Pergamon

Tetrahedron Letters 39 (1998) 1339–1340

TETRAHEDRON LETTERS

Stereocontrolled Approach to Quinuclidine Derivatives

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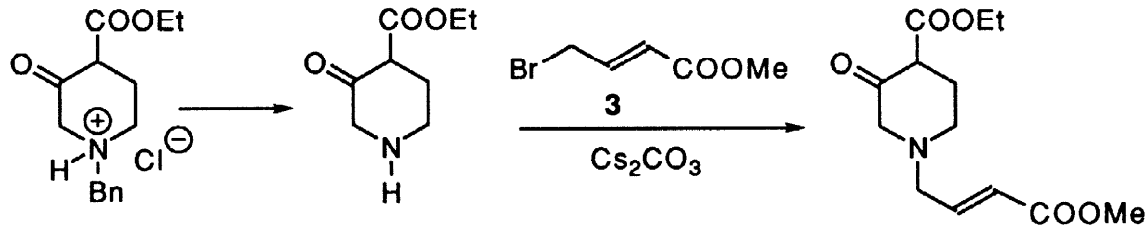
Received 24 November 1997; accepted 8 December 1997

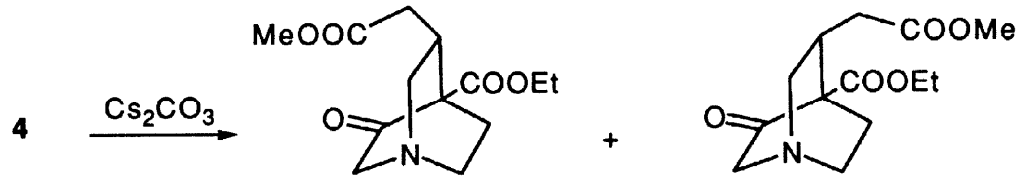
Abstract *: Asymmetric Michael-type cyclization of chiral enamino ester (S)-7 furnished the quinuclidinone derivative (3R, 4S)-5, with a high degree of stereoselectivity.*

The quinuclidine nucleus is the bridged bicyclic core of naturally occurring *Cinchona* alkaloids.[2] We reasoned that quinuclidine derivatives might be elaborated through the bridging annulation of β-enamino ester **7**, prepared from β-keto ester **4**. The latter compound was efficiently synthesized in two steps, starting from the commercially available 3-piperidone derivative **1**. Hydrogenolysis of **1** ($Pd(OH)_2$, 5 bars of H_2, CH_2Cl_2, 24 h at 20 °C, then Na_2CO_3) gave with a 84 % yield compound **2**, which upon *N*-alkylation with bromobutenoate (*E*)-**3** (Cs_2CO_3, CH_2Cl_2, 24 h at 20°C), furnished with a 65 % yield the requisite β-keto ester (*E*)-**4**.



1 **2** **4**

Base-induced cyclization of **4** was first investigated. While strong bases (KH, LDA) proved to be inefficient, the use of Cs_2CO_3 (0.6 eq., 8 h in THF at reflux) led with a 44 % yield to an inseparable mixture of diastereomeric, *racemic* quinuclidinones **5** and **6**. The diastereomeric ratio **5/6** (1:1.5) was established by ^1H and ^{13}C NMR spectroscopy.



(±)-5 **(±)-6**

Encouraged by this result, we next examined the cyclization of the chiral β-enamino ester (*S*)-**7**, prepared from keto ester **4** and (*S*)-(-)-1-phenylethylamine (10 h in refluxing benzene, in the presence of a

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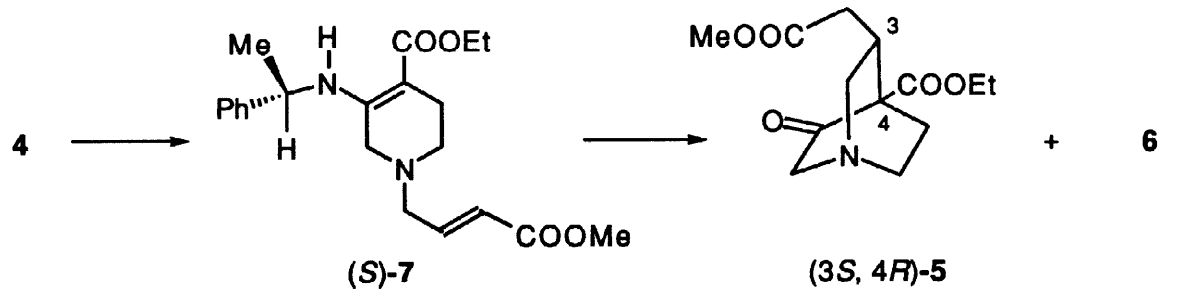
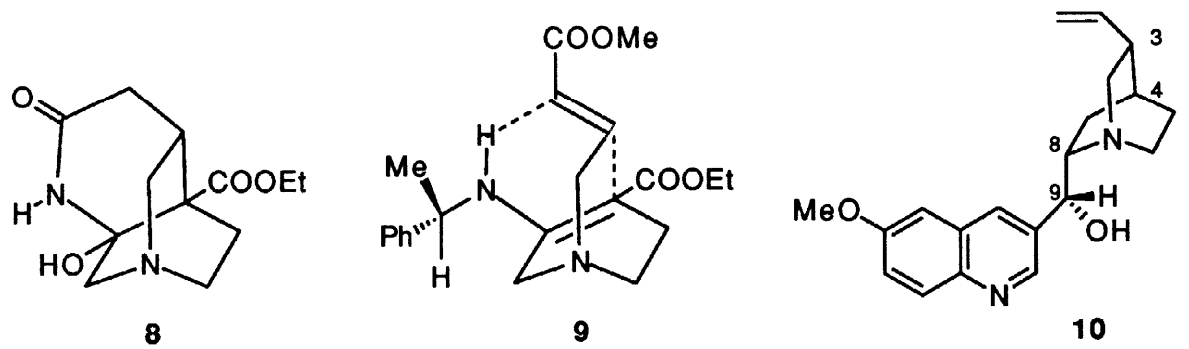
0040-4039/98/$19.00
PII: S0040-4039(97)10812-7

catalytic amount of *p*-TsOH, 72 % yield). After extensive experimentation, we discovered that $ZnCl_2$-promoted cyclization of **7** (0.3 eq. of $ZnCl_2$, THF-toluene, 12 h at 80 °C, then hydrolytic work-up) furnished with a 68 % yield the quinuclidinone (3*R*, 4*S*)-**5**, in 90 % enantiomeric purity (determined on the lactam derivative **8**), accompanied with *ca* 10 % of its stereomer **6**.



The *syn* relationship between the acetate side chain at C-3 and the keto group in **5** was definitely proved through its derivatization into the tricyclic lactam **8** (NH_3 in EtOH, 3 days at 20 °C, 70 % yield). The ee in **8** was established by ^1H NMR spectroscopy, having added (+)-2,2,2-trifluoro-1-(9-anthryl)ethanol as chiral solvating agent.[3] The absolute configuration in adduct (3*R*, 4*S*)-**5**, although not definitely established, was easily predictable on the basis of the six-membered, "aza-ene-synthesis-like" transition state **9**.[4] According to this mechanism, the alkylation took place predominantly on the less hindered enamine π-face of **7** (*anti* to the bulky phenyl group of the chiral moiety). The transfer of the NH proton to the α-vinylic center of the butenoate appendage, *more or less concerted with the creation of the C-C bond*, simultaneously ensured the stereocontrol of the acetate side chain at C-3 in resulting adduct **5**.



The present cyclization of (*S*)-**7** into quinuclidinone (3*R*, 4*S*)-**5** thus constitutes an efficient stereoselective access to quinuclidine derivatives. Syntheses of *Cinchona* alkaloids, exemplified by the traditional antimalarial drug (-)-quinine **10**,[2] based on the stereocontrolled aldol condensation of the above quinuclidinone and related molecules,[5] are currently in progress in our laboratory.

Notes and References

1 CAPES postdoctoral Fellow, on leave from the University of Recife, PE (Brazil).
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