Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 1107–1110
Tetrahedron Letters

One-pot hydrosilylation–protodesilylation of functionalized diarylalkynes: a highly selective access to *Z*-stilbenes. Application to the synthesis of combretastatin A-4

Anne Giraud [a], Olivier Provot [a,b,*], Abdallah Hamzé [a,b], Jean-Daniel Brion [a,b], Mouâd Alami [a,b,*]

[a] *Univ Paris-Sud, BioCIS, UMR 8076, Laboratoire de Chimie Thérapeutique, Faculté de Pharmacie, rue J.B. Clément, Châtenay-Malabry F-92296, France*
[b] *CNRS, BioCIS, UMR 8076, Laboratoire de Chimie Thérapeutique, Faculté de Pharmacie, rue J.B. Clément, Châtenay-Malabry F-92296, France*

Received 16 November 2007; revised 10 December 2007; accepted 12 December 2007
Available online 8 January 2008

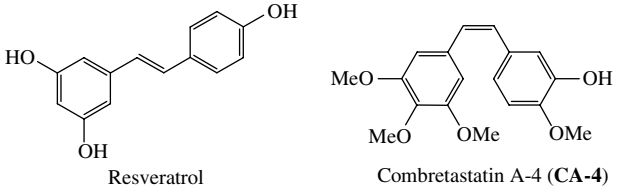
Abstract

An efficient stereoselective synthesis of *Z*-stilbenes has been developed from diarylalkynes via a new hydrosilylation–protodesilylation process. The scope and limitation of this method is presented to stereoselectively prepare a wide range of (*Z*)-stilbenes in a one-pot way is presented. A concise application to the preparation of combretastatin A-4 (**CA-4**), a vascular targeting agent inhibitor of tubulin polymerisation is described.

Keywords: Combretastatin A-4; (*Z*)-Stilbenes; Hydrosilylation; Desilylation; Platinum

A large number of stilbene (1,2-diphenylethylene) derivatives have been isolated from various plant species and exhibit a large panel of biological activities such as, antineoplastic, antiangiogenesis, cytotoxic and inhibition of cell proliferation.[1] Beside *trans* stilbene derivatives and one of their leader, resveratrol, a large number of their *cis* homologues were isolated, synthesized and evaluated. The most promising of these stilbenes thus far are combretastatins and particularly the combretastatin A-4 (**CA-4**) due to its biological activities combined to its structural simplicity (Scheme 1).[2]

If the access of *trans* stilbenes is well documented,[3] there are only few methodologies that give access to their *cis* counterparts. The most popular approach is based on the *Z* selective-Lindlar[4] semi-reduction of diarylalkynes but it suffers from several drawbacks as (*Z*) to (*E*) isomerization, overreduction to the alkane making purifications tedious and problems with reproductibility.



Scheme 1.

As a part of our research devoted to anticancer agents[5] which target tubulin,[6] we wished to synthesize the natural product **CA-4** as a reference molecule since, to our knowledge, **CA-4** is not commercially available anymore. The chemical synthesis of **CA-4** has been tackled in a variety of ways.[1b,7] While these reactions are suitable methods, many of them either display low stereoselectivity or do not tolerate sensitive functionalities. Therefore, alternative routes for the synthesis of **CA-4** are welcome. A recent

* Corresponding authors. Tel.: +33 1 46835847; fax: +33 1 46835828 (O.P.).
E-mail addresses: olivier.provot@u-psud.fr (O. Provot), mouad.alami@u-psud.fr (M. Alami).

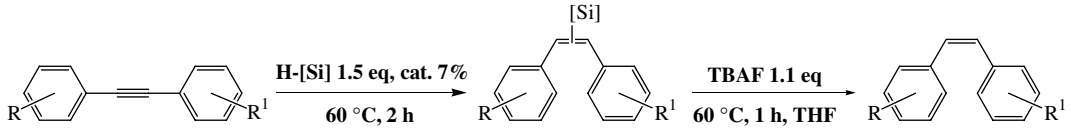
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.12.057

work describing the synthesis of **CA-4** and analogues by hydrolysis of Ti(II)–alkynes complexes[8] prompted us to publish our preliminary results in the *Z*-semi-reduction of alkynes field.

Recently, we showed that heterogeneous platinum oxide (PtO_2) is a very efficient catalyst for the hydrosilylation of *para* and *ortho* substituted diarylalkynes. The H–Si bond addition proceeds in a stereoselective *cis*-fashion[9] and the regioselectivity of the reaction was found to be governed by *ortho*-directing effects (ODE)[10] rather than the nature of the platinum catalysts. We reasoned that this efficient hydrosilylation of internal arylalkynes could be efficiently exploited to give, after linkage of the C–Si bond, *Z*-stilbenes of high biological interest. We present in this communication a convenient one-pot procedure for the *Z*-selective semi-reduction of diarylalkynes via a hydrosilylation–protodesilylation sequence.

To define optimal reaction conditions, we have studied initially the hydrosilylation of diarylalkynes **1a** and **1b** as model substrates and their subsequent desilylation. The results are summarized in Table 1. Preliminary experiment was carried out using $HSiEt_3$ (1.5 equiv), PtO_2 (7 mol %) at 60 °C in the absence of solvent as we previously reported.[9] In this case, a mixture of vinylsilanes was obtained in a quantitative yield after purification on silica gel. However, the desilylation of the vinylsilanes mixture using TBAF (1.5 equiv) at 60 °C afforded a moderate yield of *Z*-**3a** together with significant amounts of *E*-**3a** (entry 1). A survey of the sequence hydrosilylation–protodesilylation sequence of alkyne **1a** under the same conditions in the presence of other representative silanes, including $HSiPh_2Me$, $HSi(OEt)_3$ and $HSiOEtMe_2$ was conducted (entries 2–4). In these cases, we were pleased to observe the formation of a single *Z*-**3a** stereoisomer whatever the nature of the silane used and the better overall yield was obtained with the non-toxic[11] $HSiOEtMe_2$ (77% for the two steps, entry 4). Encouraged by this result, the effect of $PtCl_4$, $PtCl_2$ and Pt/C on the outcome of the hydrosilylation reaction was investigated. None of these platinum catalysts led to better results than those achieved with PtO_2 (entries 5–7). One can note that H_2PtCl_6 (Speier's catalyst), which is considered to be the catalyst of choice for *cis*-hydrosilylation of internal alkynes,[12] was not efficient and led to a complex mixture (entry 7). Having defined the best conditions [PtO_2 (7 mol %), $HSiOEtMe_2$ (1.5 equiv), 60 °C then TBAF (1.5 equiv), 0 °C] *Z*-stilbene **3b** bearing a 3,4,5-trimethoxyaryl moiety was prepared and isolated in good yield (entry 9). Careful inspection of the ^1H NMR spectrum of the crude reaction mixture indicated that the stilbene **3b** was formed in a 98:2/*Z*:*E* ratio. A similar result was obtained when using $HSi(OEt)_3$ instead of $HSiOEtMe_2$ (entry 10). Finally, the best result in terms of yield and *Z*-stereoselectivity was observed when the desilylation step of vinylsilane **2b-4** was achieved at room temperature (entry 11). In this case, *Z*-stilbene **3b** was obtained as a single *Z* stereoisomer in a 77% overall isolated yield (based on alkyne **1b**). We then applied this two stage process to prepare the target natural product **CA-4**[13] from diarylalkyne **1c**. We were delighted to observe that the hydrosilylation–protodesilylation proceeded

Table 1
Hydrosilylation–protodesilylation sequence; access to *Z*-stilbenes **3**



1 **2** **3**

Entry	Diarylalkyne **1**	H-[Si]	Catalyst	Yield[a] of **2**[b] (%)		Yield[a] of **3** (%)		*Z*/*E* ratio[c]
1	**1a** R = 4-OMe, R^1 = H	**1**: $HSiEt_3$	PtO_2	**2a-1**	97	**3a**	58	85/15
2	**1a** R = 4-OMe, R^1 = H	**2**: $HSiPh_2Me$	PtO_2	**2a-2**	93	**3a**	49	100/0
3	**1a** R = 4-OMe, R^1 = H	**3**: $HSi(OEt)_3$	PtO_2	**2a-3**	70	**3a**	80	100/0
4	**1a** R = 4-OMe, R^1 = H	**4**: **$HSiOEtMe_2$**	**PtO_2**	**2a-4**	**86**	**3a**	**90**	100/0
5	**1a** R = 4-OMe, R^1 = H	**4**: $HSiOEtMe_2$	$PtCl_2$	**2a-4**	44	**3a**	nd[d]	nd[d]
6	**1a** R = 4-OMe, R^1 = H	**4**: $HSiOEtMe_2$	Pt/C	**2a-4**	38	**3a**	—	—
7	**1a** R = 4-OMe, R^1 = H	**4**: $HSiOEtMe_2$	$PtCl_4$	**2a-4**	56	**3a**	—	—
8	**1a** R = 4-OMe, R^1 = H	**4**: $HSiOEtMe_2$	H_2PtCl_6	**2a-4**	Mixture	**3a**	—	—
9	**1b** R = 2,3,4-OMe, R^1 = H	**4**: $HSiOEtMe_2$	PtO_2	**2b-4**	87	**3b**	77	98/2
10	**1b** R = 2,3,4-OMe, R^1 = H	**3**: $HSi(OEt)_3$	PtO_2	**2b-3**	78		84	98/2
11	**1b** R = 2,3,4-OMe, R^1 = H	**4**: $HSiOEtMe_2$	PtO_2	**2b-4**	87		88[e]	100/0
12	**1c** R = 2,3,4-OMe, R^1 = 3-OH, 4-OMe	**4**: $HSiOEtMe_2$	PtO_2	**2c-4**	70[f]	**CA-4**	69	100/0

[a] Isolated yield.
[b] Mixture of regioisomers (ratio not determined).
[c] *Z*:*E* Ratios quoted as a percentage composition of total yield as estimated from ^1H NMR spectra.
[d] Not determined.
[e] Protodesilylation was achieved at rt.
[f] 4 equiv of $HSiOEtMe_2$ were required.

Table 2
One-pot access to *Z*-stilbenes **3** from diarylalkynes **1**

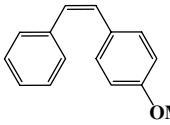
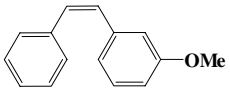
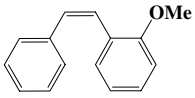
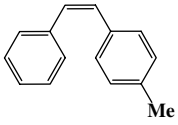
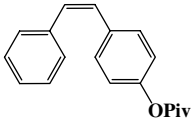
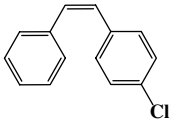
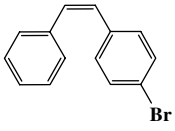
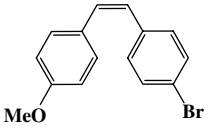
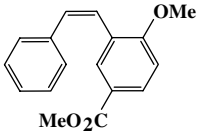
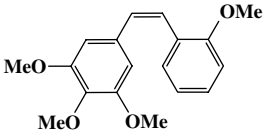
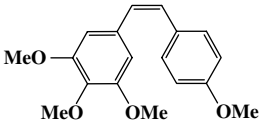
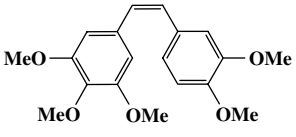
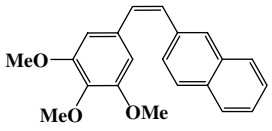
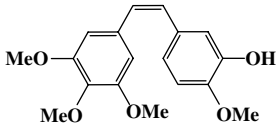
Entry	Alkynes	Stilbenes		*Z*/*E* Ratio[a]	Yield[b]
1	**1a**		**3a**	100/0	77
2	**1d**		**3d**	100/0	90
3	**1e**		**3e**	100/0	75
4	**1f**		**3f**	100/0	51
5	**1g**		**3g**	100/0	49[c]
6	**1h**		**3h**	100/0	65
7	**1i**		**3i**	100/0	79
8	**1j**		**3j**	>95/5	51
9	**1k**		**3k**	100/0	95
10	**1l**		**3l**	>95/5	62
11	**1m**		**3m**	>95/5	75
12	**1n**		**3n**	90/10	73

Table 2 (*continued*)

Entry	Alkynes	Stilbenes		*Z*/*E* Ratio[a]	Yield[b]
13	**1o**		**3o**	88/12	78
14	**1c**		**CA-4**	90/10	67

[a] *Z*:*E* Ratios quoted as a percentage composition of total yield as estimated from ^{1}H NMR spectra.
[b] Isolated yield.
[c] Unoptimized yield.

extremely efficiently to give the desired **CA-4** as a single *Z*-isomer in good yield (entry 12).

From a practical point of view of the synthetic chemist, we explored the process in a one-pot manner. Thus, after the hydrosilylation step, the excess of the volatile $HSiOEtMe_2$ was removed to achieve the protodesilylation step with TBAF (3 equiv) at 0 °C for a better *Z*-stereoselectivity. Scope and limitations of this one-pot process using various functionalized diarylalkynes **1** are summarized in Table 2.

Diarylalkynes **1a**, **1d–f** substituted with an electron donating group (OMe, Me) have been transformed successfully into their corresponding stilbenes **3** in good yields (entries 1–4). It should be noted that the position of the substituent on the aromatic ring had no influence on the *Z*-stereochemistry of the stilbenes formed (entries 1–3). A similar result (total *Z*-stereocontrol) has been obtained from **1g** bearing a pivaloyl ester function but with a moderate unoptimized 49% yield (entry 5). We were also pleased to observe that halogenated substituted arylalkynes **1h** and **1i** afforded the expected stilbenes **3h** and **3i**, respectively, in acceptable yields and again as single *Z*-stereoisomers (entries 6 and 7). When the push–pull diarylalkynes **1j** was employed as a substrate, it was found that the *Z*-stereochemistry of this one-pot process was slightly reduced. In this case, traces of the *E*-stilbene were detected by ^{1}H NMR spectroscopy. This PtO_2-catalyzed hydrosilylation–protodesilylation one-pot process can be performed also with alkyne **1k** bearing a methoxycarbonyl group as illustrated in entry 9. In this case again a total *Z*-stereochemistry associated with a nearly quantitative yield was observed (95%).

We next embarked on the utilization of this process for the conversion of 3,4,5-trimethoxyarylalkynes to their corresponding *Z*-stilbenes, analogues of **CA-4**. Starting from 3,4,5-trimethoxyarylalkynes **1l** and **1m** bearing an ortho or a para methoxy group, respectively, it was noted that the 3,4,5-trimethoxyaryl unit smoothly affected the *Z*-stereoselectivity (>95%, entries 10 and 11) providing **3l**

and **3m**[14] in good yields. Similarly, we succeeded in the one-pot preparation of known biologically active analogues of **CA-4**, **3n**[15] and **3o**[16] in good yields and high *Z*-stereocontrol (entries 12 and 13).

On account of the large scope of this one-pot procedure, we then attempted to synthesize **CA-4** from the corresponding **1c** having a free phenolic function. Because of the side silylation of the phenol moiety, the desilylation step was conducted at 60 °C. As shown in entry 14, **CA-4** was obtained with fortunately an excellent *Z*-stereoselectivity (*Z*:*E*/90:10) and in a good yield. Careful separation on silica gel afforded pure **CA-4**, which could be used as reference for biological evaluation of analogues that would be reported in due course.

In summary, we have developed a new, mild and efficient method for the synthesis of *Z*-stilbenes from diarylalkynes. This method is complementary to the existing procedures and sometimes could be the method of choice because of its chemoselectivity, simplicity and its excellent *Z*-stereoselectivity. The ease by which several *Z*-stilbenes were obtained with a total *Z*-stereocontrol and in good yields encouraged us to prepare efficiently the natural stilbene **CA-4** by this way. Moreover, we also demonstrated that this hydrosilylation–protodesilylation sequence could be achieved in a one-pot way from various diarylalkynes.

Acknowledgements

The CNRS is gratefully acknowledged for financial support of this research and the MNSER for a doctoral fellowship to A.G.

References and notes

1. (a) Jang, M.; Cai, L.; Udeani, G. O.; Slowing, K. V.; Thomas, C. F.; Beecher, C. W. W.; Fong, H. H. S.; Farnworth, R. N.; Kinghorn, A. D.; Metha, R. G.; Moon, R. C.; Pezzuto, J. M. *Science* **1997**, *275*, 218; (b) Pettit, G. R.; Rhodes, M. R.; Herald, D. L.; Hamel, E.; Schmidt, J. M.; Pettit, R. K. *J. Med. Chem.* **2005**, *48*, 4087 and references cited therein.
2. (a) Pettit, G. R.; Cragg, G. M.; Singh, S. B. *J. Nat. Prod.* **1987**, *50*, 386; (b) Pettit, G. R.; Singh, S. B.; Hamel, E.; Lin, C. M.; Alberts, D. S.; Garcia-Kendall, D. *Experientia* **1989**, *45*, 209; (c) Pettit, G. R.; Singh, S. B.; Boyd, M. R.; Hamel, E.; Pettit, R. K.; Schmidt, J. M.; Hogan, F. *J. Med. Chem.* **1995**, *38*, 1666.
3. Ferré-Filmon, K.; Delaude, L.; Demonceau, A.; Noels, A. F. *Coord. Chem. Rev.* **2004**, *248*, 2323.
4. (a) Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446; (b) Lindlar, H.; Dubuis, R. *Org. Synth.* **1973**, *5*, 880.
5. LeBras, G.; Radanyi, C.; Peyrat, J.-F.; Brion, J.-D.; Alami, M.; Marsaud, V.; Stella, B.; Renoir, J.-M. *J. Med. Chem.* **2007**, *50* http://dx.doi.org/10.1021/jm0707774.
6. Provot, O.; Giraud, A.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron Lett.* **2005**, *46*, 8547.
7. (a) Robinson, J. E.; Taylor, R. J. K. *Chem. Commun.* **2007**, 1617; (b) Harrowven, D. C.; Guy, I. L.; Howell, M.; Packham, G. *Synlett* **2006**, 2977; (c) Gaukroger, K.; Hadfield, J. A.; Hepworth, L. A.; Lawrence, N. J.; McGown, A. T. *J. Org. Chem.* **2001**, *66*, 8135; (d) Lawrence, N. J.; Abdul Ghani, F.; Hepworth, L. A.; Hadfield, J. A.; McGown, A. T.; Pritchard, R. G. *Synthesis* **1999**, 1656; (e) Fürstner, A.; Nikolakis, K. *Liebigs Ann.* **1996**, 2107.
8. Lara-Ochoa, F.; Espinosa-Pérez, G. *Tetrahedron Lett.* **2007**, *48*, 7007.
9. (a) Hamze, A.; Provot, O.; Brion, J.-D.; Alami, M. *Synthesis* **2007**, 2025; (b) Hamze, A.; Provot, O.; Alami, M.; Brion, J.-D. *Org. Lett.* **2005**, *7*, 5625.
10. (a) Liron, F.; Le Garrec, P.; Alami, M. *Synlett* **1999**, 246; (b) Alami, M.; Liron, F.; Gervais, M.; Peyrat, J.-F.; Brion, J.-D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1578; (c) Liron, F.; Gervais, M.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron Lett.* **2003**, *44*, 2789; (d) Bujard, M.; Ferri, F.; Alami, M. *Tetrahedron Lett.* **1998**, *39*, 4243; (e) Hamze, A.; Provot, O.; Brion, J.-D.; Alami, M. *J. Org. Chem.* **2007**, *72*, 3868.
11. Dodd, D. E.; Stuart, B. O.; Rothenberg, S. J.; Kershaw, M.; Mann, P. C.; James, J. T.; Lam, C. W. *Inhal. Toxicol.* **1994**, *6*, 151.
12. Speier's catalyst is well known to provide *cis*-addition processes for internal and terminal alkynes; see: Tsipis, C. A. *J. Organomet. Chem.* **1980**, *187*, 427.
13. *Procedure for the synthesis of* **CA-4**: In a 10 mL flask, PtO_2 (10 mg, 0.0035 mmol) and arylalkyne **1c** (0.5 mmol) were placed under nitrogen atmosphere. Dimethylethoxysilane (304 μL, 2 mmol) was introduced via syringe and the mixture was stirred at 60 °C in an oil bath for 1 h. The residue was concentrated and then purified by column chromatography over silica gel to yield the vinylsilanes as a mixture of regioisomers (147 mg; 70%). The mixture of vinylsilanes (147 mg, 0.35 mmol) was treated with TBAF in THF (1 mL, 1 N) at 60 ° C for 1 h. After concentration in vacuo, the crude product was purified by column chromatography (SiO_2, cyclohexane/EtOAc: 70/30) to afford **CA-4** as a single *Z*-stereoisomer (75 mg; 69%). TLC: R_f 0.46 (cyclohexane/EtOAc: 70/30, 1/1, SiO_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 6H), 3.84 (s, 3H), 3.86 (s, 3H), 5.50 (br s, 1H, OH), 6.40 (d, 1H, $J = 12.1$ Hz), 6.47 (d, 1H, $J = 12.1$ Hz), 6.53 (s, 2H), 6.72 (d, 1H, $J = 8.2$ Hz), 6.80 (dd, 1H, $J = 8.2$ Hz, $J = 1.8$ Hz), 6.92 (d, 1H, $J = 1.8$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.9 (2C), 56.1, 60.9, 106.0 (2C), 110.3, 115.0, 121.1, 129.0, 129.5, 130.6, 132.7, 137.1, 145.2, 145.8, 152.8 (2C).
14. Cushman, M.; Nagarathnam, D.; Gopal, D.; Chakraboti, A. K.; Lin, C. M.; Hamel, E. *J. Med. Chem.* **1991**, *34*, 2579.
15. Lin, C. M.; Singh, S. B.; Chu, P. S.; Dempcy, R. O.; Schmidt, J. M.; Pettit, G. R.; Hamel, E. *Mol. Pharmacol.* **1988**, *34*, 200.
16. Maya, A. B.; Del Rey, B.; De Clairac, R. P.; Caballero, E.; Barasoain, I.; Andreu, J. M.; Medarde, M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2549.