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Application of the tandem Stryker reduction–aldol cyclization strategy to the asymmetric synthesis of lucinone

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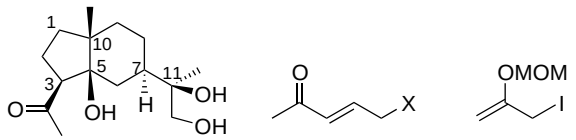
Abstract—The tandem conjugate reduction–aldol cyclization using Stryker's reagent has been employed as the key-step in an asymmetric total synthesis of lucinone.

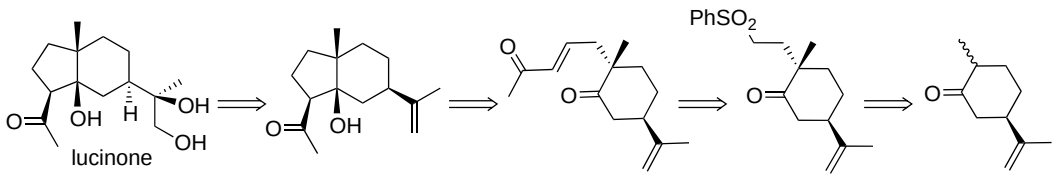
Tandem reactions add tremendous efficiency to the total syntheses of natural products by inducing multiple transformations of substrates in one operation.[1] We reported on the first example of a tandem conjugate reduction intramolecular aldol cyclization employing Stryker's reagent $[Ph_3PCuH]_6$,[2,3] and subsequently, we have undertaken a study of the scope of this cascade reaction.[4] In general, it has proven to be highly efficient, and has afforded superior yields of the aldol product. The use of this reductive aldol strategy allows the unambiguous site-selective formation of enolates in polycarbonyl substrates, which is the context of intramolecular aldol reactions. To highlight the efficiency and stereoselectivity of this reaction, we have undertaken the total synthesis of an iphionane sesquiterpenoid, lucinone.



Lucinone **1** **4**

Lucinone was isolated in 1995 from the aerial parts of *Jasonia glutinosa*, an annual medicinal plant in the Iberian Peninsula traditionally used as an antispasmodic drug.[5] The relatively simple structure of this iphionane nevertheless bears five stereocenters in its small sesquiterpenoid framework. In the paper documenting its isolation and characterization, the configuration at C11 was not assigned.[5] However, lucinone is likely to be biogenetically related to the other eudesmane alcohols isolated from the same species; therefore, the stereochemistry at C11 is presumably the same as that in the fully characterized eudesmanoids, which is (*R*) as shown.[6]

The enantioselective synthesis of lucinone employed (+)-dihydrocarvone as the starting material. The base-induced alkylation of dihydrocarvone is known to occur *syn* to the propenyl substituent;[7] therefore it was necessary to redirect the facial selectivity of the alkylation. The enantioselective alkylation of the (+)-methylbenzylamine enamine of cyclohexanones with Michael acceptors such as α,β-unsaturated esters or ketones is known.[8] Our synthesis, however, requires alkylation using a homologated α,β-unsaturated ketone such as **1** in order to build a tethered α,β-unsaturated ketone that produces the requisite five-membered ring upon reduction. We decided to achieve this in two stages, via the



Scheme 1. Retrosynthetic analysis of lucinone.

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alkylation of the chiral enamine with a vinyl sulfone, then further homologation of the sulfone to afford the α,β-unsaturated ketone (Scheme 1).

Thus, dihydrocarvone was converted to the enamine **2** using (+)-methylbenzylamine and treated with phenyl vinyl sulfone (Scheme 2). A 9:1 mixture of epimers at the α-position was generated as judged by the ^{1}H NMR of the crude product, with the desired diastereomer **3a** being the major product. The diastereomers were too similar in polarity for effective separation by column chromatography at this stage, so the synthesis was continued using the mixture of **3a** and **3b**. Protection of the ketone as the acetal prepared the substrate for chain extension exclusively at the sulfone terminus. Deprotonation using *n*-BuLi, alkylation with the acetonyl equivalent **4**,[9] followed by an acidic workup, produced **5** in 63% yield over two steps.

Treatment of the β-sulfonyl ketone **5** with triethylamine induced the elimination of the sulfone and resulted in exclusively the *trans*-α,β-unsaturated methyl ketone. At this stage, the epimers were separated by flash chromatography, and an 81% yield of enantiomerically pure ketone **6** was thus obtained. Deprotection of the ketal proceeded smoothly to yield enedione **7**, the substrate for the key copper hydride induced reductive aldol cyclization.[10]

The treatment of substrate **7** with two hydride equivalents of Stryker's reagent in toluene at 0°C to room temperature proceeded as anticipated to afford stereoselectively a quantitative yield of aldol **8**, in which four of the five stereocenters in the target molecule have been installed.[11] The *syn* relationship between the hydroxyl group and the acyl moiety was evidenced by intramolecular hydrogen bonding of the carbonyl functionality (1699 cm^{-1}) in the IR spectrum of hydroxyketone **8** under high dilution. In addition, a long-range ^{1}H–^{1}H coupling between the hydroxylic proton and the angular methyl group observable in the COSY spectrum established the *syn* stereochemistry of the ring junction in intermediate **8**.

The asymmetric dihydroxylation of the olefin was the final step leading to lucinone.[12] However, treatment of substrate **8** with either ADmix-α or ADmix-β gave essentially the same 2:3 ratio of diastereomeric triols in good combined yields.[13] After careful chromatographic separation of the closely related triols, it was found that NMR data of the minor isomer in both AD reactions corresponded to that of lucinone in the literature.[14] Dihydroxylation of olefin **8** in the absence of chiral ligands also yielded lucinone as the minor diastereomer (2:3, 95% combined yield).

Thus, the asymmetric total synthesis of lucinone has been achieved in seven steps. This synthesis serves to highlight the efficiency and the stereoselectivity of the tandem Stryker reduction–aldol cyclization to assemble the iphionane skeleton. This overall reductive–aldol methodology should be a useful general strategy for organic synthesis.

Acknowledgements

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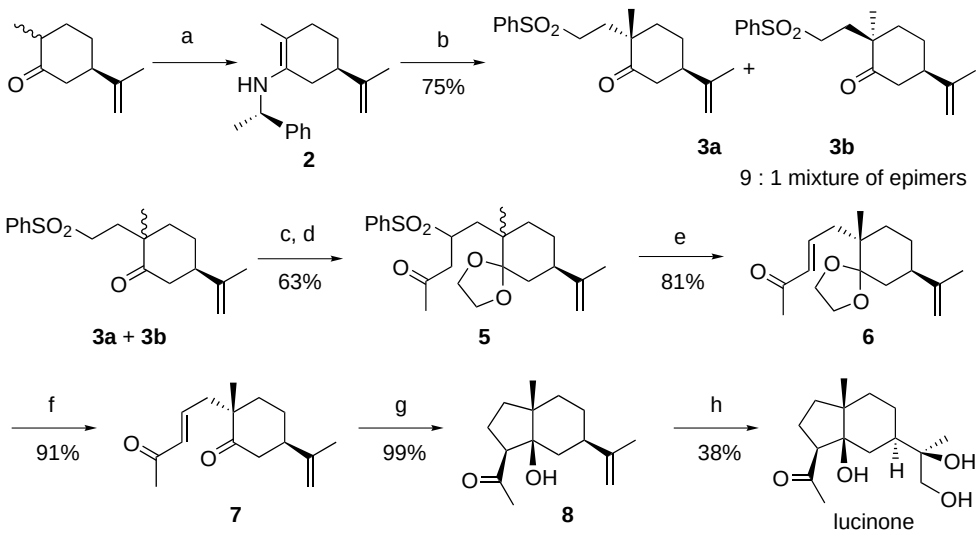

Scheme 2. *Reagents and conditions*. (a) (+)-Methylbenzylamine, PhMe, reflux; (b) i. phenyl vinyl sulfone, 35°C, ii. AcOH/H_2O; (c) ethylene glycol, PhH, reflux; (d) i. *n*-BuLi, THF, HMPA, −78°C, ii. **4**, iii. 1% H_2SO_4, rt; (e) Et_3N, CH_2Cl_2, separation of diastereomers; (f) dilute H_2SO_4, SiO_2, CH_2Cl_2; (g) Stryker's reagent, PhMe; (h) cat. OsO_4, $K_3Fe(CN)_6$.

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10. **7**: pale yellow oil; R_f (25% EtOAc in hexane) = 0.60; $[\alpha]_D^{22}$ +35.8 (*c*, 1.3 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (1H, dt, J = 15.9, 7.9 Hz), 6.06 (1H, dd, J = 15.9, 1.0 Hz), 4.77 (1H, t, J = 1.3 Hz), 4.72 (1H, s), 2.26–2.53 (4H, m), 2.23 (3H, s), 1.62–1.81 (5H, m), 1.74 (3H, s), 1.18 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.03, 198.46, 147.20, 144.67, 134.12, 109.98, 47.74, 46.11, 43.26, 41.18, 37.11, 26.88, 26.19, 23.24, 20.56; IR (CCl_4, cm^{-1}) 2937, 1710, 1678, 1644, 1629, 1455, 1426, 1359, 1253, 1180, 988, 896. HRMS: calcd for $C_{15}H_{22}O_2$ [M^+]: 234.1620; obtained: 234.1620.
11. Stryker's reduction–aldol cyclization of **7**: $[Ph_3PCuH]_6$ (83 mg, 0.042 mmol) was transferred to an oven-dried round bottom flask in a dry box. Enedione **7** (21.6 mg, 0.0921 mmol) in 1 mL anhydrous toluene was added at 0°C. The reddish reaction mixture was stirred at 0°C for 20 minutes, then at 25°C for 40 minutes. The reaction was quenched by the addition of 1 mL of saturated ammonium chloride aqueous solution, then stirred for 2 hours while open to air. The mixture was filtered through a silica gel plug, and the residue was washed with ethyl acetate. The filtrate was extracted with ethyl acetate (10 mL×2). The organics were combined and dried over anhydrous $MgSO_4$. Concentration in vacuo produced a residue which was purified by flash chromatography (10–20% EtOAc in hexane) to give **8** (21.9 mg, 99% yield). **8**: pale yellow oil; R_f (25% EtOAc in hexane) = 0.60; $[\alpha]_D^{22}$ = +31.9 (*c*, 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.71 (2H, m), 3.79 (1H, s), 3.36 (1H, t, J = 9.3 Hz), 2.18 (3H, s), 1.95–2.12 (3H, m), 1.82–1.95 (2H, m), 1.72 (3H, s), 1.61–1.39 (6H, m), 1.01 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.64, 149.02, 108.95, 82.48, 54.78, 45.51, 42.73, 37.65, 36.71, 36.60, 31.37, 27.26, 24.21, 20.81, 18.30; IR (CCl_4, cm^{-1}) 3503, 2937, 2864, 1699, 1645, 1361, 1176, 892. HRMS: calcd for $C_{15}H_{24}O_2$ [M^+]: 236.1776; obtained: 236.1731.
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14. An authentic sample of lucinone was not available for direct comparison.