employed without zinc as a co-catalyst).

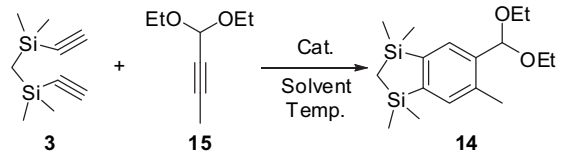
As Table 1 shows, the [2+2+2] cycloaddition reaction of **3** with **15** in the presence of a catalytic amount of CoI_2/Zn in refluxing acetonitrile afforded **14** in good yield (run 1). This was readily converted into **11** via conventional acid hydrolysis. Interestingly, the yield of **14** was significantly better than those reported for the syntheses of **7b** and **12**.[9b,9e,10d] Use of solvents, such as THF or acetone did not yield the desired product (runs 2 and 3), and reactions at lower reaction temperature (runs 4 and 5) resulted in a lower yield of **14** or no reaction at all. It is interesting to note that $CoBr_2$/Zn and $CoCl_2$/Zn catalysis also afforded **14** in refluxing acetonitrile (runs 6 and 7). Use of the $CoBr_2$/Zn system resulted in a very similar yield of **14** to that obtained with CoI_2/Zn. Because $CoBr_2$ is less expensive and more readily available than CoI_2, it is the more suitable catalyst for the synthesis of **14** via a cobalt-catalyzed [2+2+2] cycloaddition reaction. In contrast to these results, the cycloaddition reaction did not proceed in the presence of other metal catalysts (runs 9–11).

It has been reported that side reactions can lead to cyclic polymers of diyne and/or monoalkyne as by-products in [2+2+2] cycloaddition reactions, which significantly affects the yield of the desired product. In the synthesis of 1,3-disilaindanes and 1,4-disila-1,2,3,4-tetrahydronaphthalenes utilizing cobalt-catalyzed [2+2+2] cycloaddition reactions, Tacke et al. reported by-products resulting from a dimerization or trimerization of **3**.[9a] To suppress the formation of such by-products, a solution of **3** and $CoBr_2$ in acetonitrile was added slowly to a refluxing solution of monoalkyne **15** and zinc



Scheme 3. Synthetic routes to compound **2**.

Table 1
Investigation of the cobalt-catalyzed [2+2+2] cycloaddition reaction of **3** with **15**[a]



3 **15** **14**

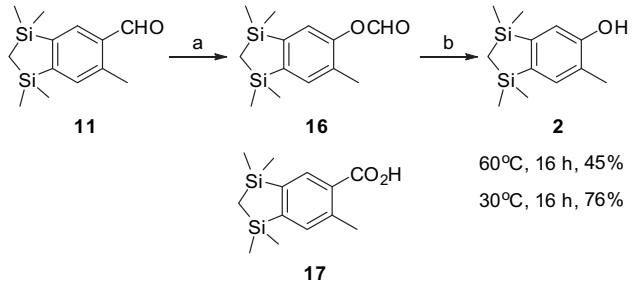
Run	Cat.	Solvent	Conditions	Time	Yield of **14**
1	CoI_2 (0.05 equiv), Zn (0.1 equiv)	CH_3CN	Reflux	2 h	70%
2	CoI_2 (0.05 equiv), Zn (0.1 equiv)	THF	Reflux	6 h	No reaction
3	CoI_2 (0.05 equiv), Zn (0.1 equiv)	Acetone	Reflux	2 h	Complex mixture
4	CoI_2 (0.05 equiv), Zn (0.1 equiv)	CH_3CN	rt	6 h	No reaction
5	CoI_2 (0.05 equiv), Zn (0.1 equiv)	CH_3CN	50 °C	2 h	50%
6	$CoCl_2$ (0.05 equiv), Zn (0.1 equiv)	CH_3CN	Reflux	4 h	50%
7	$CoBr_2$ (0.05 equiv), Zn (0.1 equiv)	CH_3CN	Reflux	2 h	70%
8[b]	$CoBr_2$ (0.05 equiv), Zn (0.1 equiv)	CH_3CN	Reflux	2 h	87%
9	$Co(acac)_2$ (0.05 equiv), Zn (0.1 equiv)	CH_3CN	Reflux	6 h	No reaction
10	$Co(OAc)_2$ (0.05 equiv), Zn (0.1 equiv)	CH_3CN	Reflux	6 h	No reaction
11	Cp*RuCl(cod)[c,d] (0.05 equiv)	CH_3CN	Reflux	6 h	Trace[e]

[a] Compounds [**3**]=0.5 M, [**15**]=0.4 M, [Cat.]=0.02 M.
[b] Slow addition of **3** into the reaction mixture.
[c] Cp*=pentamethylcyclopentadienyl.
[d] See Ref. 15.
[e] By-products were not detected.

powder in acetonitrile.[16] As we expected, this slow addition improved the yield of **14** and significant polymer formation was not detected (run 8).

2.3. Synthesis of compound 2 from 11

It is well known that the Baeyer–Villiger oxidation reaction[17] of aryl aldehydes affords the corresponding phenols and carboxylic acids. Compound **11** (prepared from **14**) was treated with formic acid (10 equiv) and aqueous 30% hydrogen peroxide (8 equiv) in toluene[18] to afford a mixture of **16** and **17** in varying ratios depending on the reaction temperature (Scheme 4). It has been found that **16** is formed in good yield under mild reaction conditions and in lower yield at higher temperatures. This is due to a significant formation of carboxylic acid **17**. The crude formic acid ester **16** obtained was then subjected to hydrolysis under basic conditions to afford **2** in 65% overall yield (for two steps).



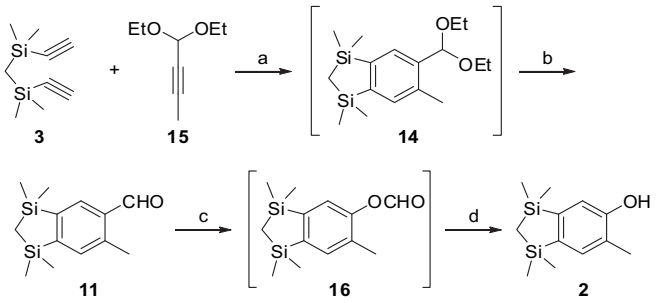
11 **16** **2** **17**

a) HCO_2H, H_2O_2, toluene; b) NaOH aq.

Scheme 4. Conversion of **11** into **2**.

2.4. Large-scale synthesis of 2

We have found that the scale-up of the $CoBr_2$/Zn-catalyzed [2+2+2] cycloaddition reaction of **3** (162.6 g, 901 mmol) with **15** (192.3 g, 1.35 mol) can be performed safely utilizing the slow addition method, as in the small-scale synthesis described above, affording **14**.[19] Compound **11** (110.4 g, 444 mmol) was obtained efficiently via in situ hydrolysis with hydrochloric acid.[20] The Baeyer–Villiger oxidation reaction of **11** (107.4 g, 432 mmol), under the previously described reaction conditions, was scaled-up without problems. The resultant crude formic ester **16** was hydrolyzed with an aqueous NaOH solution to afford **2** (76.9 g, 325 mmol) in 75% yield over two steps. Thus, a large-scale synthesis of **2** has been achieved with high efficiency (Scheme 5).



3 **15** **14** **11** **16** **2**

a) $CoBr_2$ (0.05 eq.), Zn (0.1 eq.), acetonitrile, reflux; b) HCl aq., 49% (2 steps);
c) 30% H_2O_2 aq. (8 eq.), HCO_2H (10 eq.), toluene, rt; d) NaOH aq., 75% (2 steps)

Scheme 5. Scaled-up synthesis of **2**.

3. Conclusions

An efficient, large-scale synthesis of 5-(diethoxymethyl)-1,1,3,3,6-pentamethyl-1,3-disilaindane (**14**) utilizing a $CoBr_2$/Zn-catalyzed [2+2+2] cycloaddition reaction has successfully been achieved. We have found that $CoBr_2$/Zn in acetonitrile is a useful catalytic system for the [2+2+2] cycloaddition reaction of diyne **3** and monoalkyne **15**. The formation of polymeric by-products is suppressed when a solution of **3** and $CoBr_2$ is added slowly to a refluxing mixture of **15** and zinc powder in acetonitrile, thus affording a higher yield of **14**. The Baeyer–Villiger oxidation reaction of **11** (readily obtained from **14**) under mild reaction conditions and the subsequent hydrolysis of formic ester **16** yielded **2** with high efficiency. This practical synthetic method is useful not only for the preparation of larger amounts of GnRH antagonists of the formula type **1** but also for the synthesis and development of further sila-substituted drugs derived from **11**.

4. Experimental section

4.1. General

All reactions were carried out under an argon atmosphere. Reaction workup was carried out without specific precautions against oxygen or moisture unless otherwise stated. $CoBr_2$ (WAKO Pure Chemical Industries, Ltd.; purity >97%) and Zn powder (WAKO Pure Chemical Industries, Ltd.; purity 99.9%, 75–150 μm) were reagent grade and used without further purification. Melting points were measured on a Yanaco MP-500D apparatus. ^1H, ^{13}C, and ^{29}Si NMR spectra were measured on a JEOL JMM-AL400 (^1H NMR measurements), a Bruker Avance 600 (^{13}C NMR measurements), or a Bruker Avance 400 (^{29}Si NMR measurements) NMR spectrometer using $CDCl_3$ as the solvent. Thin layer chromatography (TLC)

analyses were carried out using precoated TLC plates (silica gel 60 F_{254}, E. Merck) or basic TLC plates (NH silica gel, Fuji Sylisia Chemical Ltd.). Column chromatography was carried out using silica gel 60 (0.063–0.200 mesh, E. Merck), basic silica gel (Chromatorex, NH, 100–200 mesh, Fuji Sylisia Chemical Ltd.), or prepacked Purif-Pack columns (silica gel, Moritex Corporation).

4.2. Syntheses

*4.2.1. (1,1,3,3,6-Pentamethyl-1,3-disilaindan-5-yl)methanal (**11**).* A solution of **3** (5.00 g, 27.7 mmol) and $CoBr_2$ (152 mg, 695 μmol) in acetonitrile (40 mL) was added dropwise over a period of 1.5 h to a stirred, refluxing mixture of **15** (5.91 g, 41.6 mmol), zinc powder (181 mg, 2.77 mmol), and acetonitrile (10 mL). The reaction mixture was stirred under reflux for 30 min and then cooled to room temperature. Subsequently, 1 N hydrochloric acid (50 mL) was added, and the reaction mixture was stirred at room temperature for 30 min. The resultant mixture was extracted with ethyl acetate (100 mL), the aqueous layer was separated and extracted with ethyl acetate (50 mL), and the combined organic layers were washed sequentially with water (50 mL) and aqueous 10% NaCl solution (50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (silica gel (Moritex Corporation), 100 g; eluent, hexane/ethyl acetate (100/0 to 97/3 (v/v))) to afford **11** (6.00 g, 24.1 mmol) in 87% yield as a light yellow solid. Recrystallization from absolute ethanol gave an analytically pure product. Mp 62–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 2H), 0.31 (s, 6H), 0.32 (s, 6H), 2.69 (s, 3H), 7.44 (s, 1H), 7.95 (s, 1H), 10.32 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ −3.02, −0.28 (2C), −0.00 (2C), 19.37, 133.62, 134.56, 134.70, 139.56, 147.57, 157.64, 193.18. ^{29}Si NMR (79.5 MHz, $CDCl_3$) δ 8.70, 8.68. For the crystal structure analysis of **11**, see Supplementary data. Anal. Calcd for $C_{13}H_{20}OSi_2 \cdot 0.1H_2O$[21]: C, 62.39; H, 8.14. Found: C, 62.14; H, 7.92.

*4.2.2. 1,1,3,3,6-Pentamethyl-1,3-disilaindan-5-ol (**2**).* Aqueous 30% hydrogen peroxide solution (146 mL) was added dropwise at room temperature to a stirred mixture of **11** (44.5 g, 179 mmol), formic acid (83.8 g, 1.82 mol), and toluene (445 mL) over a period of 30 min. The reaction mixture was stirred at 30 °C for 20 h and then cooled to room temperature. The organic layer was separated, and the aqueous layer was extracted with toluene (220 mL). The combined organic extracts were washed sequentially with water (2×220 mL), aqueous 10% Na_2SO_3 solution (2×220 mL), and aqueous 10% NaCl solution (220 mL). Aqueous 8 N NaOH solution (45 mL) was then added to the organic layer, and the resulting mixture was stirred at room temperature for 30 min. The organic layer was separated, washed sequentially with water (2×45 mL) and aqueous 10% NaCl solution (45 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (basic silica gel (Chromatorex), 450 g; eluent, hexane/ethyl acetate (100/0 to 90/10 (v/v))) to afford **2** (27.4 g) in 65% yield as a pale yellow solid. Recrystallization form hexane gave an analytically pure product. Mp 93–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.06 (s, 2H), 0.26 (s, 12H), 2.27 (s, 3H), 4.69 (s, 1H), 6.94 (s, 1H), 7.32 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ −3.06, −0.27 (2C), −0.00 (2C), 116.69, 124.08, 133.87, 140.86, 149.35, 153.99. ^{29}Si NMR (79.5 MHz, $CDCl_3$) δ 8.43, 8.00. For the crystal structure analysis of **2**, see Supplementary data. Anal. Calcd for $C_{12}H_{20}OSi_2$: C, 60.95; H, 8.53. Found: C, 60.67; H, 8.53.

*4.2.3. Large-scale synthesis of (1,1,3,3,6-pentamethyl-1,3-disilaindan-5-yl)methanal (**11**).* A solution of **3** (162.6 g, 901 mmol) and $CoBr_2$ (5.10 g, 23.3 mmol) in acetonitrile (1.36 L) was added dropwise over 1.5 h to a stirred, refluxing mixture of **15** (192.3 g, 1.35 mol), zinc powder (6.20 g, 94.8 mmol), and acetonitrile (340 mL). The reaction mixture was stirred under reflux for 30 min and then cooled to room temperature. Subsequently, 2 N hydrochloric acid (820 mL) was added, and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was extracted with ethyl acetate (2.5 L), the organic layer was separated and washed sequentially with water (1 L) and brine (1 L), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (silica gel 60 (E. Merck), 1.7 kg; eluent, hexane/ethyl acetate (100/0 to 97/3 (v/v))) to afford **11** (110.4 g) in 49% yield as a light yellow solid. All spectral and analytical data were identical with those reported above.

*4.2.4. Large-scale synthesis of 1,1,3,3,6-pentamethyl-1,3-disilaindan-5-ol (**2**).* Aqueous 30% hydrogen peroxide solution (352 mL) was added dropwise at room temperature to an ice-cold stirred solution of **11** (107.4 g, 432 mmol), formic acid (202 g, 4.39 mol), and toluene (1.08 L) over a period of 30 min. The reaction mixture was stirred at room temperature for 24 h. The organic layer was separated, and the aqueous layer was extracted with toluene (220 mL). The combined organic extracts were washed sequentially with water (600 mL), aqueous 10% Na_2SO_3 solution (600 mL), and brine (600 mL). Aqueous 8 N NaOH solution (110 mL) was then added to the organic layer, and the resulting mixture was stirred at room temperature for 1 h. The resultant mixture was acidified with a 6 N hydrochloric acid, the organic layer was separated, washed sequentially with water (2×200 mL) and brine (200 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (basic silica gel (Chromatorex), 1.0 kg; eluent, hexane/ethyl acetate (100/0 to 90/10 (v/v))) to afford **2** (76.9 g) in 75% yield as a pale yellow solid. All spectral and analytical data were identical with those reported above.

Acknowledgements

We are grateful to Mr. Akihisa Maeda and Mr. Hirohiko Nishiyama (Hamari Chemical Industries Ltd.) for their helpful discussion in the scale-up of the syntheses, Ms. Mika Murabayashi (Discovery Research Center, Takeda Pharmaceutical Company Ltd.) for the measurement of the ^{29}Si NMR spectra, and Mr. Motoo Iida (Discovery Research Center, Takeda Pharmaceutical Company Ltd.) for performing the single-crystal X-ray diffraction studies.

Supplementary data

Crystal structure analyses of **2** and **11**.[22] Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.07.068.

References and notes

1. (a) Tacke, R.; Linoh, H. In *The Chemistry of Organic Silicon Compounds, Part 2*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, UK, 1989; pp 1143–1206; (b) Lukevics, E.; Ignatovich, L. *Appl. Organomet. Chem.* **1992**, *6*, 113–126; (c) Tacke, R.; Wagner, S. A. In *The Chemistry of Organic Silicon Compounds, Part 3*, Rappoport, Z., Apeloig, Y., Eds.; Wiley: Chichester, UK, 1998; Vol. 2, pp 2363–2400; (d) Tacke, R.; Heinrich, T.; Kornek, T.; Merget, M.; Wagner, S. A.; Gross, J.; Keim, C.; Lambrecht, G.; Mutschler, E.; Beckerss, T.; Bernd, M.; Reissmann, T. *Phosphorus, Sulfur, and Silicon and the Related Elements* **1999**, *150*, 69–87; (e) Bains, W.; Tacke, R. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 526–543; (f) Showell, G. A.; Mills, J. S. *Drug Discovery Today* **2003**, *8*, 551–556; (g) Mills, J. S.; Showell, G. A. *Expert Opin. Invest. Drugs* **2004**, *13*, 1149–1157; (h) Pooni, P. K.; Showell, G. A. *Mini–Rev. Med. Chem.* **2006**, *6*, 1169–1177; (i) Sieburth, S. McN.; Chen, C. A. *Eur. J. Org. Chem.* **2006**, 311–322; (j) Gately, S.; West, R. *Drug Dev. Res.* **2007**, *68*, 156–163; (k) Franz, A. K. *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 654–671.
2. (a) Tacke, R.; Daiss, J. WO2003037905, 2003; (b) Daiss, J. O.; Penka, M.; Burschka, C.; Tacke, R. *Organometallics* **2004**, *23*, 4987–4994; (c) Showell, G.A.; Miller, D.; Mandal, A.K.; Tacke, R.; Daiss, J. WO2004094436, 2004; (d) Daiss, J. O.; Burschka, C.; Mills, J. S.; Montana, J. G.; Showell, G. A.; Warneck, J. B. H.; Tacke, R. *Organometallics* **2006**, *25*, 1188–1198; (e) Showell, G. A.; Barnes, M. J.; Daiss, J. O.; Mills, J.

S.; Montana, J. G.; Tacke, R.; Warneck, J. B. H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2555–2558; (f) Daiss, J. O.; Burschka, C.; Mills, J. S.; Montana, J. G.; Showell, G. A.; Warneck, J. B. H.; Tacke, R. *J. Organomet. Chem.* **2006**, *691*, 3589–3595.
3. (a) Tacke, R.; Merget, M.; Bertermann, R.; Bernd, M.; Beckers, T.; Reissmann, T. *Organometallics* **2000**, *19*, 3486–3497; (b) Merget, M.; Günther, K.; Bernd, M.; Günther, E.; Tacke, R. *J. Organomet. Chem.* **2001**, *628*, 183–194.
4. (a) Tacke, R.; Reichel, D.; Kropfgans, M.; Jones, P. G.; Mutschler, E.; Gross, J.; Hou, X.; Waelbroeck, M.; Lambrecht, G. *Organometallics* **1995**, *14*, 251–262 and references therein; (b) Tacke, R.; Reichel, D.; Jones, P. G.; Hou, X.; Waelbroeck, M.; Gross, J.; Mutschler, E.; Lambrecht, G. *J. Organomet. Chem.* **1996**, *521*, 305–323; (c) Tacke, R.; Kornek, T.; Heinrich, T.; Burschka, C.; Penka, M.; Pülm, M.; Keim, C.; Mutschler, E.; Lambrecht, G. *J. Organomet. Chem.* **2001**, *640*, 140–165; (d) Tacke, R.; Heinrich, T. *Silicon Chem.* **2002**, *1*, 35–39; (e) Daiss, J. O.; Duda–Johner, S.; Burschka, C.; Holzgrabe, U.; Mohr, K.; Tacke, R. *Organometallics* **2002**, *21*, 803–811; (f) Tacke, R.; Handmann, V. I.; Kreutzmann, K.; Keim, C.; Mutschler, E.; Lambrecht, G. *Organometallics* **2002**, *21*, 3727–3732.
5. (a) Tacke, R.; Handmann, V. I.; Bertermann, R.; Burschka, C.; Penka, M.; Seyfried, C. *Organometallics* **2003**, *22*, 916–924; (b) Ilg, R.; Burschka, C.; Schepmann, D.; Wünsch, B.; Tacke, R. *Organometallics* **2006**, *25*, 5396–5408.
6. Heinrich, T.; Burschka, C.; Warneck, J.; Tacke, R. *Organometallics* **2004**, *23*, 361–366.
7. (a) Tacke, R.; Heinrich, T.; Bertermann, R.; Burschka, C.; Hamacher, A.; Kassack, M. U. *Organometallics* **2004**, *23*, 4468–4477; (b) Heinrich, T.; Burschka, C.; Penka, M.; Wagner, B.; Tacke, R. *J. Organomet. Chem.* **2005**, *690*, 33–47; (c) Tacke, R.; Popp, F.; Müller, B.; Theis, B.; Burschka, C.; Hamacher, A.; Kassack, M. U.; Schepmann, D.; Wünsch, B.; Jurva, U.; Wellner, E. *ChemMedChem* **2008**, *3*, 152–164; (d) Johansson, T.; Wiedolf, L.; Popp, F.; Tacke, R.; Jurva, U. *Drug Metab. Dispos.* **2010**, *38*, 73–83; (e) Tacke, R.; Nguyen, B.; Burschka, C.; Lippert, W. P.; Hamacher, A.; Urban, C.; Kassack, M. U. *Organometallics* **2010**, *29*, 1652–1660.
8. Tacke, R.; Schmid, T.; Penka, M.; Burschka, C.; Bains, W.; Warneck, J. *Organometallics* **2004**, *23*, 4915–4923.
9. (a) Doszczak, L.; Fey, P.; Tacke, R. *Synlett* **2007**, 753–756; (b) Büttner, M. W.; Penka, M.; Doszczak, L.; Kraft, P.; Tacke, R. *Organometallics* **2007**, *26*, 1295–1298; (c) Büttner, M. W.; Burschka, C.; Junold, K.; Kraft, P.; Tacke, R. *ChemBioChem* **2007**, *8*, 1447–1454; (d) Doszczak, L.; Tacke, R. *Organometallics* **2007**, *26*, 5722–5723; (e) Metz, S.; Nätscher, J. B.; Burschka, C.; Götz, K.; Kaupp, M.; Kraft, P.; Tacke, R. *Organometallics* **2009**, *28*, 4700–4712.
10. (a) Montana, J.G.; Showell, G.A.; Fleming, I.; Tacke, R.; Daiss, J. WO2004048390, 2004. (b) Montana, J.G.; Showell, G.A.; Tacke, R. WO2004048391, 2004; (c) Daiss, J. O.; Burschka, C.; Mills, J. S.; Montana, J. G.; Showell, G. A.; Fleming, I.; Gaudon, C.; Ivanova, D.; Gronemeyer, H.; Tacke, R. *Organometallics* **2005**, *24*, 3192–3199; (d) Büttner, M. W.; Nätscher, J. B.; Burschka, C.; Tacke, R. *Organometallics* **2007**, *26*, 4835–4838; (e) Lippert, W. P.; Burschka, C.; Götz, K.; Kaupp, M.; Ivanova, D.; Gaudon, C.; Sato, Y.; Antony, P.; Rochel, N.; Moras, D.; Gronemeyer, H.; Tacke, R. *ChemMedChem* **2009**, *4*, 1143–1152.
11. (a) Büttner, M. W.; Burschka, C.; Daiss, J. O.; Ivanova, D.; Rochel, N.; Kammerer, S.; Peluso–Iltis, C.; Bindler, A.; Gaudon, C.; Germain, P.; Moras, D.; Gronemeyer, H.; Tacke, R. *ChemBioChem* **2007**, *8*, 1688–1699; (b) Tacke, R.; Müller, V.; Büttner, M. W.; Lippert, W. P.; Bertermann, R.; Daiss, J. O.; Khanwalkar, H.; Furst, A.; Gaudon, C.; Gronemeyer, H. *ChemMedChem* **2009**, *4*, 1797–1802.
12. (a) Montana, J.G.; Fleming, I.; Tacke, R.; Daiss, J. WO2004045625, 2004; (b) Miller, D.J.; Showell, G.A.; Conroy, R.; Daiss, J.; Tacke, R.; Tebbe, D. WO2005005443, 2005.
13. (a) Anderson, M.B.; Vazir, H.N.; Luthin, D.R.; Paderes, G.D.; Pathak, V.P.; Christie, L.C.; Hong, Y.; Tompkins, E.V.; Li, H.; Faust, J. WO2000020358, 2000; (b) Luthin, D. R.; Hong, Y.; Pathak, V. P.; Paderes, G.; Nared-Hood, K. D.; Castro, M. A.; Vazir, H.; Li, H.; Tompkins, E.; Christie, L.; May, J. M.; Anderson, M. B. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3467–3470; (c) Luthin, D. R.; Hong, Y.; Tompkins, E.; Anderes, K. L.; Paderes, G.; Kraynov, E. A.; Castro, M. A.; Nared-Hood, K. D.; Castillo, R.; Gregory, M.; Vazir, H.; May, J. M.; Anderson, M. B. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3635–3639; (d) Li, H.; Anderes, K. L.; Kraynov, E. A.; Luthin, D. R.; Do, Q.-Q.; Hong, Y.; Tompkins, E.; Sun, E. T.; Rajapakse, R.; Pathak, V. P.; Christie, L. C.; Vazir, H.; Castillo, R.; Gregory, M. L.; Castro, M.; Nared–Hood, K.; Paderes, G.; Anderson, M. B. *J. Med. Chem.* **2006**, *49*, 3362–3367.
14. Example of a large-scale rhodium catalyzed [2+2+2] cycloaddition reaction: Nishida, G.; Ogaki, S.; Yusa, Y.; Yokozawa, T.; Noguchi, K.; Tanaka, K. *Org. Lett.* **2008**, *10*, 2849–2852.
15. Yamamoto, Y.; Ogawa, R.; Itoh, K. *Chem. Commun.* **2000**, 549–550.
16. Yamamoto, Y.; Hattori, K.; Ishii, J.; Nishiyama, H. *Tetrahedron* **2006**, *62*, 4294–4305.
17. Brink, G. J.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105–4123.
18. Tanaka, K.; Sakai, Y.; Shoji, Y.; Yoshimura, T.; Yoshimura, M. EP1209145, 2002.
19. To suppress the polymerization of **3**, an excess amount of **15** was used in the large-scale synthesis of **14**.
20. In the large-scale synthesis of **14**, significant formation of by-product(s) was not detected. More sufficient stirring and distribution of the Zn powder would give rise to a better yield of **14**.
21. The water content of **11** (0.76%) was determined by Karl Fischer titration.
22. Final crystallographic coordinates, bond distances, bond angles, structure factors, and thermal parameters have been deposited with, and can be ordered from, Cambridge Crystallographic Data Centre (CCDC-773109 (**2**) and CCDC-774798 (**11**)).