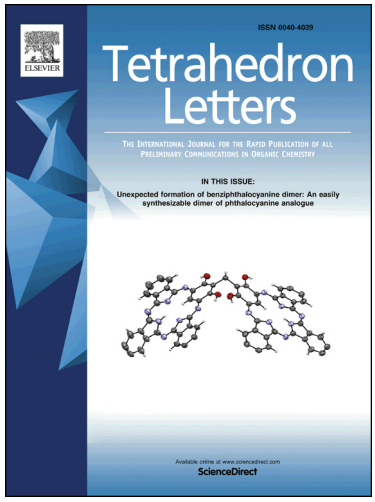

Enantiospecific total synthesis of (-)-Crotanecine

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Graphical Abstract

Enantiospecific total synthesis of (-)-Crotanecine

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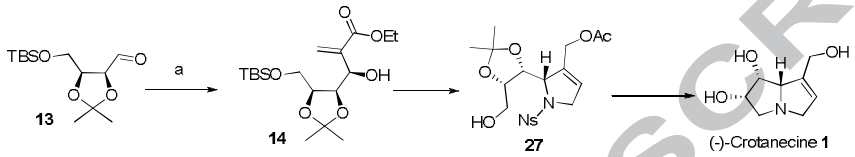

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Abstract: Crotanecine is the necine base component of a number of pyrrolizidine alkaloids. This necine subunit is an amino triol bearing a primary allylic alcohol characterized by an all-cis relationship of its stereocenters. The synthesis of crotanecine has been accomplished using simple yet versatile ring construction approach using ribose as chiral starting point.

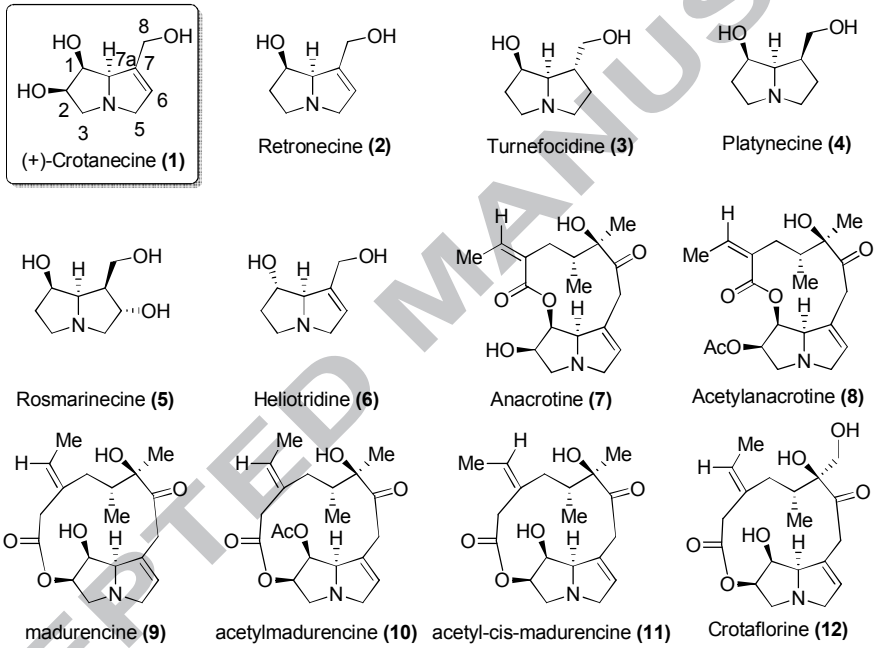

Figure-1: Structures of pyrrolizidine alkaloids and few of its derivatives

Introduction and Background:

(+)-Crotanecine **1** is found conjugated to a variety of necic acids in many pyrrolizidine alkaloids found in plants of the *Crotalaria* species. Historically pyrrolizidine alkaloids referred to as necine bases, share a common azabicyclo[3.3.0]octane core but differ based on the oxygenation pattern and whether or not saturated. Anacrotine **7** isolated from the seeds of *C. anagyroids* obtained from Sri Lanka[1,2] and from *C. incana* shrub grown in South Africa[3] afforded senecic acid and a new amino triol named crotanecine. Upon re-examination of leaves and twigs gathered

Key words: Anacrotine, crotanecine, Baylis-Hillman Reaction, Ring closing metathesis, Total synthesis.

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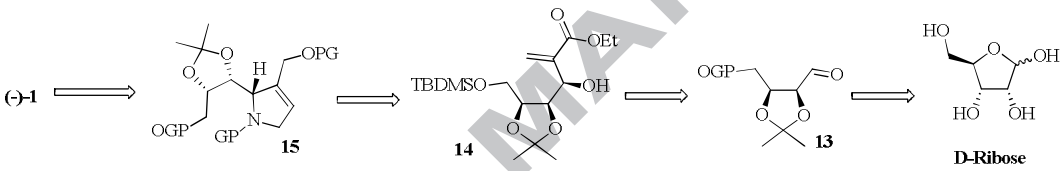
from *C. agatiflora* grown in Australia six new alkaloids were isolated, all containing (+)-crotanecine as the base (Figure 1).[4] Crotanecine bears a double bond at the C(6)-C(7) position; therefore, all the alkaloids (7-12) that contain crotanecine should be hepatotoxic, the most common biological effect of pyrrolizidine alkaloids.

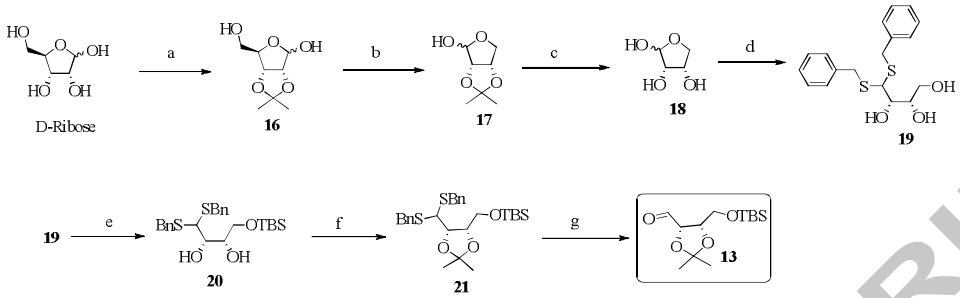
As part of our research objectives directed at development of a general synthetic methodology for functionalised indolizidine and pyrrolizidine alkaloids[5], we have become interested in developing approach for enantioselective synthesis of Crotanecine. There have been three previous synthesis[6a-c] of crotanecine **1** along with one formal synthesis[6d]. As outlined in Scheme 1 retrosynthetic analysis indicated that intermediate **13** can serve as good chiral synthon[7] as it can further manipulated using aldehyde functional group to extend the side chain to build upon. We have contemplated that Baylis-Hillman as a stereochemical determining reaction could serve the purpose to introduce the desired side chain to give **14**. Intermediate **15** can be derived from **14** *via* converting alcohol to amine followed by building the five membered ring using ring closing metathesis. After obtaining **15**, enforced cyclisation would produce crotanecine carbon framework.



Scheme 1. Retrosynthetic plan for the Crotanecine

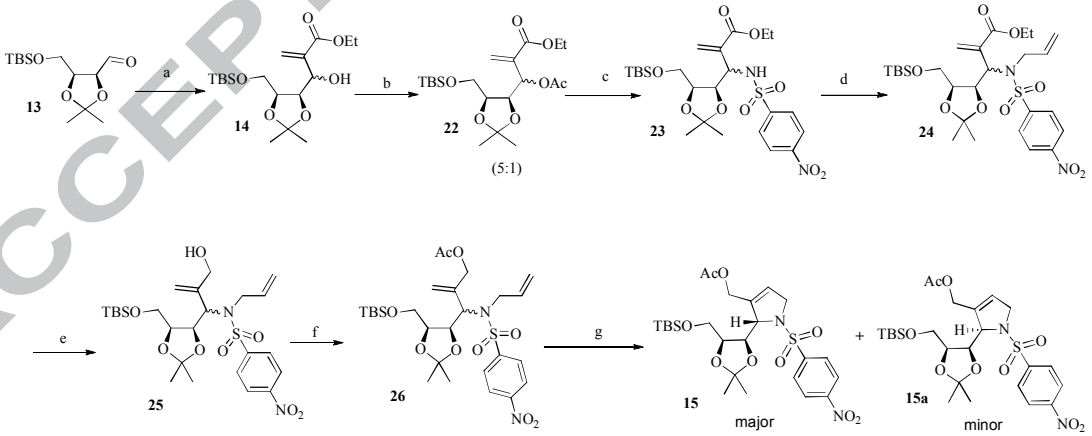
Based on retrosynthetic analysis, L-ribose was recognised as suitable chiral starting pool; however it was found to be very expensive. Hence to help our exploration efforts we have chosen the cheaper and readily available alternative chiral pool D-ribose as starting material, which eventually would lead to optical antipode of natural Crotanecine **1.** The synthesis was started with preparation of desired aldehyde **13** from known synthetic route[8,9]. However, for the practical purpose we have made several modifications in the experimental condition in order to make this route more viable and scalable. The synthesis of key intermediate **14** was started from the commercially available inexpensive D-ribose. The treatment[10] of D-ribose with catalytic amount of concentrated sulfuric acid and acetone resulted in acetonide **16** in quantitative yields (Scheme 2). Sequential reduction of **16** with $NaBH_4$ followed by oxidative cleavage of the diol with $NaIO_4$ provided hemiacetal **17**. The acetonide group was deprotected[8,9] by using 60% aqueous acetic acid to yield D-erythrose **18**. As the synthesis of diethyldithioacetate could not be conveniently scaled up due to its water solubility, we have prepared the more lipophilic dibenzyldithioacetal. Acid catalysed dithioacetalisation of the hemiacetal **18** with benzyl mercaptane, followed by chromatography on a short silica gel column gave **19**. The primary hydroxyl group in **19** was then selectively protected as silyl ether using TBDMSCl providing **20**, which on isopropylidenation using 2,2-dimethoxypropane, camphor sulfonic acid afforded **21** in good

yield. Dethioacetalisation of **21** in aqueous acetonitrile in the presence of mercury (II) chloride, gave crude aldehyde **13**. It was purified over short silica plug to obtain pure aldehyde **13** in 55% yield.



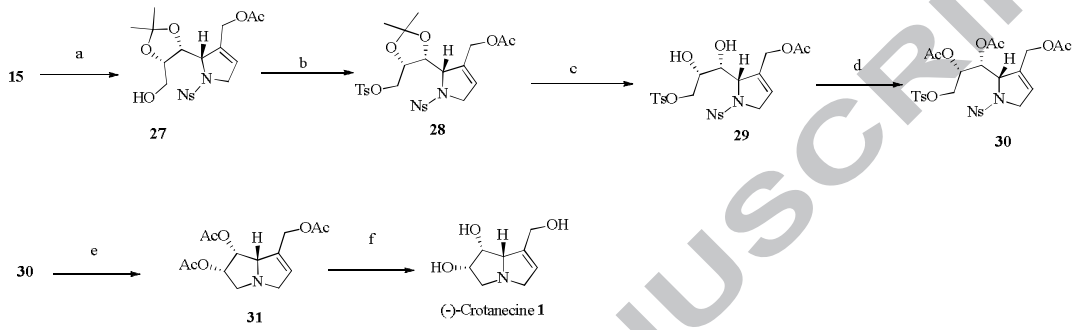
Scheme 2: *Reagents and conditions:*(a) Acetone, conc. H_2SO_4, 2h, 87%; (b) i) $NaBH_4$, MeOH, 0°C to rt, 1.5h; ii) $NaIO_4$, t-BuOH, H_2O, rt, 16h, 71%; (c) 60% aq. AcOH, H_2O, 90°C,6h; (d) Con.HCl, BnSH, -60°C to rt, 3h, 52%; (e) TBDMSCl, imidazole, DMF, RT, 3h, 58%; (f) 2,2-DMP, CSA, acetone, rt, 5h, 77%; (g) $HgCl_2$, $CaCO_3$, MeCN, H_2O, RT, 2h, 55%.

Accordingly, the Baylis-Hillman reaction[11] of **13** with ethyl acrylate in the presence of DABCO gave **14** (Scheme 3) as a mixture of two diastereomers which were acetylated to obtain inseparable diasteromeric mixture (5:1) of acetate **22**. Hence this mixture was preserved as such and considered for next reactions until a practical separation is achievable. Treatment of **22** with 4-nitrobenzesulfonamide and DABCO underwent successive S_N2'-S_N2' displacement reaction stereo specifically to give the sulfonamide **23** whose treatment with allybromide yielded inseparable diastereomeric mixture of diene **24** in 96% yield. Reduction of ester group in a mixture of **24** with diisobutylaluminium hydride at -78°C gave the primary alcohol **25** in 54% yield which was fully characterised as its acetate **26**.



Scheme 3. *Reagents and conditions:*(a) Ethyl acrylate, DABCO, DMSO, rt, 64%; (b) Ac_2O, NEt_3, DMAP,DCM, 0°C to rt, 4h, 92%; (c) 4-nitrobenzenesulfonamide, DABCO, DCM, 0°C to RT, 4h, 67%; (d) allyl bromide, K_2CO_3, DMF, 0°C tort, 4h, 96%; (e) DIBAL-H, DCM, -78°C, 15 min, 54%; (f) Ac_2O, NEt_3, DMAP, DCM, 0°C to rt, 4h, 80%; (g) Grubb's-II (5 mol%), toluene, 65°C,2h.

Initially, the monoacetate **26** was treated[12] with catalytic amount of Grubbs first generation ruthenium complex, but no progress of the reaction was observed even under refluxing toluene. On the other hand treatment of monoacetate **26** with more reactive second generation Grubb's catalyst (5 mol%) in toluene at 65°C for 2h resulted cyclic allylic acetate **15** and **15a** as a well separable mixture of diastereomers. The separation of these diastereomers were achieved by normal silica chromatography and major isomer was considered as required diastereomer **15** and taken forward for proceeding steps.



Scheme 4.*Reagents and conditions:*(a) TBAF in THF, -40°C to -10°C, THF, 1h, 80%; (b) *p*-TsCl, NEt_3, DMAP, DCM, 0°C to rt, 4h, 78%; (c) 3N aqHCl, THF, 70°C,5h; (d) Ac_2O, NEt_3, DMAP, DCM, 0°C to rt, 4h, 75%; (e) Cs_2CO_3, thiophenol, MeCN, rt, 4h, 55%; (f) NaOMe, MeOH, THF (1:3), rt, 4h, 64%.

Removal of silyl protecting group in **15** with 1M tetra-n-butylammonium fluoride solution in THF, followed by tosylation of the resulting primary alcohol in **27** furnished the tosylate **28** over two steps. For the removal of nosyl group in **28**, reaction was attempted using thiophenol and cesium carbonate in acetonitrile, which did not provide any cyclisation product, possibly due to ring strain imposed by the acetonide group. Hence, acetonide group in **28** was removed[13] by acid catalysed hydrolysis using 3N aq. HCl in THF to obtain **29**. It was then protected as acetate using acetic anhydride, triethylamine and DMAP at 0 °C at room temperature to furnish triacetate **30**. (Scheme 4)

Removal of nosyl group was achieved by treatment of **30** with thiophenol, cesium carbonate in acetonitrile, which resulted in concomitant base mediated cyclisation to afford bicyclic product **31** in 55% yield. The bicyclic triacetate **31** was fully characterized to confirm the structure. The configuration of new stereogenic centre at C(7a) in **31** was established on the basis of extensive nOe experiments (see the supporting information) and the results are displayed in (Fig. 2). Thus definite nOe interactions between C(1)H and C(2)H indicated these hydrogens are in same plane as expected based on original chiral pool stereochemistry. Further extension of nOe studies revealed strong nOe interactions between C(7a)H and C(1)H which confirmed *S* configuration at C7a centre. These studies have confirmed the all-cis relationship between C2, C1 and C7a as needed for crotanecine framework. Finally deprotection of cyclic triacetate **31** was carried out using catalytic amount of sodium methoxide in methanol/THF (1:3) at room temperature over 4 hours furnished an 64% yield of crotanecine **1**, in optical antipode form. The purification of crotanecine posed

several difficulties and it was observed that side products generated in the solvolysis promoted the decomposition of crotanecine, thereby complicating the purification. For analytical purpose flash chromatography was carried out over silica gel followed by recrystallization from ethanol/ether furnished an analytical pure sample of crotanecine (-)-1, an optical antipode of natural (+)-**1**.{$[\alpha]_D^{25}$ -65.9 (*c* 0.5, EtOH), mp 195-205 °C; Reported[6c] $[\alpha]_D^{21}$ **:** +38.7 (*c* 0.52, EtOH), mp 192-195). Based on ^{1}H NMR analytical data, the changes in chemical shift values for C(1)H, C(2)H and C(8)H are within the expected ranges. Contrary to the expectations, protons on C(3), C(5) and C(7a) have displayed the most dramatic chemical shift variances in ^{1}H NMR and minor variances in ^{13}C NMR spectra and it was understood that these proton chemical shifts are very sensitive[6c,e] to traces of moisture and method of purification[14].

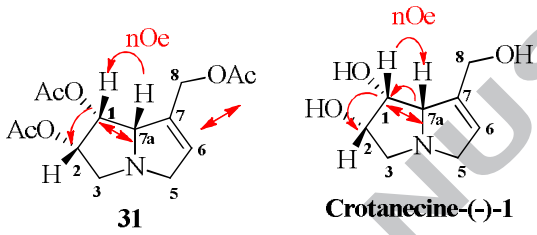


Figure 2. Observed nOe interactions in compounds **31** and **Crotanecine (-)-1**

To further confirm the carbon framework and relative stereochemistry of (-)-**1**, additional nOe studies (see the supporting information) have been considered. HMBC studies on C(8)H presented connectivity to C(8), C(6) and C(7a). In other hand C(6)H pointed strong connectivity to C(7), C(7a), C(5), C(8). The nOe studies have revealed all-cis relationship between C(7a)H, C(1)H and C(2)H indicating *S*,*R*,*S* configuration respectively. Thus 2D NMR experiments provided unambiguous structural confirmation of carbon framework and stereochemistry of synthetic crotanecine.

In summary, a short and enantiospecific synthesis of Crotanecine (-)-**1** has been achieved by deploying Baylis-Hillman reaction and ring closing metathesis as key steps. Further synthetic applications of the strategy delineated above to the indoziline and pyrrolizidine alkaloids will be reported in due course.

Acknowledgement:

Authors are grateful to the management GVK Biosciences Private Ltd., for the financial support and encouragement. We thank Dr. Sudhir Kumar Singh for his invaluable support and motivation.

Supplementary Material:

Analytical data is provided for all key intermediates along with ^{1}H, ^{13}C, NOE, HMBC and HSQC spectra for compound **31** and crotanecine **1**.

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14. For the sample obtained after silica chromatography, H-C7a signal shifted down field by 0.40 ppm with comparison to crude sample ^{1}H NMR value. When this purified sample is stirred with saturated methanolic ammonia for about 3-4h, for the resulting material the same signal is again shifted up field by about 0.20 ppm and similarly H-C3 & H-C5 have shown minor changes. To substantiate further; the pure sample was further treated with dry HCl in dioxane to form its HCl salt. The ^{1}H NMR spectrum of the HCl salt clearly indicated major change in the values of the CH and CH_2 attached to nitrogen (peaks at δ ppm 2.80, 3.11, 4.38 were shifted to δ ppm 3.95, 4.30 and 5.20 respectively, see the supporting information). We are believing these chemical shift variances are due to several factors such as presence of traces of salts or hydration or protonation on ring nitrogen which might be causing the shift variances for CH and CH_2 groups attached to nitrogen.
15. **Spectral data for selected compounds**:

Compound 31: ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 5.78 (s, 1H, H-C6), 5.10 (d, *J* = 4.4 Hz, 1H, H-C2), 5.03 (d, *J* = 2.8 Hz, 1H, H-C1), 4.51 (s, 2H, H-C8), 4.25 (br s, 1H, H-C7a), 3.75 (br d, *J* = 15.2 Hz, 1H, H-C5), 3.29-3.31 (m, 1H, H-C5), 3.04 (d, *J* = 12.0 Hz, 1H, H-C3), 2.84 (dd, *J* = 12.0, 4.4 Hz, 1H, H-C3), 1.99 (s, 3H), 1.96 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 170.0, 169.5, 169.1, 132.7 (C-7), 128.0 (C-6), 78.5 (C-2), 74.3 (C-1), 73.4 (C-7a), 62.4 (C-5), 60.3 (C-8), 58.0 (C-3), 20.6.

Crotanecine-(-)-1: White solid, mp 195-205 °C; ^{1}H NMR (CD_3OD, 500 MHz): δ = 5.66 (s, 1H, H-C6), 4.38 (br s, 1H, H-C7a), 4.18-4.21 (m, 3H, H-C2 & 8), 4.03 (dd, *J* = 4.0, 1.0 Hz, 1H, H-C1), 3.81-3.85 (dt, *J* = 15.5, 2.0 Hz, 1H, H-C5), 3.31-3.36 (m, 1H, H-C5), 3.11 (d, *J* = 11.0 Hz, 1H, H-C3), 2.80-2.83 (dd, *J* = 11.0, 4.0 Hz,1H, H-C3). ^{13}C NMR (CD_3OD, 125 MHz): δ = 139.8 (C-7), 125.6 (C-6), 79.7 (C-2), 77.0 (C-7a), 76.6 (C-1), 63.5 (C-5), 61.9 (C-4), 59.8 (C-8).

Highlights

1. Abundantly available D-Ribose is used as chiral starting material.
2. A Baylis-Hillman reaction has been used to generate new stereo-genic centre.
3. Ring closing metathesis was deployed for construction of pyrrolidine ring.
4. Base mediated method was used to remove nosyl group with concomitant cyclisation.