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Enantioselective Synthesis of 4-Aminocyclopent-2-ene-1-one from Tricyclo[5.2.1.$0^{2,6}$]decenyl Enaminones

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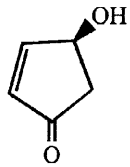
Abstract: An efficient enantioselective synthesis of 4-amino-cyclopent-2-ene-1-one **12** from enaminones **8** and and its diastereomer has been accomplished *via* a one step electron transfer reduction of the enaminone double bond and concomitant removal of an α-methylbenzyl group, followed by a [4 + 2] cycloreversion strategy.

Oxygenated monocyclic cyclopentanones and cyclopentenones are notable structures which widely occur in nature and often show intriguing activities.[1] Representative examples are the prostaglandins and the structurally related clavulones. An important building block for such cyclopentenoids is 4-hydroxycyclopentenone **1** and its derivatives.[2] These γ-oxygenated cyclopentenones can be readily obtained in enantiopure form by an appropriate oxidation of cyclopentadiene followed by enzymatic desymmetrization of the intermediate cyclopent-2-ene-1,4-diol.[3] Unlike **1**, its nitrogen analogue *viz.*, 4-aminocyclopentenone **2**, has not yet been prepared, neither racemic nor optically active. However, several N-substituted derivatives of **2**, *viz.* **3**, are known[4] and find application as synthetic building blocks in prostanoid[5] and carbanucleoside chemistry,[6] as well as in the synthesis of an important intermediate for Merck's synthesis of thienamycin and antiviral dipeptide isosteres.[7] For the synthesis of **3**, two general approaches can be distinguished: (a) the cycloaddition of appropriate nitroso compounds with cyclopentadiene followed by hydrolysis and oxidation,[7] and (b) inter- or intramolecular nucleophilic 1,4-addition of amines to appropriately functionalized 4-hydroxycyclopentenone **1**.[8,9] Using the latter approach and starting from enantiopure **1**, optically active γ-aminocyclopentenone **4** has been reported in a patent.[9]



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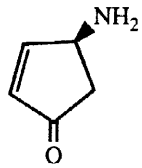

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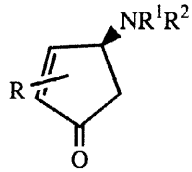

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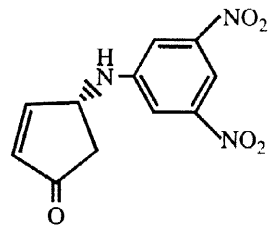

4

Recently, we described the asymmetric desymmetrization of *pseudo-meso-endo*-tricyclodecadienone **5** by chiral amines affording tricyclic enaminones of the type **6** and **7** (Scheme 1).[10] Selective reduction of the

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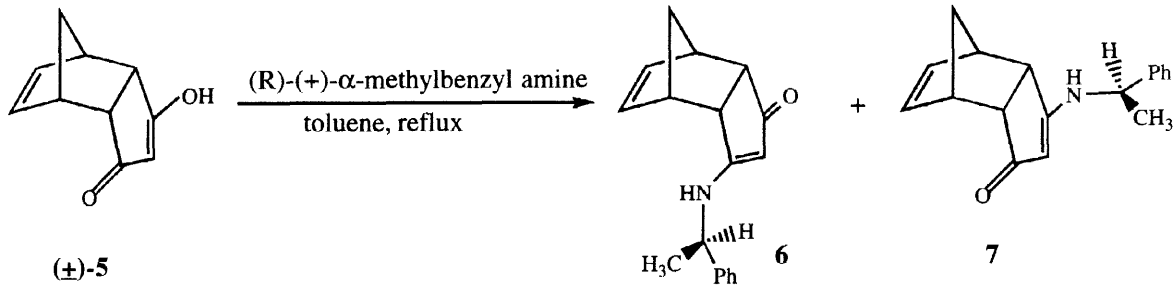
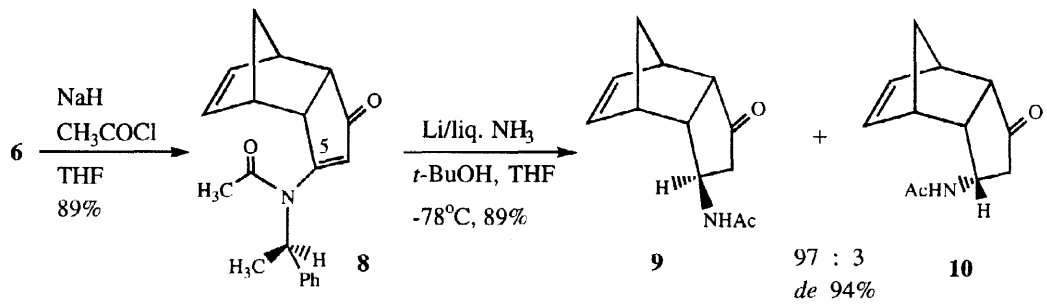
enaminone double bond followed by a retro Diels-Alder reaction is a conceivable and attractive route for the synthesis of homochiral **2** and N-substituted derivatives **3**. In this communication, we disclose an enantioselective synthesis of **2**, starting from enantiopure enaminones **6** and **7** *via* a unique one step reduction process and applying the cycloreversion methodology.[11]



Scheme 1

Although a wide variety of hydride reagents have been employed for the reduction of the enaminone double bond,[12] none of them proved successful in the present case. The conventional reagents either refused to reduce the enaminone double bond in **6** and **7** at all or if reduction had occurred the resulting β-amino ketone underwent immediate elimination of the amino functionality to give the parent tricyclo[5.2.1.$0^{2,6}$]decadienone.[10] The reluctance of the enaminone moiety to undergo hydride reduction is probably due to its extended π-delocalization which requires reduction conditions which are not suitable to retain the β-amino group. Therefore, we hypothesized that the introduction of an electron withdrawing group on nitrogen might overcome this problem. Thus, the N-acetyl derivative **8** was prepared from **6** by reaction with sodium hydride and acetyl chloride in THF (Scheme 2). However, although hydride reduction proceeded much more smoothly now, unequivocal reduction of the enone double bond in **8** could not be accomplished. A highly rewarding result was obtained when an electron transfer type reduction was attempted. Reacting diastereomerically pure **8** with lithium in liquid ammonia as the reducing agent and *t*-BuOH as the proton donor,[13] a mixture of diastereomeric β-amino ketones **9** and **10** was obtained in excellent yield (89%) and with a remarkably high diastereoselectivity (*de* 94%)[14] (Scheme 2). This unexpected reduction of the enaminone double bond in **8** along with the concomitant removal of the chiral auxiliary by lithium in liquid ammonia is unprecedented.

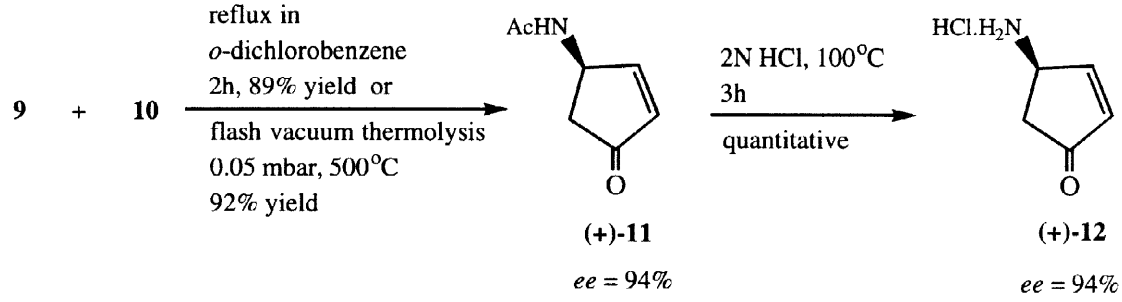


Scheme 2

Apart from being novel, this method may be general for the synthesis of optically active β-amino ketones from enaminones. Detailed NOESY studies unambiguously revealed the *exo*-stereochemistry of the amino group in the major diastereomer **9**. It is worth noting that in spite of the *endo* face being sterically

considerably hindered in **8**, proton donation at C_5 preferentially occurs from the *endo* face thus positioning the β-amino group on the *exo* side. Interestingly, the reduction of the diastereomer of **8**, obtained by the acylation of **7**, similarly gave a high yield of *ent*-**9** and *ent*-**10**, however with considerably lower diastereoselectivity (*de* = 76%) than observed for the reduction of **8**. This difference in diastereoselectivity (*de's* of 76% and 94%, respectively) indicates that the chiral α-methylbenzyl group plays a pronounced role in determining the stereochemistry of protonation of the intermediate carbanion. As a consequence, it may be concluded that the reduction of the enone moiety precedes the reductive removal of the α-methylbenzyl group.

Attempts to separate the diastereomers **9** and **10** by chromatographic methods failed, therefore the mixture (*de* 94%) was subjected to thermolysis in order to bring about the desired [4 + 2] cycloreversion. The retro Diels-Alder reaction was smoothly accomplished both under static conditions in refluxing chlorobenzene and under flash vacuum thermolytic conditions (0.05 mbar, 500°C) to give R-(+)-N-acetyl-4-aminocyclopent-2-ene-1-one **11**, $[\alpha]_D^{25}$ = +89° (*c* = 0.6, $CHCl_3$), in 89% and 92% yield, respectively (Scheme 3). In both cases the enantiomeric excess amounted to 94% showing that both under static and dynamic thermolysis no significant racemization occurred. Removal of the N-acetyl group was readily accomplished by



Scheme 3

hydrolysis in 2N aq. HCl to yield a pale yellow solid of R-(+)-4-aminocyclopent-2-ene-1-one as its hydrochloride **12**, $[\alpha]_D^{22}$ = +61.5° (*c* = 0.5, MeOH). The ^{1}H-NMR (300 MHz), ^{13}C-NMR (75 MHz) spectra of **12** in CD_3OD unequivocally established its structure and revealed this amine to be pure. Unfortunately, attempts to recrystallize this amine salt from a variety of solvents did not meet with success. In order to establish the optical purity of **12**, it was reconverted to the N-acetyl derivative **11** by treatment with acetic anhydride in the presence of triethyl amine. After purification by column chromatography, the isolated N-acetyl compound **11** showed an optical rotation identical to that of originally obtained (+)-**11** (Scheme 3) proving that during hydrolysis of (+)-**11**, no significant racemization had occurred. Using the same procedure, mixture of *ent*-**9** and *ent*-**10** afforded *ent*-**11** in 90% yield and with an *ee* of 76% $[\alpha]_D^{27}$ = -72.5° (*c* = 0.49, $CHCl_3$).

In conclusion, we have accomplished an effective and enantioselective synthesis of hitherto unknown 4-aminocyclopent-2-ene-1-one **12**. Key step in this route is the electron transfer reaction of N-α-methylbenzyl substituted enaminone **8** and its diastereomer, with lithium in liquid ammonia which not only reduces the enaminone double bond but concurrently removes the chiral auxiliary. Work is in progress to establish the generality of this reduction process for the enantioselective synthesis of β-amino ketones from the corresponding enaminones. We are also exploring these compounds as building blocks in the synthesis of 5'-nor carbocyclic nucleosides.

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11. In our laboratory, this methodology has been successfully applied for the synthesis of a variety of cyclopentanoid natural products. For an illustrative example, see ref.1.
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13. *Experimental procedure for lithium in ammonia reduction:* A 100 mL three necked flask cooled to -78°C, was charged with 50 mL of liq. ammonia. 1 mmol of enaminone **5** (307 mg) dissolved in 5 mL of THF was added followed by 296 mg (4 mmol) of *t*-BuOH in 2 mL of THF. The reaction mixture was stirred for 5 min. and 56 mg (8 mmol) of freshly cut lithium metal was added to the reaction mixture. Blue colour started appearing slowly and in 5-10 min. the reaction mixture became blue in colour. The reaction mixture was stirred at -78°C till all the blue colour had disappeared. The cooling bath was removed and ammonia was evaporated by using a water bath. The reaction mixture was then quenched with a minimum amount of water and extracted with CH_2Cl_2. The organic layer was then dried, concentrated and purified by column chromatography to yield a diastereomeric mixture of β–amino ketones **9** and **10**.
14. The diastereomeric ratios were determined by GC and ^{1}H-NMR (300 MHz). The *ee's* were determined by using chiral shift reagent $Eu(hfc)_3$ and integrating the separation of the signal due to the β-olefinic proton.