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Application of hypoiodite-mediated aminyl radical cyclization to synthesis of solasodine acetate

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ABSTRACT

Solasodine acetate, an anticancer steroidal alkaloid, was synthesized from diosgenin in 8 steps with an overall yield of 23%. A key synthetic step involves the formation of 5/6-oxazaspiroketal moiety via hypoiodite-mediated aminyl radical cyclization of a steroidal primary amine.

1. Introduction

Solasodine **1** [1], solasodine acetate **2** [2], and solarmargine **3** [3] are plant-derived steroidal alkaloids that share a 5/6-oxazaspiroketal moiety (Fig. 1) and exhibit various biological activities. Solasodine has shown antiproliferative [4], neurogenesis [5], anti-inflammatory [6], and anticonvulsant activities [7]. Solasodine acetate **2** is known to damage DNA significantly and to increase DNA repair activity [8]. DNA damage activities of solasodine acetate **2** may be ascribed to its oxazaspiroketal moiety that can produce a hypothetical imminium ion 4 (Fig. 1) [8]. Solamargine **3**, a solasodine glycoalkaloid, is highly effective at treating skin cancers [9], induces apoptosis [10], and is known to sensitize breast cancer cells to cisplatin treatment [11].

Significant biological activities of the steroidal alkaloids have prompted several research groups to undertake syntheses of solasodine-related natural products (Fig. 2). Some of these syntheses involve the use of key intermediates of steroidal diketone **6** [12], hemiacetal **7** [13], and cyclic enol ether **8** [14]. In conjunction with our ongoing efforts to develop potent steroidal anticancer agents, we recently discovered that hypoiodite-mediated radical cyclization of a primary amine **9** proceeded smoothly at 0 °C to give an oxazaspiroketal **10** in the presence of iodobenzene diacetate and iodine (Fig. 3) [15]. Since our cyclization conditions do not require a radical-stabilizing groups (e.g. acetyl, sulfonyl, and phosphoryl groups [16]) on the amino group that were typically employed in other aminyl radical cyclization methods, we expected that the radical-stabilizing group-free method would be a valuable means for efficient preparation of various oxazaspiroketal-containing natural products. Indeed, we have successfully applied the methodology in the synthesis of an analog of cephalostatin **11** [16], a bis-steroidal pyrazine anticancer agent [15]. We envisaged that solasodine acetate **2** also can be readily synthesized from diosgenin **5** via "Reduction/Oxidation" modifications and the hypoiodite-mediated aminyl radical cyclization (Scheme 1). Herein, we report a facile synthesis of solasodine acetate **2**, where hypoiodite-mediated cyclization of a nonactivated primary amine is used as a key chemical transformation.

2. Experimental

2.1. General Methods

Reagents, such as triethylsilane, boron trifluoride etherate, iodine, iodobenzene diacetate, triphenylphosphine, sodium azide, and *p*-toluenesulfonyl chloride were purchased from Aldrich Chemical Company Inc., were used as received. Acetonitrile, methylene chloride, pyridine, and triethylamine (TEA) were distilled from calcium hydride: methanol was distilled from magnesium turnings: THF was distilled from Na/benzoquinone. Sodium sulfate (Na_2SO_4) was anhydrous. All chromatographic and workup solvents were distilled.

Unless otherwise indicated, all reactions were carried out under a positive pressure of argon in anhydrous solvents and the reaction

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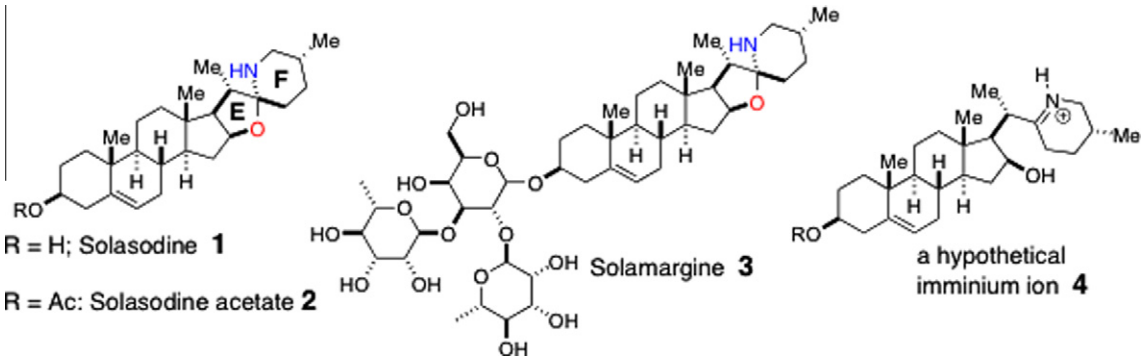


Fig. 1. Steroidal alkaloids: Solasodine **1**, solasodine acetate **2** solamargine **3** and a hypothetical imminium ion 4.

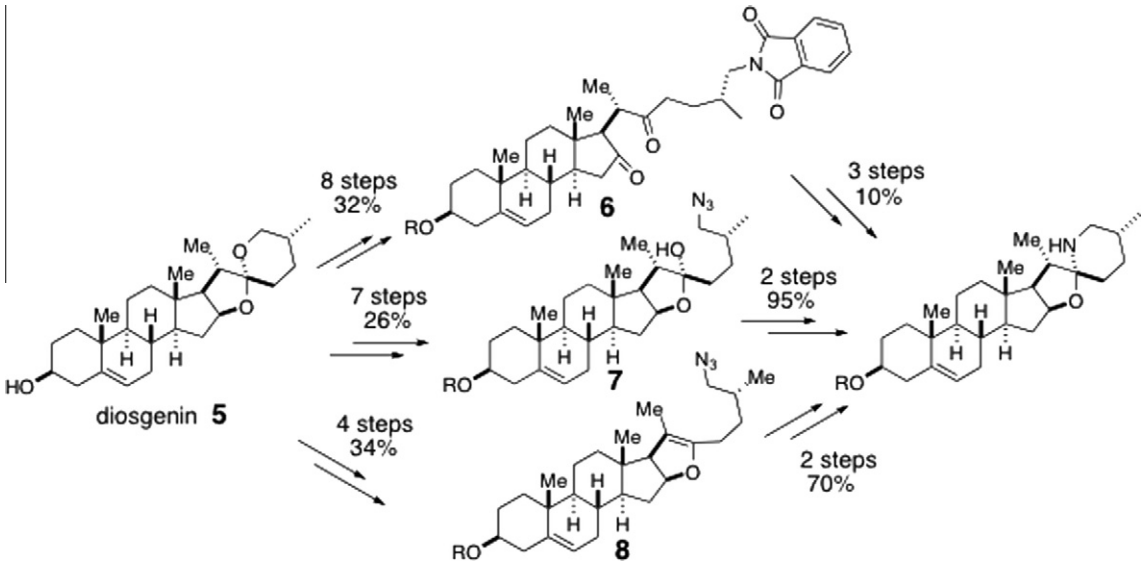


Fig. 2. Previous syntheses of natural products containing solasodine moiety.

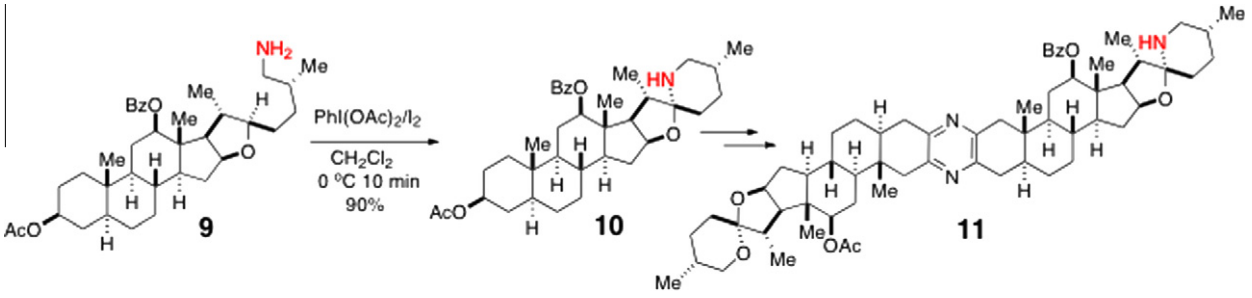
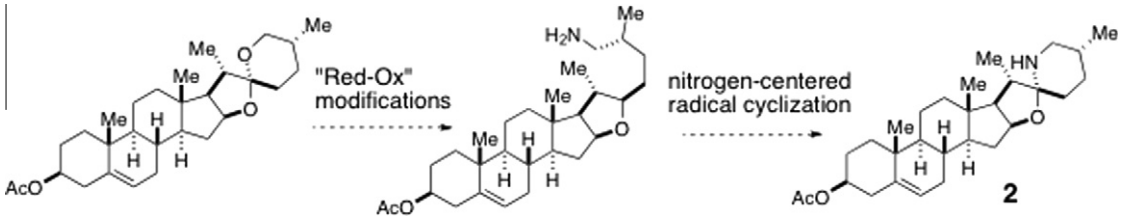


Fig. 3. Previous synthesis of oxazaspiroketal-containing cephalostatin analog **11** using a hypoiodite-mediated aminyl radical cyclization as a key reaction.

flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe. Progress of reactions was monitored by thin layer chromatography (TLC) in comparison with the starting materials. All TLC analyses were carried out on Merck Silica Gel 60 F254 TLC plates, thickness of 0.25 mm. The plates were visualized by ultraviolet illumination at 254 nm and immersion in visualizing solution. The two commonly employed TLC visualizing solutions were: (i) *p*-anisaldehyde solution (1350 mL of absolute ethanol, 50 mL of concentrated H_2SO_4, 37 mL of *p*-anisaldehyde), and (ii) permanganate solution (weight percents of 1% $KMnO_4$ and 2% Na_2CO_3 in water).

Analytical samples were obtained from flash silica gel chromatography, using about 100 grams of silica gel of 230–400 mesh size for purifying a gram of reaction mixture. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 500 (500 MHz). NMR spectra were determined in chloroform-d ($CDCl_3$) and are reported in parts per million (ppm) from the residual chloroform (7.24 ppm and 77.0 ppm) and benzene (7.16 ppm and 128.39 ppm) standard, respectively. Peak multiplicates in ^{1}H-NMR spectra, when reported, are abbreviated as s (singlet), d (doublet), t (triplet), m (multiplet), and/or ap (apparent) and/or br (broad). Mass spectra were all obtained on either a JEOL AX-505 or a JEOL SX-102.



Scheme 1. Plan for solasodine acetate synthesis.

2.2. Chemical synthesis

2.2.1. (20α,22β,25R)-3β-Acetoxyfurost-5-ene-26-(p-toluenesulfonate) 14

To a CH_2Cl_2 (50 mL) solution of diosgenin acetate **12** (4.03 g, 8.83 mmol) and triethylsilane (2.86 mL, 17.6 mmoL) was added dropwise boron trifluoride diethyl etherate (2.50 g, 17.6 mmoL) in CH_2Cl_2 (20 mL) at 0 °C. After stirring the resulting mixture for 12 h at an ambient temperature, the reaction was quenched by slow addition of aqueous saturated sodium bicarbonate (200 mL). Extraction of aqueous layer with CH_2Cl_2 (3 × 200 mL), washing with brine, drying over anhydrous sodium sulfate, and concentration under reduced pressure gave a crude primary alcohol **13**, which was subjected to the next reaction without further purification. To a CH_2Cl_2 (70 mL) solution of alcohol **13** were added triethylamine (3.68 mL, 26.5 mmol), 4-dimethylaminopyridine (107 mg, 0.88 mmol), and *p*-toluenesulfonyl chloride (2.50 g, 13.2 mmol), and the resulting mixture was vigorously stirred at 25 °C. After 6 h, the reaction mixture was concentrated under reduced pressure, and subjected to silica gel chromatography (Hexane/EtOAc = 8:1) to give tosylate **14** (4.62 g, 7.75 mmol) as a white solid (mp, 116–119 °C) in 85% yield. ^{1}H and ^{13}C NMR chemical shifts values of compound 2 were consistent with the previously reported values [17].

2.2.2. (20α,22β,25R)-3β-Acetoxy-5-ene-26-azidofurostane 15

To a DMF (6 mL) solution of tosylate **14** (660 mg, 1.07 mmol) was added sodium azide (208 mg, 3.20 mmol) and the mixture was stirred for 3 h at 60 °C. The reaction mixture was then partitioned between water (50 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the combined organic extracts were washed with saturated lithium chloride (50 mL). After removal of the organic solvents under reduced pressure, the residue was subjected to silica gel chromatography (Hexane/EtOAc = 8:1) to give azide **15** (350 mg, 0.72 mmol) as an off-white solid (mp, 60–63 °C) in 67% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.34 (1H, d, *J* = 3 Hz), 4.56 (1H, m), 4.27 (1H, m), 3.28 (1H, m), 3.22–3.06 (2H, m), 2.30 (3H, s), 1.00 (3H, s), 0.97 (3H, d, *J* = 3.9 Hz), 0.93 (3H, d, *J* = 4.2 Hz), 0.78 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 170.5, 139.7, 122.3, 90.0, 83.2, 73.8, 65.1, 57.7, 56.9, 50.0, 40.6, 39.4, 38.0, 37.9, 37.0, 36.7, 33.7, 32.2, 31.9, 31.5, 31.1, 30.7, 29.7, 27.7, 21.4, 20.6, 19.3, 18.9, 17.6, 16.4. HRMS for $C_{29}H_{46}N_3O_3$ (M+H), calcd: 484.3534, found: 484.3530.

2.2.3. (20α,22β,25R)-3β-Acetoxy-5-ene-26-aminofurostane 16

To a MeOH (10 mL) solution of (20α,22β,25R)-3β-acetoxy-5-ene-26-azidofurostane **15** (100 mg, 0.21 mmol) was added triphenylphosphine (550 mg, 2.1 mmol) at an ambient temperature. The mixture was heated and stirred for 15 h at 60 °C. The precipitates were filtered through sintered glass, the filtrates were concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (EA/MeOH/TEA = 1:1:0.02) to give (20α,22β,25R)-3β-acetoxy-5-ene-26-aminofurostane **16** (60 mg, 0.13 mmol) as an off-white solid (mp, 100–103 °C) in 64% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.36 (1H, m), 4.53 (1H, m), 4.26 (1H, m), 3.28 (1H, m), 2.60 (1H, dd, *J* = 5.4, 12.6 Hz), 2.48 (1H, dd, *J* = 5.9, 12.5 Hz), 2.28 (2H, d, *J* = 7.2 Hz), 1.99 (3H, s), 1.00 (3H, s), 0.96 (3H, d, *J* = 6.7 Hz), 0.87 (3H, d, *J* = 6. 7 Hz), 0.77 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 170.5, 139.6, 122.4, 90.2, 83.1, 73.9, 65.1, 56.8, 50.0, 48.1, 40.6, 39.3, 38.0, 37.8, 36.9, 36.6, 36.2, 32.2, 31.9, 31.5, 31.1, 30.8, 27.7, 24.1, 21.4, 20.6, 19.2, 18.9, 17.2, 16.4.

HRMS for $C_{29}H_{48}NO_3$ (M+H), calcd: 458.3628, found: 458.4634.

2.2.4. (20α,22β,25R)-3β-Acetoxy-5,6-epoxy-26-azidofurostane 17

To a stirred solution of trisubstituted alkene **15** (313 mg, 0.65 mmol) and $NaHCO_3$ (273 mg, 3.25 mol) in 10 mL of CH_2Cl_2 was added portionwise *m*-chloroperoxybenzoic acid (319 mg, 1.30 mmol) over 10 min at 0 °C. After vigorously stirring the mixture for 3 h at the same temperature, the reaction was quenched by adding saturated sodium thiosulfate (10 mL). The reaction mixture was extracted with ethyl acetate (3 × 30 mL), washed with brine, dried over anhydrous sodium sulfate, concentrated *in vacuo*, and subjected to silica gel chromatography (Hexane/EtOAc = 4:1) to give an inseparable mixture of diasteromeric epoxide **17** (280 mg, α:β = 2:1 based on 1H NMR integration of C3–H) as a colorless foam in 87% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.92 (0.66H, m, C3–H of the α epoxide), 4.66 (0.33H, m, C3-H of the β epoxide), 3.21 (1H, m), 3.15 (1H, d, *J* = 5.9 Hz), 3.03 (2H, m), 2.82 (1H, d, *J* = 4.1 Hz), 1.93 (3H, s), 1.02 (3H, d, *J* = 6.7 Hz), 0.92 (3H, d, *J* = 7.7 Hz), 0.67 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 170.3, 170.0, 89.8, 82.8, 71.1, 64.9, 64.7, 63.1, 62.2, 58.8, 57.5, 56.9, 56.2, 50.8, 42.2, 40.5, 39.3, 38.8, 37.8, 37.7, 36.5, 36.0, 35.0, 34.9, 33.5, 32.4, 32.0, 31.9, 31.0, 30.5, 29.4, 39.3, 28.7, 27.0, 21.4, 21.2, 20.1, 18.8, 17.4, 17.0, 16.2, 16.1, 15.7. HRMS for $C_{29}H_{46}N_3O_4$, (M+H), calcd: 500.3483, found: 500.3481.

2.2.5. (20α,22β,25R)-3β-Acetoxy-26-amino-5,6-epoxy-furostane 18

To azide **17** (260 mg, 0.54 mmol) in THF/H_2O (10 mL/0.2 mL) was added triphenylphosphine (757 mg, 2.9 mmol), and the resulting mixture was stirred at 25 °C for 24 h. The reaction mixture was concentrated under reduced pressure, and subjected to silica gel chromatography (EtOAc/MeOH/TEA = 10:1:0.05) to provide a primary amine **18** (230 mg, 0.49 mmol) as a colorless foam in 87% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.85–4.58 (1H, m), 4.14 (1H, m), 3.16 (1H, m), 2.94–2.75 (1H, m), 2.41 (2H, m), 1.87(3H, s), 0.96 (3H, s), 0.84 (3H, d, *J* = 6.7 Hz), 0.76 (3H, d, *J* = 6.4 Hz), 0.61(1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 170.1, 170.0, 90.0, 82.7, 71.0, 64.8, 64.6, 63.1, 62.1, 58.7, 56.7, 56.0, 50.7, 48.0, 42.1, 40.4, 40.3, 39.2, 38.7, 37.6, 36.4, 36.1, 35.8, 34.9, 34.8, 32.3, 31.9, 30.8, 30.5, 29.3, 29.1, 28.6, 26.9, 21.2, 21.0, 19.9, 18.7, 17.0, 16.8, 16.1, 16.0, 15.6. HRMS for $C_{29}H_{48}NO_4$ (M + H), calcd: 474.3578, found: 474.3585.

2.2.6. 5,6-epoxy-solasodine-3β-acteate 19

Iodobenzene diacetate (232 mg, 0.72 mmol) and I_2 (181 mg, 0.72 mmol) were dissolved in CH_2Cl_2 (3 mL) by vigorous stirring

for 30 min at room temperature. The mixture was then cooled down to 0 °C and a CH_2Cl_2 solution (3 mL) of primary amine **18** (170 mg, 0.36 mmol) was added. After stirring for 2 h at 0 °C, the reaction was quenched by adding saturated sodium thiosulfate (20 mL), and the reaction mixture was extracted with CH_2Cl_2 (3×20 mL) and dried over anhydrous Na_2SO_4. Concentration and purification by silica gel chromatography (Hexane/EtOAc = 1:1) gave an oxazaspiroketal **19** (100 mg, 0.21 mmol) as an off-white solid (mp, 175–178 °C) in 77% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.96 (1H, m), 4.74 (1H, m), 3.06–2.63 (2H, m), 2.86 (1H, m), 1.98 (3H, s), 1.06 (3H, s), 0.98 (3H, s), 0.87 (3H, d, J = 6.4 Hz), 0.72 (3H, d, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 170.4, 170.1, 99.8, 99.7, 83.9, 77.4, 71.2, 65.1, 64.9, 63.2, 62.4, 61.1, 58.7, 56.0, 55.3, 50.6, 45.5, 42.0, 41.9, 40.9, 40.8, 38.5, 37.8, 35.9, 35.0, 34.6, 33.2, 32.0, 31.8, 31.5, 29.5, 29.3, 28.7, 27.8, 27.1, 25.2, 22.6, 21.3, 20.1, 18.5, 17.0, 16.6, 16.0, 15.8, 14.0. HRMS for $C_{29}H_{46}NO_4$ (M+H), calcd: 472.3421, found: 472.3423.

2.2.7. Solasodine-3β-acetate **2**

To a CH_2Cl_2 (2 mL) solution of epoxide 19 (25 mg, 0.055 mmol) was added triphenylphosphine (39 mg, 0.15 mmol) and iodine (38 mg, 0.15 mmol) and the mixture was stirred for 1 h at 25 °C. The reaction mixture was quenched by adding saturated sodium thiosulfate (5 mL), extracted with CH_2Cl_2 (3×5 mL) and dried over anhydrous sodium sulfate. Concentration and purification by silica gel chromatography (Hexane/EtOAc = 1:1) afforded the target solasodine acetate *2* (16 mg, 0.04 mmol) as a white solid (mp, 190–194 °C [lit mp 189–190 °C ref [14]]) in 73% yield. ^{1}H and ^{13}C NMR chemical shifts values of compound **2** were consistent with the previously reported values [14].

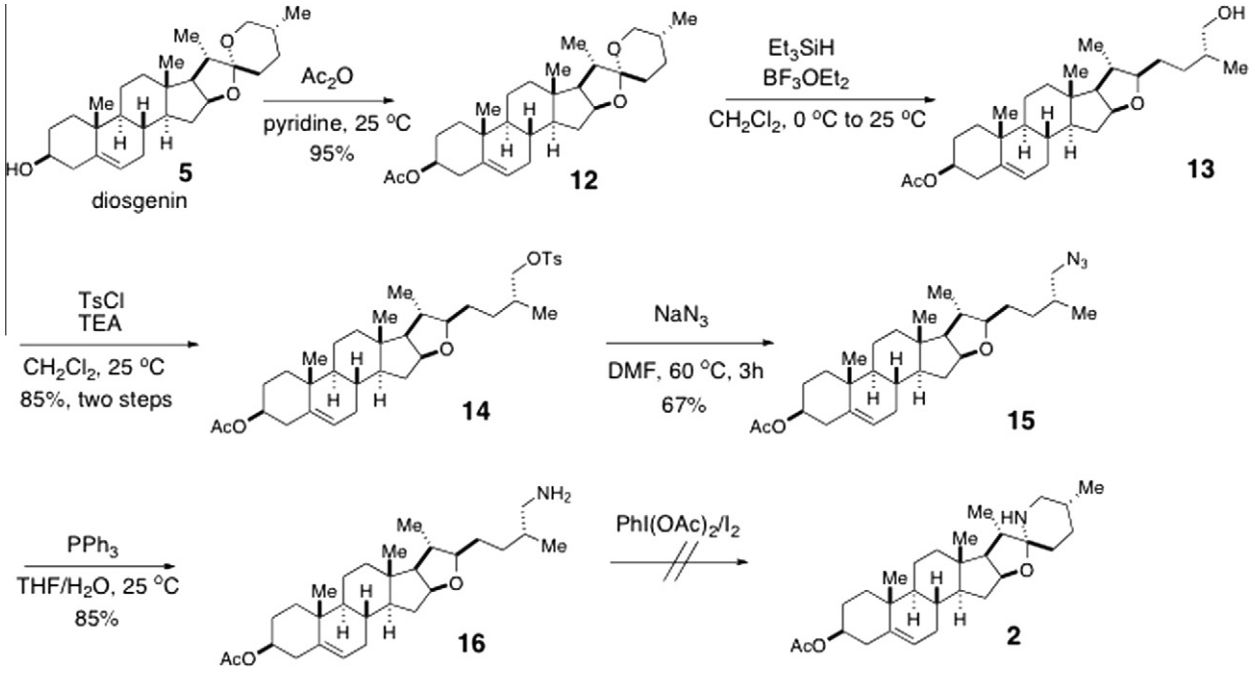
3. Results and discussion

Synthesis of solasodine acetate **2** started with acetylation of commercially available diosgenin **5** [17] followed by boron trifluoride etherate/triethylsilane-mediated reductive ring opening of 5/6 spiroketal **12** to stereoselectively give primary alcohol **13** [18]. The alcohol **13** was converted into the corresponding azide **15** via sequential tosylation of the alcohol 13 and nucleophilic substitution of the tosylate group with azide (Scheme 2). Staudinger reduction [19] of alkyl azide **15** yielded a primary amine **16**, which set the stage for a crucial aminyl radical cyclization. Unfortunately, when the steroidal amine **16** was treated with iodobenzene diacetate and iodine, the reaction gave a complex mixture of products with no indication of formation of solasodine acetate **2**. Proton and carbon NMR spectra indicate that Δ^5 olefin moiety was affected under the influence of iodobenzene diaceate and iodine [20], and this led us to seek a revised synthetic plan involving protection of Δ^5 olefin moiety with oxirane group prior to hypoiodite-mediated cyclization (Scheme 3).

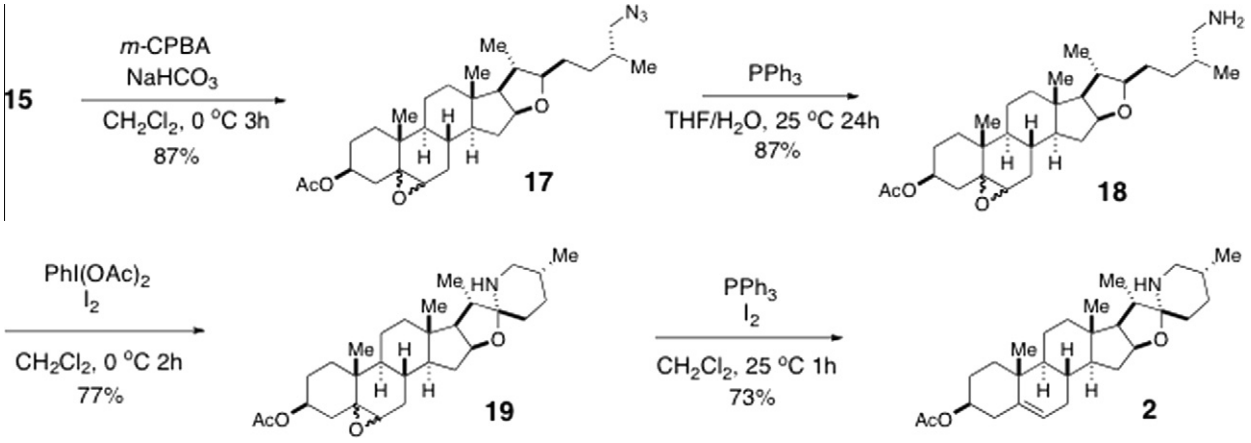
Our revised synthesis of solasodine acetate **2** began with an oxidation of a trisubstituted alkene **15** with *m*-chloroperoxybenzoic acid [21] to give a diasteromeric mixture (α:β = 2:1) of 5,6-epoxides **17** in 87% yield (Scheme 3). The resulting oxirane-azide **17** was then subjected to Staudinger reduction [19] to afford primary amine **18**. Gratifyingly, when the olefin moiety was protected with an oxirane group, the hypoiodite-mediated intramolecular radical cyclization [15] occurred smoothly at 0 °C to stereoselectivley furnish 5/6 oxazaspiroketal **19** in 77% yield. Deoxygenation of oxirane group in **19** with triphenylphosphine and iodine [22] smoothly provided the target solasodine acetate **2** in 73% yield.

A potential mechanism for the formation of 5/6 oxazaspiroketal **19** via hypoiodite-mediated aminyl radical cyclization of 18 is shown in Scheme 4. The action of $PhI(OAc)_2$ and I_2 on the primary amine **18** produces *N*-iodoamine **20**, which generates an aminyl radical **21** and an iodine radical via a homolytic cleavage of the N–I bond. Transposition of the aminyl radical **21** via 1,6-hydrogen atom transfer gives a carbon radical **22**, which is stabilized by the adjacent oxygen atom in the THF ring. The carbon radical reacts with iodine radical to give iodocyclic ether **23**, which undergoes oxygen atom-assisted removal of iodine to generate oxacarbenium ion **24**. The oxacarbenium ion is then quenched by the neighboring primary amine to produce 5/6 oxazaspiroketal **19** stereoselectively.

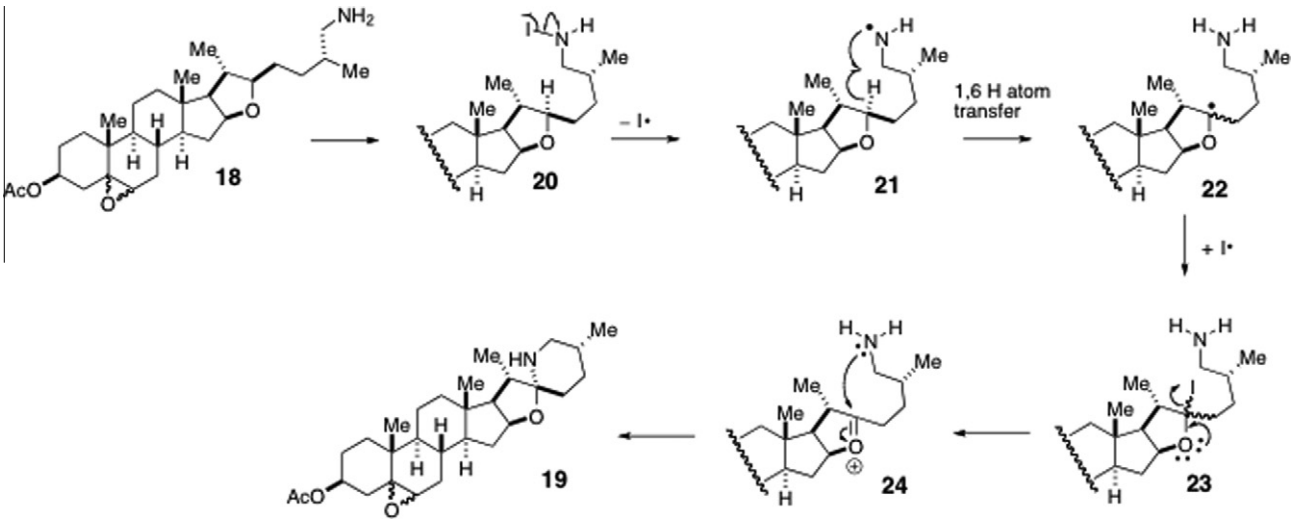
In summary, we have developed an efficient synthetic route for solasodine acetate **2**, where hypoiodite-mediated cyclization of a



Scheme 2. Initial attempts for solasodine acetate synthesis.



Scheme 3. Synthesis of solasodine acetate **2**.



Scheme 4. A potential reaction mechanism for oxazaspiroketal formation.

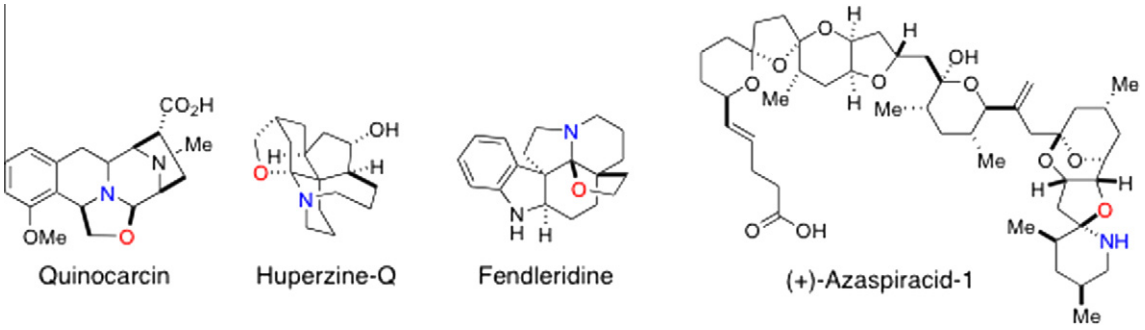


Fig. 4. oxazaketal or oxazaspiroketal-containing natural products.

primary amine was used as a key transformation. Solasodine acetate **2** has been prepared in 8 steps with an overall yield of 23%. Oxazaketal or oxazaspiroketal moieties, found in many biologically active natural products, such as quinocarcin, huperizine-Q, fendleridine, and azaspiracid (Fig. 4) have been implicated to be important for the bioactivities of these natural products. We are currently applying the hypoiodite-mediated aminyl radical cyclization to synthesize oxazaspiroketal-containing natural products, and the results will be reported elsewhere in due course.

Acknowledgements

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