Indian Journal of Chemistry
Vol. 60B, June 2021, pp. 866-873

An effective total synthesis of four angiotensin-converting enzymes containing silanediols

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Received 9 September 2020; accepted (revised) 5 April 2021

Four angiotensin-converting enzymes (ACE) containing silanediols **1** have been synthesized successfully in 8% overall yield in 8 steps from inexpensive starting materials such as diphenyldichlorosilane **5**, β-methylallylic alcohol **7** and Ellman sulfinimine **9**.

Keywords: Angiotensin-converting enzymes, silandiol, Ellman sulfinimine, diphenyldichlorosilane, β-methylallylic alcohol, total synthesis

A part from similarity, there are a lot of differences between silicon and carbon. In general, the hydrated sp^3 hybridization form of carbonyl group is energetically disfavored over their trigonal unhydrated sp^2 counterparts. In contrast, silicon species strongly prefersp^3 geometry to sp^2 geometry[1]. Therefore, silandiol containing compounds have been synthesized for some decades to test for some biological activity purposes based on modification of enzymes[2-4]. For example, silanediol inhibitors of the serine protease coagulation cascade enzyme FXIa[5], human neutrophil elastase[6,7], serine protease[8], anthrax lethal factor[9], angiotensin-converting enzyme[10] and the metalloprotease thermolysin[11,12] and human immunodeficiency virus-1 protease[13] were synthesized successfully. Moreover, silanediols have been investigated as acid-based catalysts. For instance, silanediols were active in catalyzing Diels-Alder reactions[14-16]. From these examples, four angiotensin-converting enzymes (ACE) containing silanediols got most our attention since three of them inhibited interestingly angiotensin-converting enzymes at IC_{50} values (3.8-207 nM); the fourth diastereomer exhibited inhibition of angiotensin-converting enzymes at 3200 nM that all paralleled with identical ketones.

The first synthesis of these four silanediols was successfully synthesized in 2005 by Kim, J. *et al.* The ACE inhibitors (*R*,*S*,*S*)-**1**, (*R*,*R*,*S*)-**1,** (*S*,*S*,*S*)-**1** and (*S*,*R*,*S*)-**1**+** were carried out following that rout required from 13 linear steps in % over all.

In this synthesis, one stereo center was purchased and the other was formed without control[10]. In 2011, a short and asymmetric synthesis of (*R*,*S*,*S*)-**1**'s precursor was reported through an asymmetric synthesis of silyl ether gave an (*S*)-silafuran in 90% (94 ee%). It suffered from the high cost of ferrotane catalyst; the instability of asymmetric hydrosilylation and scale of reactions[17]. In this paper, a quick and inexpensive access for synthesis of these silanediols is reporting.

In Figure 1, the silanediolprecursor **2** would be treated with strong acid to hydrolyze the two phenyl-silicon bonds and the *tert*-butyl ester to form diflourosilane derivatives that would be easily converted to silanediols **1**[11]. The silane sulfinimide**3** would be derived from Ellman sulfinimine and silyl lithium that is prepared when silane **4** reacts with lithium. The silane **4** would be synthesized from inexpensive commercially available dichlorodiphenyl silane **5**.

Results and Discussion

First of all, dichlorodiphenylsilane **5** was converted into diphenylsilane (**6**). This step was scaled up to 120g (100mL) of dichlorodiphenylsilane (**5**). It is worth to know that the Fieser&Fieser helps to work

** **Note**: (*S*,*S*,*S*)-**1**, (*R*,*S*,*S*)-**1**, (*S*,*R*,*S*)-**1**, (*R*,*R*,*S*)-**1** were denoted for absolute cofiguration in order from left to right of the structures.

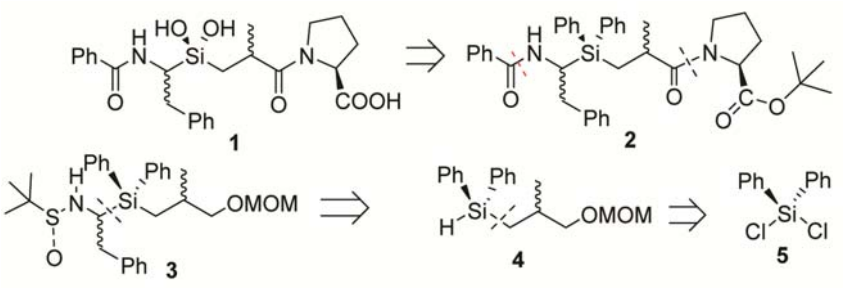


Figure 1 — Synthetic plan for silanediols 1

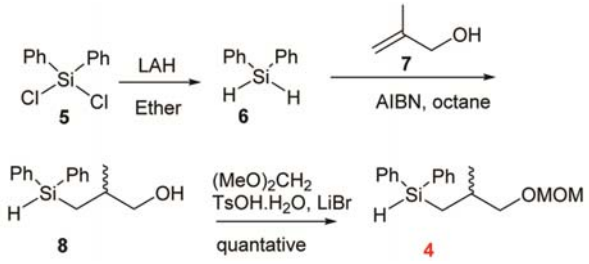
up with $LiAlH_4$ (LAH) in safe. Product diphenylsilane (**6**) was distilled with Kugelrohr apparatus in 95% yield. Azobisisobutyronitrile (AIBN) initiated the radical substitution reaction between silane **6** and β-methylallylic alcohol **7** [18] to obtain alcohol (±)-**8**, without further purification, the alcohol was protected with a methoxymethyl (MOM) group using the method of Gras *et al*. to give silane (±)-**4** in 73% yield over three steps (Scheme I) [19].

To take advantages of reaction of silyl lithium and sulfinimine[20], the silane (±)-**4** reacted with lithium metal in anhydrous tetrahydrofuran (THF) to form the silyllithium that was reacted with Ellman sulfinimine (*R*)-9 at –78°C to give sulfinamide 10 as a mixture of two diastereomers (*R*,*R*,*R*)-10 and (*R*,*R*,*S*)-10 in 45% yield (Scheme II).

The Ellman auxiliary and MOM group of **10** were removed with 4 M HCl in dioxane to yield a crude amine salt[21] followed bySchotten-Baumann benzoylation gave the desired amide **11** in moderate yield. (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (Tempo) and bis(acetoxy)iodobenzene (BAIB)[22,23] were the first used to oxidize the primary alcohol **11** to carboxylic acid **12** in moderate yield. The coupling reaction between acid **12** and L-proline usingdiethyl cyanophosphonate formed a mixture of amides **2** which were separated via a flash column chromatography. The retention factors of (*R*,*R*,*S*)-**2** (R_f = 0.47)and (*R*,*S*,*S*)-**2**(R_f = 0.25)were different by 0.2, allowing for an easy separation with flash column chromatography (Scheme II) [10,17,24]. The absolute configuration of (*S*,*S*,*S*)-**2**and (*S*,*R*,*S*)-**2** were determined by comparing with the known-diastereomers[11,17].

Similar to synthesis of (*S*,*S*,*S*)-**2** and (*S*,*R*,*S*)-**2** in Scheme II, (*S*,*R*,*S*)-**2** and (*S*,*S*,*S*)-**2** were synthesized easily using Ellman sulfinimine (*S*)-**9** (Scheme III).

Since each diastereomer had a known stereogeniccenter on the proline moiety, X-Ray diffraction of (*S*,*S*,*S*)-**2** was recorded (Figure 2). Therefore, the other was (*S*,*R*,*S*)-**2** diastereomer.



Scheme I — Synthesis of silane 4

Dearylation of compounds **2** was accomplished with 60 equivalents of triflic acid (TfOH), followed by addition of NH_4OH and HF to produce stable diflurosilanes**14**, as stable crystalline products, easily stored and easily hydrolyzed to the silanediols **1** (Scheme IV) [10].

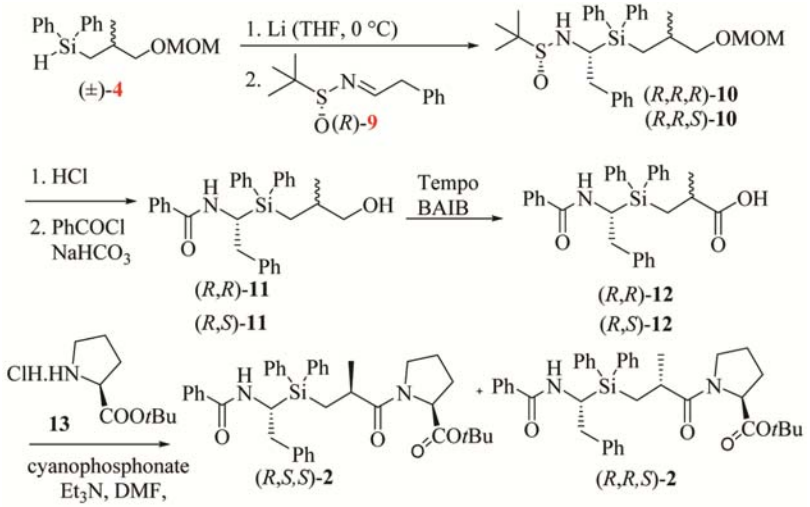
Experimental Section

General

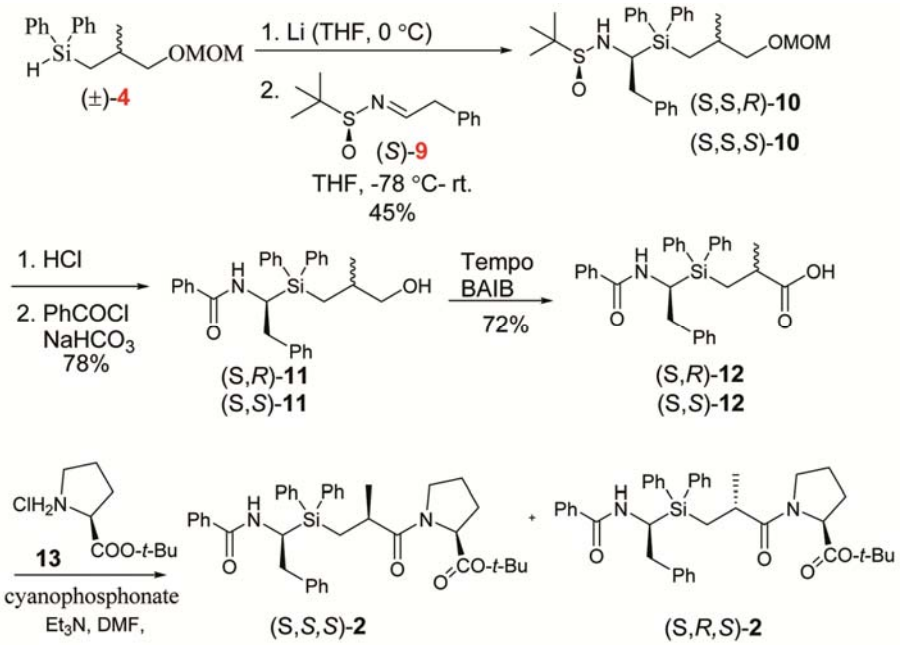
Reagents and solvents were purchased from Gelest, Aldrich, Fisher Scientific, Alfa Aesar, and Acros. Reaction solvents were purified using a 'Grubbs-style' solvent dispensing system purchased from Glass Contour. Chromatography was conducted over silica gel (170e400 mesh, 60A) or basic alumina (activated 50e200 micron). Analytical thin layer chromatography utilized Analtech Uniplate Silica Gel GF (250 micron) pre-coated glass plates. TLC visualization was conducted with UV light, iodine, and phosphomolybdic acid solution. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance 400 spectrometer and Bruker Avance III 500 spectrometers. Chemical shifts were measured relative to the residual solvent resonance. IR spectra were recorded on Mattson 4020 GALAXY Series FT-IR. Mass spectra were obtained with an Agilent 6520B. Accurate-Mass Q-TOF LC/MS and from the Mass Spectrometry Facility of University of California at Riverside.

Preparation of diphenylsilane, 6

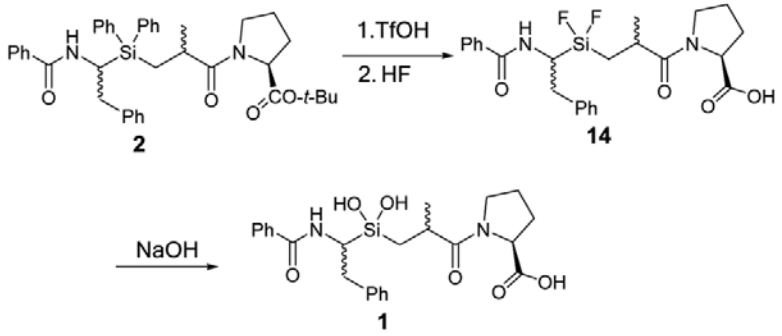
To a mixture of lithium aluminium hydride (LAH, 20.0 g, 0.521 mol) in anhydrous ether (500 mL) was



Scheme II — Synthesis of (*R*,*S*,*S*)-2 and (*R*,*R*,*S*)-2



Scheme III — Synthesis of (*S*,*S*,*S*)-2 and (*S*,*R*,*S*)-2



Scheme IV — Synthesis of silanediols 1

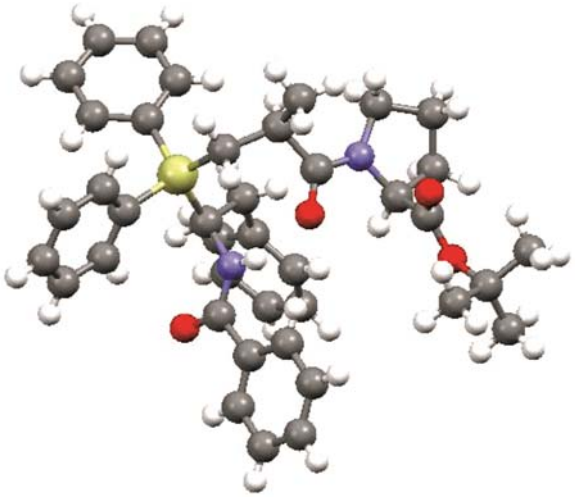


Figure 2 — X-ray diffraction of (*S*,*S*,*S*)-2

cooled down at 5ºC, then dichlorodiphenylsilane (**5**, 100 mL, 0.474 mol) was added slowly within 30 min. The resulting solution was refluxed for 1h. The reaction solution was iced at 0ºC followed by adding slowly water (20 mL), 15% aqueous sodium hydroxide (20 mL), water (60 mL). The mixture was gradually warmed to rt. and stirred for 15 min, added some anhydrous magnesium sulfate. The suspension was filtrated to obtain mother liquid through celite. Ether was removed *in vacuo.* Diphenylsilane (**6**) was distilled at 95-97°C at 13-15 mmHg as a clear liquid (83 mL, ~95%).

Preparation of (3-(methoxymethoxy)-2-methylpropyl) diphenylsilane, (±)-4

Step 1: Preparation of 3-(diphenylsilyl)-2-methylpropan-1-ol, (±)-8

To a solution of diphenylsilane (**6**) (10.0 g, 54.3 mmol) in heptane (150 mL) was added β-methyl allylic alcohol (5.5 mL, 65.2 mmol), *tert*-dodecylmercaptan (1.2 mL, 5.4 mmol) and AIBN (0.44 g, 0.26 mmol). The resulting mixture was heated at 75°C for 19 h, and then concentrated *in vacuo* to give a mixture **A**. A small part of the mixture **A** was purified for analysis. Flash column chromatography using a gradient eluent (100:1 to 95:5 hexane and ethyl acetate) gave alcohol **8** (85%) as a colorless oil. R_f = 0.6 (hexane / ethyl acetate 6:1); IR: 3334(br), 3068, 301, 2929, 2873, 2117, 1535, 1427, 1116, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.6-7.3 (m, 10H), 5.0 (t, *J* = 4.5 Hz, 1H), 3.5 (ddd, *J* = 10.0, 6.1 Hz, 2H), 1.9-1.8 (m, 1H), 1.6 (br, 1H), 1.36 (dt, *J* = 14.6, 4.6 Hz, 1H), 1.05 (dd, *J* = 10.0, 4.6 Hz, 1H), 1.02 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.3, 135.2, 134.9, 134.7, 129.7, 128.2, 70.3, 32.7, 19.3, 16.8; Exact mass: $[M\text{-}Na]^+$calcd. for $[C_{16}H_{20}NaOSi]^+$ 279.1176, found 279.1189.

Step 2: Preparation of 3-(diphenylsilyl)-2-methylpropan-1-ol ((±)-4) from 3-(diphenylsilyl)-2-methylpropan-1-ol, (±)-8

To a solution of alcohol **(±)-8** (the rest of the mixture A in step 1) in dimethoxymethane (20 mL) was added $TsOH.H_2O$ (1.48 g, 6.8 mmol) and LiBr (0.66 g, 6.8 mmol). The solution was stirred at rt for 30min, diluted with diethyl ether (100 mL). The aqueous layer was extracted with ether (3 x 30 mL). The combined organic layers were washed with 10% $NaHCO_3$ (3 x 10 mL) and brine (20 mL), dried over with sodium sulfate, concentrated *in vacuo*. Column chromatography gave pure (3-(methoxymethoxy)-2-methylpropyl) diphenylsilane**(±)-4** (11.0 g, 95%) as a colorless oil.

Preparation of (*R*)-*N*-{[(3-(Methoxymethoxy)-2(*R/S*)-2-methylpropyl)diphenylsilyl]-2(*R*)-2-phenyl ethyl}-2-methyl-2-propanesulfinamide (*R*,*R*,*S*)-10 and (*R*,*R*,*R*)-10

Lithium (90 mg, 13 mmol) was washed with THF (3 × 5 ml), added solution of compound (±)-**4** (1.0 g, 3.3 mmol) in THF (7 mL). The mixture was stirred at 0 °C. Progress of reaction was monitored by ^{1}H NMR. The silyllithium solution was transferred *via* syringe to (*R*)-**9** (0.225 g, 1.1 mmol) in THF (5 mL) at -78ºC. The resulting solution was stirred at -78 °C for 3h and at rt for overnight. The solution was quenched by adding saturated NH_4Cl solution (50 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL). Combined organic layers were washed with water (3 x 10 mL), brine (2 x 10 mL), dried over with $MgSO_4$, and then concentrated *in vacuo*. Flash chromatography with eluent gave **11** (0.2 g, 40%) as a mixture of two diastereomers. R_f = 0.43 (hexane / ethyl acetate 1:1); IR (neat): 3068, 2953, 2883, 1504, 1454, 1427, 1149, 1068, 920, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.20 (m, 15H), 4.44-4.43(d, *J* = 1.2 Hz (one diastereomer), d, *J* = 2.2 Hz, (another diastereomer), 2H), 3.84-3.77 (m, 1H), 3.256 and 3.248 (s, 3H (two diastereomers)), 3.17-2.97 (m, 4H), 1.72-1.65 (m, 1H), 1.26-1.16 (m, 1H), 1.00-0.99 (s, 9H (two diastereomers)), 0.9-0.8 (m, 1H) 0.71-0.69 (d, *J* = 5.6 Hz, d, *J* = 5.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.4, 136.0, 133.5, 133.4, 130.1, 128.7, 128.3, 128.2, 126.8, 96.7, 75.3 (75.29), 56.9, 55.4, 47.9 (47.7), 40.0, 30.0, 23.0, 20.5, 17.1 (17.09); Exact mas: $[M\text{-}H]^+$calcd. for $[C_{30}H_{42}NO_3SSi]^+$ 524.2649, found 524.2655.

Preparation of (*S*)-*N*-{[(3-(Methoxymethoxy)-2(*R/S*)- 2-methylpropyl)diphenylsilyl]-2(*R*)-2-phenylethyl}-2-methyl-2-propanesulfinamide (*S,S,R*)-10 and (*S,S,S*)-10

Following the procedure for synthesis of compound **10**, using **(±)-4** (5.0 g, 16.7 mmol), Li (1.4 g, 167 mmol), and (*S*)-**9** (1.2 g, 5.6 mmol) gave sulfinamides (*S,S,R*) and (*S,S,S*)-**10** (1.4 g, 50%). R_f = 0.34 (hexane / ethyl acetate1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.7-7.2 (m, 15H), 4.44-4.43 (m, 2H), 3.84-3.78 (m, 1H), 3.2 (s, 3H), 3.1-2.8 (m, 4H), 1.73-1.65 (m, 1H), 1.2-1.0 (m, 1H), 1.0 (s, 9H), 0.9-0.8 (m, 1H), 0.75-0.64 (m, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 139.1, 135.9, 133.4, 133.2, 129.9, 128.5, 128.2, 128.0, 126.6, 96.5, 75.1 (75.0), 56.7, 55.2, 47.7 (47.5), 39.8, 29.8, 22.8 (22.6), 20.3, 16.9.

Preparation of compound (*R,S*)-11 and (*R,R*)-11

To a solution of two diastereomers (*R,R,S*)-**10** and (*R,R,R*)-**10** (1.0 g, 1.9 mmol) in a flask was added 1.25M HCl (6.0 mL, 7.6 mmol) in methanol[#1]. The solution was stirred at rt for 5 h, concentrated *in vacuo*, dissolved in ethyl acetate (8 mL), added saturated $NaHCO_3$ (3 ml) followed benzoyl chloride (0.26 mL, 2.28 mmol). The mixture was stirred at rt. for 3h, diluted with water (30 ml). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). Combined organic layers were washed with water (3 × 10 mL), brine (2 × 10 mL), dried over with Na_2SO_4, and then concentrated *in vacuo*. Column chromatography gave (*R,S*)-**11** (327 mg, 35%) and (*R,R*)-**11** (227 mg, 25%).

Or using aqueous HCl in MeOH

Preparation of Mixture of (*S,R*)-11 and (*S,S*)-11

Following the procedure for synthesis of(*R,S*)-**11** and (*R,R*)-**11**, using the mixture of two diastereomers (*S,S,S*)-**10** and (*S,S,R*)-**10** (1.0 g, 1.9 mmol), 1.25M HCl (6.0 mL, 7.6 mmol). Column chromatography gave (*S,R*)-**11** and (*S,S*)-**11** mixture (637 g, 70% yield). R_f = 0.5 (hexane / ethyl acetate 1:1).

Preparation of 3-(((*R*)-1-benzamido-2-phenylethyl) diphenylsilyl)-2(*R*)-methylpropanoic acid ((*R,R*)-12) and 3-(((*R*)-1-benzamido-2-phenylethyl) diphenylsilyl)-2(*S*)-methylpropanoic acid ((*R,S*)-12)

To a solution of (*R,S*)-**11** and (*R,R*)-**11** (0.5 g, 1.04 mmol) in acetonitrile and water (2/1, 10 mL) at rt was added (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO, 32 mg, 0.2 mmol), and bis(acetoxy)iodobenzene (BAIB, 0.73 g, 2.2 mmol). The solution was stirred at rt for 2 h, quenched with 30% $Na_2S_2O_3$ (20 mL). The aqueous layer was extracted with DCM (3 × 10 mL). The combined DCM layers were washed with water (3 × 10 mL), brine (2 × 5 mL), dried over with $MgSO_4$, and then concentrated *in vacuo*. Column chromatography gave (*R,S*)-**12** and (*R,R*)-**12** (369 mg, 72%); R_f = 0.31 (hexane / ethyl acetate 3:1).

Following the procedure for synthesis of (*R,S*)-**12** and (*R,R*)-**12**, using the mixture of (*S,R*)-**11** and (*S,S*)-**11** (1.0 g, 2.1 mmol), TEMPO (62 mg, 0.4 mmol), and BAIB (1.4 g, 4.4 mmol) gave a mixture of (*S,R*)-**12** and (*S,S*)-**12** (750 mg, 72%yied); R_f = 0.29 (tail) (hexane / ethylacetate 3:1).

Preparation of (*S*)-*tert*-Butyl-1-{(*S*)-3-[(*R*)-1-benzamido-2-phenylethyl)diphenylsilyl]-2-methylpropanoyl} pyrrolidine-2-carboxylate (*R,S,S*)-2

To a 0°C solution of acid (*R,S*)-**12** (0.5 g, 1.0 mmol) and **13** (0.21 g, 1.0 mmol) in DMF (10 mL) was added 90% diethyl cyanophosphonate (0.23 mL, 1.2 mmol) followed by triethylamine (0.46 mL, 3.3 mmol). The reaction was stirred at 0°C for 3 h, and at rt overnight. The mixture was diluted with ethyl acetate (30 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with 5% HCl (3 × 10 mL), saturated $NaHCO_3$ (3 x 10 mL), water (3 × 10 mL), brine (10 mL), dried over with Na_2SO_4, and concentrated *in vacuo*. Column chromatography gave (*R,S,S*)-**2** (0.53 g, 80%) as a colorless foam. R_f = 0.6 (hexane / ethyl acetate 3:1); ^{1}H NMR (400 MHz, $CDCl_3$):δ 7.82-7.00 (m, 21H, included NH), 4.69-4.63 (m, 1H), 3.55 (dd, *J* = 8.4, 3.6 Hz, 1H), 3.05-3.02 (m, 1H), 2.99 (dd, *J* = 14.0, 4.4 Hz, 1H), 2.77 (dd, *J* = 14.0, 9.2 Hz, 1H), 2.42-2.37 (m, 1H), 2.30-2.25 (m, 1H), 1.63-1.51 (m, 5H), 1.35 (s, 9H), 1.23-1.19 (m, 1H), 1.12 (d, *J* = 6.8 Hz, 3H).

Preparation of (*S*)-*tert*-Butyl-1-((*R*)-3-(((*R*)-1-benzamido-2-phenylethyl)diphenylsilyl)-2-methylpropanoyl) pyrrolidine -2-carboxylate (*R,R,S*)-2

Following the procedure for synthesis of(*R,S,S*)-**2**, using acid (*R,R*)-**12** (0.5 g, 1.0 mmol), proline salt **13** (0.21 g, 1.0 mmol) in DMF (10 mL), 90% diethyl cyanophosphonate (0.23 mL, 1.2 mmol), triethylamine (0.46 mL, 3.3 mmol) gave (*R,R,S*)-**2** (0.53 g, 80%) as a colorless foam. R_f = 0.31 (hexane / ethyl acetate 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74-7.13 (m, 20H), 5.96 (d, *J* = 9.6 Hz, 1H), 4.78-4.72 (m, 1H), 3.00 (dd, *J* = 14.2, 4.0 Hz, 1H), 3.61 (dd, *J* = 7.9, 3.8 Hz, 1H), 3.13-3.06 (m, 8H),

2.85-2.71 (m, 3H), 2.60-2.32 (m, 5H), 2.08-2.01 (m, 1H), 1.81-1.38 (m, 12H), 1.35 (s, 9H), 1.34 (s, 9H), 1.09 (d, *J* = 6.8 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H).

Following the procedure for synthesis of(*R*,*S*,*S*)-**2** (p.182), using mixture of acid (*S*,*R*)-**12** and (S,*S*)-**12** (0.8 g, 1.6 mmol), salt **13** (0.33 g, 1.6 mmol) in DMF (10 mL), diethyl cyanophosphonate (0.4 mL, 3.2 mmol), triethylamine (0.67 mL, 4.8 mmol) gave (*S*,*S*,*S*)-**2** (0.22 g, 41%) and (*S*,*R*,*S*)-**2** (0.2 g, 37%) after flash column chromatography.

Preparation of (*S*)-*tert*-Butyl 1-{(*S*)-3-[((*S*)-1-benzamido-2-phenylethyl)diphenylsilyl]-2-methylpropanoyl} pyrrolidine -2-carboxylate (*S*,*S*,*S*)-2

R_f = 0.45 (hexane / ethyl acetate 2:1)

^{1}H NMR (400 MHz, $CDCl_3$):δ 7.59-7.12 (m, 20H), 6.56 (d, *J* = 10.0 Hz, 1H), 4.75 (dt, *J* = 11.1, 4.0, Hz, 1H), 4.20 (dd, *J* = 8.4, 4.0 Hz, 1H), 3.37-3.32 (m, 1H), 3.19 (dd, *J* = 14.0, 4.0 Hz, 1H), 2.97- 2.91 (m, 1H), 2.70-2.64 (m, 1H), 2.52 (dd, *J* = 14.0, 11.2 Hz, 1H), 2.02-1.72 (m, 5H), 1.43 (s, 9H), 1.29-1.24 (m, 1H), 1.20 (d, *J* = 6.5 Hz, 3H).

Preparation of (*S*)-*tert*-Butyl 1-{(*R*)-3-[((*S*)-1-benzamido-2-phenylethyl)diphenylsilyl]-2-methylpropanoyl} pyrrolidine-2-carboxylate (*S*,*R*,*S*)-2

R_f = 0.27 (hexane / ethyl acetate 2:1); ^{1}H NMR (400 MHz, $CDCl_3$):δ 7.74-7.13 (m, 40H), 6.00 (d, *J* = 10.0 Hz, 1H), 4.78-4.72 (m, 2H), 4.23 (dd, *J* =8.4, 3.6 Hz, 1H), 3.61 (dd, *J* = 8.0, 3.8 Hz, 1H), 3.13-3.06 (m, 8H), 2.85-2.71 (m, 3H), 2.60-2.32 (m, 5H), 2.08-2.01 (m, 1H), 1.81-1.38 (m, 12H), 1.35 (s, 9H), 1.34 (s, 9H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.04 (d, *J* = 6.5 Hz, 3H).

(*S*)-1-{(*S*)-3-[((*R*)-1-benzamido-2-phenylethyl) difluoro sily-l]-2-methylpropanoyl}pyrrolidine-2-carboxylic acid (*R*,*S*,*S*)-14

To a 0°C solution of (*R*,*S*,*S*)-**2** (0.2 g, 0.3 mmol) in DCM (10 mL) was added trifluoromethane sulfonic acid (3.8 mL, 18 mmol). The solution was stirred for 1h at 0 °C, diluted with DCM (10.0 mL) followed by 14.8 N NH_4OH (1.0 mL) and stirred for 35min at 0 °C, and then added 48% HF solution (0.6 mL) to give a pH of 2-3. Stirring was continued for 10 min. After addition of DCM (20 mL), the solution was washed with water (10 mL), saturated NaCl (10 mL), dried over Na_2SO_4, concentrated to give (*R*,*S*,*S*)-**14** (145 mg, 92%) as a light yellow foam. ^{1}H NMR (400 MHz, DMSO-d_6):*δ*10.1 (br, 1H), 7.91-7.17 (m, 10H), 4.0 (dd, *J* = 7.2, 4.1 Hz, 1H), 3.47-3.45 (m, 2H), 3.1 (dd, *J* = 14.0, 4.2 Hz, 1H), 3.0-2.98 (m, 1H), 2.9 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.8-2.7(m, 1H), 1.84 – 1.69 (m, 4H), 1.0 (d, *J* = 6.9 Hz, 3H), 0.9-0.8 (m, 1H), 0.7-0.6 (m, 1H).

Preparation of (*S*)-1-{(*R*)-3-[((*R*)-1-Benzamido-2-phenylethyl)difluorosilyl]-2-methylpropanoyl} pyrrolidine-2-carboxylic acid (*R*,*R*,*S*)-14

Following the procedure for synthesis of(*R*,*S*,*S*)-**14**, using (*R*,*R*,*S*)-**2** (0.2 g, 0.3 mmol) in DCM (10 mL), trifluoromethane sulfonic acid (1.8 mL, 8.4 mmol), 14.8 N NH_4OH (1.0 mL), and 48% HF solution (0.6 mL) gave (*R*,*R*,*S*)-**14** (145 mg, 92%) as a light yellow foam. ^{1}H NMR (400 MHz, CD_3CN): δ 8.10 (brs, 1H), 7.80-7.21 (m, 10H), 4.42 (dd, *J* = 8.0, 2.8 Hz, 1H), 3.47 (m, 2H), 3.18 (dd, *J* = 14.0, 3.4 Hz, 1H), 3.12-3.08 (m, 1H), 2.85- 2.82 (m, 1H), 2.77 (dd, *J* = 13.6, 10.0 Hz, 1H), 2.17-2.11 (m, 1H), 2.01-1.96 (m, 1H), 1.88-1.68 (m, 2H), 1.30-1.15 (m, 1H), 1.12 (d, *J* = 6.4 Hz, 3H), 0.99-0.93 (m, 1H).

Preparation of (*S*)-1-{(*S*)-3-[((*S*)-1-benzamido-2-phenylethyl)difluorosilyl]-2-methylpropanoyl} pyrrolidine-2-carboxylic acid (*S*,*S*,*S*)-14

Following the procedure for synthesis of(*R*,*S*,*S*)-**14** (p.185), using (*S*,*S*,*S*)-**2** (0.2 g, 0.3 mmol) in DCM (10 mL), trifluoromethane sulfonic acid (1.8 mL, 8.4 mmol), 14.8 N NH_4OH (1.0 mL), and 48% HF solution (0.6 mL) gave (*S*,*S*,*S*)-**14** (145 mg, 92%) as a light yellow foam. ^{1}H NMR (400 MHz, acetone_d_6): δ 8.2 (br s, 1H), 7.99-7.20 (m, 10H), 4.15 (dd, *J* = 8.0, 2.8 Hz, 1H), 3.56-3.47 (m, 2H), 3.24-3.15 (m, 2H), 2.93-2.73 (m, 2H), 1.86-1.81 (m, 2H), 1.60-1.56 (m, 2H), 1.22-1.18 (m, 1H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.04-1.01 (m, 1H).

Preparation of (*S*)-1-{(*R*)-3-[((*S*)-1-benzamido-2-phenylethyl)difluorosilyl]-2-methylpropanoyl} pyrrolidine-2-carboxylic acid (*S*,*R*,*S*)-14

Following the procedure for synthesis of(*R*,*S*,*S*)-**14** (p.185), using (*S*,*R*,*S*)-**2** (0.2 g, 0.3 mmol) in DCM (10 mL), trifluoromethane sulfonic acid (1.8 mL, 8.4 mmol), 14.8 N NH_4OH (1.0 mL), and 48% HF solution (0.6 mL) gave (*S*,*R*,*S*)-**14** (145 mg, 92%) as a light yellow solid. ^{1}H NMR (400 MHz, acetone_d_6): δ 8.27 (br s, 1H), 7.9-7.3 (m, 10H), 4.5 (dd, *J* = 8.0, 2.9 Hz, 1H), 3.76 (m, 1H), 3.63 (m, 1H), 3.3 (dd, *J* =14.0, 3.6 Hz, 1H), 3.2-3.1 (m, 1H), 3.07-3.02 (m, 1H), 2.96-2.85 (m, 1H), 2.2-2.17 (m, 1H), 2.1-2.06 (m, 1H), 2.04-1.97 (m, 1H), 1.88-1.79 (m, 1H), 1.4-1.29 (m, 1H),1.28 (d, *J* = 6.4 Hz, 3H), 1.08- 0.92 (m, 1H).

Preparation of Sodium (*S*)-1-((*S*)-3-(((*R*)-1-benzamido-2-phenylethyl)dihydroxysilyl)-2-methylpropanoyl) pyrrolidine-2-carboxylate (*R,S,S*)-1

To a 0 °C solution of acid (*R*,*S*,*S*)-**14** (9.0 mg, 19.0 μmol) in 1:99 CD_3CN/D_2O (0.4 mL) was added a 0.2 M NaOH solution in D_2O (0.3 mL, 57.0 μmol). The reaction was monitored by ^{19}F NMR, and gave silanediol sodium salt (*R*,*S*,*S*)-**1**. ^1H NMR (400 MHz, 1% CD_3CN in D_2O): δ 7.47-7.10 (m, 10H), 4.02 (dd, *J* = 8.7, 4.4 Hz, 1H), 3.66 (dd, *J* = 13.0, 3.2Hz, 1H), 3.43-3.29 (m, 2H), 3.07 (dd, *J* = 14.0, 3.2Hz, 1H), 2.72-2.66 (m, 2H), 1.97-1.92 (m, 1H), 1.76-1.65 (m, 2H), 1.60-1.54 (m, 1H), 1.08 (d, *J* = 6.5 Hz, 3H), 0.78 (dd, *J* = 14.8, 3.6 Hz, 1H), 0.58 (dd, *J* = 15.0, 10.8 Hz, 1H).

Preparation of Sodium (*S*)-1-((*R*)-3-(((*R*)-1-benzamido-2-phenylethyl)dihydroxysilyl)-2-methylpropanoyl) pyrrolidine-2-carboxylate (*R,R,S*)-1

^1H NMR (400 MHz, 1% CD_3CN in D_2O): δ 7.50-7.10 (m, 10H), 4.12 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.58 (dd, *J* = 13.0, 3.6 Hz, 1H), 3.51-3.31 (m, 2H), 3.01 (dd, *J* =14.0, 3.2 Hz, 1H), 2.87-2.86 (m, 1H), 2.70 (t, *J* = 13.0 Hz, 1H), 2.14-2.08 (m, 1H), 1.89-1.69 (m, 3H), 1.03 (d, *J* = 6.0 Hz, 3H), 0.76 (dd, *J* = 15.2, 4.4 Hz, 1H), 0.60 (dd, *J* = 15.0, 10.5 Hz, 1H).

Preparation of Sodium (*S*)-1-{(*S*)-3-[((*S*)-1-benzamido-2-phenylethyl)dihydroxysilyl]-2-methylpropanoyl} pyrrolidine-2-carboxylate (*S,S,S*)-1

^1H NMR (400 MHz, 1% CD_3CN in D_2O): δ 7.49-7.11 (m, 10H), 4.08 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.62 (dd, *J* = 13.0, 3.6 Hz, 1H), 3.53-3.32 (m, 2H), 3.05 (dd, *J* = 14.0, 3.6 Hz, 1H), 2.86-2.79 (m, 1H), 2.68 (t, *J* = 13.0 Hz, 1H), 2.04-2.00 (m, 1H), 1.82-1.62 (m, 3H), 1.06 (d, *J* = 6.5 Hz, 3H), 0.76 (dd, *J* = 15.1, 4.4 Hz, 1H), 0.60 (dd, *J* = 15.0, 10.0 Hz, 1H).

Preparation of Sodium (*S*)-1-{(*R*)-3-[((S)-1-benzamido-2-phenylethyl)dihydroxysilyl]-2-methylpropanoyl} pyrrolidine-2-carboxylate (*S,R,S*)-1

^1H NMR (400 MHz, 1% CD_3CN in D_2O): δ 7.50-7.10 (m, 10H), 4.28 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.61 (dd, *J* = 12.8, 3.0 Hz, 1H), 3.34- 3.28 (m, 2H), 2.97 (dd, *J* =14.0, 3.0 Hz, 1H), 2.70-2.67 (m, 1H), 2.63 (t, *J* = 7.6 Hz, 1H), 2.05-1.84 (m, 2H), 1.63-1.56 (m, 2H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.83 (dd, *J* = 15.2, 4.0 Hz, 1H), 0.68 (dd, *J* = 15.2, 5.0 Hz, 1H).

Conclusion

In summary, four diastereomers of the ACE silanediol inhibitors **1** were synthesized via an addition of a silyllithium to an Ellman sulfinimine to control the first stereogenic center. Simple column chromatography could separate each pair of diastereomers **2**. The synthesis is 8 linear steps from inexpensive starting material-dichlorodiphenylsilane (**5**) in over all yield 8%.

Conflict of interest

The authors confirm that this article content has no conflict of interest.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

Acknowledgements

The authors thank Dr. Frank David, Dr. Michael J. Zdillaat Temple University and Dr. Annaliese K. Franz at University of California Davis for valuable discussions. The authors thank Temple University for funding.

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