Pergamon

Tetrahedron Letters, Vol. 36, No. 23, pp. 4059-4062, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00680-X

Thermal Rearrangement of Enantioenriched α-Hydroxy Imines -I. Enantiocontrolled Synthesis of α-Substituted α-Amino Ketones.

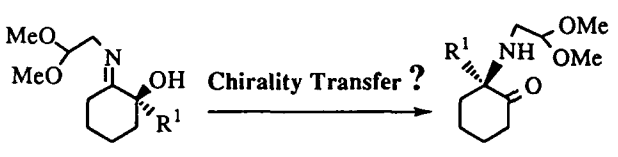
Philippe Compain, Jacques Goré and Jean-Michel Vatèle*

Laboratoire de Chimie Organique I , associé au CNRS, Université Claude Bernard CPE-Lyon, 43 Bd. du 11 Novembre 1918, 69622 Villeurbanne, France.

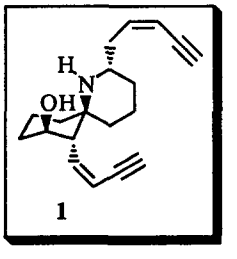
Abstract : Enantioenriched 2-allyl- and 2-(3-trimethylsilylpropargyl)-2-hydroxycyclohexanone were respectively obtained by resolution from the corresponding diastereomeric acetal derived from C_2-symmetrical diol or from the camphanate ester. Study of the rearrangement of their corresponding imine derivatives has shown that it occurred with complete retention of the stereogenicity.

The azaspiro[5.5]undecane skeleton is found in a variety of natural alkaloids[1] which display quite interesting biological properties. Among them, histrionicotoxin **1** and its congeners, isolated from the skin extracts of the Colombian dart frogs, *Dendrobates histrionicus*[1b]. Both histrionicotoxin **1** and its fully hydrogenated analog, perhydrohistrionicotoxin, have been used to study the mechanism involved in the transsynaptic transmission of neuromuscular impulses[2].

In connection with our efforts devoted to the synthesis of the histrionicotoxins, we recently described an efficient method to synthesize α-aminocyclohexanone derivatives bearing an allyl or a silylated propargyl group, good candidates for the elaboration of 1-azaspiro[5.5]undecane ring system[3]. This method involves a benzylic-type rearrangement with a 1,2-allyl or propargyl shift (scheme 1).



R^1 = Allyl, 3-Me_3Sipropargyl



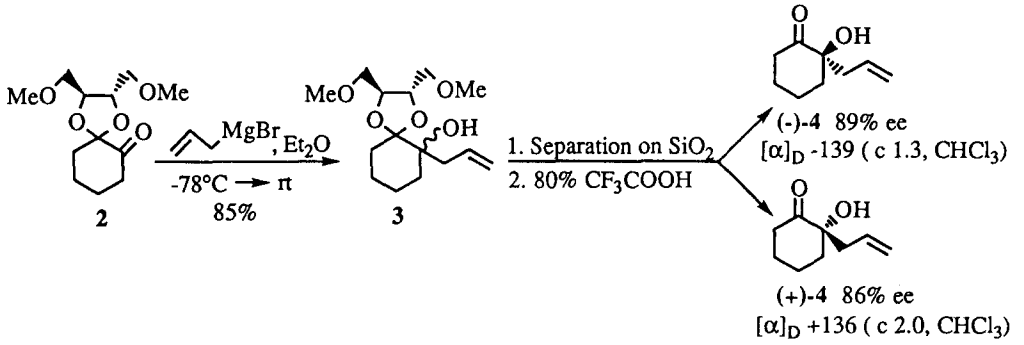
Scheme 1

Herein, we wish to report our results on the study of the stereochemical outcome of the rearrangement of optically active α-allyl and α-TMSpropargyl α-hydroxy imines.

The transposition of α-hydroxy imines has been well studied by Stevens *et al.*[4] from a theoretical standpoint mainly with phenyl as a migrating group. From kinetic studies[5] and experimental data[6], the rearrangement was envisioned as proceeding in an intramolecular concerted manner. Only one report dealing with

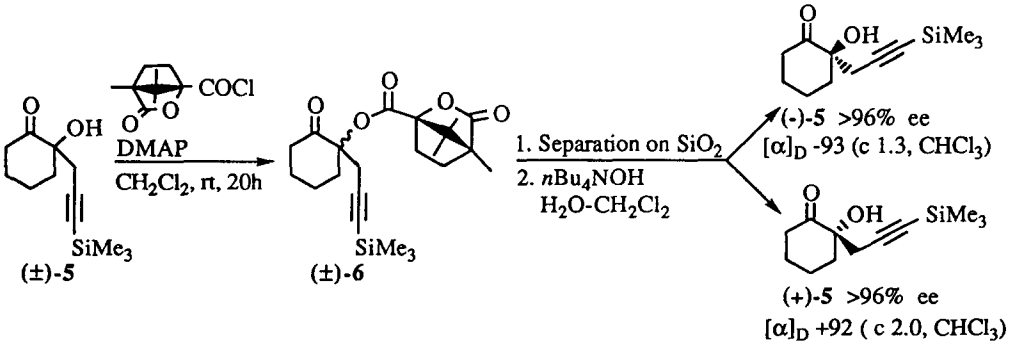
the asymmetric induction of thermal rearrangement of an optically active open-chain α-hydroxy imine with 1,2-phenyl shift has confirmed this mechanism[7].

In order to know whether the rearrangement of α-hydroxy imines involving an allyl or propargyl migrating groups also occurs through a highly ordered transition state, allowing in principle a 1,2-chirality transfer, we synthesized enantioenriched α-ketols **4** and **5**. As outlined in Scheme 2, (R and S) α-allyl-α-ketol **4** was prepared from chiral α-keto acetal **2**, available in 2 steps from α-hydroxycyclohexanone[8] and (2S,3S)-1,4-dimethoxy-2,3-butanediol[9] in 54% yield. In contrast with what had been reported with other organometallic reagents[10], addition of allylmagnesium bromide in ether to the ketone **2**, at -78°C, occurred with almost no diastereoselectivity (8% de). Chromatographic separation of diastereomeric α-hydroxy acetals **3** on silica gel followed by treatment with 80% aqueous CF_3CO_2H provided enantioenriched (+) and (-) **4**[11].



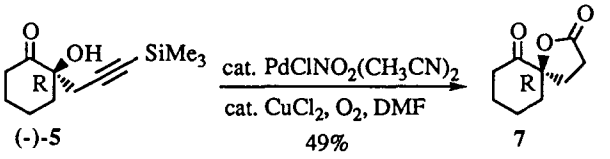
Scheme 2

Resolution of the racemic mixture of **5** [3] from its diastereomeric α-hydroxy acetal derived from C_2 symmetrical diol was unsuccessful. Pure enantiomers of α-ketol **5** could be nevertheless obtained by resolution *via* diastereomeric camphanate esters[14] (scheme 3). Esterification of (±)-**5** was effected with (-)-camphanic acid chloride in the presence of 2.4 equiv. of DMAP[15] which allowed the reaction to be carried out at room temperature. Easy separation of the diastereomeric esters **6** by flash chromatography followed by saponification with *n*Bu4NOH in a two-phase system[14] afforded pure(-) and (+)-**5**[16] respectively in 33% and 27% yield from racemic **5**.



Scheme 3

The absolute configuration of (-) **5** was determined by its conversion to the known(-)-γ-butyrolactone **7**[17] $[\alpha]_D$ -44 (c 1.65, AcOEt) [litt.[17] $[\alpha]_D$ -44 (c 6, AcOEt)], *via* a method we recently described and involving a Wacker-type reaction[18] (Scheme 4).

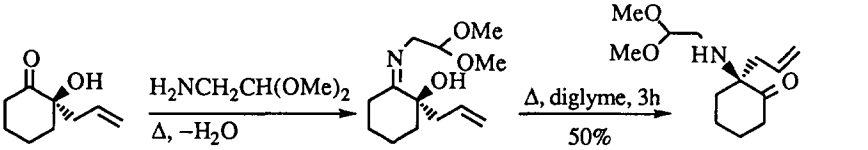


(-)-5 7

Scheme 4

Having in hands enantioenriched **4** and **5**, we next turned our attention to the study of the extent of the transfer of stereogenicity during the rearrangement of α-hydroxyimines **8**, **10**.

As depicted in scheme 5, condensation of (-)-**4** with 1.5 equiv. of 2-aminoacetaldehyde dimethylacetal in refluxing toluene under Dean-Stark conditions afforded quantitatively imine **8**. The crude imine was heated in refluxing diglyme for 3 h to provide, after purification on silica gel, α-amino ketone **9**, $[\alpha]_D$ -15 (c 1.47, $CHCl_3$), in 50% yield (10% of the starting material was recovered)[20]. The optical purity of (-)-**9** (90%), determined by ^{1}H-NMR experiments in the presence of Eu(hfc)3, showed that the rearrangement occurred with a complete transfer of chirality.

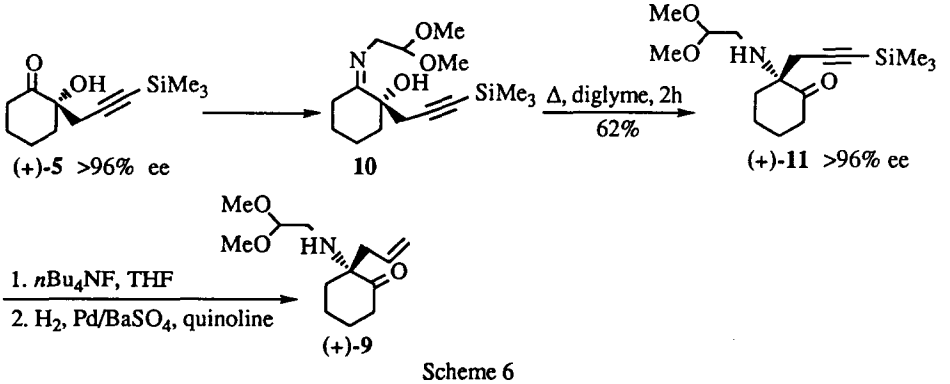


(-)-4 89% ee 8 (-)-9 90% ee

Scheme 5

Then, imine **10**, obtained from (+)-**5**, subjected to the rearrangement conditions (2h, refluxing diglyme) gave α-amino ketone (+)-**11** in 62% yield, $[\alpha]_D$ + 30 (c 2.8, $CHCl_3$) (Scheme 6). The optical purity of (+)-**11** (>96%) was established[21] by its transformation, in 2 steps, to the α-allyl α-amino ketone **9** and comparison of its optical rotation[22] with that of the compound obtained by rearrangement of **8**.

As in the case of α-hydroxyimine **8**, 1,2-shift of the silylated propargyl group during rearrangement of **10** proceeded with total asymmetric transmission.



(+)-5 >96% ee 10 (+)-11 >96% ee (+)-9

Scheme 6

In summary,we have demonstrated that the transposition of α-hydroxy imines **8** and **10** happens with a total 1,2-chirality transfer. Moreover, the 1,2-shift is suprafacial with inversion of configuration as it will be shown in the following paper.

Finally, this rearrangement allows the facile and rapid asymmetric preparation of potential intermediates of the histrionicotoxin synthesis. Work directed to a more efficient enantioselective synthesis of **4** and **5** is in progress in our laboratory.

Acknowledgments. One of us (P.C.) thanks Ministère de l'Enseignement Supérieur et de la Recherche for a fellowship.

References and notes :

1. For examples of alkaloids containing a 1- or 2-azaspiro[5.5] undecane ring system see : (a) Keppens, M. ; De Kimpe, N. Synlett, **1994**, 285-286 and references cited therein (nitramine and its congeners). (b) Daly, J.W. *in Fortschifte der Chemie Organisher Naturstoffe*, ed. Herz, W. ; Grisebach, H. and Kirby, G.W. *Springer Verlag*, New-York **1982**, vol. 41, pp 205-340 (the histronicotoxin family).
2. Spivak, C.E. ; Maleque, M.A. ; Oliviera, A.C. ; Masukawa, L. ; Tokuyama, K. ; Daly, J.W. ; Albuquerque, E.X. *Mol. Pharmacol.* **1982**, *21*, 351. Takahashi, K.; Witkop, B. ; Brossi, A. ; Maleque, M.A. and Albuquerque, E.X. *Helv.Chim.Acta* **1982**, *65*, 252-261.
3. Vatèle, J.M. ; Dumas, D. and Goré, J. *Tetrahedron Lett.*, **1990**, *31*, 2277-2280.
4. Stevens, C.L. ; Pillai, P.M. ; Munk, M.E. and Taylor, K.G. *Mech.Mol.Migr.*, **1971**, *3*, 271-296.
5. Stevens, C.L. ; Hanson, H.T. and Taylor, K.G. *J.Am.Chem.Soc.* **1966**, *88*, 2769-2774.
6. Stevens, C.L. ; Thuillier, A. and Daniher, F.A. *J.Org.Chem* **1965**, *30*, 2962 ; Stevens, C.L. ; Klundt, I.L. ; Munk, M.E. and Pillai, M.D. *J.Org.Chem.* **1965**, *30*, 2967-2972 ; Stevens, C.L. ; Ash, A.B. ; Thuillier, A. ; Amin, J.H. ; Balys, A. ; Dennis, W.E. ; Dickerson, J.P. ; Glinski, R.P. ; Hanson, H.T. ; Pillai, M.D. and Stoddard, J.W. *J.Org.Chem.* **1966**, *31*, 2593-2601.
7. Yamada, S.I. ; Mizuno, H. and Terashima,S. *J.Chem.Soc.chem.Comm.* **1967**, 1058-1060.
8. Cohen, T. and Tsuji, T. *J.Org.Chem.* **1961**, *26*, 1681.
9. Seebach, D. ; Kalinowski, H.O. ; Bastani, B. ; Grass, G. ; Daum, H. ; Dörr, H. ; Du Preez, N.P. ; Ehrig, V. ; Langer, W. ; Nüssler, C. ; Oei, H. and Schmidt, M. *Helv.Chim.Acta* **1977**, *60*, 301-325.
10. Tamura, Y. ; Kondo, H. ; Annoura, H. ; Takeuchi, R. and Fujioka, H. *Tetrahedron Lett.* **1986**, *27*, 81-82.
11. The absolute configuration of (+)-and(-) **4** was established by correlation of the sign of their specific rotation with those of similarly constituted chiral molecules[12] (Freudenberg's rule of shift[13]). Their optical purity was determined by ^{1}H NMR of their corresponding O-methoxyacetate by LIS experiments (Eu(hfc)$_3$).
12. Fujisawa, T. ; Watanabe, M. and Sato, T. *Chem.Lett.* **1984**, 2055-2058.
13. Eliel, E.L. ; Wilen, S.H. and Mander, L.N. in *Stereochemistry of Organic Compounds*, Wiley J., New York, **1944**, pp 1080-1083.
14. Kolb, H.C. and Hoffmann, H.M.R. *Tetrahedron : Asymmetry*, **1990**, *1*, 237-250.
15. Grawronski, J.K. ; Madhava Reddy, S. and Walborsky, H.M. *J.Amer.Chem.Soc.*, **1987**, *109*, 6726-6730.
16. The optical purity of (+) and (-)-**5** was determined from their corresponding camphanate ester by ^{13}C NMR spectroscopy.
17. Desmaële, D. and d'Angelo, J. *Tetrahedron Lett.* , **1989**, *30*, 345-348.
18. Compain, P. ; Vatèle, J.M. and Goré, J. *Synlett* , **1994**, 943-945.
19. All new compounds gave satisfactory elemental analyses and their spectra data (IR, ^{1}H and ^{13}C NMR) agree with the proposed structures.
20. As shown by C.I. Stevens *et al.*, the rearrangement of α-hydroxyimines to α-amino ketones is an equilibrated reaction[5]. Depending very much of the substrate we recovered between 5 to 50% of the starting α-ketol (Vatèle, J.M., unpublished results).
21. Determination of the optical purity of (+)-**11** by LIS-NMR experiments was unsuccessful.
22. Compound **9** obtained from (+)-**11** has a specific rotation value of + 17 (c 0.8, $CHCl_3$).

(*Received in France* 8 *March* 1995; *accepted* 7 *April* 1995)