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Chiral N-acyliminium ions as new tools in the asymmetric synthesis of CNS-active compounds

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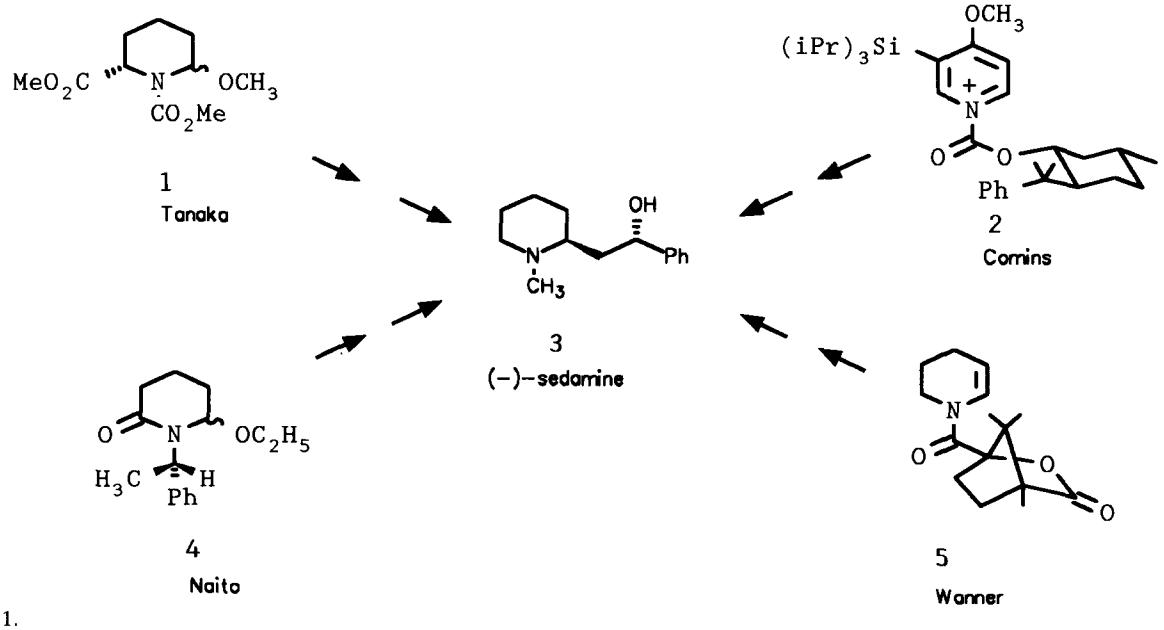
The addition reaction of a nucleophile to an N-acyliminium ion is a very efficient and valuable method for the synthesis of both α-substituted amides and α-substituted amines. This process, known for almost a century (Hellman, 1957), has been termed α-amidoalkylation. The last decade has witnessed the development of various methods of asymmetric syntheses on the basis of this reaction. These asymmetric syntheses employ three main strategies which differ mainly in the location of the chiral information needed for the asymmetric induction. They can nicely be illustrated by the synthesis of (–)-sedamine (**3**) which is a biologically active constituent of *Sedum acre* (Scheme 1).

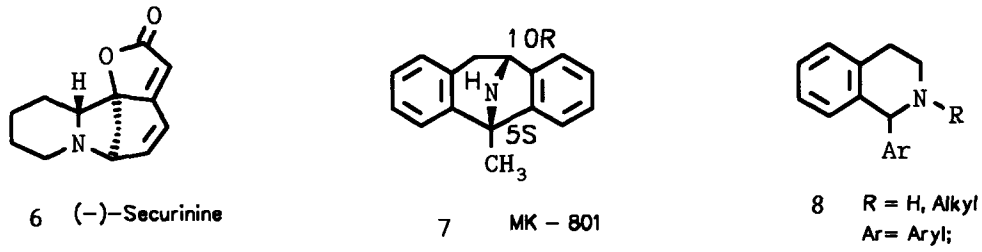
In one instance acyliminium ion precursors containing a chiral N-alkyl group which later becomes part of the final product (Irie et al., 1985) are used (see **1**). This process corresponds to a chiral pool synthesis. In another more general approach the N-alkyl group also contains the chiral information, but this group is designed as a mere chiral auxiliary which consequently will be removed upon completion of the asymmetric synthesis (see **4**) (Kiguchi et al., 1990). Finally, we ourselves relied on a concept wherein an N-acyl group represents the chiral auxiliary (see **5**). The first reagent we developed for this purpose is shown as **5** (Wanner and Kärtner, 1987). In this case the chiral auxiliary can easily be removed and the method as such may readily be applied to the preparation of a whole range of different nitrogen heterocycles. Recently others have also made use of this concept by employing carbamate-derived iminium ions as starting materials (**2**) (Comins and Hong, 1993).

As the above methods provide access to substituted amines they appear to be of particular value in the synthesis of CNS-active compounds such as (–)-securinine (**6**). This compound (see Scheme 2) is representative of a small group of alkaloids produced by plants of the family Euphorbiaceae and is known to act as a CNS-stimulant and as a convulsive. Only recently it



Scheme 1.

SSDI 0928-0987(94)00037-Z

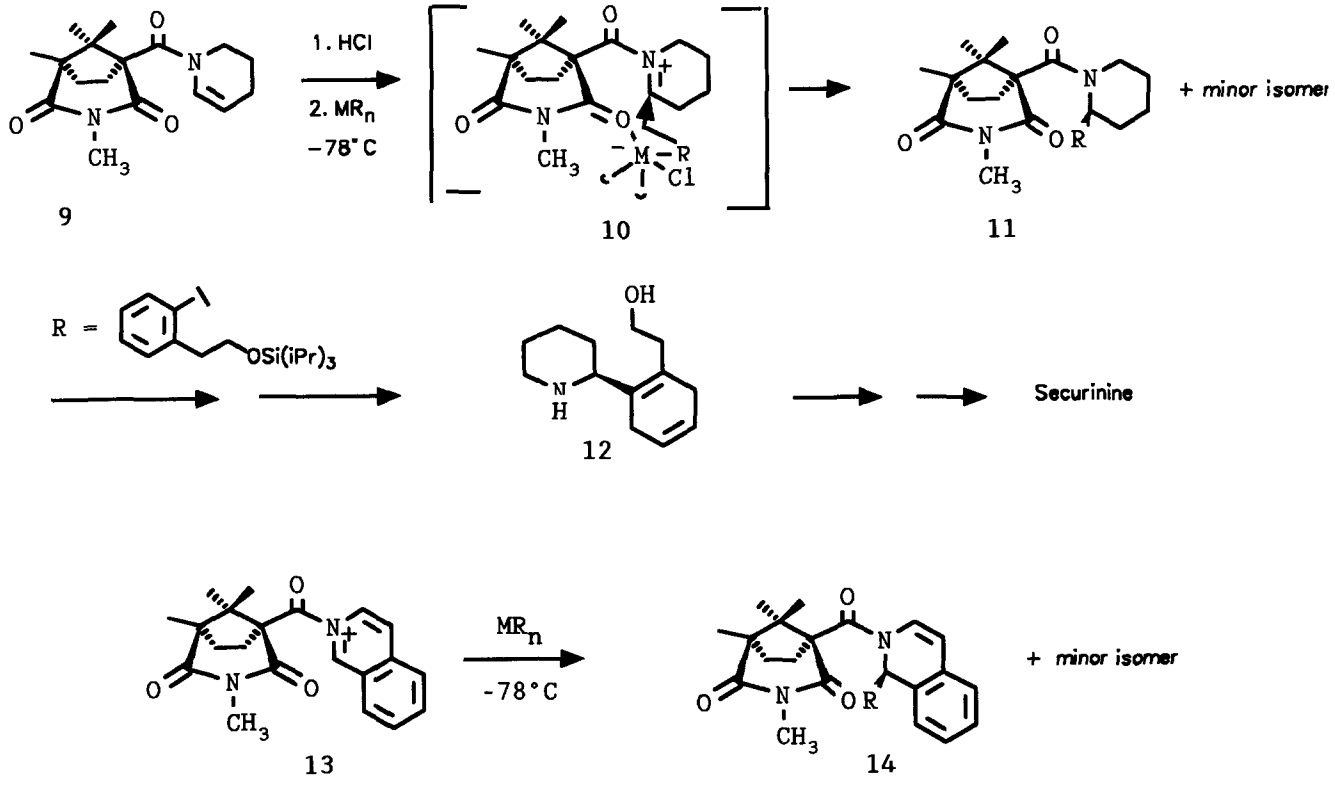


Scheme 2.

has been found to be a $GABA_A$-receptor antagonist acting at the GABA recognition site (Beutler and Brubaker, 1987). (–)-Securinine (**6**) with its unique ring skeleton thus appears to be a valuable lead for the development of new antagonists for the ligand binding site of the $GABA_A$-receptor. We report herein on our attempts directed towards a total synthesis of (–)-securinine (**6**) and the preparation of compounds with corresponding substructures as potential ligands for the $GABA_A$-receptor.

In addition to the above studies we are also engaged in the asymmetric synthesis of 1-aryl substituted tetrahydroisoquinolines (**8**). In a recent paper, representatives of this class of compounds have been reported to be noncompetitive NMDA antagonists (ion channel site) (Gray et al., 1989). They are related to MK-801 (**7**) which is a selective blocker of the NMDA receptor-associated ion channel. Its binding is stereoselective, the affinity of the (+)-enantiomer being seven times higher than that of the (–)-counterpart thereof (Wong et al., 1986). We wondered whether this was also true for the 1-aryl-isoquinolines (**8**). The binding data that have been reported until now related to racemic material only (Gray et al., 1989).

We chose compound (**12**) (Scheme 3) as key intermediate in our synthesis of securinine since we expected it to prove access both to the alkaloid and to substructures thereof. The homoallylic alcohol moiety was designated as synthetic precursor for the γ-lactone subunit whereas the second double bond was intended to serve as branching point in our synthesis. On the one hand, the latter was to afford the ring



Scheme 3.

skeleton of the alkaloid by a ring closure reaction with the amine nitrogen also present in the molecule and, on the other hand, e.g., by cleavage thereof, the double bond appeared to be useful in the preparation of derivatives of the natural product. The chiral amidoalkylation reagent (**9**) served as starting point of our synthesis. The chiral auxiliary of (**9**) is derived from camphoric acid and the decisive step for stereodifferentiation in this case is precomplexation (see **10**) (Wanner and Painter, 1994). We tested various organometallic reagents such as nucleophiles in this reaction and most of them were found to add smoothly to (**9**) (after its activation with HCl) giving (**11**) in high yields and with satisfactory diastereoselectivity. By proceeding in the manner just described, we also were able to obtain an addition product (**11**) (for R see Scheme 3) which could be further processed to afford the intermediate (**12**). Our efforts are now directed towards the synthesis of securinine and of substructures thereof for biological testing.

The chiral auxiliary of (**9**) proved useful also in the synthesis of 1-aryl substituted isoquinolines (**8**) the stereoselectivity of the addition step (**13**→ **14**) reaching 95/5. We finally converted the corresponding addition products to the free tetrahydroisoquinolines. Our next studies will concentrate on their affinity for the ion-channel set of the NMDA receptor.

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