COMMUNICATION

Face selective reduction of the exocyclic double bond in isatin derived spirocyclic lactones†

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We report an unusual face selective reduction of the exocyclic double bond in the α-methylene-γ-butyrolactone motif of spiro-oxindole systems. The spiro-oxindoles were assembled by an indium metal mediated Barbier-type reaction followed by an acid catalyzed lactonization.

The α-methylene-γ-butyrolactone motif is present in a number of biologically active sesquiterpene lactone natural products, many of which possess useful biological properties (Fig. 1 left side).[1] Presence of this lactone moiety with the exocyclic double bond in the natural products is considered to be a major factor in the observed biological activity such as anti-cancer, antiviral, and anti-inflammatory activities.[2] Studies have shown that certain proteins with accessible cysteine functionality tend to bind irreversibly to these natural products.[3] Due to its biological relevance, many methods have been reported for the synthesis of α-methylene-γ-butyrolactones.[4]

The oxindole framework bearing a spirocyclic quaternary stereocenter at the C3 position represents a privileged structure commonly found in clinical pharmaceuticals and natural products (Fig. 1 right side).[5] Oxindole derivatives have been reported to have a range of biological activities such as tyrosine kinase inhibition, cyclin-dependent kinases (CDKs) inhibition, and anti-angiogenic properties.[6]

Based on these observations, we postulated that a novel hybrid pharmacophore compound containing both α-methylene-γ-butyrolactones and oxindole presents an interesting scaffold for biological screens. This hybridization concept of conjugating two privileged scaffolds has been successfully applied towards the identification of novel scaffolds/compounds with anticancer, antimalarial and antimicrobial properties.[7] To build this novel hybrid pharmacophore, we carried out an indium mediated Barbier-type reaction with isatin (**1**) and methyl 2-(bromomethyl)acrylate (**2**).

Previous reports with aldehydes/ketones and methyl 2-(bromomethyl)acrylate (**2**) yielded cyclic products in a single step.[8] However, in our case, reaction of **1a** and methyl 2-(bromomethyl)acrylate (**2**) yielded acyclic and cyclic compounds in a 6 : 1 ratio in 97% yield (Scheme 1).

Nevertheless, the acyclic product **3a(I–II)** when subjected to *p*-toluenesulfonic acid in dichloromethane at room temperature was easily converted to the cyclic product **4a(I–II)** in excellent yield. When a mixture of enantiomers **4a(I–II)** was subjected to hydrogenation, we expected to see two sets of
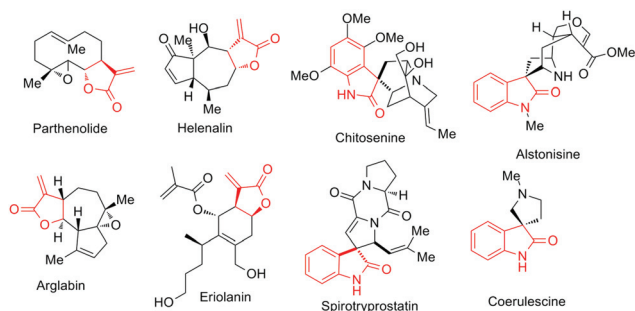

Fig. 1 Biologically relevant α-methylene-γ-butyrolactones and oxindole motifs.

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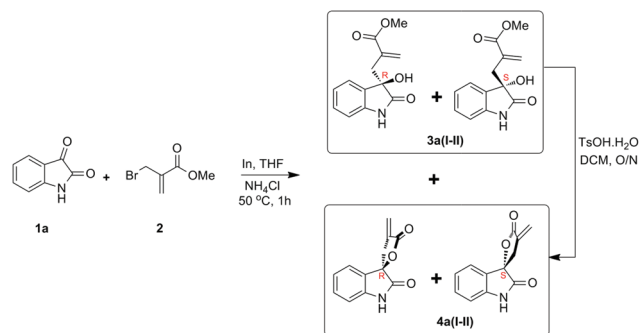
Scheme 1 Indium metal mediated Barbier-type reaction between isatin and methyl 2-(bromomethyl)acrylate.

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diastereomers **6a(I–IV)** (Scheme 2) and thus two sets of doublets for the exocyclic methyl group protons by nuclear magnetic resonance (NMR) spectroscopy. To our surprise, NMR spectra showed only one doublet (~1.5 ppm) that corresponds to the exocyclic methyl group (Fig. 2 top panel). This suggested possible face selective reduction of the double bond.

To test if indeed we observe face selective reduction of **4a(I–II)**, we reversed the sequence of reactions, *i.e.*, reduction followed by cyclization (Scheme 2). Acyclic compound **3a(I–II)** was hydrogenated in the presence of 5% Pd/C in THF, which resulted in two sets of inseparable diastereomers **5a(I–IV)** in 85% yield (two ester methyl peaks were observed at 3.4 to 3.6 ppm by NMR spectroscopy). Treatment of this inseparable reaction mixture with *p*-toluenesulfonic acid in dichloromethane gave two sets of inseparable diastereomers **6a(I–IV)** in 92% yield, which were clearly resolved by NMR spectroscopy (two doublets at 1.4 and 1.5 ppm respectively, Fig. 2 second panel), thus suggesting a face selective reduction in the former case (**4a**).

To establish the stereochemistry of the newly created stereocenter alpha to the carbonyl in the lactone ring of compound **6a(I–IV)** we conducted Nuclear Overhauser Effect (NOE) experiments. Since the lactone and oxindole rings are perpendicular to each other, we expected to observe crosspeaks between the proton at the C4 position of the oxindole and the protons on the methyl group in only one set of **6a(I–IV)** diastereomers.

Unfortunately, NOE experiments with **6a(I–IV)** at different mixing times showed no crosspeaks between the proton at the C4 position of the oxindole and the protons on the methyl group. Alternatively, it is known that 1D NOE difference NMR

experiments allow long distance transfer of magnetization, therefore a 1D NOE difference NMR experiment was
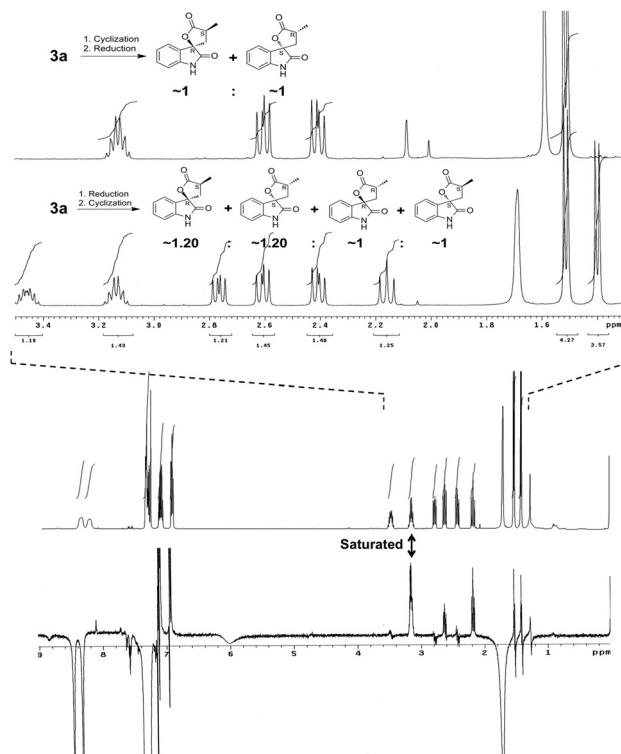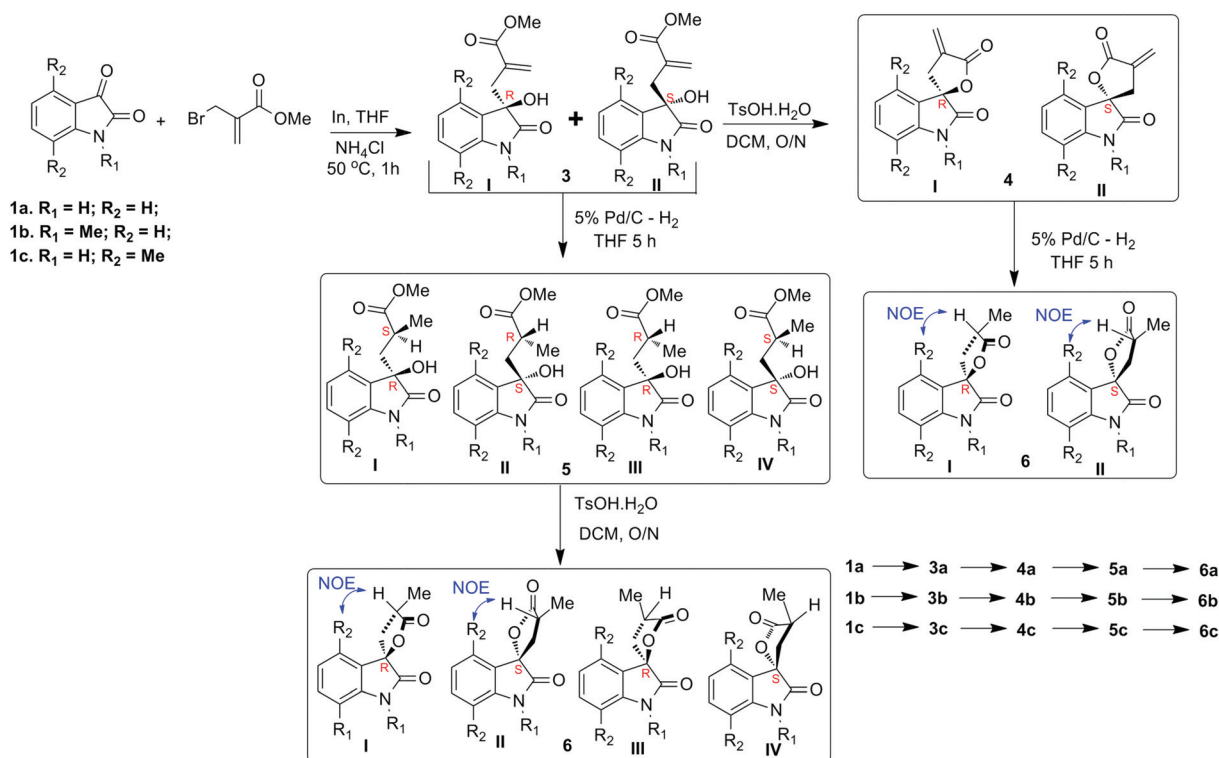

Fig. 2 Overlay of ¹H-NMR and 1D-NOE difference NMR spectra.

Scheme 2 Overall routes to study different configurations.

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conducted.[9] For compound **6a(I–IV)**, upon saturation of the aromatic region proton (∼7.3 ppm), only one set of C–H protons (∼3.2 ppm) alpha to the carbonyl was saturated while the other (∼3.5 ppm) was not (Fig. 2 bottom panel). This suggests that the proton alpha to the carbonyl on the lactone ring is closer to the aromatic protons in the saturated set of diastereoisomers (RS and SR), while the other set of diastereoisomers (RR and SS) has the methyl group closer to the aromatic C–H. No saturation of signal was observed for either of the exocyclic methyl groups (∼1.5 and ∼1.4 ppm). At the present time, it is unclear why we did not observe saturation of at least one set of the exocyclic methyl groups.

The same experiment with **6a(I–II)** showed saturation of the C–H proton at ∼3.2 ppm. Together the data confirm that the reduction of the double bond in the cyclized product **4a(I–II)** yields only one set of diastereoisomers **6a(I–II)** (RS and SR) in which the methyl group is pointing away from the aromatic ring. We speculated that the source of the facial selectivity during reduction could be due to the orientation of the compound on the catalyst. To investigate this, we synthesized two additional isatin derivatives with methyl groups on the nitrogen atom (**1b**) and on the C4 and C7 atoms (**1c**) of the aromatic ring.[10] We repeated similar sets of experiments with these substituted isatins (cyclization followed by reduction and reduction followed by cyclization) and carried out 1D NOE difference NMR experiments. The results were similar to what was observed with the unsubstituted isatin compound.

The reaction of **1b** and **2** in the presence of indium metal yielded acyclic **3b(I–II)** and cyclic **4b(I–II)** in a 3 : 1 ratio in 98% overall yield. Acyclic compound **3b(I–II)** was easily converted to cyclic compound **4b(I–II)** using *p*-toluenesulfonic acid. When the mixture of enantiomers **4b(I–II)** was subjected to hydrogenation, ^{1}H NMR spectra showed only one doublet (∼1.5 ppm) that corresponds to the exocyclic methyl group (ESI†). On the other hand, reduction of **3b(I–II)** to **5b(1–IV)** followed by cyclization gave a mixture of diastereoisomers **6b(I–IV)** in 94% yield. Two sets of doublets for exocyclic methyl groups at 1.5 and 1.4 ppm were clearly resolved by NMR spectroscopy (ESI†). Similarly, when **1c** was subjected to a reaction with **2**, **3c(I–II)** was obtained in 92% yield. **3c(I–II)** upon reaction with *p*-toluenesulfonic acid gave cyclic product **4c(I–II)** in 96% yield. When the mixture of enantiomers **4c(I–II)** was subjected to hydrogenation, ^{1}H NMR spectra of product **6c(I–II)** showed only one doublet (∼1.59 ppm) that corresponds to the exocyclic methyl group (ESI†). On the other hand, reduction of **3c(I–II)** followed by cyclization gave a mixture of inseparable diastereoisomers **6c(I–IV)** in 74% yield, which were clearly resolved by NMR spectroscopy (two doublets at 1.6 and 1.4 ppm respectively). This suggested that substitutions on isatin do not contribute to the observed facial selectivity during the reduction of the double bond.

Conclusions

We used isatin analogs and methyl 2-(bromomethyl)acrylate to synthesize the oxindole-α-methylene-γ-butyrolactone compounds (hybrid pharmacophore) by an indium mediated Barbier type reaction. Irrespective of isatin substitutions, a face selective reduction of the exocyclic double bond in the lactone ring was observed. Using 1D NOE difference NMR experiments, we established the stereochemistry of the newly created stereocenter alpha to the lactone carbonyl group. Synthesis and the structural–activity relationship of functionally modified spiro-oxindole compounds are currently under investigation and will be reported in due course.

Acknowledgements

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