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DOUBLY ALLYLIC STRAIN - CONTROLLED DIASTEREOSELECTIVE INTRAMOLECULAR MICHAEL ADDITION AND A SYNTHESIS OF (±)-IRIDOMYRMECIN

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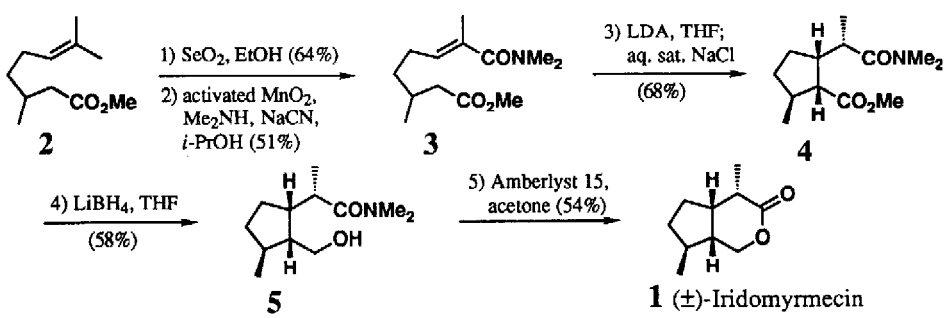
Abstract: Diastereoselective construction of four contiguous asymmetric centers assembled in a trisubstituted cyclopentane ring has been achieved *via* a doubly $A^{(1,3)}$-strain - controlled intramolecular Michael addition, and the resulting compound has been converted into (±)-iridomyrmecin in two steps.

Recently we have reported the effectiveness of the allylic strain - controlled cyclic hydroboration to prepare polyketide segments with three contiguous asymmetric centers.[1] Encouraged by the successful results, we proceeded to apply the same conception to other reactions. We here report a diastereoselective intramolecular Michael addition directed by the allylic 1,3-strain,[2] and a convenient synthesis of (±)-iridomyrmecin (**1**).[3]

Methyl (±)-citronellate (**2**) was converted into the ester amide **3** in 33% yield in two steps. An α,β-unsaturated amide was chosen as the Michael acceptor and an ester as the donor because (i) the two carbonyl functionalities should be differentiated for further processing, and (ii) an enolate, not a dienolate, should be generated by the base treatment.

The intramolecular Michael donor - acceptor precursor **3** was treated with 1.1 mole equivalent of lithium diisopropylamide (LDA) in THF at -78 °C for 30 min. After quenching the reaction by addition of aqueous saturated sodium chloride followed by workup and purification, an intramolecular Michael adduct **4** was obtained in 68% yield as a single stereoisomer.[4] The structure of **4** was assumed based on ^1H and ^{13}C NMR, IR and mass spectra, and confirmed by converting **4** into (±)-iridomyrmecin (**1**) as shown below.

The cyclopentanecarboxylate **4** was reduced with lithium borohydride in refluxing THF to give a hydroxy amide **5** in 58% yield. Treatment of **5** with Amberlyst® 15 ion exchange resin in refluxing acetone[5] for 2 h afforded a lactone in 54% yield, whose spectral data were identical with those of (±)-iridomyrmecin (**1**).[6]

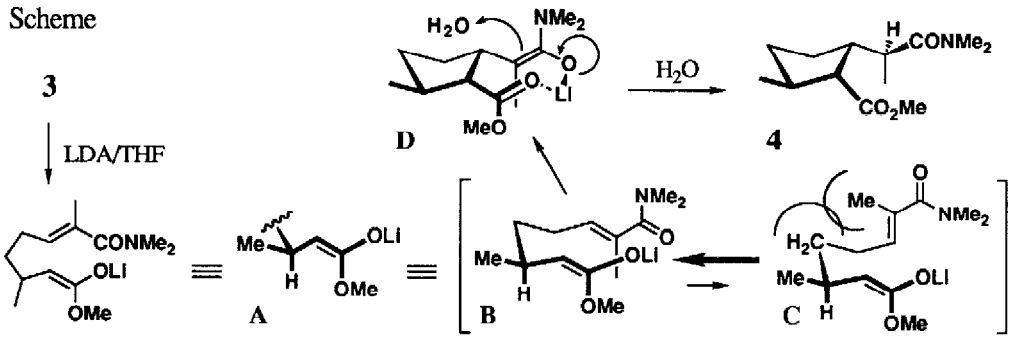


2 **3** **4** **5** **1** (±)-Iridomyrmecin

Although a number of papers dealing with the intramolecular Michael addition has been published,[7] little work has been reported on the diastereoselective reactions controlled by the allylic strain.[8,9] The reasonable

pathway of the intramolecular Michael addition mentioned above is shown in Scheme. Through avoiding the allylic 1,3-strain between the methoxyl group and the allylic substituents,[10] the conformation around the enolate should be as given in **A**. The most favorable conformation of the enolate to give rise to the cyclization (*i.e.*, substantial overlap of the orbitals is possible) is therefore **B**, since **C** suffers another allylic strain between the olefinic methyl and one of the methylene groups.[11] Coordination of the bidentate Michael product to the lithium cation fixed its conformation as **D** until the addition of water, so that the configuration of the newly formed secondary methyl group on the side chain was thus controlled.

Scheme



Thus, an allylic strain-controlled intramolecular Michael addition has been shown to proceed with high stereoselectivity to afford only one diastereomer of a trisubstituted cyclopentane with four contiguous asymmetric centers, and culminated in a synthesis of (±)-iridomyrmecin from methyl (±)-citronellate.

References and Notes

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4 **4**: IR (neat) 1722, 1630 cm^{-1}. ^1H NMR ($CDCl_3$); δ 1.07 (3H, d, *J*=6.60 Hz), 1.08 (3H, d, *J*=7.59 Hz), 2.95 and 3.06 (each 3H, s, NMe_2), 3.68 (3H, s, OMe). ^{13}C NMR ($CDCl_3$); δ 17.07, 22.03, 30.66, 33.60, 35.58, 36.44, 37.52, 39.21, 47.01, 51.28, 52.60, 176.33, 176.58. MS *m/z* 241 (M^+, 2%), 109 (C_8H_{13}, 45%), 101 ($C_5H_{11}ON$, 100%). Found: *m/z* 241.1732. Calcd for $C_{13}H_{23}O_3N$: 241.1678.

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