Studies towards the synthesis of hyperireflexolide A

G. Hari Mangeswara Rao¹,²

Full Research Paper

Address:
¹Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur-208016, India and ²Department of Chemistry, Texila American University, Georgetown, Guyana

Email:
G. Hari Mangeswara Rao - harimangesh@gmail.com

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Abstract
The first approach to hyperireflexolide A, based on the synthesis of γ-lactone-fused cyclopentane 5, a functionalized key intermediate, is presented. Compound 5 is involved in hydrolysis, α-allylation at C-8 and α-methylation at C-10 stereoselectively from the convex face. Then it is subjected to cross metathesis to give α,β-unsaturated ketone 11 as precursor in the total synthesis of hyperireflexolide A.

Introduction
Hyperireflexolide A (1) [1] is a spiroterpenoid, isolated from hypericum reflexum, plants of the genus hypericum (Figure 1). Hyperireflexolide A is widely used in folk medicine, displays antifungal [2] and cytotoxic activities [3].

γ-Lactone-fused cyclopentanes are of vital importance in organic synthesis and are the most abundant substructures found in various naturally occurring molecules [4,5]. A cis-cyclopentane ring-fused γ-lactone is the key structural unit of many complex and challenging biologically active natural products [6-19]. The γ-lactone-fused cyclopentane ring system is also an important component for the synthesis of a variety of cyclopentanoid natural and unnatural products [20-24].

In the literature, numerous synthetic methods are reported to attain γ-lactone-fused cyclopentanes [25-31]. Earlier from our lab, we reported a short and efficient methodology for the synthesis of γ-lactone-fused cyclopentane 5 [32]. The cis-ring junction of this carbocyclic ring system offers a high degree of selectivity for the assemblage of various substituents on the convex surface. The lactone part can serve as a useful tool to append various side chains.

Results and Discussion
The presence of a γ-lactone-fused cyclopentane moiety in hyperireflexolide A (1) attracted our attention. In fact, the ketal moiety in 5 could not only act as a surrogate for C-9 carbonyl but also facilitate installation of an angular methyl group.

The retrosynthetic analysis for hyperireflexolide A is depicted in Scheme 1. We envisioned that hyperireflexolide A (1) could be synthesized by metal-catalyzed opening of the epoxide 2
with 2-bromopropene followed by lactonization. Enone 3 could be synthesized from 4 by installation of the methyl group at C-10 followed by cross metathesis reaction. Compound 4 could be obtained from the γ-lactone-fused cyclopentane 5 by deprotection of C-9 followed by allylation at C-8.

Previously, we reported from our laboratory the synthesis of γ-lactone-fused cyclopentane derivative 5 from the respective Diels–Alder adduct in 5 steps with an overall yield of 29% [32]. Hydrolysis of dimethyl ketal 5 with MeSO₂H in 1,2-DCE furnished γ-lactone-fused cyclopentanone 6 in 97% yield. Cyclopentanone 6 exists in its tautomeric enol form 7, observed in the ¹H NMR spectrum after column chromatographic purification (6 and 7 were not separated) as represented in Scheme 2 [33].

In order to check the feasibility of the alkylation reaction of γ-lactone-fused β-ketoester 6, initially a mixture of 6 and 7 was subjected to methylation using 1.1 equiv of K₂CO₃ in the presence of methyl iodide (MeI). The α-methylated β-ketoester 8 was obtained in good yield. In the ¹H NMR, 8 showed a signal at 3.70 ppm as doublet for C-10 (ring junction) proton confirming the selective methylation at C-8. Further, installation of the methyl group at C-10 was achieved by treatment of 8 with 1.1 equiv of K₂CO₃ in the presence of MeI to give bis-methylated γ-lactone-fused β-ketoester 9 in 72% yield.

**Figure 1:** Hyperireflexolide A.

**Scheme 1:** Retrosynthetic strategy.

**Scheme 2:** Hydrolysis of dimethyl ketal 5.
Now the stage has been set for allylation of γ-lactone fused cyclopentanone 6. Treatment of 6 with K$_2$CO$_3$ in the presence of allyl bromide at 0 °C afforded α-allylated γ-lactone-fused β-ketoester 4 in 88% yield. In the $^1$H NMR a signal appeared at 3.64 ppm as doublet for ring junction (C-10) proton confirmed that selective allylation occurred at C-8. Compound 4 was then subjected to methylation at C-10 using K$_2$CO$_3$ and Mel to obtain the requisite γ-lactone fused cyclopentanone 10 in excellent yield (Scheme 4). Allylation and methylation both were occurred stereoselectively from the convex face to give α,α'-cis stereochemistry. The allyl derivative 10 was then subjected to cross metathesis reaction with ethyl vinyl ketone. Initially, the reaction performed using Grubbs’ 1st generation catalyst (3–20 mol %) was unsuccessful. Treatment of 10 with ethyl vinyl ketone using Grubbs’ 2nd generation catalyst (3 mol %) in the presence of CH$_2$Cl$_2$ furnished (E)-enone 11 in 77% yield as shown in Scheme 4. In the $^1$H NMR spectrum, 11 showed a signal at 6.13 ppm as doublet with coupling constant 15.8 Hz (trans-configuration) for the α-proton of enone [34-37].

After successfully synthesizing the side chain via cross-metathesis, our next task was the stereoselective epoxidation of (E)-enone 11. Unfortunately, the stereoselective epoxidation of 11 under basic conditions were unsuccessful [38], which prevented completion of the proposed synthetic sequence.

**Conclusion**

In conclusion, synthetic studies towards hyperireflexolide A, the synthetic precursor α,β-unsaturated ketone 11 was synthesized. Failure of the stereoselective epoxidation of 11 prevented completion of the proposed synthetic sequence. Future studies...
of the reaction was monitored by tlc. The reaction was diluted with water (3 mL) and the organic layer was extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine solution (2 mL) and dried over anhydrous Na₂SO₄. The solvent was concentrated in vacuo to furnish a residue which was purified by silica gel column chromatography (25% EtOAc/hexane) to afford 8 in 71% yield. Viscous liquid; 

$^1$H NMR (400 MHz, CDCl₃) δ 3.72 (s, 3H, CO₂Me), 3.70 (d, J = 1.9 Hz, 1H), 2.98–2.91 (m, 1H), 2.52 (dd, J = 13.2, 11.2 Hz, 1H), 2.11–2.04 (m, 1H), 1.50 (s, 3H, Me), 1.47 (s, 3H, Me), 1.37 (s, 3H, Me); $^{13}$C NMR (100 MHz, CDCl₃) δ 203.4 (C=O), 171.0, 167.7, 84.5, 58.0, 55.6, 52.8, 44.9, 35.1, 29.3, 22.3, 18.7; IR (neat): 2900, 1760, 1740, 1440 cm⁻¹; HRMS (m/z): [M]$^+$ calcd for C₁₂H₁₆O₂, 240.0998; found, 240.1001.

**Methyl 1,1,3a,5-tetramethyl-3,4-dioxohexahydro-1H-cyclopenta[c]furan-5-carboxylate (9):** To a solution of the γ-lactone-fused cyclopentanone 8 (15 mg, 0.07 mmol) in dry acetone (0.4 mL) under argon was added anhydrous K₂CO₃ (9.7 mg, 0.07 mmol) and methyl iodide (12 mg, 0.08 mmol) at 0 °C. The reaction was stirred at 0 °C for 21 h. Completion of the reaction was monitored by tlc. The reaction was diluted with water (4 mL) and the organic layer was extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine solution (2 mL) and dried over anhydrous Na₂SO₄. The solvent was concentrated in vacuo to furnish a residue which was purified by silica gel column chromatography (20% EtOAc/hexane) to afford 9 in 72% yield. 

$^1$H NMR (400 MHz, CDCl₃) δ 3.70 (s, 3H, CO₂Me), 2.66 (t, J = 8.6 Hz, 1H), 2.55 (dd, J = 13.9, 8.8 Hz, 1H), 2.05 (dd, J = 13.9, 8.4 Hz, 1H), 1.64 (s, 3H, Me), 1.50 (s, 3H, Me), 1.49 (s, 3H, Me), 1.36 (s, 3H, Me); $^{13}$C NMR (100 MHz, CDCl₃) δ 201.4 (C=O), 169.3, 168.4, 80.2, 59.2, 56.4, 53.5, 44.4, 36.5, 28.7, 22.6, 19.8, 18.7; IR (neat): 2900, 1760, 1740, 1440 cm⁻¹; HRMS (m/z): [M]$^+$ calcd for C₁₅H₂₁O₇, 254.1154; found, 254.1155.

**Methyl 5-allyl-1,1-dimethyl-3,4-dioxohexahydro-1H-cyclopenta[c]furan-5-carboxylate (4):** To a solution of the γ-lactone-fused cyclopentanone 6 (75 mg, 0.331 mmol) in dry acetone (1 mL) under argon was added anhydrous K₂CO₃ (55 mg, 0.3972 mmol) and allyl bromide (48 mg, 0.3972 mmol) at 0 °C. The reaction was stirred at 0 °C for 21 h. Completion of the reaction was monitored by tlc. The reaction was diluted with water (4 mL) and the organic layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine solution (3 mL) and dried over anhydrous Na₂SO₄. The solvent was concentrated in vacuo to furnish a residue which was purified by silica gel column chromatography (15% EtOAc/hexane) to afford 4 in 88% yield. Viscous liquid; 

$^1$H NMR (500 MHz, CDCl₃) δ 5.72–5.64 (m, 1H), 5.18–5.12 (m, 2H), 3.71 (s, 3H, CO₂Me), 3.64 (d, J = 7.2 Hz, 1H),
Methyl 5-allyl-1,1,3a-trimethyl-3,4-dioxohexahydro-1H-cyclopenta[e]furan-5-carboxylate (10): To a solution of the γ-lactone-fused cyclopentanone 4 (29 mg, 0.109 mmol) in dry acetone (0.6 mL) under argon was added anhydrous K₂CO₃ (16.5 mg, 0.1199 mmol) and methyl iodide (18.5 mg, 0.1308 mmol) at 0 °C. The reaction was stirred at room temperature for 14 h. Completion of the starting material was monitored by tlc. The reaction was diluted with water (3 mL) and the organic layer was extracted with EtOAc (3 × 4 mL). The combined organic layers were washed with brine solution (3 mL) and dried over anhydrous Na₂SO₄. The solvent was concentrated in vacuo to furnish a residue which was purified by silica gel column chromatography (10% EtOAc/hexane) to afford 10 in 94% yield. Viscous liquid; ¹H NMR (500 MHz, CDCl₃) δ 5.69–5.61 (m, 1H), 5.17–5.11 (m, 2H), 3.69 (s, 3H, OMe), 2.66 (dd, J = 13.9, 6.5 Hz, 1H), 2.57 (t, J = 8.5 Hz, 1H), 2.49 (dd, J = 14.0, 8.5 Hz, 1H), 2.35 (dd, J = 13.9, 7.5 Hz, 1H), 2.19 (dd, J = 14.0, 8.5 Hz, 1H), 1.59 (s, 3H, Me), 1.53 (s, 3H, Me), 1.50 (s, 3H, Me); ¹³C NMR (100 MHz, CDCl₃) δ 206.0, 171.8, 170.3, 131.9, 120.1, 84.0, 60.7, 60.1, 52.8, 50.4, 37.8, 30.5, 30.2, 23.7, 22.5; IR (neat): 3400–2600 cm⁻¹; HRMS (m/z): [M⁺] calcd for C₁₅H₂₅O₅S, 280.1311; found, 280.1310.

Methyl 1,1,3a-trimethyl-3,4-dioxo-hexahydro-1H-cyclopenta[e]furan-5-carboxylate (11): To a solution of the compound 10 (110 mg, 0.327 mmol) in CH₂Cl₂ (0.8 mL) was added ethyl vinyl ketone (31 mg, 0.3597 mmol) and 3 mol % Grubbs’ 2nd generation catalyst (8.5 mg, 0.00981 mmol), then the reaction mixture at 40 °C for 8 h (monitored by tlc). The solvent was concentrated in vacuo to furnish a residue which was purified by silica gel column chromatography (15% EtOAc/hexane) to afford 11 in 77% yield. Viscous liquid; ¹H NMR (500 MHz, CDCl₃) δ 6.67–6.61 (m, 1H), 6.13 (d, J = 15.8 Hz, 1H, -C(O)-CH=CH₂), 3.70 (s, 3H, CO₂Me), 2.80–2.75 (m, 1H), 2.59–2.51 (m, 4H), 2.48–2.43 (m, 1H), 2.12 (dd, J = 13.1, 7.4 Hz, 1H), 1.58 (s, 3H, Me), 1.53 (s, 3H, Me), 1.49 (s, 3H, Me), 1.07 (t, J = 7.4 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 205.6, 200.3, 171.5, 169.9, 139.1, 134.0, 84.1, 60.3, 60.1, 53.5, 50.5, 36.1, 33.5, 31.0, 30.3, 23.7, 22.5, 7.8; IR (neat): 2900, 1760, 1720, 1460 cm⁻¹; HRMS (m/z): [M⁺] calcd for C₁₅H₂₅O₅S, 336.1573; found, 336.1576.

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References
38. Epoxidation of enone 11 with 30% aq H₂O₂ solution using NaHCO₃ afforded a 6:1 of two diastereomers (determined by ¹H NMR analysis of the crude reaction mixture) of α,β-epoxy ketone in very low yield (10%). Changing the base from NaHCO₃ to aq NaOH solution (1 N) did not improve the yield. Then the diastereomeric mixture of α,β-epoxy ketone was subjected to nucleophilic addition of Grignard reagent derived from 2-bromopropene in the presence of CuI led to the formation of an intractable mixture.