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A CONVERGENT AND STRAIGHTFORWARD SYNTHETIC METHOD TO PREPARE DEAZA-ANALOGS OF SQUALENE EPOXIDASE INHIBITORS

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Abstract: a general route to deaza-analogs of squalene epoxidase inhibitors of general formula **A** is described using a very convergent synthetic scheme illustrated by the preparation of compound **2b**. A Heck reaction, and an enolate condensation with an appropriate electrophile are the key steps of the expedient elaboration of **2b** or analogs.

As part of our search for new hypocholesterolemic and antiatherosclerotic agents, we focused our efforts on inhibitors of squalene epoxidase (SE, EC 1.14-99.7), which plays a key role in cholesterol biosynthesis.[1] Inhibitors of this enzyme include antifungal agents that selectively inhibit fungal squalene epoxidase such as terbinafine **1a** (Figure 1).[2] Beside, we have recently reported a novel series of (aryloxy)methylsilane derivatives including **2a** as potent mammalian SE inhibitors able to control cholesterol biosynthesis *in vitro* and *in vivo* (Figure 1).[3] Recent studies[4] have shown that the nitrogen atom found in terbinafine was not essential for squalene epoxidase inhibition such as in compound **1b** (Figure 1) but

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play a central role in the process of penetration of the fungal envelope. In order to gain better insights about the importance of a basic nitrogen for mammalian SE inhibition, we have prepared the analog **2b** (Figure 1).

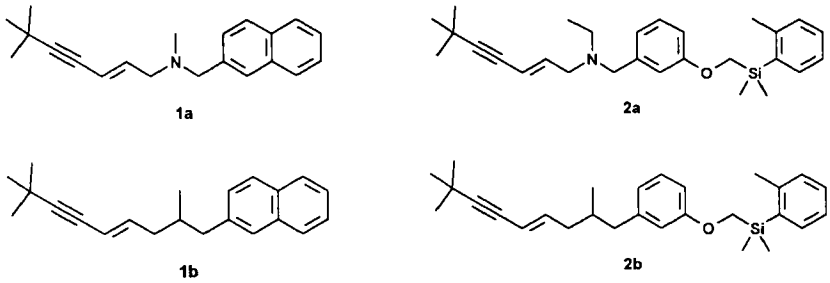


Figure 1

In this letter, we wish to report on a new, general approach to prepare aromatic enyne derivatives of general formula **A** (Figure 2) illustrated by the synthesis of **2b** and which turned out to be superior to the one proposed[4] previously to access carba-analogs of terbinafine.

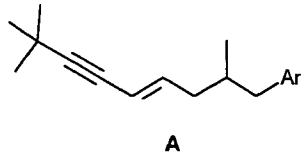
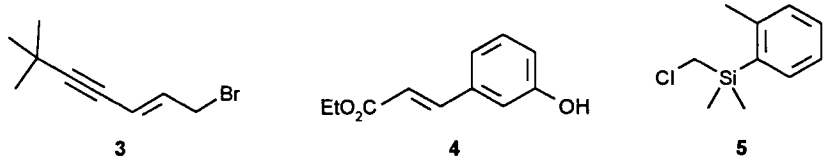


Figure 2

A retrosynthetic analysis led us to fragment compound **2b** in three units, **4** being the principal anchor (Figure 3). A palladium-catalyzed cross-coupling reaction between 3-halogenated phenol and ethylacrylate could lead to the intermediate **4**. Alkylation of the phenolic part of **4** with (chloromethyl)(2-methylphenyl)dimethylsilane **5** should afford the right wing of **2b** while enoiate

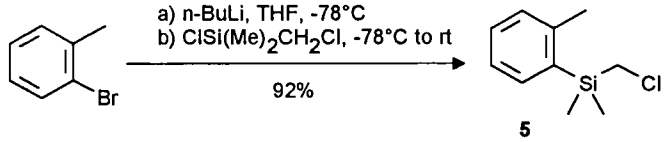
condensation of its ester moiety (after reduction of the double bond) with the enyne **3** should complete the construction of **2b** in a very efficient manner. C-alkylation of an ester enolate is a very attractive method since the stereochemistry of the formed chiral center can be easily controlled by taking advantage of existing enantioselective methods for enolate condensation.[5]



3 **4** **5**

Figure 3

Chlorosilane **5** was prepared in high yield (92 % after distillation) by reacting n-butyllithium at -78°C with *o*-bromotoluene followed by the addition of (chloromethyl)dimethylchlorosilane in tetrahydrofuran (Scheme 1).[6,7]

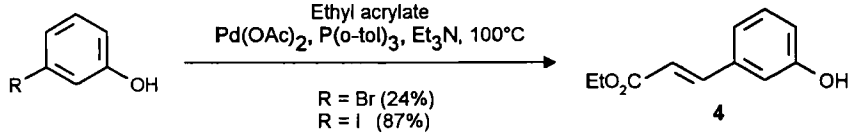


5

Scheme 1

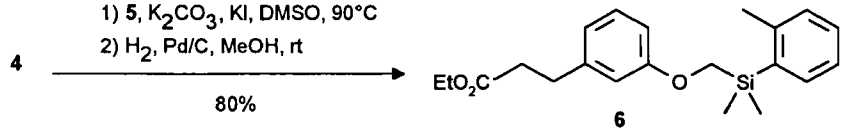
A known procedure[8] was employed for the synthesis of the enyne unit **3**: addition of the lithio derivative of 3,3-dimethylbutyne on acrolein led quantitatively to a secondary allylic alcohol which was rearranged in **3** by treatment with phosphorus tribromide in aqueous hydrobromic acid.

The elaboration of the pivot intermediate **4** was envisioned via a Heck reaction[9] (Scheme 2). Our first attempts using $Pd(OAC)_2/P(o\text{-}tol)_3$ provided the expected phenol **4** in low yield (24%) even after a prolonged time at 100°C. Replacement of 3-bromophenol by 3-iodophenol proved to be satisfying, leading in a very high yield to compound **4**.



Scheme 2

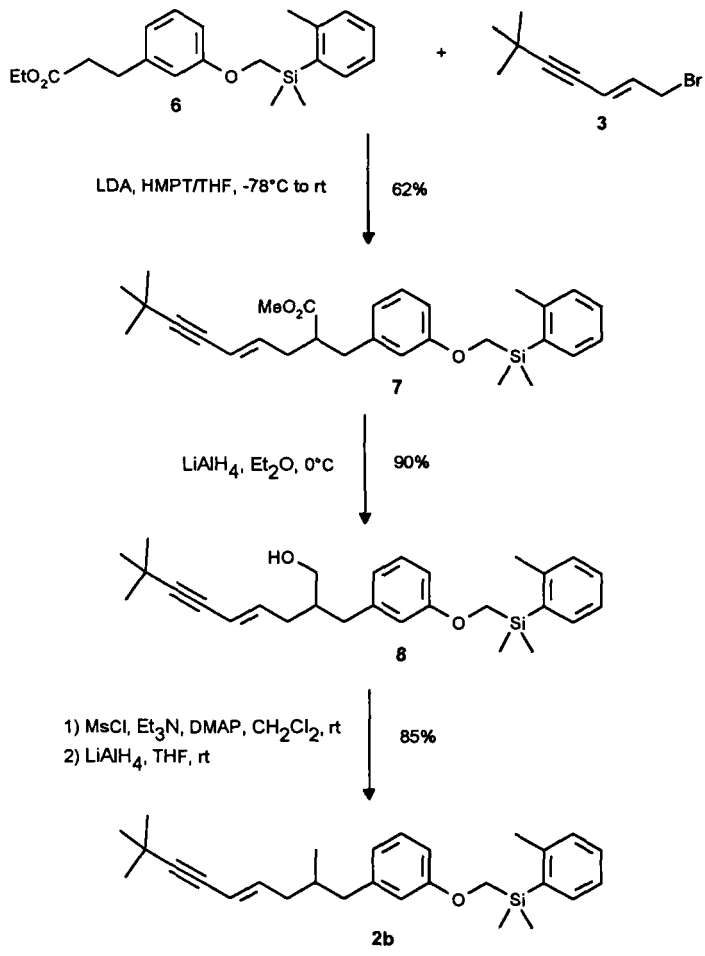
Alkylation of the phenolic part of **4** with silane **5** required to treat compound **4** with potassium carbonate. and a stoechiometric amount of potassium iodide in dimethylsulfoxide (DMSO) at 90°C (Scheme 3). Quantitative reduction of the double bond by using hydrogen and palladium on charcoal provided ester **6** (Scheme 3) in a high yield two steps sequence.



Scheme 3

Scheme 4 summarizes the final stages in the synthesis of aryloxysilane carba-analog **2b**. The key step was the condensation of the ester enolate derived from **2** with allylic bromide **3** to generate the enyne structural element. When compound **6** was treated with lithium diisopropylamide in tetrahydrofuran at -70°C followed by quenching the expected enolate intermediate[10] with bromide **3**, the yield was low and numerous by-products were formed. Performing the reaction in the same conditions with HMPT as co-solvent enhances the reactivity of the enolate and led to **7** in good yield.

A classical three steps reduction mesylation-reduction sequence (Scheme 4) allows an easy and straightforward transformation of the ester group to a methyl group and thus to the isolation of final compound **2b** in a 47% global yield from **6**.



Scheme 4

In conclusion, the proposed synthesis of carba-analog **2b** described in this paper appears as a fully convergent approach, and offers a new, general and very straightforward method of elaboration of compound of type **A**.

Experimental[11]

Chloromethyl(2-methylphenyl)dimethylchlorosilane 5

To a solution of 2-bromotoluene (10 g, 58 mmol) in anhydrous tetrahydrofuran (60

mL) was added n-butyllithium (10 M in hexanes, 7 mL, 70 mmol, 1.2 equiv) at -70°C. The reaction mixture was then stirred for 30 minutes at this temperature and treated with (chloromethyl)dimethylchlorosilane (8.5 mL, 65 mmol, 1.1 equiv.) in tetrahydrofuran (10 mL). The resulting mixture was allowed to warm to room temperature over a period of 2 h and partitioned between ether (200 mL) and a saturated aqueous ammonium chloride solution (50 mL). The organic layer was washed with a saturated aqueous sodium chloride solution (100 mL) then dried over magnesium sulfate, filtered and concentrated *in vacuo*. Vacuum distillation of the crude oil (1 mbar, 65°C) provided the title compound (10.6 g, 92%) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 7.32-6.84 (m, 4H), 3.04 (s, 2H) , 2.51 (s, 3H), 0.45 (s, 6H).

(E)-Ethyl-2-(3-hydroxyphenyl)propenoate 4

A mixture of 3-iodophenol (5 g, 23 mmol), triethylamine (6 mL), ethyl acrylate (3 mL, 34 mmol, 1.5 equiv), palladium acetate (51 mg, 0.23 mmol, 0.01 equiv) and tris(o-tolyl)phosphine (420 mg, 1.38 mmol, 0.06 equiv) was heated for 24 h to 100°C in a pressure-safety bottle. After cooling, the mixture was diluted in ethyl acetate (200 mL) and washed with an aqueous solution of 1N hydrochloric acid (15 mL) to reach neutral pH. The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. Column chromatography on silica gel (80/20 petroleum ether/ethyl acetate; Rf = 0.23) gave **4** (3.8 g 87 %) as a pale yellow solid: ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 16.0 Hz, 1H), 7.13-6.81 (m, 4H), 6.32 (d, J = 16.0 Hz, 1H), 5.72 (s, 1H), 4.33 (q, J = 7.2 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H). Calculated for $C_{11}H_{12}O_3$: C, 68.73; H, 6.30 Found: C, 68.83; H, 6.36.

Ethyl-3-[((2-methylphenyl)dimethylsilyl)methoxy]propionate 6

A mixture of phenol **4** (500 mg, 2.6 mmol), and finely ground potassium carbonate

(1.8 g, 13 mmol, 5 equiv) in dimethylsulfoxide (10 mL) was heated at 90°C for 30 min. After cooling, potassium iodide (458 mg, 3.9 mmol, 5 equiv) and (chloromethyl)(2-methylphenyl)dimethylsilane (510 mg, 3.9 mmol, 1.5 equiv) in dimethylsulfoxide (10 mL) were successively added. The reaction was stirred for 5 h at 90°C and then, after cooling, partitioned between ethyl acetate and water. Separation of the layers and washing of the ethyl acetate layer with water was continued until the aqueous phase reached pH=7. The aqueous fractions were extracted with ethyl acetate (x2) and the combined organic layers dried over magnesium sulfate. Filtration and solvent removal *in vacuo* gave the crude product which was purified by column chromatography (SiO_2, 92/8 petroleum ether/ether) to afford *(E)-ethyl-3-[((2-methylphenyl)dimethylsilyl)methoxy]-propenoate* as an oil (830 mg, 90 %): Rf = 0.55 (80/20 petroleum ether/ethyl acetate). ^1H NMR ($CDCl_3$) δ 7.65 (d, J = 16 Hz, 1H), 7.55-6.95 (m, 8H), 6.42 (d, J = 16 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 3.87 (s, 2H), 2.51 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H), 0.45 (s, 6H). IR (film, cm^{-1}): 2960, 1713, 1250, 840. Calculated for $C_{21}H_{26}O_3Si$: C, 71.25; H, 7.34 Found: C, 71.02; H, 7.37.

A solution of the α,β-unsaturated ester previously obtained (700 mg, 1.96 mmol) and palladium on charcoal (5%, 120 mg) in methanol (10 mL) was stirred 10 h under an atmosphere of hydrogen at room temperature. The mixture was then filtered over Celite and evaporated *in vacuo* to afford **6** as a colorless oil (630 mg, 90 %) pure enough to be used in the next step without further purification: Rf = 0.54 (80/20 petroleum ether/ethyl acetate). ^1H NMR ($CDCl_3$) δ 7.53-6.75 (m, 8H), 4.26 (q, J = 7.2 Hz, 2H), 3.87 (s, 2H), 2.92 (t, J = 8 Hz, 2H), 2.62 (t, J = 8 Hz, 2H), 2.51 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H), 0.45 (s, 6H). IR (cm^{-1}): 2960, 1735, 1250, 840. Calculated for $C_{21}H_{23}O_3Si$: C, 70.85; H, 7.86 Found: C, 70.59; H, 8.17.

Ethyl-2-{[(2-methylphenyl)dimethylsilyl)methoxy]benzyl}-8,8-dimethyl-non-4-ene-5yne-oate 7

To a solution of lithium diisopropylamide [prepared by treatment of diisopropylamine (0.76 mL, 5.4 mmol, 1.3 equiv) in tetrahydrofuran (10 mL) with n-butyllithium (1.6 M in hexanes, 3 mL, 4.8 mmol, 1.15 equiv) at -20°C] was added dropwise ester **6** (1.5 g, 4.21 mmol) in tetrahydrofuran (10 mL) at - 70°C. The reaction mixture was stirred 1 h at this temperature and a solution of the bromide[8] (1 g, 5 mmol, 1.2 equiv) in hexamethylphosphorotriamide (HMPT) (0.74 mL, 4.21 mmol, 1 equiv) was introduced slowly at -70°C. After stirring 1 h at this temperature, the mixture was allowed to warm to room temperature (2 h) and diluted in ethyl acetate (200 mL).

Drying over magnesium sulfate, filtration and concentration afford a crude oil which was subjected to a column chromatography (SiO_2, 95/5 petroleum ether/ether) to provide **7** as a yellow oil (1.23 g, 62 %): Rf = 0.66 (80/20 petroleum ether/ethyl acetate). ^1H NMR ($CDCl_3$) δ 7.72-7.16 (m, 5H), 6.85-6.74 (m, 3H), 6.12 (dt, J = 16.2, 8 Hz, 1H), 5.54 (d, J = 16.2 Hz, 1H), 3.81 (q, J = 7.2 Hz, 2H), 3.8 (s, 2H), 2.92-2.65 (m, 3H), 2.5 (s, 3H), 2.42-2.25 (m, 2H), 1.21 (s, 9H), 1.15 (t, J = 7.2 Hz, 3H), 0.45 (s, 6H). IR(cm^{-1}): 2960, 2200, 1735, 1250, 849. Calculated for $C_{30}H_{40}O_3Si$: C, 75.69; H, 8.47. Found: C, 75.87; H, 8.23.

2-{3-[((2-methylphenyl)dimethylsilyl)methoxy]benzyl}-8,8-dimethyl-non-4-enen-5-ynoate 8

A solution of lithium aluminium hydride (1 M in ether, 2.3 mL, 2.26 mmol, 1.1 equiv) was dropwise added at 0°C to a solution of ester **7** (980 mg, 2.05 mmol) in ether (15 mL). After completion of the reaction (2 h), the mixture was quenched with addition of sodium sulfate decahydrate. The etheral solution was then filtered, concentrated *in vacuo* and the crude product purified by column chromatography

on silica gel (80/20 petroleum ether/ethyl acetate; Rf = 0.32) to afford alcohol **8** (800 mg, 90 %) as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 7.72-7.16 (m, 5H), 6.85-6.74 (m, 3H), 6.12 (dt, J = 16.2, 8 Hz, 1H), 5.54 (d, J = 16.2 Hz, 1H), 4.82 (s, 1H), 3.81 (s, 2H), 3.53-3.50 (m, 2H), 2.58 (d, J = 8 Hz, 2H), 2.5 (s, 3H), 2.18-1.86 (m, 3H), 1.21 (s, 9H), 0.45 (s, 6H). IR (cm^{-1}): 3400, 2950, 1250, 840 Calculated for $C_{28}H_{38}O_2Si$: C, 77.37; H, 8.81. Found: C, 76.95; H, 8.88.

2-{3-[((2-methylphenyl)dimethylsilyl)methoxy]benzyl}-8,8-dimethyl-non-4-ene-6-yne 2b

To a 0°C cooled solution of alcohol **8** (230 mg, 0.53 mmol), triethylamine (0.18 mL, 1.06 mmol, 2 equiv) and 4-dimethylaminopyridine (15 mg, 0.11 mmol, 0.2 equiv) in dichloromethane (5 mL) was added dropwise methanesulfonyl chloride (0.05 mL, 0.635 mmol, 1.2 equiv). The reaction mixture was stirred 30 min at room temperature diluted in ether (100 mL) and washed successively with a saturated aqueous solution of copper sulfate and a saturated aqueous sodium chloride solution. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was filtered over silica gel (fast plug, 100% ether). Evaporation of the solvent afforded the crude mesylate (290 mg; 100%) pure enough to be used in the next step without further purification.

A solution of mesylate (290 mg, 0.57 mmol) in tetrahydrofuran cooled at - 10°C was treated with lithium aluminium hydride (1 M in tetrahydrofuran, 0.6 mL, 0.57 mmol, 1 equiv) for 4 h. The mixture was quenched with addition of sodium sulfate decahydrate. The etheral solution was then filtered, concentrated *in vacuo* and the crude product purified by column chromatography on silica gel (70/20 petroleum ether/ethyl acetate, Rf = 0.68) to provide the expected carba-analog **2b** (190 mg, 85%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.53-7.16 (m, 5H), 6.85-6.74 (m, 3H), 6.12 (dt, J = 16.2, 8 Hz, 1H), 5.54 (d, J = 16.2 Hz, 1H), 3.81 (s, 2H), 2.59

(dd, J = 13.1, 6.1 Hz, 1H), 2.5 (s, 3H), 2.31 (dd, J = 13.1, 7.8 Hz, 1H), 2.18-1.86 (m, 3H), 1.21 (s, 9H), 0.84 (d, J = 6.1 Hz, 3H), 0.45 (s, 6H). Calculated for $C_{29}H_{38}OSi$: C, 80.32; H, 9.15 Found C: 80.33; H, 9.45.

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