Pure & Appl. Chem., Vol. 66, Nos 10/11, pp. 2159–2162, 1994.
Printed in Great Britain.

Asymmetric synthesis of natural products monitored by chiral sulfoxides

Guy Solladié*, Antonio Almario, Carmen Dominguez

Ecole Européenne des Hautes Etudes des Industries Chimiques, Laboratoire de Stéréochimie associé au CNRS, 1, Rue Blaise Pascal, 67008 Strasbourg, France

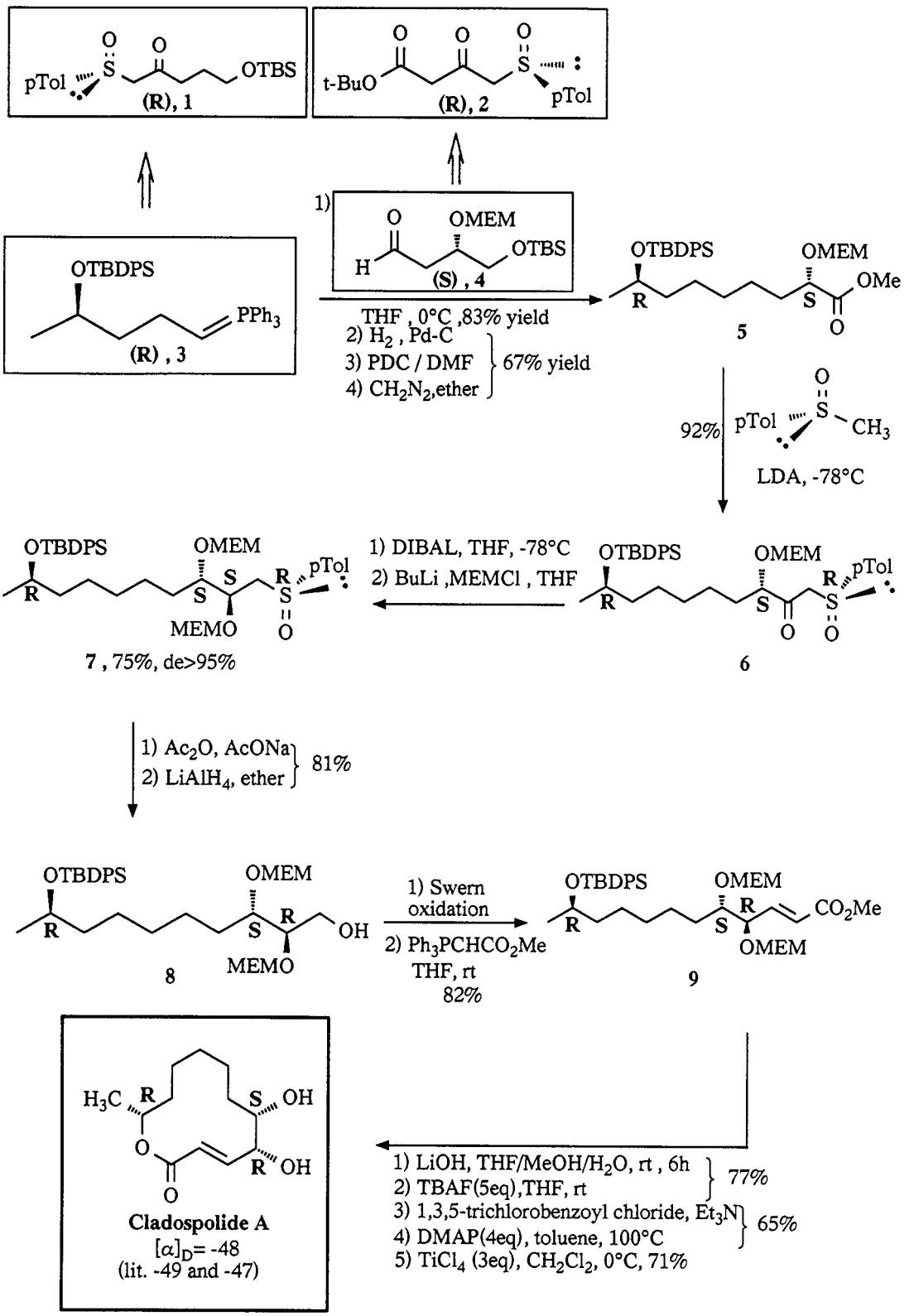
Abstract : The macrolide cladospolide A and of (+) (2S, 3S, 6R, 8R) - nonactic and (-) (2R, 3R, 6S, 8R)-epi-nonactic acids were, enantioselectively prepared. The formation of the chiral centers was controlled by a chiral sulfoxide group.

The stereoselective reduction of optically active β-ketosulfoxides is now a well documented reaction (1) and several applications to total synthesis of natural products have already been published (2).

The macrolide cladospolide A, **1**, a root-growth inhibitor of lettuce seedlings produced by *cladosporium cladosporioides* FI-113 (3), shows interesting structural features for the synthetic organic chemist : three chiral hydroxylic centers with particularly an anti 1,2-diol moiety.
The main new point of the synthesis of **1**, with respect to our preceding work on the reduction of β-ketosulfoxides (2), will be the asymmetric synthesis of the anti 1,2-diol part monitored by chiral sulfoxides.

As shown on scheme I, protected methyl (2S, 8R) 2,8-dihydroxy nonanoate was obtained by a Wittig condensation of the phosphorus ylide (R)-**3** and the aldehyde (S)-**4**, readily obtained by reduction of the β-ketosulfoxides (R)-**1** and (R)-**2** (4), followed by double bond reduction, oxidation of the primary alcohol and esterification.

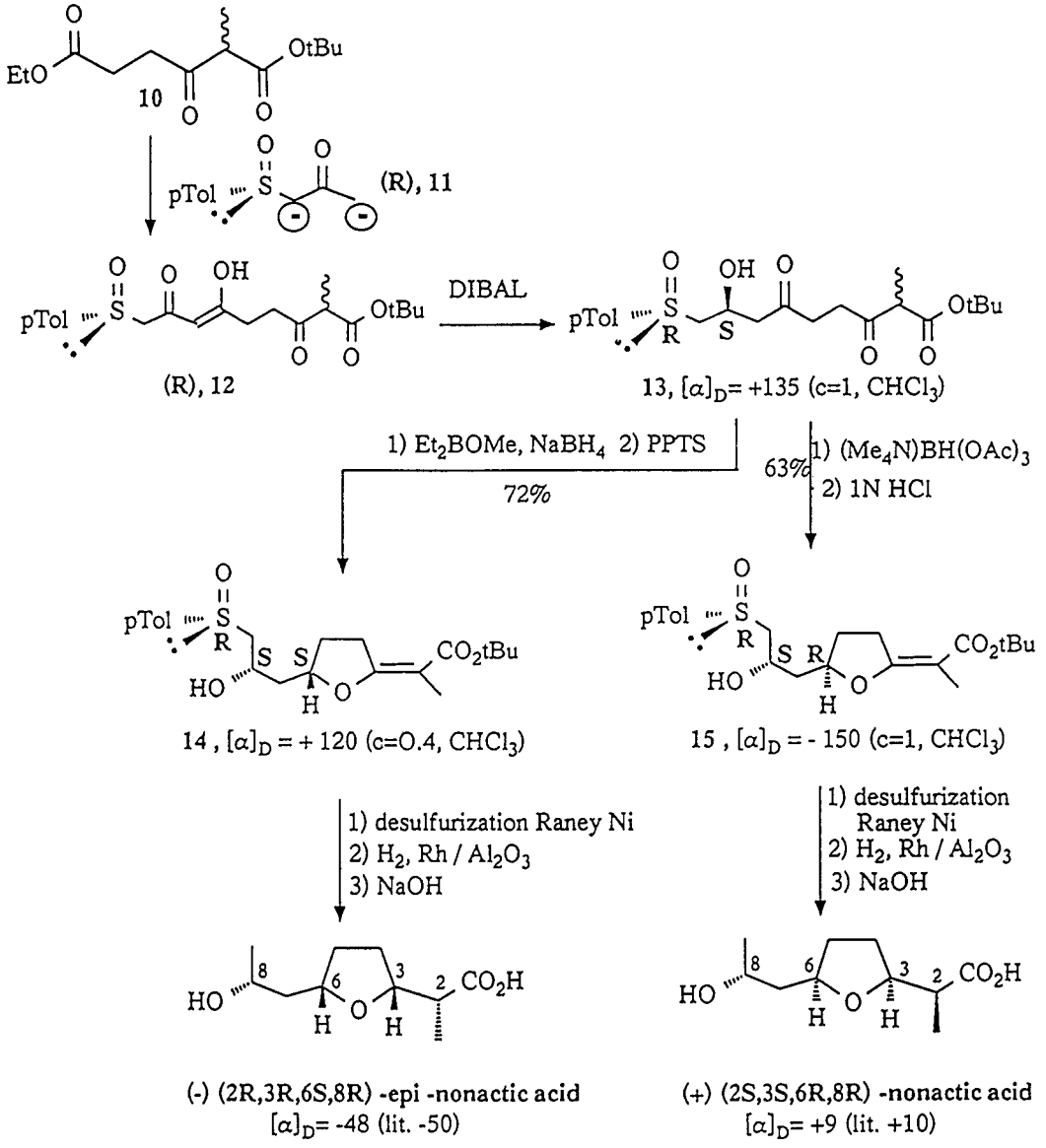
Condensation of (+)(R) methyl p-tolylsulfoxide on the ester lead to the β-ketosulfoxide **6** which gave upon DIBAL reduction and protection of the created OH group, the trihydroxy sulfoxide **7** as the unique diastereomer, as shown by ^1H NMR (only one ABX system could be detected for the methylene α to the sulfoxide). The stereochemistry of the reduction was completely controlled by the sulfoxide (5). The S absolute configuration of the created hydroxylic center was deduced from our preceding work (1,2) and will be confirmed by correlation with cladospolide A. Pummerer rearrangement followed by $LiAlH_4$ reduction


pTol
OTBS
(R), 1
t-BuO
pTol
(R), 2
OTBDPS
PPh3
(R) , 3
1)
OMEM
OTBS
(S) , 4
THF , 0°C ,83% yield
2) H2 , Pd-C
3) PDC / DMF
4) CH2N2,ether
67% yield
OTBDPS
OMEM
OMe
5
92%
pTol
CH3
LDA, -78°C
OTBDPS
OMEM
pTol
MEMO
7 , 75%, de>95%
1) DIBAL, THF, -78°C
2) BuLi ,MEMCl , THF
OTBDPS
OMEM
pTol
6
1) Ac2O, AcONa
2) LiAlH4, ether
81%
OTBDPS
OMEM
OH
MEMO
8
1) Swern oxidation
2) Ph3PCHCO2Me
THF, rt
82%
OTBDPS
OMEM
CO2Me
9
H3C
OH
OH
Cladospolide A
[α]D= -48
(lit. -49 and -47)
1) LiOH, THF/MeOH/H2O, rt , 6h
2) TBAF(5eq),THF, rt
77%
3) 1,3,5-trichlorobenzoyl chloride, Et3N
4) DMAP(4eq), toluene, 100°C
65%
5) TiCl4 (3eq), CH2Cl2, 0°C, 71%

Scheme I

afforded the compound 8. Swern oxidation and Wittig reaction gave the seco-ester 9 which was finally cyclized, using procedures described in the literature (6), to cladospolide A showing all the known characteristics (6).

The ionophoric macrolide antibiotic Nonactin, isolated from a variety of *streptomyces* cultures (7) is composed of two subunits of (+) nonactic acid and two subunits of (-) epi-nonactic acid. We now report the enantioselective synthese of both (+) (2S, 3S, 6R, 8R). nonactic acid and (-) (2R, 3R, 6S, 8R)-epi-nonactic acid via the asymmetric reduction of the β,δ-diketosulfoxide (R)-12, using our recent discovery that β,δ-diketosulfoxides could lead, in a highly stereoselective manner, to optically pure syn and anti 1,3-diols (8) (Scheme II).



Scheme II

The sulfoxide (R)-12 was prepared by condensation of the dianion of (R) p-tolylsulfinyl propanone 11 (9) on the methyl t-butyl 2-methyl-3,6-diketo-octanedioate 10. As expected (9), the δ-carbonyl was totally enolized. DIBAL reduction resulted in the stereoselective reduction

of the β-carbonyl (8) (DIBAL being chelated of the sulfoxide oxygen reduces only the β-carbonyl) to give compound **13** as a unique diastereomer in 60% yield (only one ABX sytem for the CH_2 a to the sulfoxide was detected by ^1H NMR). The reagent, $Et_2BOMe/NaBH_4$, which is known to stereoselectively give syn 1,3-diols from 1,3-hydroxyketones (10) was then used. However in our case, the resulting diol spontaneously reacted, in the reaction medium, with the carbonyl β to the ester, to give the corresponding five membered lactol which was dehydrated with PPTS to give the furane **14** as a unique diastereomer.

Desulfurization, double bond reduction and saponification afforded (-)(2R,3R,6S,8R)-epi-nonactic acid (12). On the other hand, using the Evans reagent, $(Me_4N)BH(OAC)_3$, which is known to give anti 1,3-diols from 1,3-hydroxyketones (11), we observed in this case cyclisation of the resulting diol to the corresponding bicyclic acetal which was converted into **15** with acid, probably through the corresponding lactol. Furane **15** was finally transformed by the procedure used in the diastereomeric series into (+)(2S,3S,6R,8R)-nonactic acid (12).

In conclusion, we have shown in this work the powerful utility of chiral sulfoxides in total synthesis of natural products to create optically pure syn and anti 1,2 and 1,3-diols. Furthermore, we have been able to report one of the shortest asymmetric synthesis of nonactic and epi-nonactic acids.

References.

1) a) Solladié, G. ; Demailly, G. ; Greck, C., *Tetrahedron Lett.* **26**, 435-438 (1985); b) Solladié, G. ; Demailly, G. ; Greck, C. ; *J. Org. Chem.* **50**, 1552-1554 (1985); c) Solladié, G. ; Fréchou, C. ; Demailly, G. ; Greck, C., *J. Org. Chem.* **51**, 1912-1914 (1986); d) Solladié-Cavallo, A. ; Suffert, J. ; Adib, A. ; Solladié, G., *Tetrahedron Lett.* **31**, 6649-6652 (1990).

2) Solladié, G. ; Rubio, A. ; Carreño, M.C. ; Garcia-Ruano, J.L., *Tetrahedron Asym.* **1**, 187-198 (1990); Solladié, G.; Maestro, M.C; Rubio, A.; Pedregal, C.; Carreño, M.C.; Garcia-Ruano, J.L., *J. org. Chem.*, **56**, 2317 (1991); Solladié, G.; Almario, A.; Colobert, F., *Synlett*, 167, (1992); Solladié, G.; Stone, G.B.; C. Hamdouchi, C., *Tetrahedron Lett.*, **34**, 1807-1810 (1993); Solladié, G.; C. Ziani-Chérif, C., *J. Org. Chem.*, **58**, 2181-2185 (1993).

3) Hirota, A. ; Isogai, A. ; Sokai, H., Agric. Biol. chem. **45**, 799 (1981) and **49**, 731 (1985).

4) Solladié, G.; Almario, A., *Tetrahedron Lett.*, **33**, 2477 (1992).

5) Solladié, G.; Almario, A., unpublished results.

6) Mori, K. ; Maemoto, S., Liebigs Ann. Chem. 863-869 (1987).

7) Dominguez, J. ; Dunitz, J.D. ; Gerlach, H. ; Prelog, V., Helv. Chim. Acta. **45**, 129 (1962) ; Gerlach, H. ; Prelog, V., Liebigs Ann. Chem. **669**, 121 (1963).

8) Solladié, G. ; Ghiatou, N., *Tetrahedron Lett.* **33**, 1605 (1992).

9) Solladié, G. ; Ghiatou N., *Tetrahedron Asym.* **3**, 33 (1992).

10) Chen, K. ; Harttmann, G. ; Prasad, K. ; Repic, O. ; Shapiro, H.J., *Tetrahedron Lett.* **28**, 155 (1987).

11) Evans, D.A. ; Chapman, K.T. ; Carreira, E.M.T., *J. Am. Chem. Soc.* **110**, 3560 (1988).

12) Ireland, R.E. ; Vevert, J.P., *Can. J. Chem.* **59**, 572-583 (1981).