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A facile and efficient method for the synthesis of solasodine from diosgenin

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ABSTRACT

A facile and high-yielding route for the synthesis of solasodine from diosgenin is devised. Ring opening of steroidal spiroketal under mild conditions with trifluoroacetyl trifluoromethanesulfonate (TFAT) provides an applicable protocol to prepare key intermediates **4** or 3-Ac-solasodine, which can potentially serve as a platform for the selective functionalization of C(3)–OH and N–H of solasodine. The simple operations without purification by column chromatography make this method suitable to scale up.

1. Introduction

The steroidal alkaloid solasodine glycosides derived from a plant Devil's Apple, such as solasonine and solamargine, show significant anticancer activities in cell cultures of animals and in humans.[1] In Australia, the cream Curaderm^{BEC5}, which containing solasonine and solamargine, have been approved for skin cancers.[2] In China, *Solamaceous* herbs rich in solasodine glycosides, are widely used as traditional antitumor drugs. Moreover, Liu reported that the hydrochlorate solasodine has been in preclinical trial as an anticancer agent.[3] Roelink reported that solasodine showed moderate inhibition activity against sonic hedgehog (Shh) pathway, just 15–20-fold less active than another steroidal alkaloid cyclopamine, which is currently in clinical studies as an anticancer agent.[4,5]

However, solasodine occurs extremely rarely in plant (0.03%).[6] Therefore, it is important to develop an effective method for the synthesis of solasodine and its analogues. In 1953, Uhle[7] first reported the conversion of diosgenin to solasodine in 5% total yield. Recently, Sun and Tian groups, respectively, gave a method for the synthesis of solasodine from diosgenin (five steps, 25% overall yield; nine steps, 21% overall yield, respectively).[8,9] However, these methods so suffer from one or more drawbacks, such as harsh reaction conditions, cumbersome workup procedures, and long reaction time. Furthermore, these methods are not economical to prepare abundant solasodine derivatives due to low yields. Their major strategy from diosgenin to solasodine is as follows: (1) opening of the steroidal spiroketal ring; (2) activation of C(26)–OH; (3) introduction of *N*-source and ring-closure. By Uhle and Sun, acetic anhydride was used to acetylize the spiroketal ring.[7,9] The reaction conditions were violent, which caused many side reactions. Furthermore, the regioselectivity between C(3)–OH and C(26)–OH was low when the hydroxyl of C(26) was activated. These problems made the intermediates difficult to purification, which reduced the overall yield. Keeping these in mind, we try to develop a more efficient method to prepare solasodine for our medicinal chemical research. If we exploit some acid anhydride, which can open the spiroketal ring and activate the C(26)–OH in one step, it would be facile to avoid the problems mentioned above. Fuchs et al. have screened a series of reagents (e.g., Tf_2O, TMSOTf, $(CF_3CO)_2O$, *p*-$NO_2C_6H_4OTf$, etc.), and found that the spiroketal could be opened in the presence of TFAT (trifluoroacetyl trifluoromethanesulfonate).[10,11] As we know, the resulting trifluoroacetate can be replaced by azide directly.[12] Herein, we wish to report a convenient and efficient method for synthesis of solasodine from diosgenin.

2. Results and discussion

The strategy for synthesis of steroidal alkaloids solasodine from diosgenin is shown in Scheme 1. Firstly, in order to achieve selective derivatization between C(3)–OH and C(26)–OH, the hydroxyl of C(3) was protected by ester. Treatment of diosgenin **1** with acetic anhydride in pyridine, afforded a quantitative yield of diosgenin acetate. Secondly, to transform spirostan to pseudospirostan, ring opening of the steroidal spiroketal was studied. As we know, Gould reported that the conversion could be performed at 200 °C in the

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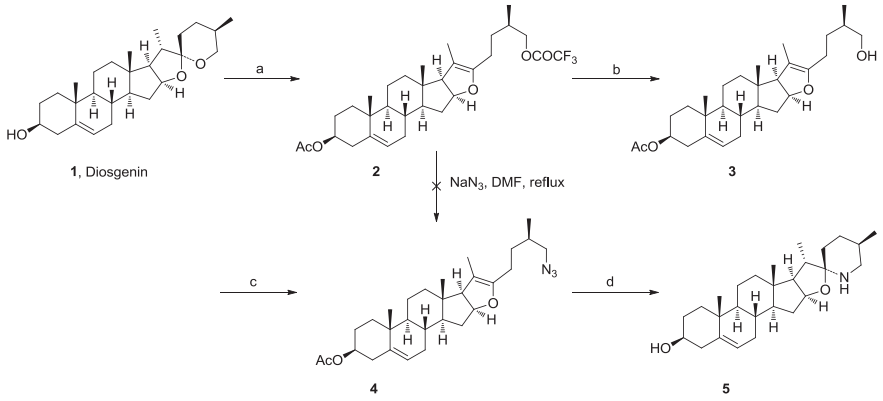
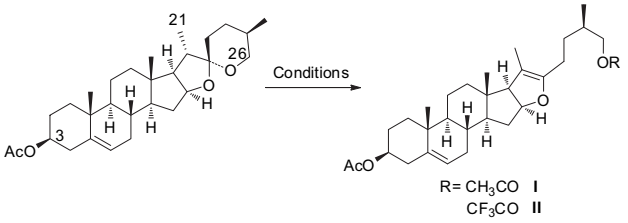


Scheme 1. Synthesis of solasodine from diosgenin: a. (i) Py, Ac_2O; (ii) TFAT (1.5 equiv), DCM, −40 °C, 90% (two steps); b. $NaHCO_3$, MeOH/H_2O, 98%; c. (i) Py, TsCl, DCM, rt; (ii) NaN_3, DMF, 60 °C, 90% (two steps); d. (i) NaOH, MeOH/H_2O; (ii) NaI, CH_3CN, TMSCl, 72% (two steps).

presence of Lewis acids, such as acetyl chloride and aluminum chloride.[13] However, the high reaction temperature led to further acetylation of the resulting enol ether. Moreover, the side reactions were difficult to be controlled, and the byproducts were troublesome to be removed. Meanwhile, Duben and Wall developed improved protocol that could be performed at low temperature in the presence of pyridinium hydrochloride or ammonium chloride/pyridine.[14] Although the yield was increased, the products still needed to be chromatographed. Hence, these methods were not suitable to scale up. In 2003, Fuchs reported that TFAT could be used to open the steroidal spiroketal under mild reaction conditions.[10] In our group, investigation was carried out to confirm whether the pseudodiosgenin trifluoroacetyl ester **2** was easy to obtain in quantitative yield by reaction with TFAT. As shown in Table 1, the yield of pseudospirostan from spirostan developed by Fuchs (entry 4) was much higher than that through refluxing with acetic anhydride and Lewis acids (entries 1–3). In addition, the resulting byproducts acids (TFA/TfOH) were easily removed by washing. The yield of **2** from **1** was 90%.

Table 1
Investigation on ring opening of the steroidal spiroketal



Entry	Conditions	Time (h)	Yield[a]
1	Ac_2O, AcCl (1 equiv), 200 °C (sealed tube)	12	**I**, 43%
2	Ac_2O, Pyridine/HCl (1 equiv), 140 °C	8	**I**, 67%
3	Ac_2O, Pyridine/NH_4Cl (1 equiv), 140 °C	8	**I**, 73%
4	TFAT (1.5 equiv), CH_2Cl_2, −40 °C	2	**II**, 96%

[a] Isolated yields.

Unfortunately, we only obtained the hydrolysis product 3-acetyl pseudodiosgenin **3**, when trying to turn trifluoroacetyl ester **2** directly into azide by treatment with sodium azide in anhydrous DMF under reflux as mentioned by Zwierzak.[12] The displacement reaction did not work yet under improved reaction conditions. Therefore, we decided to introduce azide through activating C(26)–OH by *p*-toluenesulfonyl. In view of activation of C(26)–OH by *p*-TsCl in need of acid-binding agent pyridine, we utilized pyridine as base to hydrolyze trifluoroacetyl ester **2**, but observed that the ester was partially converted to **3** at 100 °C overnight. Finally, $NaHCO_3$ was chose to hydrolyze **2** to provide **3** in 98% yield. Next 26-*p*-toluenesulfonate was prepared in good yield through treatment with 1.2 equiv *p*-TsCl for in pyridine 5 h, and then generated into azido derivative **4** by reaction with NaN_3 in DMF at 60 °C for 3 h. The reaction temperature should not be too high, otherwise byproducts were produced. The yield of **4** from **3** was 90%.

After hydrolysis of ester group of **4** by 5 N NaOH, the azide was reduced to amine by the system of chlorotrimethylsilane (TMSCl)/NaI in MeCN at rt. Under the acidic conditions, the resulting primary amine was prone to cyclize automatically in situ to give a crude product. The crude product was recrystallized in ethanol to give a white solid in 72% yield. By comparison of the various spectroscopic data of the authentic sample, the white solid was deduced to be solasodine ((3β, 22α, 25*R*)-spirosol-5-en-3-ol). The diastereoselectivity of the ring-closure to solasodine could be rationalized by the model proposed by Saito et al. in the similar ring-closure reaction from pseudosarsasapogenin to sarsasapogenin.[15]

3. Conclusion

We have reported a method for the synthesis of solasodine from diosgenin in seven steps with 57% overall yield, much higher than that reported before. Our strategy avoids using rigorous spiroketal ring-opening reaction conditions, which usually result in byproducts. In addition, the simple operations without purification by column chromatography make this method suitable to scale up. Furthermore, it is easy to selectively derive between C(3)–OH and N–H of solasodine with the azide **4** as a key intermediate. The C(3)–OH of **4** could be selectively modificated to other functional groups, and then conveniently converted to solasodine derivates. This protocol can be applicable to SAR study of anticancer on steroidal alkaloids solasodine analogues.

4. Experimental section

4.1. General

Reagents and all solvents were analytically pure grade and were used without further purification. ^1H NMR, ^{13}C NMR spectra were recorded at 400 MHz for ^1H, at 100 MHz for ^{13}C with Bruker AMX-400 instruments in deuterated solutions. HRMS (ESI) was carried out using Micromass Q-Tof Global mass spectrometers. MS (ESI) were recorded on a Bruker Esquire 3000 Plus spectrometer. Optical rotations were measured on a Perkin–Elmer 341 polarimeter.

4.2. General experimental procedure

*4.2.1. 3-Ac-26-TFA-pseudodiosgenin (**2**).* The mixture of diosgenin **1** (5.00 g, 12.08 mmol), acetic anhydride (6 mL), and pyridine (10 mL) was stirred at rt for 6 h, and then was poured into water. The resulting white precipitate was filtered, and washed with water for three times. The crude product 3-Ac-diosgenin (5.30 g) was used in next step without further purification.

To a solution of 3-Ac-diosgenin (4.50 g, 9.87 mmol) in dried CH_2Cl_2 was added TFAT (3.65 g, 1.5 equiv) at −40 °C. The mixture was stirred for 3 h, and then quenched with water. Dilution with CH_2Cl_2, the organic layer was washed with water and brine, dried over sodium sulfate, and concentrated to yield white solid **2** (4.98 g, 90% two steps). The crude product **2** was used in next step without further purification; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.37 (d, J=4.8 Hz, 1H), 4.69–4.75 (m, 1H), 4.58–4.62 (m, 1H), 4.22 (dd, J=10.8, 5.8 Hz, 1H), 4.15 (dd, J=10.8, 6.6 Hz, 1H), 2.45 (d, J=10.8 Hz, 1H), 2.22 (d, J=10.2 Hz, 2H), 2.05–2.18 (m, 4H), 2.00 (s, 3H), 1.58 (s, 3H), 1.04 (s, 3H), 0.98 (d, J=6.6 Hz, 3H), 0.68 (s, 3H); MS (ESI) m/z 575.5 $[M+Na]^+$; HRMS (ESI) m/z 575.2968 $[M+Na]^+$ (calcd for $C_{26}H_{30}NaO_7$, 575.2960).

*4.2.2. 3-Ac-pseudodiosgenin (**3**).* The solid 3-Ac-26-TFA-pseudodiosgenin **2** (2.00 g, 3.6 mmol) was dissolved in methanol (10 mL), and then saturated aqueous $NaHCO_3$ (20 mL) was added. After stirring for 3 h, methanol was evaporated. The resulting precipitate was filtered, washed with water, and dried in oven. The crude product **3** (1.61 g, 98%) was used in next step without further purification; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.37 (d, J=4.8 Hz, 1H), 4.64–4.78 (m, 1H), 4.58–4.62 (m, 1H), 3.40–3.54 (m, 1H), 2.45 (d, J=10.8 Hz, 1H), 2.28 (d, J=12.8 Hz, 2H), 2.03–2.20 (m, 4H), 2.00 (s, 3H), 1.55 (s, 3H), 1.03 (s, 3H), 0.94 (d, J=6.6 Hz, 3H), 0.76 (s, 3H); MS (ESI) m/z 479.5 $[M+Na]^+$; HRMS (ESI) m/z 479.3140 $[M+Na]^+$ (calcd for $C_{26}H_{30}NaO_7$, 479.3137).

*4.2.3. 3-Ac-26-azide-pseudodiosgenin (**4**).* To a solution of 3-acetyl pseudodiosgenin **3** (1.20 g, 2.6 mmol) in pyridine (5 mL) and CH_2Cl_2 (25 mL) was added TsCl (0.60 g, 2 equiv) at −30 °C in two portions. After conversion was completed indicated by TLC, the mixture was washed with 2 N HCl and brine. The organic layer was dried by sodium sulfate and concentrated to afford yellow solid 3-Ac-26-Ts-pseudodiosgenin (1.50 g, 95%). The crude product was used in next step without further purification.

A mixture of 3-Ac-26-Ts-pseudodiosgenin (1.30 g, 2.1 mmol) and NaN_3 (0.40 g, 3 equiv) in DMF was heated to 60 °C for 3 h. Then ice-water was added to the mixture at rt. After 15 min, the resulting precipitate was filtered, washed with water, and dried. The crude product **4** (0.94 g, 93%) was used in next step without further purification; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.37 (d, J=4.8 Hz, 1H), 4.78–4.73 (m, 1H), 4.58–4.72 (m, 1H), 3.22 (dd, J=12.0, 5.7 Hz, 1H), 3.10 (dd, J=12.0, 4.8 Hz, 1H), 2.47 (d, J=10.8 Hz, 1H), 2.30 (d, J=10.8 Hz, 2H), 2.05–2.18 (m, 4H), 2.02 (s, 3H), 1.58 (s, 3H), 1.04 (s, 3H), 0.96 (d, J=6.6 Hz, 3H), 0.68 (s, 3H); MS (ESI) m/z 481.7 $[M+Na]^+$; HRMS (ESI) m/z 481.3328 $[M+Na]^+$ (calcd for $C_{26}H_{30}NaO_7$, 481.3304).

*4.2.4. Solasodine (**5**).* The solid 3-Ac-26-azide-pseudodiosgenin **4** (0.90 g, 1.87 mmol) was dissolved in methanol (10 mL), and then 5 N NaOH (4 mL) was added. After stirring for 1 h, methanol was evaporated. The resulting precipitate was filtered, washed with water, and dried. The crude product 26-azide-pseudodiosgenin (0.80 g, 98%) was used in next step without further purification.

To a solution of 26-azide-pseudodiosgenin (0.70 g, 1.60 mmol) in CH_3CN, NaI (0.50 g, 2 equiv) was added. After 30 min, a solution of Me_3SiCl (0.45 mL, 2 equiv) in CH_3CN was added dropwise, and the resulting yellow mixture was stirred at rt for 2 h. Then the reaction was quenched with 10% aqueous $Na_2S_2O_3$, and then 5 N NaOH was added to adjust the pH to 9. After removal of CH_3CN, the mixture was extracted with $CHCl_3$. The organic layer was washed with water and brine, dried over sodium sulfate, and concentrated to give yellow solid. The solid was recrystallized in ethanol to give solasodine **5** (0.45 g, 72%); mp 198–200 °C; $[\alpha]_D^{20}$ −98 (c 0.35, methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.34 (d, J=4.8 Hz, 1H), 4.33–4.30 (m, 1H), 3.55–3.47 (m, 1H), 2.18–2.57 (m, 1H), 2.00–2.18 (m, 4H), 1.58 (s, 3H), 1.02 (s, 3H), 0.98 (d, J=7.2 Hz, 3H), 0.84 (d, J=6.0 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.77, 121.38, 98.24, 78.80, 71.68, 62.67, 56.46, 50.01, 47.57, 42.22, 41.20, 40.48, 39.89, 37.18, 36.60, 33.97, 32.12, 31.57, 31.36, 31.27, 30.19, 20.85, 19.39, 19.28, 16.40, 15.26; MS (ESI) m/z 414.5 $[M+H]^+$; HRMS (ESI) m/z 414.3375 $[M+H]^+$ (calcd for $C_{26}H_{31}O_7$, 414.3372).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.06.058.

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