Tetrahedron Letters,Vol.25,No.47,pp 5377-5380,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

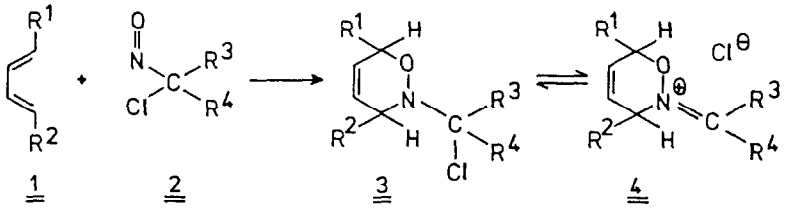
ASYMMETRIC DIELS - ALDER REACTIONS WITH α-CHLORONITROSO COMPOUNDS - I. APPLICATION OF α-CHLORONITROSO EPIANDROSTERONE IN SYNTHESIS

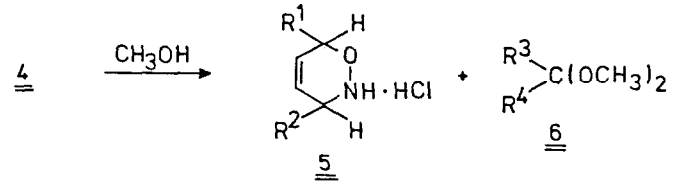
Mahmud Sabuni, Günter Kresze* and Heinz Braun
Organisch-chemisches Institut der Technischen Universität München
Lichtenbergstraße 4, D-8046 Garching

Abstract: The Diels - Alder reaction of 1,3-cyclohexadiene (9) with the enantiomerically pure α-chloronitroso compound 8, synthesized from epiandrosterone (7a), gives the adduct 10a with 1-(R),4-(S) configuration in 69 % chemical yield and ⩾95 % enantiomeric excess.

In connection with our work directed toward the synthesis of streptamine analogues[1], which are interesting building blocks for mutasynthesis of antibiotics, we have investigated asymmetric Diels - Alder reactions with α-chloronitroso compounds. Diastereoselective Diels - Alder reactions using chiral dienophiles or dienes have received considerable attention during the last years[2]. In most cases[3], high asymmetric induction is achieved by the formation of a complex with rigid conformation between reaction partners and a Lewis acid (Lewis acid promoted [4+2] cycloadditions[4]).

With nitroso compounds as dienophiles, there is another possibility of reaching high diastereoselectivity, as we have pointed out in describing the first example of such an asymmetric synthesis[5]: By use of an α-chloronitroso compound with rigid molecular framework and bulky groups in the vicinity of the C(Cl)NO - moiety, the free rotation around the C-NO - bond may be suppressed. The diene in its least hindered orientation then attacks preferentially one side of the nitroso group. In the case of an enantiomerically pure nitroso derivative, this results in a diastereoselectivity if the 1,3-diene is substituted in 1- or 1,4-position.

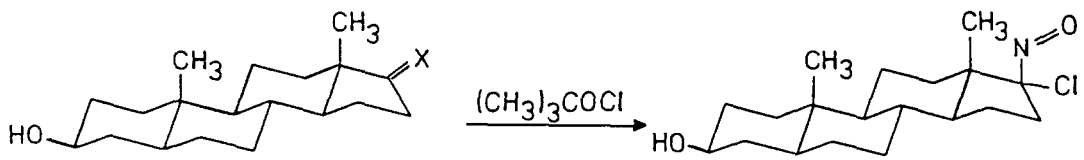




There are several advantages in the use of chiral α-chloronitroso compounds in cycloadditions:

- The dienophilic reactivity of the nitroso group is high enough to allow reaction to proceed under mild conditions with a variety of dienes, even with severely hindered ones[6].
- The nitroso group is directly attached to a center of chirality, with properly designed nitroso compounds this attachment should favour high asymmetric induction.
- By solvolysis of the isomeric immonium salt 4 of the adduct 3, the nitrogen-carbon bond is cleaved. Thereby, the cycloaddition becomes irreversible, on the one hand, and, on the other hand product 5 does no longer contain the chiral center(s) of the reagent.
- Finally, by this solvolysis reaction, the group formerly attached to the nitroso group is converted into the acetal 6 of the corresponding ketone. In this way, a reuse of the starting material is possible, which may be important in the case of expensive educts.

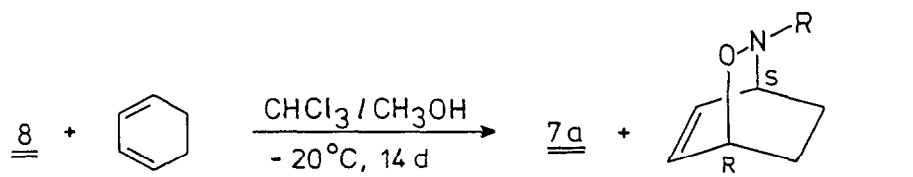
Following this reasoning we have designed a model reagent useful for effecting asymmetric synthesis.



7a, X = O
b, X = NOH

8

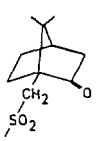
The compound chosen was 17-chloro-17-nitroso-3β-hydroxy-5α-androstane (8), which may be prepared easily by treating the oxime of epiandrosterone 7b[7] with tert.-butyl hypochlorite (CH_2Cl_2, 6 h at -30°C, then 48 h at -18°C). The resulting mixture of diastereomeric nitroso compounds is separated by HPLC (silicagel, 10-40μ, n-hexane/ethylacetate 5:1) and the main product ($[\alpha]_D^{20}$+449° (c = 0.93), m.p. 138 - 140°C dec.)[8] is isolated in 50 % yield.
We ascribe the 17α-chloro-17β-nitroso configuration to 8. The given stereochemistry is based on the ^{13}C NMR spectrum of 8 (C-17: δ = 128 ppm)[9].



9

10a, R = H·HCl

b, R =

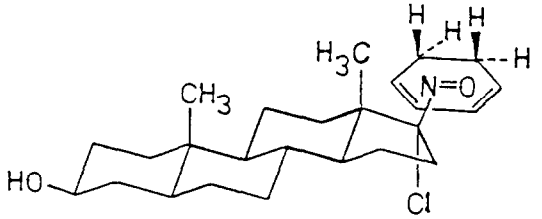


By reaction of the blue compound 8 with cyclohexadiene (9) (molar ratio 1:5) in $CHCl_3$ solution in the presence of CH_3OH (2 weeks at -20°C for total decoloration), an optically active adduct 10a is formed. The crystalline mixture of the adduct 10a and epiandrosterone dimethylacetal was separated by treating it with diluted HCl and $CHCl_3$. From the aqueous solution 69 % hydrochloride 10a (m.p. 163° from ethanol, $[\alpha]_D^{20}$ -24° (c = 5.0 CH_3OH) was isolated and from the $CHCl_3$ phase 72 % epiandrosterone (7a) could be recovered.

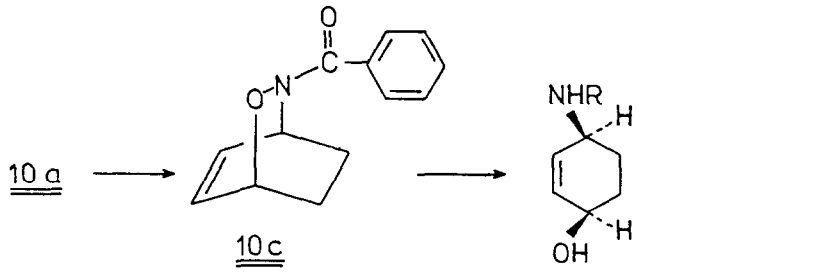
To ascertain the optical purity of 10a, we prepared its D-camphor-10-sulfonyl derivative 10b (m.p. 120°C from ether/petrolether). Whereas the sulfonamide derived from the racemic adduct (prepared identically from 9 and α-chloronitrosocyclohexane[6]) showed two AB type signals (δ = 3.54/2.83 and 3.44/2.99) for the 10-methylene group in the 200 MHz ^1H NMR spectrum with equal intensity, the derivative 10b of the optically active adduct gave only one AB system (δ = 3.44/2.99 ppm) with measurable intensity. Taking into account the known uncertainty of quantitative NMR measurements, we may state that the reaction described proceeds with an enantiomeric excess of at least 95 %.

The configuration of (-)10a had been proven previously[10] by chemical degradation to N-trifluoroacetylglutaric acid diisopropylester to be 1-(R),4-(S).

This configuration is to be expected if the approach of the diene to the nitroso compound occurs in the way shown in the picture.



The easy accessibility of optically active adducts with 1-(R),4-(S) configuration as well as with 1-(S),4-(R) configuration[11] offers attractive possibilities for the synthesis of chiral conduramines[12] and streptamine analogues[1].



11a, R = H

b, R = COC_6H_5

Benzoylation of 10a and reductive cleavage of the N-O-bond of 10c[13] by a method introduced by Keck[13] gives the products 11b or 11a in excellent yields. 11b or 11a allow the introduction of two further heteroatom substituents, for example by hydroxylation of the double bond[1,12]. Starting the Diels-Alder reaction of 8 with 1,3-cyclohexadienes already containing heteroatom substituents in position 5 and 6 and treatment of the adducts as described above, may afford optically active streptamine analogues with well defined stereochemistry. This work is in progress.

Acknowledgement:
We are indebted to Dr. R. Charles for GC measurements with chiral columns.
Financial support of this work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

References and Notes

1) G. Kresze, M. Weiß, and W. Dittel, Liebigs Ann. Chem. 1984, 203 and references cited therein.
2) Recent reviews: a) Y. I. Mori, J. Synth. Org. Chem., Jpn. 40, 321 (1982). b) P. Welzel, Nachr. Chem. Tech. Lab. 31, 979 (1983). c) H. Wurziger, Kontakte (Darmstadt) 1984 (2) 3.
3) For exceptions see: W. Choy, L. A. Reed, and S. Masamune, J. Org. Chem. 48, 1139 (1983).
4) Leading references: a) W. Oppolzer, Ch. Chapuis, and M. Kelly, Helv. Chim. Acta 66, 2358 (1983).
b) S. Masamune, L. A. Reed, J. T. Davis, and W. Choy, J. Org. Chem. 48, 4441 (1983).
c) B. M. Trost, D. O'Krongly,and J. C. Belletire, J. Am. Chem. Soc. 102, 7595 (1980).
5) H. Nitsch, and G. Kresze, Angew. Chem., Int. Ed. Engl. 15, 760 (1976).
6) G. Kresze, and J. Firl, Fortschr. Chem. Forsch. 11, 245 (1969).
7) L. Ruzicka, M. Goldberg, J. Meyer, H. Brüngger, and E. Eichenberger, Helv. Chim. Acta 17, 1395 (1934).
8) All new compounds described in this publication gave correct elementary analysis and spectral data.
9) The large shift indicates normally a severely hindered position of the nitroso group: G. Kresze, T. Bosch, H. Nitsch, and V. Arndt, unpublished.
10) U. Dederer, Dissertation TU München 1984. GC measurements by Dr. R. Charles, Rehovoth.
11) H. Felber, G. Kresze, H. Braun, and A. Vasella, Tetrahedron Lett. 1984, following paper.
12) a) G. Kresze, W. Dittel, and H. Melzer, Liebigs Ann. Chem. 1981, 224.
b) G. Kresze, and W. Dittel, Liebigs Ann. Chem. 1981, 610.
13) G. E. Keck, S. Fleming, D. Nickell, and P. Weider, Synthetic Commun. 9, 281 (1979).

(Received in Germany 23 August 1984)