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Total Synthesis

Concise Asymmetric Construction of C_2-symmetric 1,9-Diarylnonanoids Using a Hypervalent Silicon Complex: Total Synthesis of (−)-Ericanone

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Abstract: By using a phosphine oxide-catalyzed enantioselective double aldol reaction, we achieved the concise construction of C_2-symmetric 1,9-diarylnonanoids, enabling the synthesis of (−)-ericanone from *p*-hydroxybenzaldehyde in 6 steps with 65% overall yield. The enantioselective double aldol reaction is useful for establishing C_2-symmetric 1,9-diaryl-3,7-dihydroxy-5-nonanones with a single operation. Furthermore, the use of *o*-nosyl-protected *p*-hydroxybenzaldehyde and a 4,4′-disubstituted BINAP dioxide catalyst dramatically improved the reactivity and selectivity in the double aldol reaction, enabling the total synthesis of (−)-ericanone with high yield and with excellent enantiopurity.

(−)-Ericanone (**1**) is a C_2-symmetric 1,9-diarylnonanoid, isolated in 2011 from the acetone extract of the aerial parts of fresh *Erica Cinerea* L. (Figure 1).[1] While the structure of (−)-**1** appears simple and characteristic with a linear C_2-symmetry, it is in fact quite rare in nature. Several 1,9-diarylnonanoids have recently been discovered.[2] However, the bioactivities of these 1,9-diarylnonanoid families remain unexplored. Nevertheless, they are expected to possess useful bioactivities because 1,7-diarylheptanoids represented by curcumin have efficient bioactivities

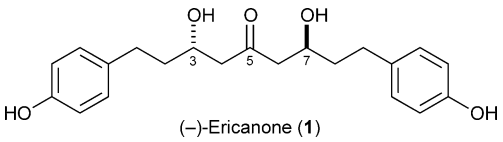

Figure 1. Structure of (−)-ericanone (**1**).

such as antioxidant and antitumor properties.[3] The first synthesis of (−)-**1** was achieved by Dias and co-workers in 2013.[4] They conducted the total synthesis of (−)-**1** from *p*-hydroxybenzaldehyde in 10 steps with 16% overall yield and assigned its absolute configuration as 3*S*,7*S*. Key elements of their synthetic approach constituted achieving the C_2-symmetric structure using the stereoselective allylation/aldol reaction sequence (i.e., stepwise manipulation).

Our research group has previously demonstrated the utility of chiral phosphine oxides as Lewis base organocatalysts.[5] Phosphine oxide coordinates with a chlorosilane to form a hypervalent silicon complex in dynamic equilibrium and catalyzes various asymmetric transformations.[6–8] In addition, we have recently developed the asymmetric double aldol reaction of ketone **2** with aromatic aldehyde **3** using the hypervalent silicon complex to obtain 3-pentanone derivative **4** with high stereoselectivity (Figure 2).[9,10] The hypervalent silicon complex **6**, generated from phosphine oxide (*S*)-**5** and silicon tetrachloride, first promotes the asymmetric aldol reaction. Phosphine oxide **5** is dislocated from the complex to yield silyl aldolate **7** and then regenerates **6** with another silicon tetrachloride, which further promotes the second aldol reaction of silyl aldolate **7** with aldehyde **3** to afford **4** in a highly stereoselective fashion. The stereochemical relationship between the two hydroxy moieties of **4** as well as those of **1** is 1,5-*anti*. Therefore, it is expected that the double aldol reaction of acetone (**2**) and a cinnamaldehyde derivative directly furnished the core skeleton of (−)-**1** with C_2-symmetric 1,9-diarylnonanoid structure. Herein, we report the enantioselective synthesis of (−)-ericanone (**1**) by means of the phosphine oxide-catalyzed asymmetric double aldol reaction.

We first explored the reactivity of aldehydes in the double aldol reaction. The reaction, conducted by treating three equivalents of 3-phenylpropanal with ketone **2** in the presence of 10 mol% (*S*)-**5**, four equivalents of silicon tetrachloride, and five equivalents of *N*,*N*-diisopropylethylamine in dichlorome-

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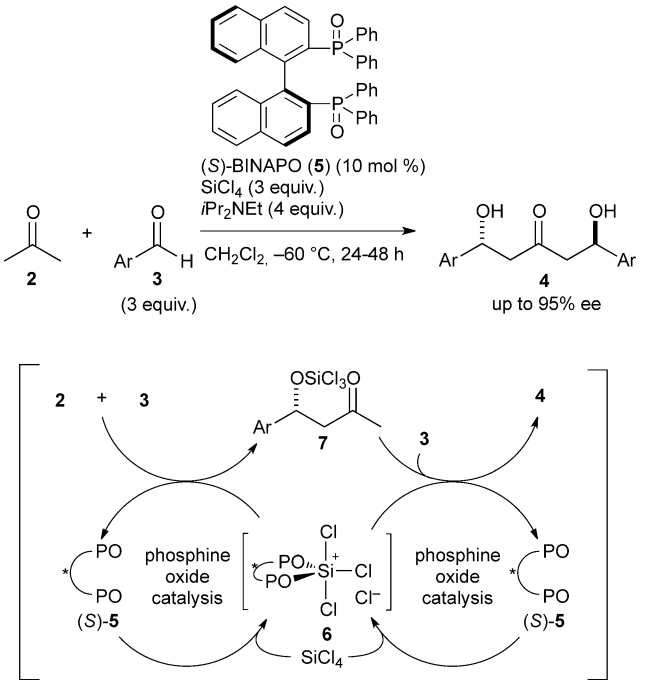
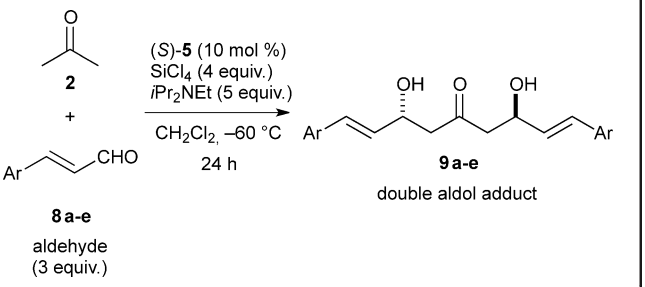


Figure 2. Phosphine oxide-catalyzed double aldol reaction.

Table 1. Enantioselective double aldol reaction of cinnamaldehyde derivatives **8**.[a]



Entry	Aldehyde, Ar		Double Aldol Adduct	Yield [%]	*Ee* [%][b]
1	**8a**	Ph	**9a**	68	88
2[c]	**8b**	4-TIPSO-C_6H_4	**9b**	41	84
3	**8c**	4-BnO-C_6H_4	**9c**	2	–[d]
4	**8d**	4-Br-C_6H_4	**9d**	86	87
5	**8e**	4-NsO-C_6H_4	**9e**	99	78
6[e]	**8e**	4-NsO-C_6H_4	**9e**	99	93

[a] Unless otherwise noted, the reactions were carried out by adding $SiCl_4$ (0.4 mmol) to a solution composed of ketone **2** (0.1 mmol), aldehyde **8** (0.3 mmol), catalyst (*S*)-**5** (0.01 mmol), and iPr_2NEt (0.5 mmol) in CH_2Cl_2 at −60 °C. [b] Determined by HPLC. [c] Aldehyde (5.0 equiv). [d] Not determined. [e] **8e** (2.3 equiv) at −78 °C.

thane at −60 °C, did not yield 1,9-diphenyl-3,7-hydroxy-5-nonanone owing to the in situ formation of a less electrophilic chlorohydrin in the reaction media.[11] On the other hand, the conjugate aldehyde cinnamaldehyde (**8a**) reacted smoothly to furnish double aldol adduct **9a** in good yield and with high enantioselectivity (Table 1, entry 1). Thus, we chose a cinnamaldehyde derivative **8** as an electrophile for the double aldol reaction. The carbon–carbon double bonds, which are not necessary for the total synthesis, would be hydrogenated during the later stage of the sequence. We then conducted the double aldol reaction of *p*-triisopropylsilyloxycinnamaldehyde (**8b**) toward the total synthesis of (−)-**1** (entry 2).[12] The corresponding double aldol product **9b** was obtained with good selectivity. However, the product yield was insufficient compared to the result obtained with the parent aldehyde **8a**.[13]

The unexpected decrease in the product yield in the double aldol reaction of **8b** was rationalized as summarized in Figure 3. The hypervalent silicon complex **6**, generated from (*S*)-**5** and silicon tetrachloride, coordinates with the aldehyde **8b** to form an intermediate **10**, owing to the electron-donor effect of the silyloxy group. A chloride anion attacks the intermediate **10** through path A to furnish **11**, which decomposes to aldehyde **12**. The addition of the chloride anion through paths B and C yields less electrophilic chlorosilyl species **13** and **14**, leading to the starting material **8b** after workup. The isolations of **12** and **8b** also support this suppression mechanism. Thus, the strong electron-donating functionality of the aldehyde **8b** facilitates the undesirable addition of chloride, suppressing the double aldol reaction.

To confirm the substituent effect of cinnamaldehydes, we conducted the double aldol reaction with several cinnamaldehyde derivatives (Table 1, entries 3–6). *p*-Benzyloxycinnamaldehyde (**8c**) bearing an electron-donating group was much less reactive than aldehyde **8b** (entry 3). In contrast, the use of *p*-bromocinnamaldehyde (**8d**) bearing an electron-withdrawing atom remarkably improved both the yield and enantioselectivity (entry 4). Thus, we introduced the 2-nitrobenzenesulfonyl (Ns) group as a removable electron-withdrawing group for the phenolic hydroxyl group (entry 5).[14,15] Expectedly, aldehyde **8e** was highly reactive at −60 °C to furnish the double aldol adduct **9e** with quantifiable yield. Lowering the reaction tem-

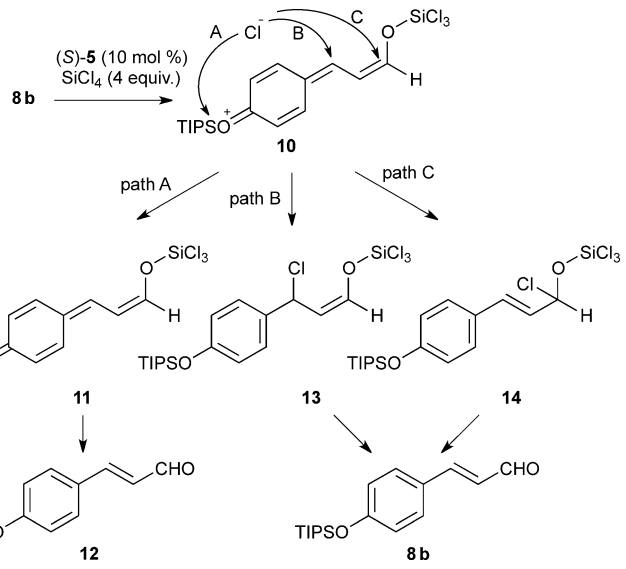
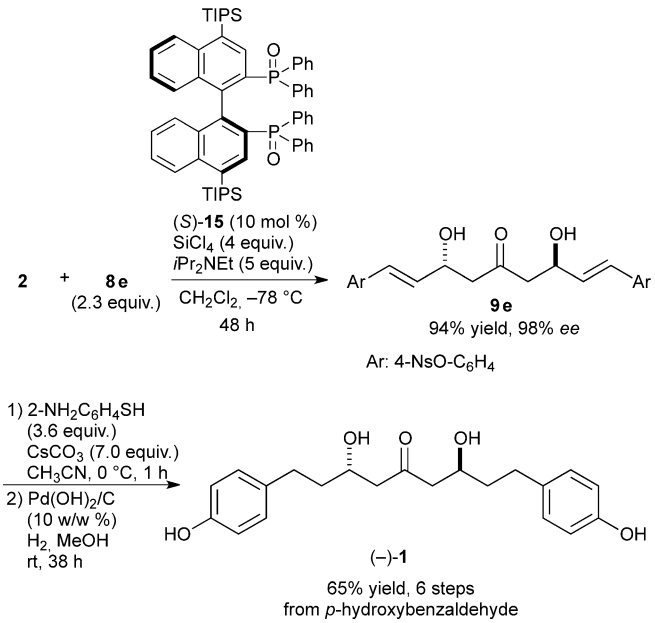


Figure 3. Suppression mechanism in the double aldol reaction of aldehyde **8b**.

perature to −78 °C resulted in the production of C_2-symmetric 1,9-diaryl-5-nonanone **9e** with high enantioselectivity (entry 6). We found that the use of the Ns group dramatically improved the reactivity in the double aldol reaction, and thereby realized high-yielding and stereoselective construction of the C_2-symmetric 3,7-*anti*-1,9-diaryl-3,7-dihydroxy-1,9-nonanoid structure.

In the double aldol reaction between ketone **2** and aldehyde **8e**, it was found that the use of 4,4′-TIPS$_2$-BINAPO (**15**) as a phosphine oxide catalyst further improved the enantioselectivity to 98% *ee* (Scheme 1).[16] The C_2-symmetric 1,9-diaryl-5-nonanone **9e** obtained was transformed to (−)-**1** by the removal of the Ns groups,[17] followed by hydrogenation with Pearlman catalyst. Thus, we completed the enantioselective total synthesis of (−)-**1** from *p*-hydroxybenzaldehyde in 6 steps with 65% overall yield. The spectroscopic data of the prepared (−)-**1** was identical to that of the naturally derived material in all respects.[1,4]



Scheme 1. Enantioselective total synthesis of (−)-ericanone (**1**).

In conclusion, we have achieved the enantioselective total synthesis of (−)-ericanone from *p*-hydroxybenzaldehyde in 6 steps with 65% overall yield. Key results of the study include great improvements in the reactivity with the 2-nitrobenzenesulfonyl group and improvement in selectivity by introducing the triisopropylsilyl group in the 4,4′-positions of BINAPO in the asymmetric double aldol reaction. The double aldol reaction using the chiral hypervalent silicon complex presents a concise and convenient strategy for constructing the C_2-symmetric molecule via a simple procedure. Current and future work is directed towards applying the developed strategy to related targets and probing the biochemical potential of (−)-ericanone.

Experimental Section

Typical procedure for the enantioselective double aldol reaction of ketone 2 and aldehyde 8e with (*S*)-TIPS$_2$-BINAPO (15): To a solution of aldehyde **8e** (76.6 mg, 0.23 mmol, 2.3 equiv), (*S*)-TIPS$_2$-BINAPO (**15**) (9.7 mg, 0.01 mmol, 10 mol%), ketone **2** (37 μL, 0.1 mmol) and *N*,*N*-diisopropylethylamine (0.08 mL, 0.5 mmol, 5 equiv) in CH_2Cl_2 (5.0 mL), and silicon tetrachloride (0.05 mL, 0.4 mmol, 4 equiv) were added at −78 °C, and the reaction mixture was stirred for 48 h. The reaction was quenched with an aqueous solution composed of 1.5 M KF/3.0 M HCO_2H (5.0 mL), and the slurry was stirred for 0.5 h. The two-layer mixture was extracted with ethyl acetate (EtOAc; 3×20 mL) and the combined organic layers were washed with 10% HCl (20 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL), and then dried over Na_2SO_4. After filtration and concentration, the crude product was purified by column chromatography (hexane/EtOAc = 4:1, SiO_2: 10 g) to afford product **9e** (67.9 mg, 94% yield, 98% *ee*) as yellow prisms.

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Keywords: 1,9-diarylnonanoids · aldol reaction · C_2-symmetry · hypervalent silicon complex · phosphine oxides

[1] B. Bennini, A. J. Chulia, M. Kaouadji, P. Fondaneche, D. P. Allais, *Tetrahedron Lett.* **2011**, *52*, 1597–1600.
[2] For papers regarding 1,9-diarylnonanoid families, see: a) M. Kaouadji, B. Bennini, A. J. Chulia, *Tetrahedron Lett.* **2012**, *53*, 3663–3667; b) M. Kaouadji, B. Bennini, A. J. Chulia, *Tetrahedron Lett.* **2013**, *54*, 1873–1876.
[3] For papers regarding 1,7-diarylheptanoid families, see: a) P. Rüedi, M. Juch, *Curr. Org. Chem.* **1999**, *3*, 623–646; b) J. Ishida, M. Kozuka, H. Tokuda, H. Nishino, S. Nagumo, K.-H. Lee, M. Nagai, *Bioorg. Med. Chem.* **2002**, *10*, 3361–3365; c) K.-S. Chun, K.-K. Park, J. Lee, M. Kang, Y.-J. Surh, *Oncol. Res.* **2002**, *13*, 37–45; d) H.-J. Kim, S.-H. Yeom, M.-K. Kim, J.-G. Shin, I.-N. Paek, M.-W. Lee, *Arch. Pharmacal Res.* **2005**, *28*, 177–179; e) H. Matsuda, S. Ando, T. Kato, T. Morikawa, M. Yoshikawa, *Bioorg. Med. Chem.* **2006**, *14*, 138–142.
[4] L. C. Dias, P. K. Kuroishi, E. C. Polo, E. C. de Lucca, Jr., *Tetrahedron Lett.* **2013**, *54*, 980–982.
[5] For examples of phosphine oxide-catalyzed asymmetric transformations conducted in this laboratory, see: a) M. Nakajima, S. Kotani, T. Ishizuka, S. Hashimoto, *Tetrahedron Lett.* **2005**, *46*, 157–159; b) S. Kotani, S. Hashimoto, M. Nakajima, *Synlett* **2006**, 1116–1118; c) S. Kotani, S. Hashimoto, M. Nakajima, *Tetrahedron* **2007**, *63*, 3122–3132; d) K. Nakanishi, S. Kotani, M. Sugiura, M. Nakajima, *Tetrahedron* **2008**, *64*, 6415–6419; e) S. Kotani, Y. Shimoda, M. Sugiura, M. Nakajima, *Tetrahedron Lett.* **2009**, *50*, 4602–4605; f) Y. Shimoda, T. Tando, S. Kotani, M. Sugiura, M. Nakajima, *Tetrahedron: Asymmetry* **2009**, *20*, 1369–1370; g) M. Sugiura, N. Sato, Y. Sonoda, S. Kotani, M. Nakajima, *Chem. Asian J.* **2010**, *5*, 478–481; h) S. Kotani, S. Aoki, M. Sugiura, M. Nakajima, *Tetrahedron Lett.* **2011**, *52*, 2834–2836; i) S. Aoki, S. Kotani, M. Sugiura, M. Nakajima, *Chem. Commun.* **2012**, *48*, 5524–5526; j) K. Osakama, M. Sugiura, M. Nakajima, S. Kotani, *Tetrahedron Lett.* **2012**, *53*, 4199–4201; k) S. Kotani, H. Furusho, M. Sugiura, M. Nakajima, *Tetrahedron* **2013**, *69*, 3075–3081; l) S. Kotani, M. Sugiura, M. Nakajima, *Chem. Rec.* **2013**, *13*, 362–370;

m) S. Kotani, S. Aoki, M. Sugiura, M. Ogasawara, M. Nakajima, *Org. Lett.* **2014**, *16*, 4802 – 4805.

[6] For other examples of phosphine oxide-catalyzed asymmetric transformations, see: a) S. Rossi, M. Benaglia, A. Genoni, T. Benincori, G. Celentano, *Tetrahedron* **2011**, *67*, 158 – 166; b) S. Rossi, M. Benaglia, F. Cozzi, A. Genoni, T. Benincori, *Adv. Synth. Catal.* **2011**, *353*, 848 – 854; c) M. Bonsignore, M. Benaglia, F. Cozzi, A. Genoni, S. Rossi, L. Raimondi, *Tetrahedron* **2012**, *68*, 8251 – 8255; d) J. Chen, D. Liu, D. Fan, Y. Liu, W. Zhang, *Tetrahedron* **2013**, *69*, 8161 – 8168; e) S. Cauteruccio, D. Dova, M. Benaglia, A. Genoni, M. Orlandi, E. Licandro, *Eur. J. Org. Chem.* **2014**, 2694 – 2702; f) S. Rossi, M. Benaglia, E. Massolo, L. Raimondi, *Catal. Sci. Technol.* **2014**, *4*, 2708 – 2723; g) S. Rossi, R. Annunziata, F. Cozzi, L. M. Raimondi, *Synthesis* **2015**, 2113 – 2124.

[7] For reviews on Lewis base organocatalysis, see: a) G. Chelucci, G. Murineddu, G. A. Pinna, *Tetrahedron: Asymmetry* **2004**, *15*, 1373 – 1389; b) S. Rendler, M. Oestreich, *Synthesis* **2005**, 1727 – 1747; c) A. V. Malkov, P. Kočovský, *Eur. J. Org. Chem.* **2007**, 29 – 36; d) S. E. Denmark, G. L. Beutner, *Angew. Chem. Int. Ed.* **2008**, *47*, 1560 – 1638; *Angew. Chem.* **2008**, *120*, 1584 – 1663; e) M. Benaglia, S. Guizzetti, L. Pignataro, *Coord. Chem. Rev.* **2008**, *252*, 492 – 512; f) M. Benaglia, S. Rossi, *Org. Biomol. Chem.* **2010**, *8*, 3824 – 3830.

[8] For reviews on silicon tetrachloride-mediated reactions, see: S. Rossi, M. Benaglia, A. Genoni, *Tetrahedron* **2014**, *70*, 2065 – 2080.

[9] a) Y. Shimoda, S. Kotani, M. Sugiura, M. Nakajima, *Chem. Eur. J.* **2011**, *17*, 7992 – 7995; b) Y. Shimoda, T. Kubo, M. Sugiura, S. Kotani, M. Nakajima, *Angew. Chem. Int. Ed.* **2013**, *52*, 3461 – 3464; *Angew. Chem.* **2013**, *125*, 3545 – 3548; c) S. Kotani, M. Sugiura, M. Nakajima, *Synlett* **2014**, *25*, 631 – 640.

[10] For examples of Lewis base-catalyzed asymmetric double aldol reactions by other laboratories, see: a) A. Genoni, M. Benaglia, S. Rossi, G. Celentano, *Chirality* **2013**, *25*, 643 – 647; b) P. Zhang, Z. Han, Z. Wang, K. Ding, *Angew. Chem. Int. Ed.* **2013**, *52*, 11054 – 11058; *Angew. Chem.* **2013**, *125*, 11260 – 11264; c) F. Maier, O. Trapp, *Angew. Chem. Int. Ed.* **2014**, *53*, 8756 – 8760; *Angew. Chem.* **2014**, *126*, 8901 – 8905.

[11] S. E. Denmark, S. B. D. Winter, W. Su, K.-T. Wong, *J. Am. Chem. Soc.* **2002**, *124*, 13405 – 13407.

[12] The phenolic hydroxyl group of *p*-hydroxybenzaldehyde was protected with the triisopropylsilyl group, followed by HWE reaction with cyanomethylphosphonate and sodium hydride in toluene leading to cinnamonitrile. Reduction with DIBAL-H yielded aldehyde **8b** in three steps.

[13] While the double aldol adduct **9b** was converted into (−)-**1** in two steps, the overall yield hardly improved compared to Dias' route.

[14] a) R. Ishikawa, N. Yoshida, Y. Akao, Y. Kawabe, M. Inai, T. Asakawa, Y. Hamashima, T. Kan, *Chem. Lett.* **2014**, *43*, 1572 – 1574; b) Y. Kawabe, R. Ishikawa, Y. Akao, A. Yoshida, M. Inai, T. Asakawa, Y. Hamashima, T. Kan, *Org. Lett.* **2014**, *16*, 1976 – 1979.

[15] We slightly modified the synthesis procedure of cinnamaldehyde **8e**. A sequence of *o*-nosyl protection and HWE reaction by treating *p*-hydroxybenzaldehyde with *o*-nosyl chloride and cyanomethylphosphonate, respectively, in the presence of Hünig's base, gave the corresponding cinnamonitrile with 99% yield (*E*/*Z* = 3:1) in a one-pot process. The nitrile was reduced with DIBAL-H, leading to aldehyde **9e** with 84% yield. The *Z*-isomer of cinnamonitrile was isomerized into the *E*-isomer after reduction of DIBAL-H; see the Supporting Information.

[16] We have recently disclosed that 4,4′-substituents of the binaphthyl moiety in BINAPO efficiently improved the stereoselectivities, see: ref. 5m.

[17] a) T. Fukuyama, C.-K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6373 – 6374; b) Y. Aihara, A. Yoshida, T. Furuta, T. Wakimoto, T. Akizawa, M. Konishi, T. Kan, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4171 – 4174.

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