A divergent asymmetric approach to aza-spiropyran derivative and (1S,8aR)-1-hydroxyindolizidine

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Abstract

Background: Spirophets and the corresponding aza-spirophets are the structural features found in a number of bioactive natural products, and in compounds possessing photochromic properties for use in the area of photochemical erasable memory, self-development photography, actinometry, displays, filters, lenses of variable optical density, and photomechanical biomaterials etc. And (1R,8aS)-1-hydroxyindolizidine (3) has been postulated to be a biosynthetic precursor of hydroxylated indolizidines such as (+)-lentiginosine 1, (-)-2-epilentiginosine 2 and (-)-swainssonine, which are potentially useful antimetastasis drugs for the treatment of cancer. In continuation of a project aimed at the development of enantiomeric malimide-based synthetic methodology, we now report a divergent, concise and highly diastereoselective approach for the asymmetric syntheses of an aza-spiropyran derivative 7 and (1S,8aR)-1-hydroxyindolizidine (ent-3).

Results: The synthesis of aza-spiropyran 7 started from the Grignard addition of malimide 4. Treatment of the THP-protected 4-hydroxybutyl magnesium bromide with malimide 4 at -20°C afforded N,O-acetal 5a as an epimeric mixture in a combined yield of 89%. Subjection of the diastereomeric mixture of N,O-acetal 5a to acidic conditions for 0.5 h resulted in the formation of the desired functionalized aza-spiropyran 7 as a single diastereomer in quantitative yield. The stereochemistry of the aza-spiropyran 7 was determined by NOESY experiment. For the synthesis of ent-3, aza-spiropyran 7, or more conveniently, N,O-acetal 5a, was converted to lactam 6a under standard reductive dehydroxylation conditions in 78% or 77% yield. Reduction of lactam 6a with borane-dimethylsulfide provided pyrrolidine 8 in 95% yield. Compound 8 was then converted to 1-hydroxyindolizidine ent-3 via a four-step procedure, namely, N-debenzylation/O-mesylation/Boc-cleavage/cyclization, and O-debenzylation. Alternatively, amino alcohol 8 was mesylated and the resultant mesylate 12 was subjected to hydrogenolytic conditions, which gave (1S,8aR)-1-hydroxyindolizidine (ent-3) in 60% overall yield from 8.

Conclusion: By the reaction of functionalized Grignard reagent with protected (S)-malimide, either aza-spiropyran or (1S,8aR)-1-hydroxyindolizidine skeleton could be constructed in a concise and selective manner. The results presented herein constitute an important extension of our malimide-based synthetic methodology.
Background
Spiroketalts of general structure A (Scheme 1) constitute key structural features of a number of bioactive natural products isolated from insects, microbes, fungi, plants or marine organisms.[1-3] The corresponding aza-spiroketal (cf: general structure B) containing natural products, while less common, are also found in plants, shellfish and microbes.[4,5] For example, pandamari lactone-1 and pandamarine were isolated from the leaves of Pandanus amaryllifolius[6] solasodine and its derivatives were isolated from Solanum umbelliferum, which exhibited significant activity toward DNA repair-deficient yeast mutants.[7] Azaspiracids are marine phycotoxins isolated from cultivated mussels in Killary harbor, Ireland.[8] and chlorofusin A is a novel fungal metabolite showing the potential as a lead in cancer therapy.[9] In addition, azaspiropyran C, being able to equilibrate with the corresponding non-spiro analogue D, is a well known class of compounds possessing photochromic properties for use in the area of photochemical erasable memory,[10] and also found applications as self-development photography, actinometry, displays, filters, lenses of variable optical density,[11] and photomechanical biomaterials etc.[12]

On the other hand, hydroxylated indolizidines [13-20] such as castanospermine, (-)-swainsonine, (+)-lentiginosine [21-23] (1) and (-)-2-epilentiginosine [21-26] (2) constitute a class of azasugars showing potent and selective glycosidase inhibitory activities. [13-20] (1R,8aS)-1-Hydroxyindolizidine 3 has been postulated as a biosynthetic precursor [21-26] of (+)-lentiginosine (1), (-)-2-epilentiginosine (2) and (-)-swainsonine, a potentially useful antimetastasis drug for the treatment of cancer.[15] In addition, these molecules serve as platforms for testing synthetic strategies, and several asymmetric syntheses of both enantiomers of 1-hydroxyindolizidine (3) have been reported. [27-34] In continuation of our efforts in the development of enantiomeric malimide-based synthetic methodologies, [35-38] we now report concise and highly diastereoselective syntheses of an aza-spiropyran derivative 7 and (1S,8aR)-1-hydroxyindolizidine (ent-3).

Results and discussion
Previously, we have shown that the addition of Grignard reagents to N,O-dibenzyl malimide 4 leads to N,O-acetals 5 in high regioselectivity (Scheme 2), and the subsequent reductive dehydroxylation gives 6 in high trans-diastereoselectivity.[35] On the other hand, treatment of N,O-acetals 5 with an acid furnished enamides E, which can be transformed stereoselectively to either hydroxylactams F or G under appropriate conditions. [36-38] It was envisioned that if a C₄-bifunctional Grignard reagent was used, both aza-spiroketal H (such as aza-spiropyran, n = 1, path a) and indolizidine ring systems I (path b) could be obtained.

Scheme 2: Synthetic strategy based on N,O-dibenzy1malimide (4).

The synthesis of aza-spiropyran 7 started from the Grignard addition of malimide 4. Treatment of the THP-protected 4-hydroxybutyl magnesium bromide with malimide 4 at -20°C for 2.5 h afforded N,O-acetal 5a as an epimeric mixture in 7:1 ratio and with a combined yield of 89% (Scheme 3). If the reaction was allowed to stir at room temperature overnight, the diastereomeric ratio was inversed to 1:1.8. Subjection of the diastereomeric mixture of the N,O-acetal 5a to acidic conditions [1sOH (cat.)/CH₂Cl₂, r.t.] for 0.5 h resulted in the formation of the desired functionalized aza-spiropyran derivative 7 as a single diastereomer in quantitative yield. The result means that a tandem dehydration-THP cleavage-intramolecular nucleophilic addition occurred. When the stirring was prolonged to 2 h, about 5% of another epimer (no shown) was also formed according to the ¹H NMR analysis.
Scheme 3: Stereoselectivity synthesis of aza-spiropyran 7.

The stereochemistry of the aza-spiropyran 7 was determined on the basis of the NMR analysis. This was done firstly by a 1H-1H COSY experiment to confirm the proton assignments, and then by NOESY experiment. As shown in Figure 1, the strong NOE correlation of H-9a (δH 3.59) and H-4 (δH 4.22) indicates clearly O4/O5-trans relationship in compound 7.

These findings are surprising comparing with our recent observations. In our previous investigations, it was observed that the treatment of N,O-acetals 5 with an acid leads to the dehydration products E (Scheme 1), and the two diastereomers of 5 shows different reactivities towards the acid-promoted dehydration. [36-38] The trans-diastereomer reacts much more slower than the cis-diastereomer, and some un-reacted trans-epimer was always recovered even starting with a pure cis-diastereomer. In the present study, not only both two diastereomers have been completely converted to the aza-spiropyran 7, what is equally surprising is that no dehydration product was observed under acidic conditions!

For the synthesis of ent-3, aza-spiropyran 7, a cyclic N,O-acetal, was converted to lactam 6a under standard reductive dehydroxylation conditions (Et3SiH, BF3·OEt2, -78°C, 6 h; warm-up, yield: 78%) (Scheme 4). Under the same conditions, N,O-acetal 5a was converted to lactam 6a in 77% yield. It was observed that during the reaction of 5a, 7 was first formed as an intermediate after the addition of Et3SiH and BF3·OEt2, and stirring for 1 hour.

Scheme 4: Stereoselective synthesis of (1S,8aR)-1-hydroxyindolizidine (ent-3).

Reduction of lactam 6a with borane-dimethylsulfide provided pyrrolidine derivative 8 in 95% yield. Compound 8 was then converted to (1S,8aR)-1-hydroxyindolizidine.
(ent-3) [α]D 27 + 50 (c 0.90, EtOH); lit.[29] [α]D +51.0 (c 0.54, EtOH); lit.[32] -49.7 (c 0.95, EtOH) for the anti-pode} via a four-step procedure, namely, one-pot N-debenzylation-N-Boc formation/O-mesylation/Boc-cleavage/cyclization, and O-debenzylation.

In searching for a more concise method, amino alcohol 8 was mesylated (MsCl, NEt3, 0°C) and the resultant labile mesylate 12 was subjected to catalytic hydrogenolysis (H2, 1 atm, 10% Pd/C, r.t.), which gave (1S-mesylate (12) functionalized Grignard reagent with the protected (ent-3) functionalization leading to 2-pyrrolidinones 6, and the acid-promoted dehydration leading to (E)-enamides E (and then F, G), acid treatment of the N,O-acetal 5a could provide, chemoselectively and quantitatively, the aza-spiropyran ring system 7. The results presented herein constitute a valuable extension of our malimides-based synthetic methodology.

Conclusion

In summary, we have demonstrated that by the reaction of functionalized Grignard reagent with the protected (S)-malimide 4, either aza-spiropyran derivative 7 or (1S,8aR)-1-hydroxyindolizidine skeleton (ent-3) can be constructed in a concise and selective manner. It is worthy of mention that in addition to the reductive dehydroxylation leading to 2-pyrrolidinones 6, and the acid-promoted dehydration leading to (E)-enamides E (and then F, G), acid treatment of the N,O-acetal 5a could provide, chemoselectively and quantitatively, the aza-spiropyran ring system 7. The results presented herein constitute a valuable extension of our malimides-based synthetic methodology.

See Additional File 1 for full experimental procedures and characterization data of the synthesized compounds.

Additional material

Additional file 1

Experimental. Experimental procedures for the synthesis of all compounds described, and characterization data for the synthesized compounds.

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