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An Efficient Asymmetric Synthesis of Trisubstituted Cyclohexenones and Trisubstituted Cyclopentenones from Chiral 2,2-Dialkyl 1,4- and 1,5-Diketones*

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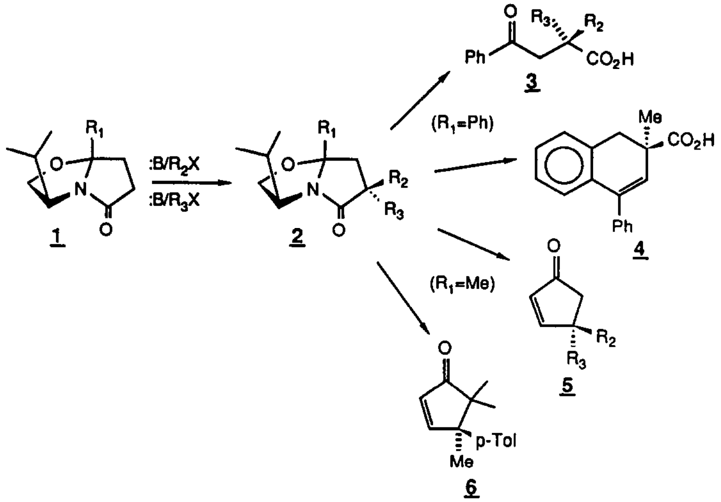
Summary: Addition of organolithium reagents to the chiral bicyclic lactams 2 and 9 leads to the title compounds in high enantioselectivity.

Our recent studies on chiral bicyclic lactams 1, 2, 7, 8 and 9 have provided a useful approach to a variety of chiral, non-racemic compounds containing quaternary carbons at the stereocenter.[1-6] Thus, 1, readily available from γ-ketoacids and S-valinol has been doubly alkylated with lithium bases and two different alkyl halides affording 2 in high diastereomeric ratios (> 95%). Acidic hydrolysis gave the enantiomerically pure keto acids 3[1] and dihydronaphthalenes 4,[1] whereas reduction of 2 followed by base-catalyzed aldolization gave the cyclopentenones 5.[2] The synthesis of (-)-α-cuparenone 6 was recently described using this methodology.[3] Furthermore



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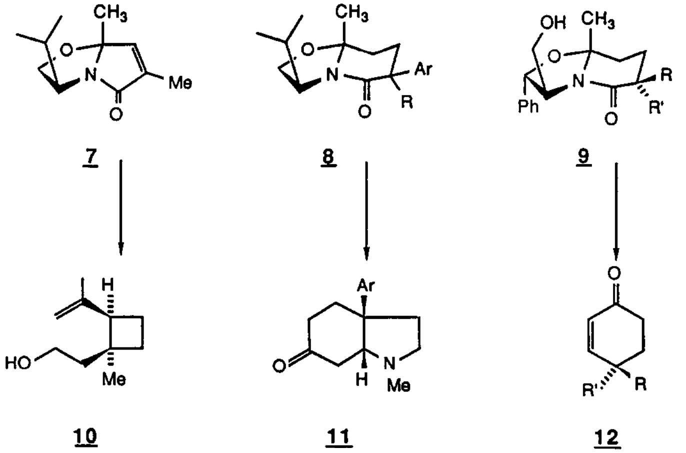
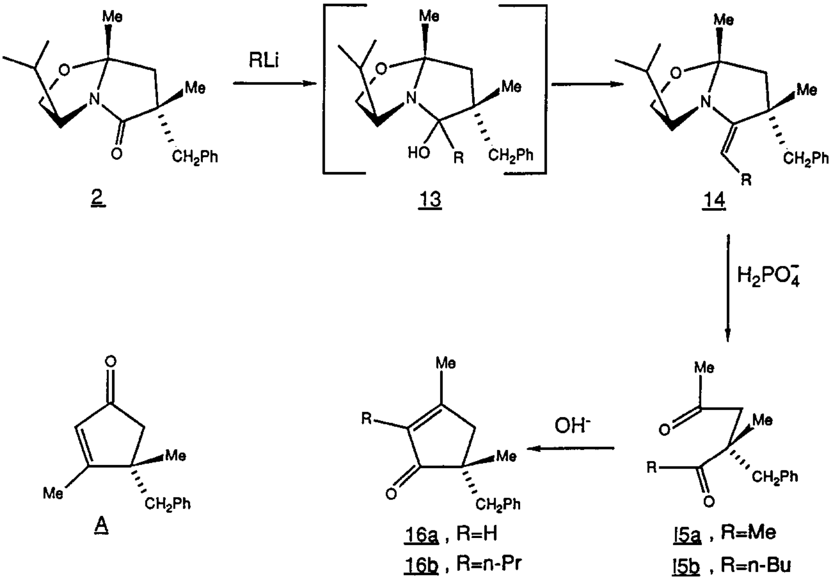
*Dedicated to Professor Teruaki Mukaiyama on the occasion of his 60th birthday.

other bicyclic lactams 7-9 were employed in the asymmetric synthesis of (-)-grandisol 10,[4] (+)-mesembrine 11,[5] and 4,4-dialkylcyclohexenones 12,[6] respectively. We now report that the bicyclic lactams 2 and 9 react smoothly with organolithium reagents by adding to the carbonyl

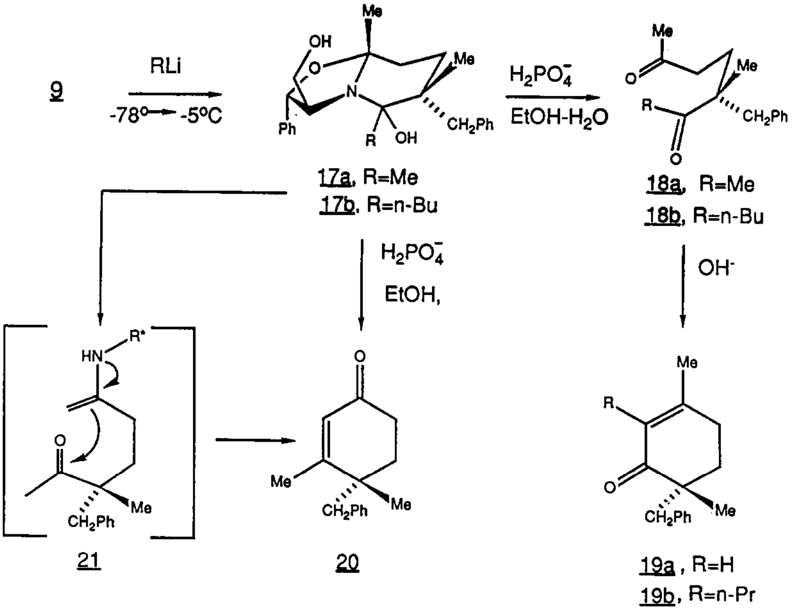


group affording, after cleavage, the 1,4 or 1,5-diketones (15 or 18) which cyclize to the enantiomerically pure cyclohexenones (19 and 20) and cyclopentenones, 16 (a,b). Thus,



addition of RLi to 2 (-78° THF) gave the carbinolamine 13 which, on aqueous workup (sat'd NH_4Cl) furnished the enamines 14 in >99% crude yield. Hydrolysis using 1M $Bu_4NH_2PO_4$ in aqueous ethanol (1:2:1) led to the ketones 15a [$[\alpha]_D$ -35.6° (c 1, EtOH)] and 15b [$[\alpha]_D$ -36.8° (c 0.6, EtOH)] in 80 and 91% yield respectively, after flash chromatography on silica gel (10% EtOAc-hexane). The chiral diketones were cyclized to cyclopentenones 16a [$[\alpha]_D$ 93.6° (c 0.76, EtOH)] and 16b [$[\alpha]_D$ 96.6° (c 1, EtOH)] in 89 and 84% yields, respectively.[7,8]

The analogous bicyclic lactam 9,[6] reacted with 2-3 equiv of organolithium reagents (THF) to furnish 17. The crude carbinolamines, formed in near quantitative yields, were hydrolyzed as above, using aqueous ethanol with $Bu_4NH_2PO_4$ producing the 1,5-diketones 18a [$[\alpha]_D$ -13.5° (c 0.8, EtOH)] and 18b [$[\alpha]_D$ -23.4° (c 1, EtOH)] in 67 and 60% yields, respectively. Treatment with a trace of ethanolic KOH in THF gave the cyclohexenones 19a [$[\alpha]_D$ -12.6° (c 0.31, EtOH) and 19b [[α] 9.5° (c 0.4, EtOH) in 83 and 80% yields, respectively.[9]



When the carbinolamine 17a was hydrolyzed, in the absence of water, using $Bu_4NH_2PO_4$ in anhydrous ethanol and heating to reflux (16 h), only the 3,4,4-substituted cyclohexenone 20 was obtained [67% from 9, $[\alpha]_D$ -52.0° (c 1, EtOH)] . Thus, the cleavage of 17a under anhydrous conditions proceeded through a different pathway (posssibly the enamine 21). This variation in regiochemistry on aldolization of diketones has been observed earlier in related systems.[10]

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References

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7) Cyclization of 15a to the isomeric ketone, A has only been accomplished in 28% yield using anhydrous $Bu_4NH_2PO_4$ in n-butanol. Optimum conditions for this isomeric product are still eluding us and work is continuing in this regard.
8) The bicyclic lactams 2 and 9 were diastereomerically pure prior to addition of organolithiums. All products gave satisfactory spectral and elemental analyses and the diketones and cycloenones are assumed to be >99% enantiomerically pure.
9) Attempted addition of RLi to bicyclic lactam 8 failed to give any product, a result also observed when 8 was treated with metal hydrides (see ref. 5).
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