Published in final edited form as:

European J Org Chem. 2014 October 1; 2014(30): 6761–6768. doi:10.1002/ejoc.201402812.

A convergent synthesis of carbocyclic sinefungin and its C5 epimer

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Abstract

A convergent synthesis of carbocyclic sinefungin **2** and its C5 epimer **3** is described. The key features in our synthesis include the use of commercial available L-methionine and readily available (1*R*, 4*S*)-4-hydroxy-2-cyclopentenyl acetate as starting materials, cross-metathesis coupling, enzymatic kinetic resolution and Staudinger reduction. The current synthesis is flexible and therefore provides convenient access to the synthesis of various carbocyclic SIN analogues for biological evaluation.

Keywords

sinefungin; synthesis; methyltransferase; enzyme resolution; carbocyclic derivative

Introduction

Sinefungin (**1**, SIN, **Figure 1**) was isolated from the fermentation broth of *Streptomyces griseoleus* NRRL 3739 at Lilly research Laboratories in 1973.^[1] It is structurally similar to *S*-adenosyl-methionine (AdoMet) and *S*-adenosyl-homocysteine (AdoHcy). It is a highly potent and competitive inhibitor of AdoMet dependent methyltransferase (MTase).^[2] Preliminary bioassays of sinefungin displayed antifungal,^[3] antitumor,^[4] antiviral,^[5] and antiparasitic activity.^[6] However, toxicological studies showed that the therapeutic and lethal dose of SIN are very close in goats, causing severe nephrotoxic side effects.^[7] Sinefungin showed a short plasma half-life.^[8] Intravenous administration of SIN in rats showed that the blood clearance time was less than 270 min and 50% of the SIN dose was eliminated by excretion in the urine.^[9] Schneller and co-workers synthesized carbocyclic SIN (**Figure 1**), which replaced the ribosyl oxygen of SIN to its isosteric methylene unit.^[10] Such modification may alleviate metabolic instability associated with sinefungin.

Recently, Li and co-workers reported the X-ray crystal structure of the flavivirus MTase in complex with SIN.^[11] Analysis of the SIN-MTase complex structure revealed an additional pocket that is adjacent to the AdoMet-binding pocket. Based upon this molecular insight, it

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Supporting Information: (see footnote on the first page of this article): Copies of ¹H and ¹³C NMR spectra of all synthetic compounds.

has been proposed that modification of the adenine base of SIN may show enhanced binding affinities, there by leading to more potent and specific inhibitors of flavivirus MTase.^[11]

We therefore, planned to design and synthesize a series of carbocyclic SIN derivatives in which different substitution will be introduced to the adenine base of SIN. We sought to develop an efficient and flexible synthesis of carbocyclic SIN for analog preparation. Herein, we report convergent syntheses of carbocyclic SIN and its C5 epimer **3**. The present synthesis utilized commercial available L-methionine **7** and readily available (1*R*, 4*S*)-4-hydroxy-2-cyclopentenyl acetate **8** as starting materials. Other key reactions include cross-metathesis, enzymatic resolution and Staudinger reduction.

Results and Discussion

Our retrosynthetic analysis of carbocyclic SIN and its derivatives is outlined in Scheme 1. We planned to introduce the adenine base in a late stage via SN² substitution of **4a-b**. These derivatives could be synthesized utilizing the cross-metathesis of the segment **5** and olefin **6a-b**. The fragment **5** would be prepared from L-methionine **7**. The alcohol **6a-b** could be derived from (1*R*, 4*S*)-4-hydroxy-2-cyclopentenyl acetate **8**.

The synthesis of vinyl glycine derivative **5** is shown in scheme 2. L-methionine **7** was converted to methyl ester **9** using thionyl chloride in methanol according to reported literature procedure.^[12] Protection of the amine group as Cbz-derivative followed by oxidation of the sulfide in the presence of NaIO₄ provided sulfoxide **10**.^[13] Boc-protected sulfoxide **11** was prepared by following similar course of reactions. For the subsequent elimination in mesitylene at 170 °C, the Boc-protected derivative **11** provided a complex mixture of unidentified products along with a trace amount of olefin **5**. The Cbz-protected derivative **10** however, provided the desired terminal alkene **12** in 60% yield.^[14] We then converted the Cbz-protected derivative **12** to Boc-protected derivative **5**.

The synthesis of segment **6a-b** is shown in Scheme 3. It began with (1*R*, 4*S*)-4-hydroxy-2-cyclopentenyl acetate **8** which is readily available in high enantiomeric purity on a large scale from cyclopentadiene according to literature procedures.^[15] As shown in Scheme 3, coupling of **8** with methyl chloroformate, followed by selective palladium-catalyzed nucleophilic substitution in the presence of sodium hydride providing the *cis*-adduct **13**.^[16] Decarboxylation of **13** in DMF in the presence of KI at 150 °C afforded ester **14**. Dihydroxylation with OsO₄ and subsequent protection of *cis*-diol with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-TsOH afforded isopropylidene derivative **15**.^[17] Saponification of **15** with potassium hydroxide in methanol and THF furnished alcohol **16**. The (*R*)-alcohol **16** was inverted to (*S*)-alcohol **17** upon oxidation with Dess-Martin reagent and selective reduction with sodium borohydride. Treatment of the (*S*)-alcohol **17** with PMBCl and sodium hydride yielded the PMB-protected derivative **18**. Reduction of **18** with DIBAL followed by treatment of the resulting aldehyde with vinylmagnesium chloride resulted in allyl alcohol **19** as a mixture of diastereomers (1:1). This mixture could not be separated by silica gel chromatography. Oxidation of allyl alcohol **19** with Dess–Martin periodinane afforded enone **20**, which was then subjected to Corey-Bakshi-Shibata reduction using (*R*)-2-Me-CBS and borane dimethylsulfide complex (BMS)

affording segment **6a** in excellent distereoselectivity (15:1 dr, by ^1H and ^{13}C NMR analysis).^[18] Allylic alcohol **6a** was obtained in 55% yield along with olefin-reduced by product. We also investigated this reaction using borane tetrahydrofuran complex or catecholborane instead of BMS, however, the yield was not improved.

In an alternative route, we attempted the separation of diastereomeric alcohol **19** by enzymatic kinetic resolution.^[19] As shown in Scheme 4, alcohol **19** was treated with Amano lipase in the presence of vinyl acetate in dimethoxyethane. The resolution afforded (*R*)-isomer **6b** (13:1 dr, by ^1H and ^{13}C NMR analysis) and acetate derivative **21** (15:1 dr, by ^1H and ^{13}C NMR analysis) in a good yield and distereoselectivity. The stereochemistry can be predicted by Kazlauskas' rule,^[20] and the result is consistent with that of Corey-Bakshi-Shibata reduction. Acetate derivative **21** was hydrolyzed by treatment with aqueous NaOH to afford the desired (*S*)-isomer **6a**.

With segment **5** and **6a-b** in hand, we then turned our attention to construct the C3-C4 bond of the target compound. As shown in Scheme 5, cross-metathesis of these two fragments proceeded smoothly in the presence of Grubbs' second-generation catalyst to afford alkene **22a-b**.^[21] A homodimer was also formed from **6a-b** in this reaction, even when the ratio of **6a-b** to **5** was decreased to 1 : 4. The unreacted homodimer was recycled under the same conditions affording alkene **22a-b** in 75-78% total yields. Mesylation of alkene **22a-b** followed by treatment with sodium azide did not provide the expected azide derivatives **23a-b**, instead resulted in the elimination of the hydroxyl group along with other byproduct.

To circumvent this problem, we first carried out hydrogenation of alkene **22a-b** to provide saturated alkane **24a-b**. Mesylation of the respective alcohol to mesylate followed by displacement of mesylate with azide proceeded well to afford azide **25a-b**. Deprotection of the PMB group on azide **25a-b** with DDQ in DCM afforded cyclopentanol **4a-b** as shown in Scheme 6.

Treatment of cyclopentanol **4a-b** with triflic anhydride and pyridine in DCM followed by S_{N}^2 substitution afforded the protected carbocyclic SIN **26a-c**. However, the S_{N}^2 substitution using NaH as base following literature procedure gave a low yield.^[10a] We found that carbocyclic SIN **26a-c** could be obtained in good yield using K_2CO_3 and 18-Crown-6 in DMF [at 50 °C].^[22] Staudinger reduction of **26a-c** converted the azide to an amine.^[23] The removal of the acetonide and Boc protecting group by exposure to trifluoroacetic acid provided the corresponding amine. Saponification of methyl ester with aqueous LiOH furnished carbocyclic SIN **2** and **3**.

Conclusions

In summary, a convergent synthesis of carbocyclic sinefungin **2** and its C5 epimer **3** is described. The key features in our syntheses include the use of commercially available L-methionine and readily available (1*R*, 4*S*)-4-hydroxy-2-cyclopentenyl acetate **8** as starting materials, cross-metathesis coupling, enzymatic kinetic resolution and Staudinger reduction. The current synthesis is flexible and therefore provides a convenient access to the synthesis of various carbocyclic SIN analogues for biological evaluation. Further study of the

chemistry and biology of carbocyclic SIN derivatives is an active area of research in our laboratory.

Experimental Section

Aminoester 5. A solution of **12** (2.49 g, 10 mmol) in hydrobromic acid solution (4 mL) was stirred for 2 h at room temperature, then diluted with DCM and condensed under reduced pressure to get the crude product as a brown oil. The crude product was dissolved in 1, 4-dioxane (20 mL) and H₂O (15 mL), then slowly adjusted to pH 12 with NaHCO₃ at 0 °C. A solution of Boc₂O (4.36 g, 20 mmol) in 1, 4-dioxane (10 mL) was added at the same temperature. The above mixture was stirred overnight at room temperature and concentrated under reduced pressure. The residue was treated with H₂O (15 mL), and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated. The residue was purified via silica gel chromatography (15:1 hexanes/EtOAc) to afford **5** (1.39 g, 65%, 2 steps) as a colorless oil. $[\alpha]_D^{20} +3.2$ (c 1, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 5.89 (m, 1H), 5.35 (d, *J* = 17.2, 1H), 5.26 (d, *J* = 10.4 Hz, 1H), 5.23 (brs, 1H), 4.87 (brs, 1H), 3.76 (s, 3H), 1.45 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) 171.10, 154.86, 132.55, 117.27, 79.92, 55.64, 52.42, 28.14; HRMS (ESI), *m/z* (M+Na)⁺ Calcd for C₁₀H₁₇O₄Na: 238.1055, found 238.1059.

Compound 13. To a stirred solution of **8** (1.00 g, 7.0 mmol) in anhydrous DCM (20 mL) was added pyridine (0.85 mL, 10.5 mmol) and methyl chloroformate (0.82 mL, 10.5 mmol) at 0 °C. The mixture was stirred for 1 h at the same temperature, and quenched with 5% HCl (10 mL). The resulting mixture was extracted by DCM (3 × 20 mL), and the combined extracts were dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified via silica gel chromatography (10:1 hexanes/EtOAc) to afford a colorless oil.

To a suspension of NaH (60% in mineral oil, 840 mg, 21 mmol) in THF (20 mL) was added dropwise a solution of dimethyl malonate (1.60 mL, 14 mmol) in THF (20 mL) at 0 °C, and the mixture was stirred for 30 min at room temperature. This reaction mixture was added to a solution of Pd(Ph₃P)₄ (404 mg, 0.35 mmol) and the above oil in THF, and then stirred for 3 h at room temperature. Then the reaction mixture was quenched with 5% HCl (20 mL). The resulting mixture was extracted by DCM (3 × 20 mL), and the combined extracts were dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified via silica gel chromatography (10:1 hexanes/EtOAc) to afford compound **13** (1.49g, 83%) as a colorless oil. $[\alpha]_D^{20} +17.5$ (c 1.01, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 6.02-6.00 (m, 1H), 5.89-5.87 (m, 1H), 5.63-5.59 (m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.36-3.26 (m, 2H), 2.58 (dt, *J* = 14.5, 7.5 Hz, 1H), 2.02 (s, 3H), 1.56 (dt, *J* = 14.5, 4.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 170.63, 168.51, 168.44, 137.21, 131.36, 78.71, 56.75, 52.44, 52.38, 43.45, 34.56, 21.09; LRMS (ESI), *m/z* 279.1 (M+Na)⁺

Acetate derivative 14. To a stirred solution of **13** (240 mg, 0.94 mmol) in DMF (15 mL) was added KI (468 mg, 2.82 mmol) and H₂O (1.5 mL) at room temperature under argon. The mixture was heated to 150 °C and stirred for 8 h, then cooled to room temperature and diluted with water. The mixture was extracted with Et₂O, and the combined extracts were

dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified via silica gel chromatography (10:1 hexanes/EtOAc) to afford compound **14** (130 mg, 70%) as a colorless oil. $[\alpha]_D^{20} +23.3$ (*c* 1.05, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 6.01 (d, *J* = 6.0 Hz, 1H), 5.86-5.82 (m, 1H), 5.65-5.60 (m, 1H), 3.73 (s, 3H), 3.08-3.01 (m, 1H), 2.59 (dt, *J* = 14.5, 7.6 Hz, 1H), 2.48 (dd, *J* = 15.6, 7.0 Hz, 1H), 2.38 (dd, *J* = 15.6, 8.2 Hz, 1H), 2.07 (s, 3H), 1.46 (dt, *J* = 14.1, 4.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 172.57, 170.71, 139.43, 130.07, 79.32, 51.50, 40.40, 40.34, 36.34, 21.17; HRMS (ESI), *m/z* (M+Na)⁺ Calcd for C₁₀H₁₄O₄Na: 221.0790, found 221.0786.

Isopropylidene derivative **15**. To a stirred solution of **14** (110 mg, 0.56 mmol) in acetone (5 mL) was added *N*-methymorpholine-*N*-oxide (195 mg, 1.67 mmol) and OsO₄ (4% in water, 25 μL) at 0 °C, and the resulting mixture was stirred for 6 h at room temperature. To the reaction mixture was added NaHSO₃, and stirred for additional 30 minutes. The mixture was diluted with EtOAc (10 mL), filtered and concentrated. The residue was dissolved in 0.5 M H₂SO₄ (10 mL), extracted with EtOAc (3 × 20 mL). The combined extracts were dried over anhydrous Na₂SO₄, filtered and concentrated to get a brown oil.

The above oil was dissolved in 2, 2-dimethoxypropane (3 mL) at room temperature. To the mixture was added TsOH (10 mg, 0.06 mmol), and stirred for 2 h. The reaction mixture was quenched by saturated aqueous NaHCO₃ solution, and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated. The residue was purified via silica gel chromatography (3:2 hexanes/EtOAc) to afford **15** (102 mg, 68%, 2 steps) as a colorless oil. $[\alpha]_D^{20} -6.7$ (*c* 1, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 5.03 (d, *J* = 3.0 Hz, 1 H), 4.52 (d, *J* = 5.6 Hz, 1H), 4.44 (d, *J* = 5.5 Hz, 1H), 3.68 (s, 3H), 2.65-2.31 (m, 4H), 2.04 (s, 3H), 1.58 (d, *J* = 16.1 Hz, 1H), 1.44 (s, 3H), 1.27 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 172.35, 169.79, 110.94, 84.78, 84.53, 79.54, 51.61, 41.01, 37.41, 33.98, 26.45, 24.08, 21.06; HRMS (ESI), *m/z* (M+Na)⁺ Calcd for C₁₃H₂₀O₆Na: 295.1158, found 295.1163.

Alcohol **16**. To a stirred solution of **15** (500 mg, 1.8 mmol) in MeOH (10 mL) and THF (10 mL) was added KOH (110 mg, 2.0 mmol) at room temperature, and the resulting mixture was stirred for 30 min. The reaction mixture was adjusted to pH 6.0 with 5% HCl, diluted with water (15 mL), and extracted by EtOAc (3 × 30 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated. The residue was purified via silica gel chromatography (3:2 hexanes/EtOAc) to afford **16** (400 mg, 95%) as a colorless oil. $[\alpha]_D^{20} +1.4$ (*c* 1, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 4.48-4.45 (m, 2H), 4.24-4.22 (m, 1H), 3.69 (s, 3H), 2.70-2.45 (m, 3H), 2.29 (dt, *J* = 13.8, 6.2 Hz, 1H), 1.53 (d, *J* = 14.0 Hz, 1H), 1.43 (s, 3H), 1.28 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 173.02, 110.54, 87.10, 85.02, 77.47, 51.54, 41.24, 37.96, 36.49, 26.51, 24.13; LRMS (ESI), *m/z* 253.1 (M+Na)⁺.

Compound **17**. To a stirred solution of **16** (40 mg, 0.17 mmol) in DCM (3 mL) was added Dess-Martin periodinane (110 mg, 0.26 mmol) at room temperature. The mixture was stirred for 3 h at the same temperature, and quenched with saturated aqueous NaHCO₃ (3 mL) and Na₂S₂O₄ (3 mL) solutions. The resulting mixture was extracted by DCM (3 × 20 mL), and the combined extracts were dried over anhydrous Na₂SO₄, and filtered. The filtrate was

concentrated under reduced pressure. The residue was purified via silica gel chromatography (3:1 hexanes/EtOAc) to afford ketone as a colorless oil.

To a stirred solution of the above oil in THF (3 mL) was added sodium borohydride (10 mg, 0.26 mmol) at 0 °C. The mixture was stirred for 20 min at the same temperature, quenched with saturated aqueous NH₄Cl solution, and extracted by DCM. The combined extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified via silica gel chromatography (2:1 hexanes/EtOAc) to afford **17** (37 mg, 93%) as a colorless oil. [α]_D²⁰ −7.6 (c 0.8, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 5.75-5.65 (t, *J* = 5.7 Hz, 1H), 4.38 (dd, *J* = 6.1, 1.5 Hz, 1H), 4.09-4.03 (m, 1H), 3.68 (s, 3H), 2.55-2.48 (m, 1H), 2.40 (d, *J* = 5.3 Hz, 1H), 2.31 (dd, *J* = 15.5, 7.9 Hz, 1H), 2.25 (dd, *J* = 15.5, 7.8 Hz, 1H), 1.95 (dt, *J* = 13.3, 7.7 Hz, 1H), 1.50 (s, 3H), 1.33 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.21, 111.84, 84.10, 79.05, 70.98, 51.65, 37.93, 36.63, 36.49, 25.97, 24.25; LRMS (ESI), *m/z* 231.3 (M+H)⁺.

Compound **18**. To a stirred solution of NaH (6 mg, 0.15 mmol) in DMF (2 mL) was added a solution of **17** (30 mg, 0.13 mmol) in DMF (1 mL) and 4-Methoxybenzyl chloride (20 μL, 0.15 mmol) at 0 °C under argon. The mixture was stirred for 3 h, quenched with saturated aqueous NH₄Cl solution (5 mL), and extracted by DCM (3 × 10 mL). The combined extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified via silica gel chromatography (3:1 hexanes/EtOAc) to afford **18** (40 mg, 88%) as a colorless oil. [α]_D²⁰ −16.1 (c 0.9, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.29 (d, *J* = 8.7 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 4.60 (d, *J* = 11.9 Hz, 1H), 4.55-4.51 (m, 2H), 4.28 (d, *J* = 5.6 Hz, 1H), 3.80 (s, 3H), 3.78-3.74 (m, 1H), 3.66 (s, 3H), 2.46-2.41 (m, 1H), 2.22 (dd, *J* = 15.3, 8.3 Hz, 1H), 2.21-2.09 (m, 2H), 1.63-1.60 (m, 1H), 1.52 (s, 3H), 1.31 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 172.29, 159.15, 130.17, 129.41, 113.66, 111.08, 83.74, 78.33, 71.26, 55.17, 51.67, 37.85, 37.04, 32.45, 29.59, 26.21, 24.26; HRMS (ESI), *m/z* (M+Na)⁺ Calcd for C₁₉H₂₆O₆Na: 373.1627, found 373.1630.

Alcohol **19**. To a stirred solution of **18** (50 mg, 0.14 mmol) in DCM (3 mL) was added dropwise DIBAL (1 M in hexanes, 0.16 mL) under argon at −78 °C. The reaction mixture was stirred for 10 min, then treated with H₂O (1 mL), and warmed to room temperature. The mixture was diluted with DCM (10 mL) and washed with water (4 mL) and brine (4 mL), then dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified via silica gel chromatography (10:1 hexanes/EtOAc) to afford aldehyde as a colorless oil, which was subject to the next step immediately.

To a stirred solution of the above colorless oil in anhydrous THF (5 mL) was added dropwise vinylmagnesium chloride (1 M in THF, 0.16 mL) over 5 min at 0 °C. The reaction mixture was stirred for 1 h at the same temperature, quenched with saturated aqueous NH₄Cl solution (20 mL), and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated. The residue was purified via silica gel chromatography (3:2 hexanes/EtOAc) to afford **19** (37 mg, 75%, 2 steps) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) 7.30 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 5.90-5.79 (m, 1H), 5.27-5.20 (m, 1H), 5.13-5.10 (m, 1H), 4.70-4.48 (m, 3H), 4.37-4.38 (m, 1H), 4.15-4.13 (m, 1H), 3.80 (s, 3H), 3.80-3.78 (m, 1H), 2.07-2.02 (m, 3H), 1.78-1.50 (m,

2H), 1.52 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.10, 140.72, 140.61, 130.39, 129.37, 129.33, 115.07, 114.97, 113.65, 111.22, 84.79, 84.49, 78.60, 77.50, 72.04, 71.46, 71.30, 55.16, 39.85, 39.77, 38.32, 37.60, 33.49, 26.26, 24.43; HRMS (ESI), m/z ($\text{M} + \text{Na}$) $^+$ Calcd for $\text{C}_{20}\text{H}_{28}\text{O}_5\text{Na}$: 371.1834, found 371.1837.

Enzymatic kinetic resolution of compound **19**. To a stirred solution of **19** (0.53 g, 1.52 mmol) in dimethoxyethane (30 mL) was added vinyl acetate (2.80 mL, 30.4 mmol) and Amano lipase (2.65 g) at room temperature. The reaction mixture was stirred for 24 h, and filtered. The filtrate was concentrated, and the residue was purified via silica gel chromatography (4:1 to 3:2 hexanes/EtOAc) to afford **6b** (2.49 g, 47%) and **21** (2.91 g, 48%) as colorless oils.

Compound **6b**, $[\alpha]_{\text{D}}^{20}$ -40.3 (c 1.01, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 7.27 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 5.79 (ddd, J = 17.2, 10.4, 6.8 Hz, 1H), 5.19 (d, J = 17.2 Hz, 1H), 5.07 (d, J = 10.0 Hz, 1H), 4.59 (d, J = 12.0 Hz, 1H), 4.53-4.45 (m, 2H), 4.32 (d, J = 6.0 Hz, 1H), 4.10-4.08 (m, 1H), 3.77 (s, 3H), 3.77-3.75 (m, 1H), 2.18-2.04 (m, 3H), 1.64-1.50 (m, 2H), 1.49 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.09, 140.82, 130.39, 129.36, 114.85, 113.64, 111.13, 84.78, 78.51, 77.38, 71.87, 71.27, 55.14, 39.83, 38.20, 33.40, 26.25, 24.43; LRMS (ESI), m/z ($\text{M} + \text{Na}$) $^+$

Compound **21**, $[\alpha]_{\text{D}}^{20}$ -34 (c 1.02, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 7.29 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 5.79 (ddd, J = 17.2, 10.4, 6.8 Hz, 1H), 5.26-5.16 (m, 3H), 4.61 (d, J = 12.0 Hz, 1H), 4.53-4.45 (m, 2H), 4.25-4.23 (m, 1H), 3.78 (s, 3H), 3.77-3.75 (m, 1H), 2.15-2.04 (m, 6H), 1.64-1.50 (m, 2H), 1.46 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.04, 159.12, 135.74, 130.36, 129.40, 117.46, 113.65, 110.98, 84.47, 78.20, 77.49, 73.40, 71.31, 62.07, 55.15, 37.27, 36.89, 32.67, 26.15, 24.26, 21.12; HRMS (ESI), m/z ($\text{M} + \text{Na}$) $^+$ Calcd for $\text{C}_{22}\text{H}_{30}\text{O}_6\text{Na}$: 413.1940, found 413.1944.

Alcohol **6a**. To a solution of **21** (273 mg, 0.70 mmol) in THF (4 mL) and H_2O (4 mL) was added NaOH (84 mg, 2.10 mmol) at room temperature. The reaction mixture was stirred for 4 h at the same temperature, poured into H_2O (8 mL). The aqueous phase was extracted with DCM (3×10 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (3:2 hexanes/EtOAc) to afford **6a** (238 mg, 98%) as a colorless oil. $[\alpha]_{\text{D}}^{20}$ -25.8 (c 1.00, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 7.29 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.82 (ddd, J = 17.2, 10.4, 6.8 Hz, 1H), 5.22 (d, J = 17.2 Hz, 1H), 5.11 (d, J = 10.4 Hz, 1H), 4.61 (d, J = 12.1 Hz, 1H), 4.56-4.47 (m, 2H), 4.28 (d, J = 5.9 Hz, 1H), 4.17-4.10 (m, 1H), 3.79 (s, 3H), 3.79-3.77 (m, 1H), 2.20-2.02 (m, 3H), 1.78-1.50 (m, 2H), 1.51 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.11, 140.60, 130.44, 129.32, 115.12, 113.65, 111.24, 84.54, 78.64, 77.48, 71.55, 71.28, 55.17, 39.76, 37.65, 33.50, 26.28, 24.44; LRMS (ESI), m/z ($\text{M} + \text{Na}$) $^+$.

Compound **22a**. To a stirred solution of **6a** (174 mg, 0.50 mmol) in anhydrous DCM (10 mL) was added **5** (537 mg, 2.50 mmol) and Grubbs 2nd (26 mg, 0.03 mmol) at room temperature under argon. The reaction mixture was stirred for 24 h at the same temperature, and then concentrated. The residue was purified via silica gel chromatography (1:1 hexanes/

EtOAc) to afford **22a** (201 mg, 75%) as a colorless oil. $[\alpha]_D^{20} -3.1$ (c 1, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.74-5.68 (m, 2H), 5.27 (brs, 1H), 4.82 (brs, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.52-4.45 (m, 2H), 4.23 (d, *J* = 5.3 Hz, 1H), 4.17 (brs, 1H), 3.79 (s, 3H), 3.77-3.75 (m, 1H), 3.73 (s, 1H), 2.18-2.08 (m, 2H), 1.58-1.54 (m, 1H), 1.49 (s, 3H), 1.39-1.36 (m, 2H), 1.27 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 171.18, 159.10, 154.89, 133.83, 130.36, 129.33, 125.27, 113.65, 111.32, 84.36, 80.12, 78.71, 77.43, 71.31, 70.31, 55.16, 54.77, 52.55, 39.78, 37.67, 33.80, 28.20, 26.27, 24.42; HRMS (ESI), *m/z* (M + Na)⁺ Calcd for C₂₈H₄₁O₉NNa: 558.2679, found 558.2683.

Compound **22b** was obtained from **6b** and **5** in a similar manner for the preparation of **22a** as a colorless oil in 78% yield. It was used directly in the next step.

Compound **24a**. To a stirred solution of **22a** (54 mg, 0.10 mmol) in anhydrous methanol (5 mL) was added Pd/C (10% palladium on activated charcoal, 6 mg). The mixture was stirred under an atmosphere of H₂ at room temperature for 1 h, filtered, and concentrated. The residue was purified via silica gel chromatography (1:1 hexanes/EtOAc) to afford **24a** (46 mg, 85%) as a colorless oil. $[\alpha]_D^{20} -17.2$ (c 1, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.20 (brs, 1H), 4.62 (d, *J* = 11.8 Hz, 1H), 4.53-4.48 (m, 2H), 4.33 (brs, 1H), 4.25 (m, 1H), 3.84 (s, 3H), 3.83-3.80 (m, 1H), 3.66 (s, 3H), 3.65-3.63 (brs, 1H), 2.46-1.95 (m, 4H), 1.70-1.52 (m, 3H), 1.51 (s, 3H), 1.50-1.48 (m, 2H), 1.42 (s, 9H), 1.24 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 173.05, 159.08, 155.46, 130.45, 129.29, 113.64, 111.47, 84.30, 79.96, 78.94, 77.44, 71.33, 69.38, 55.16, 52.99, 52.21, 40.55, 38.02, 34.08, 32.86, 29.37, 28.20, 26.32, 24.51; LRMS (ESI), *m/z* 560.5 (M + Na)⁺.

Compound **24b**. The title compound was obtained from **22b** in a similar manner for the preparation of **24a** as a colorless oil in 80% yield. $[\alpha]_D^{20} -11.6$ (c 1, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.29 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 5.13 (brs, 1H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.54 (t, *J* = 5.2 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.30 (brs, 2H), 3.79 (s, 3H), 3.78-3.74 (m, 1H), 3.73 (s, 3H), 3.69-3.64 (brs, 1H), 2.38-1.90 (m, 4H), 1.85-1.55 (m, 3H), 1.51 (s, 3H), 1.50-1.44 (m, 2H), 1.43 (s, 9H), 1.24 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 173.15, 159.09, 155.40, 130.48, 129.29, 113.65, 111.66, 85.14, 79.81, 79.09, 71.40, 70.16, 55.15, 53.16, 52.17, 40.30, 39.10, 33.90, 32.97, 28.82, 28.20, 26.32, 24.60; LRMS (ESI), *m/z* 560.4 (M + Na)⁺.

Azide **25a**. To a stirred solution of **24a** (40 mg, 0.074 mmol) in anhydrous DCM was added triethylamine (103 μL, 0.74 mmol) and methanesulfonyl chloride (29 μL, 0.37 mmol) at 0 °C. The mixture was stirred for 5 min and then quenched with water. The aqueous phase was extracted with DCM. The combined extracts were dried over MgSO₄, filtered, and concentrated to give the crude product as a colorless oil.

The above crude product was dissolved in DMF (5 mL), and then NaN₃ (24 mg, 0.37 mmol) was added. After being stirred at 45 °C for 3.5 h, the solution was allowed to cool on ice-water bath. Then, the reaction mixture was diluted with Et₂O (10 mL) and quenched with water (5 mL). The aqueous phase was extracted with Et₂O (3 × 10 mL), and the combined organic phase was washed with water (2 × 5 mL). The organic phase was dried over

MgSO₄, filtered and concentrated. The residue was purified via column chromatography (2:1 hexanes/EtOAc) to give the desired azide compound **25a** (32 mg, 77%, for two steps) as a colorless oil. $[\alpha]_D^{20}$ -6.4 (c 1, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 5.07 (brs, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.58-4.48 (m, 2H), 4.31 (brs, 1H), 4.23 (d, *J* = 5.8 Hz, 1H), 3.79 (s, 3H), 3.76-3.60 (m, 4H), 3.28-3.22 (m, 1H), 2.40-1.60 (m, 7H), 1.51 (s, 3H), 1.50-1.46 (m, 2H), 1.43 (s, 9H), 1.30 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.72, 159.15, 155.26, 130.30, 129.35, 113.67, 111.29, 84.64, 79.98, 78.40, 77.37, 71.37, 60.28, 55.16, 52.78, 52.35, 38.31, 37.14, 32.55, 30.04, 29.28, 28.19, 26.21, 24.37; HRMS (ESI), *m/z* (M + Na)⁺ Calcd for C₂₈H₄₂O₈N₄Na: 585.2900, found 585.2903.

Azide **25b**. The title compound was obtained from **24b** in a similar manner for the preparation of **25a** as a colorless oil in 80% yield. $[\alpha]_D^{20}$ -14.5 (c 1, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 5.08 (brs, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.58-4.48 (m, 2H), 4.31-4.18 (m, 2H), 3.82 (s, 3H), 3.75-3.70 (m, 4H), 3.15-3.12 (m, 1H), 3.11 (s, 3H), 2.18-1.95 (m, 3H), 1.80-1.50 (m, 6H), 1.50 (s, 3H), 1.42 (s, 9H), 1.32 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.71, 159.14, 155.22, 130.30, 129.34, 113.68, 111.45, 84.23, 79.99, 78.66, 77.32, 71.36, 60.75, 55.16, 53.05, 52.34, 38.45, 37.30, 33.47, 30.18, 29.10, 28.19, 26.24, 24.41; LRMS (ESI), *m/z* 585.4 (M + Na)⁺.

Alcohol **4a**. To a stirred solution of **25a** (30 mg, 0.053 mmol) in anhydrous DCM (4 mL) was added DDQ (18 mg, 0.080 mmol) at room temperature. The mixture was stirred for 3 h at the same temperature, and then quenched with saturated NaHCO₃ solution (5 mL). The aqueous phase was extracted with DCM. The combined organic extracts were dried over MgSO₄, filtered, and concentrated. The residue was then purified via silica gel chromatography (3:2 hexanes/EtOAc) to afford **4a** (24 mg, 92%) as a colorless oil. $[\alpha]_D^{20}$ +10.2 (c 1, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 5.08 (brs, 1H), 4.48 (t, *J* = 6.2 Hz, 1H), 4.32-4.30 (brs, 2H), 3.80 (brs, 1H), 3.74 (s, 3H), 3.33 (brs, 1H), 2.47 (brs, 1H), 2.24-2.20 (m, 1H), 2.01-1.56 (m, 8H), 1.52 (s, 3H), 1.43 (s, 9H), 1.32 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.73, 155.25, 112.23, 85.06, 79.97, 79.24, 70.51, 60.61, 52.80, 52.36, 38.67, 36.95, 30.04, 29.21, 28.20, 26.03, 24.35; LRMS (ESI), *m/z* 443.2 (M + H)⁺.

Alcohol **4b**. The title compound was obtained from **25b** in a similar manner for the preparation of **4a** as a colorless oil in 88% yield. It was used directly in the next step.

Compound **26a**. To a stirred solution of **4a** (20 mg, 0.04 mmol) in anhydrous DCM (5 mL) was added pyridine (36 μL, 0.45 mmol) and triflic anhydride (30 μL, 0.18 mmol) at 0 °C. The mixture was stirred for 5 min and then quenched with water. The aqueous phase was extracted with DCM. The combined extracts were dried over MgSO₄, filtered, and concentrated. The residue was purified via silica gel chromatography (2:1 hexanes/EtOAc) to afford a colorless oil which was subjected to the next step immediately.

To a stirred solution of above oil in anhydrous DMF (4 mL) was added adenine (10 mg, 0.07 mmol), K₂CO₃ (48 mg, 0.35 mmol) and 18-Crown-6 (4 mg, 0.015 mmol) at room temperature. The resulting mixture was heated to 50 °C, and stirred for 5 h. The mixture was allowed to cool on ice-water bath, diluted with Et₂O (10 mL) and quenched with water (5

mL). The aqueous phase was extracted with Et₂O (3 × 10 mL), and the combined organic phase was washed with water (2 × 5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The residue was purified via column chromatography (2:1 hexanes/EtOAc) to give the compound **26a** (15 mg, 75%) as a colorless oil. [α]_D²⁰ +5.2 (c 1, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 8.35 (s, 1H), 7.85 (s, 1H), 5.76 (s, 2H), 5.17 (brs, 1H), 5.13 (dd, *J* = 5.7, 6.9 Hz, 1H), 4.74 (ddd, *J* = 11.7, 6.6, 5.1 Hz, 1H), 4.56 (t, *J* = 6.5 Hz, 1H), 4.37 (brs, 1H), 3.79 (s, 3H), 3.42 (brs, 1H), 2.50-2.40 (m, 1H), 2.35-2.30 (m, 1H), 2.02-1.55 (m, 8H), 1.59 (s, 3H), 1.46 (s, 3H), 1.33 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.76, 155.43, 152.61, 149.83, 140.06, 120.44, 114.00, 84.29, 83.26, 79.99, 61.67, 60.45, 52.81, 52.36, 41.16, 37.91, 36.69, 29.99, 29.10, 28.20, 27.42, 25.05. HRMS (ESI) calcd for C₂₅H₃₈N₉O₆ (M + H)⁺: 560.2945, found 560.2949.

Compound **26b**. The title compound was obtained from **4b** and adenine in a similar manner for the preparation of **4a** as a colorless oil in 68% yield. [α]_D²⁰ +0.8 (c 1, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 8.34 (s, 1H), 7.84 (s, 1H), 5.84 (s, 2H), 5.22 (d, *J* = 10.1 Hz), 5.13 (dd, *J* = 5.8, 6.9 Hz, 1H), 4.74 (ddd, *J* = 11.8, 6.4, 5.0 Hz, 1H), 4.52 (t, *J* = 10.1 Hz, 1H), 4.37 (brs, 1H), 3.79 (s, 3H), 3.53 (m, 1H), 2.50-2.30 (3H, m), 2.07-2.03 (m, 1H), 1.94-1.60 (m, 5H), 1.59 (s, 3H), 1.47 (s, 9H), 1.32 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.78, 155.47, 155.24, 152.62, 149.81, 140.04, 120.43, 114.16, 84.51, 83.56, 79.98, 61.49, 61.16, 53.08, 52.34, 41.70, 38.31, 37.10, 31.06, 29.24, 28.20, 27.36, 25.13. HRMS (ESI) calcd for C₂₅H₃₈N₉O₆ (M + H)⁺: 560.2945, found 560.2944.

Compound **26c**. The title compound was obtained from **4b** and *N*-(3-methylbenzyl)-9H-purin-6-amine in a similar manner for the preparation of **4a** as a colorless oil in 63% yield. [α]_D²⁰ -2.4 (c 0.5, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.38 (s, 1H), 7.72 (s, 1H), 7.24-7.15 (m, 1H), 7.09 (d, *J* = 7.3 Hz, 1H), 6.06 (brs, 1H), 5.13-5.08 (m, 2H), 4.82 (brs, 2H), 4.73-4.67 (m, 1H), 4.54-4.48 (m, 1H), 4.34 (brs, 1H), 3.55-3.48 (m, 1H), 2.50-2.40 (m, 2H), 2.37 (s, 3H), 2.36-2.35 (m, 1H), 1.75-1.60 (m, 5H), 1.52 (s, 3H), 1.43 (s, 9H), 1.29 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.75, 155.22, 154.65, 152.79, 139.34, 138.31, 138.18, 128.50, 128.35, 128.17, 124.68, 120.59, 114.15, 84.53, 83.61, 80.02, 61.49, 61.18, 60.28, 53.09, 52.36, 41.73, 38.34, 37.18, 31.06, 29.29, 28.21, 27.37, 25.14. HRMS (ESI) calcd for C₃₃H₄₅N₉O₆Na (M + Na)⁺: 686.3390, found 686.3396.

Compound **2**. To a stirred solution of **26a** (10 mg, 0.02 mmol) in anhydrous methanol (3 mL) was added triphenylphosphine at room temperature. The mixture was stirred for 4 h at the same temperature, and then trifluoroacetic acid (1.5 mL) was added. The resulting mixture was stirred for additional 2 h, and concentrated. The residue was dissolved in THF (1.5 mL), and then slowly adjusted to pH 12 with LiOH solution (1 M) at 0 °C. The mixture was stirred overnight at room temperature, adjusted to pH 7 with HCl solution (1 M), and concentrated. The residue was purified with preparation TLC (5:3:1 DCM/MeOH/NH₃H₂O) to afford carbocyclic sinefungin **2** (4 mg, 60%) as an amorphous solid. [α]_D²⁰ +3.4 (c 1, H₂O); ¹H NMR (500 MHz, D₂O) δ 8.15 (s, 1H), 8.14 (s, 1H), 4.45 (t, *J* = 7.1 Hz, 1H), 3.96 (t, *J* = 6.1 Hz, 1H), 3.73 (t, *J* = 6.0 Hz, 1H), 3.37 (td, *J* = 12.7, 6.6 Hz, 1H), 2.47-2.43 (m, 1H), 2.15-2.11 (m, 1H), 1.96-1.69 (m, 7H); ¹³C NMR (125 MHz, D₂O) δ 174.42, 155.52, 152.28, 149.18, 140.89, 118.83, 74.55, 74.48, 59.91, 54.09, 50.00, 39.48, 36.06, 31.80, 28.18, 26.18; HRMS (MALDI) calcd for C₁₆H₂₆N₇O₄ (M + H)⁺: 380.2046, found 380.2049.

Compound **3a** was obtained from **26b** in a similar manner for the preparative of **2** as an amorphous solid in 58% yield. $[\alpha]_D^{20} -5.6$ (c 0.35, H_2O); 1H NMR (500 MHz, 313 K, D_2O) δ 8.10 (s, 1H), 8.06 (s, 1H), 4.68-4.65 (m, 1H), 4.39 (dd, J = 8.0, 6.5 Hz, 1H), 3.89 (t, J = 6.1 Hz, 1H), 3.38-3.34 (m, 1H), 3.11-3.08 (m, 1H), 2.42-2.36 (m, 1H), 2.08-2.02 (m, 1H), 1.88-1.57 (m, 6H), 1.52-1.42 (m, 1H); ^{13}C NMR (125 MHz, 313 K, D_2O) δ 155.88, 152.71, 149.60, 141.20, 119.21, 75.02, 74.92, 60.26, 55.65, 49.55, 39.81, 39.28, 32.48, 29.49, 26.65. HRMS (ESI) calcd for $C_{16}H_{26}N_7O_4$ ($M + H^+$) : 380.2046, found 380.2051.

Compound **3b** was obtained from **26c** in a similar manner for the preparation of **2** as an amorphous solid in 75% yield. $[\alpha]_D^{20} -3.1$ (c 0.38, H_2O); 1H NMR (500 MHz, 313 K, D_2O) δ 8.38 (s, 1H), 8.35 (s, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.39-7.31 (m, 3H), 5.00-4.92 (m, 3H), 4.67 (t, J = 5.9 Hz, 1H), 4.18 (t, J = 5.6 Hz, 1H), 3.72 (t, J = 5.9 Hz, 1H), 3.44-3.36 (m, 1H), 2.71-2.65 (m, 1H), 2.46 (s, 3H), 2.40-2.31 (m, 1H), 2.16-1.75 (m, 7H); ^{13}C NMR (125 MHz, 313 K, D_2O) δ 152.70, 140.58, 139.09, 138.79, 128.90, 128.12, 127.66, 124.16, 74.91, 74.78, 60.17, 55.30, 49.65, 39.60, 38.23, 32.35, 29.76, 28.65, 20.54. HRMS (ESI) calcd for $C_{24}H_{33}N_7O_4$ ($M + H^+$): 484.2672, found 484.2666.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This research was supported by the National Institutes of Health (AI07079201A1). The authors would like to thank the Purdue University Center for Cancer Research which supports the shared NMR and Mass spec facilities. We also thank Dr. Hongmin Li for helpful discussions.

References

- [1]. Hameil RL, Hoehn MM. J. Antibiot. 1973; 26:463–465. [PubMed: 4792069]
- [2]. Pugh CS, Borchardt RT, Stone HO. J. Bio. Chem. 1978; 253:4075–4077. [PubMed: 659406]
- [3]. Gordee RS, Butler TF. J. Antibiot. 1973; 26:466–470. [PubMed: 4600794]
- [4]. Zingg JM, Shen JC, Yang AS, Rapoport H, Jones PA. Nucl. Acids Res. 1996; 24:3267–3275. [PubMed: 8774911]
- [5]. a) Pugh CS, Borchardt RT. Biochemistry. 1982; 21:1535–1541. [PubMed: 6282307] b) Chen H, Zhou B, Brecher M, Banavali N, Jones SA, Li Z, Zhang J, Nag D, Kramer LD, Ghosh AK, Li H. PloS one. 2013; 8:e76900. [PubMed: 24130807]
- [6]. Dube DK, Mpimbaza G, Allison AC, Lederer E, Rovis L. Am. J. Trop. Med. Hyg. 1983; 32:31–33. [PubMed: 6130709]
- [7]. Zwegarth E, Schillinger D, Kaufmann W, Rottcher D. Trop. Med. Parasitol. 1986; 37:255–257. [PubMed: 2878488]
- [8]. Deng L, Zhang L, Yao Y, Wang C, Redell MS, Dong S, Song Y. MedChemComm. 2013; 4:822–826. [PubMed: 23795283]
- [9]. Kalimouttou S, Skiba M, Bon P, Dechelotte P, Arnaud P, Lahiani-Skiba M. J. Nanosci. Nanotechnol. 2009; 9:150–158. [PubMed: 19441289]
- [10]. a) Yin X, Zhao G, Schneller SW. Tetrahedron Lett. 2007; 48:4809–4811. [PubMed: 18612331] b) Chen Q, Liu C, Shulyak TS, Schneller SW. Tetrahedron. 2014; 70:892–900.
- [11]. Dong H, Liu L, Zou G, Zhao Y, Li Z, Lim SP, Shi PY, Li H. J. Biol. Chem. 2010; 285:32586–32595. [PubMed: 20685660]
- [12]. Scully CCG, Rutledge PJ. Tetrahedron. 2010; 66:5653–5659.

- [13]. Marchand D, Martinez J, Cavelier F. *Eur. J. Org. Chem.* 2008; 18:3107–3112.
- [14]. a) Carrasco M, Jones RJ, Kamel S, Rapoport H, Truong T. *Org. Synth.* 1992; 70:29–32. b) Lumbroso A, Coeffard V, Le Grogne E, Beaudet I, Quintard JP. *Tetrahedron Lett.* 2010; 51:3226–3228.
- [15]. a) Kanko C, Sugimoto A, Tanaka S. *Synthesis.* 1974; 12:876–877. b) Deardorff DR, Windlham CQ, Craney CL. *Org. Synth.* 1996; 73:25–28.
- [16]. Ambe-Suzuki K, Ohyam Y, Shirai N, Ikeda S. *Adv. Synth. Catal.* 2012; 354:879–888.
- [17]. Marschner C, Penn G, Griengl H. *Tetrahedron.* 1993; 49:5067–5078.
- [18]. a) Corey EJ, Helal CJ. *Angew. Chem. Int. Ed.* 1998; 37:1987–2012. b) Xu S, Unabara D, Uemura D, Arimoto H. *Chem. Asian J.* 2014; 9:367–375. [PubMed: 24136879]
- [19]. Chojnacka A, Obara R, Wawrzenczyk C. *Tetrahedron Asymmetry.* 2007; 18:101–107.
- [20]. Kazlauskas RJ, Weissfloch ANE, Rappaport AT, Cuccia LA. *J. Org. Chem.* 1991; 56:2656–2665.
- [21]. Scholl M, Ding S, Lee CW, Grubbs RH. *Org. Lett.* 1999; 1:953–956. [PubMed: 10823227]
- [22]. Kim HS, Jacobson KA. *Org. Lett.* 2003; 5:1665–1668. [PubMed: 12735747]
- [23]. Chakraborty TK, Gajula PK, Koley D. *J. Org. Chem.* 2008; 73:6916–6919. [PubMed: 18672934]

Figure 1.
Design of new carbocyclic SIN derivatives.

Scheme 1.
Retrosynthesis of carbocyclic SIN and its derivatives.

Scheme 2.
Synthesis of segment **5**.

Scheme 3.
Synthesis of segment **6a**.

Scheme 4.
Enzymatic kinetic resolution of alcohol **19**.

Scheme 5.

Cross coupling and examination of azide substitution

Scheme 6.
Synthesis of azides **4a-b**.

Scheme 7.
Synthesis of carbocyclic SIN **2** and **3**.