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The Total Synthesis of (+)-Pectinatone: An Iterative Alkylation Approach Based on the SAMP-Hydrazone Method

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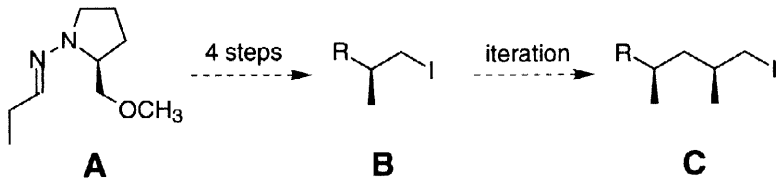
Abstract: The marine natural product (+)-pectinatone containing 'skip' 1,3-dimethyl stereocentres was synthesised via the iterative alkylation of propanal SAMP-hydrazone with β-branched iodides. Factors affecting the selectivity of the alkylation reaction and the *in situ* formation of volatile β-branched iodides are described.

We wish to report here our efforts towards the development of a general method for the stereoselective synthesis of natural products, containing a fully reduced, polypropionate derived 'skip' 1,3-dimethyl motif[1]. Although several approaches to these arrays have been reported[2], perhaps the most attractive route is that first suggested by Evans *et al.*, based on the iterative asymmetric alkylation with β-branched iodides[3]. The relatively low reactivity and instability of many chiral enolate reagents has necessitated the use of highly reactive β-branched triflates and/or the use of HMPA as co-solvent[3-5]. Recently, Myers *et al.* described the alkylation of pseudoephedrine derived amide enolates to give 'skip' 1,3-dimethyl arrays in excellent yields and selectivities[6]. Despite displaying good stability at ambient temperature, these amide enolates are still plagued by low reactivity, taking in the order of 6-20 hours at ambient temperature to react with β-branched iodides.

In contrast, the highly reactive aza-enolates derived from SAMP hydrazones react readily with secondary iodides and β-branched iodides and bromides at low temperatures[7]. We sought to apply these encouraging results to the synthesis of 'skip' 1,3-dimethyl arrays present in certain natural products. Another attractive feature of the aldehyde SAMP-hydrazone alkylation is the direct accessibility of aldehydes upon cleavage. The known hydrazone **A**, derived from propanal was utilised as the source of the methyl stereogenic centre[8]. Generation of the aza-enolate, alkylation, hydrazone cleavage, reduction to the alcohol and finally conversion into the iodide **B** gives the first methyl stereocentre. Further iteration generates the 'skip' 1,3-motif **C** (Scheme 1).



Scheme 1

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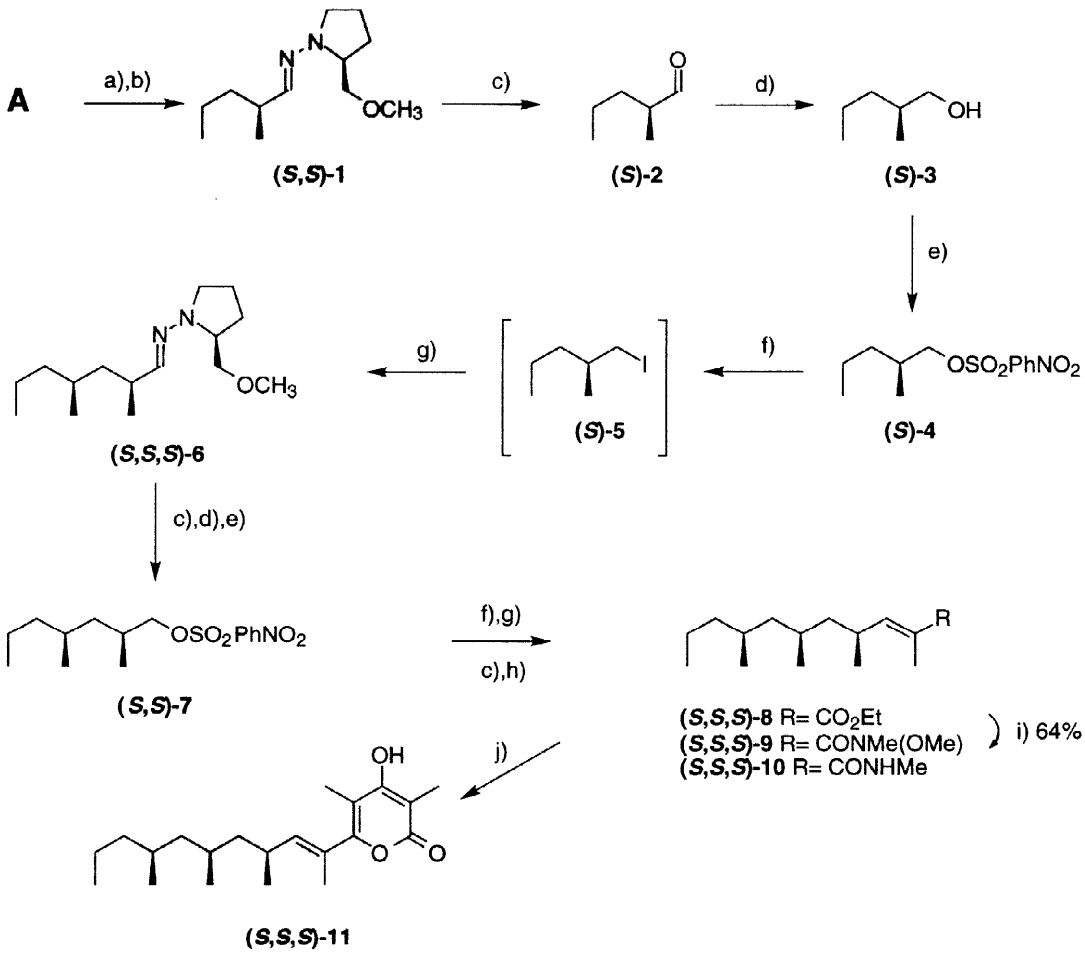
Control quench experiments indicated that treatment of the hydrazone **A** with lithium tetramethylpiperidide (LiTMP) gave complete deprotonation in less than 30 minutes at 0°C[9]. Alkylation of the aza-enolate with *n*-propyl iodide at -78°C gave the hydrazone **1** as a 97:3 mixture of diastereoisomers (94% de)[10]. Although the oxidative cleavage of the SAMP hydrazone could be conveniently achieved using ozone, the susceptibility of the liberated aldehyde to further oxidation under the reaction conditions was problematic giving variable yields[11]. We chose therefore, to employ the salt method[8] which gave good yields of the aldehyde **2** ready for subsequent transformations. Reduction of the aldehyde **2** was conveniently carried out using borane dimethyl sulfide complex[8]. The alcohol **3** was directly derivatised as the nosylate **4**. A small portion was also converted into the Mosher ester[12] which indicated that cleavage of the hydrazone and reduction of the aldehyde had proceeded with no detectable racemisation.

Upon the scale up of this 4 step sequence as a reduction by-product a sulfinic ester was obtained[13]. This by-product was formed in appreciable amounts (10-15%) from both the ozonolytic and salt cleavage methods to liberate the corresponding aldehyde from **6**. Indeed, employing tetrabutyl ammonium borohydride[14] in the reduction of the aldehyde gave this by-product in 38% overall yield. The involvement of iodide was implicated following the isolation of iodine from some reactions. Through the washing of the salt hydrolysis reaction mixture with aqueous sodium sulfite and purifying the aldehyde by filtration through a plug of silica this troublesome side reaction was effectively suppressed giving the sulfonate **4** in 30% overall yield from **A** (75% per step). All attempts to alkylate the azaenolate derived from **A** with the nosylate **4** resulted only low conversions (< 15%).

We envisaged that the *in situ* conversion of the sulfonate **4** to the iodide **5** and subsequent alkylation would prove useful in the manipulation of volatile alkyl iodides as compared with the usual PPh_3, I_2, imidazol protocol. Employing, the crystalline nosylate **4**, iodide displacement occurred rapidly at ambient temperature in THF[15]. Although, the precipitated lithium sulfonate salt appeared to adversely effect the alkylation reaction the addition of two volumes of pentane to the mixture effectively overcame this problem[16]. Inverse addition of the aza-enolate of **A** to a solution of the *in situ* iodide **5** gave the desired hydrazone **6** (86% de overall). Quaternization, acidic hydrolysis and subsequent reduction gave the alcohol which without further purification was converted into the nosylate **8** in 32% overall yield from **4** (80% per step, 86% de overall). Separation of the minor diastereoisomer by flash chromatography was unfortunately not possible at this stage[17]. *In situ* conversion into the iodide as before, alkylation with the aza-enolate derived from **A**, quaternization, acidic hydolysis and then reaction with phosphorane gave the α,β-unsaturated ester **8** in 52% overall yield (85% per step, 9:1 mixture of alkene isomers). Conversion into the Weinreb amide **9**[18] in good yield was readily achieved using the Merck protocol[19]. This intermediate has been used in the total synthesis of siphonarienone and thus represents a formal total synthesis of this natural product[5].

We chose to use this intermediate Weinreb amide **9** in the first synthesis of (+)-pectinatone (**11**) isolated from *Siphonaria sp.* molluscs which displays anti-bacterial, anti-fungal and cytotoxic activity[20]. The dialkylated acetoacetate ester required for the formation of the pyrone ring was prepared following the method of Weiler[21]. Generation of the β-ketoester dianion using LDA and addition to the amide **9** at 0°C occurred smoothly to give the tricarbonyl intermediate[22]. Warming of the reaction mixture to ambient temperature gave increasing amounts of the amide **10** as by-product. Treatment of the crude reaction mixture with DBU in boiling toluene[23] to effect cyclisation to the α-pyrone gave pectinatone **11** in 29% overall yield (35% recovered starting material) (Scheme 2). Synthetic pectinatone **11** was spectroscopically identical to the natural product[20]. In conclusion, we have demonstrated that these 'skip' 1,3 motifs can be rapidly and efficiently constructed using the SAMP hydrazone method allowing the synthesis of many of these natural products[20,24]. A full report on the iterative construction of both *syn* and *anti* 'skip' 1,3,*n* methyl stereocentres will be published in due course.



Scheme 2

Reagents and Conditions: a) LiTMP, THF, 0.5M, 0 °C, 45 min **b**) *n*-propyl iodide, -78 °C **c**) MeI, reflux, 90 min then 4N HCl,pentane, 90 min **d**) $BH_3.Me_2S$, 0 °C, then MeOH and HCl **e**) 4-nitrophenyl sulfonyl chloride, pyridine, DMAP, CH_2Cl_2, rt **f**) LiI, THF, 1M, rt, 3 h, then pentane and -78 °C **g**) hydrazone **A**, **a**) and inverse addition -78 °C **h**) $Ph_3PC(CH_3)CO_2Et$, toluene, reflux, 5 h **i**) N-methoxy, N-methyl amine.HCl, 2eq $^{i}PrMgCl$, THF, -20 °C-0 °C, 64% **j**) LDA, THF, 0 °C, $CH_3CH_2COCH(CH_3)CO_2Et$, inverse addition, then DBU, toluene, reflux, 3h, 29% overall (35% recovered starting material) and 20% amide **10**.

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[9] Control quench experiments: 1 mmol scale, 0.5 M hydrazone in THF at 0° and addition of *n*-propyl iodide at 0. Similiarly subsequent experiments showed that deprotonation using LDA (1 mmol hydrazone, 0.5M THF, 0°, and alkylation at 0°) was complete in less than 45 minutes.

[10] The effect of temperature on the selectivity in this alkylation reaction appears to be less than previously thought, -100°C gave 97:3, -78°C gave 97:3, -20°C gave 97:3 and at 0°C selectivity fell slightly to 94:6 (selectivity from 500MHz ^{1}H NMR). Similar results have been obtained for ketone SAMP-hydrazones, Job A, unpublished results. See also: Kawanami Y, Ito Y, Kitigawa T, Taniguchi Y, Katsuki T, Yamaguchi M. Tetrahedron Lett. 1984;25:857-860.

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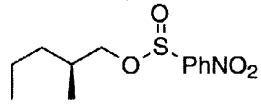
The sulfinate ester was isolated as a 1:1 mixture of diastereoisomers.



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[15] The use of TBAI, NaI, KI in 30% DMPU in THF to effect the displacement and the addition of the preformed aza-enolate of **A** in THF reduced the selectivity to between 5:1 and 2:1.

[16] The addition of this volume of pentane had no detectable effect on the stereochemistry of the alkylation reaction.

[17] All attempts to recrystallise the mixture to increase the diastereomeric purity from a variety of solvents were unsuccessful.

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[20] **11**: ^{1}H NMR (500 MHz, C_6D_6) σ = 0.84 (d, 3H, *J* = 6.7 Hz, Me), 0.86 (d, 3H, *J* = 6.2 Hz, Me), 0.88 (d, 3H, *J* = 6.4 Hz, Me), 0.92 (t, 3H, *J* = 6.7 Hz, Me), 0.80 - 1.40 (m, 8H), 1.40 - 1.60 (m, 2H), 1.80 (bs, 3H, Me), 1.97 (bs, 3H, Me), 2.04 (bs, 3H, Me), 2.47 - 2.56 (m, 1H), 5.25 (m, 1H, CH); lit. [20]: $[\alpha]_D$ = +62 (c = 0.11, $CHCl_3$). Biskupiak JE, Ireland CM. Tetrahedron Lett. 1983; 24:3055-3058. Norte M, Cataldo F, Gonzalez AG, Rodriguez ML, Ruiz-Perez C. Tetrahedron 1990; 46:1669-1678. Garson MJ, Small CJ, Skelton BW, Thinapong P, White AH, J. Chem. Soc. Perkin Trans. 1. 1990:805-807.

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