Pergamon

Tetrahedron Letters, Vol. 37, No. 39, pp. 7019-7022, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01540-7

Preparation and Use of Chiral (*Z*)-Enol Ethers in Asymmetric Bradsher Cycloaddition

Olivia Sageot, Daphnée Monteux, Yves Langlois*

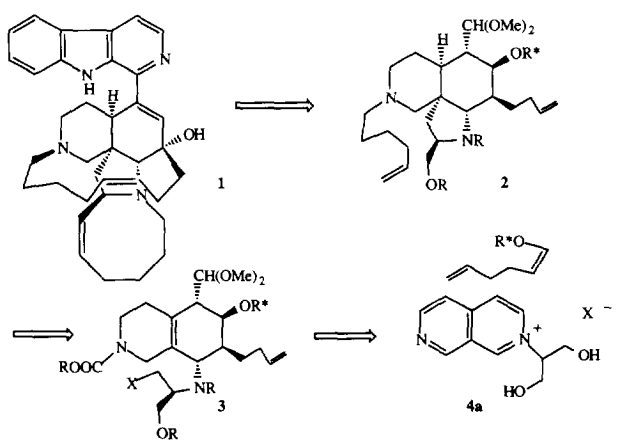
Laboratoire de Synthèse des Substances Naturelles,
Laboratoire des Réactions Sélectives sur Supports
Associés au CNRS, Bâtiment 410, Université de Paris-Sud, 91405, Orsay, France.

Claude Riche, Angèle Chiaroni.

Institut de Chimie des Substances Naturelles, CNRS,
91190, Gif sur Yvette, France

Abstract: Chiral (Z)-enol ethers **7a-7p** have been prepared in two steps. Bradsher cycloaddition between such compounds and 2,7-naphthyridinium salt **4b** in water or in *ter*-butanol-water afforded, in some cases with good yield and diastereoselectivity, highly functionalized isoquinoline derivatives, potential intermediates in Manzamine A **1** total synthesis. X-Ray analysis secured the direction of asymmetric induction with enol ether **7l**. Copyright © 1996 Published by Elsevier Science Ltd

During the course of preliminary studies toward the total synthesis of cytotoxic alkaloid Manzamine A **1**[1], we recently demonstrated[2] the synthetic potential of a Bradsher cycloaddition[3] strategy. An extension of this reaction to its asymmetric counter part could give rise in few steps to highly functionalized isoquinoline derivative **3**, potential precursor of Manzamine A **1** according to the retrosynthetic scheme (Scheme1).

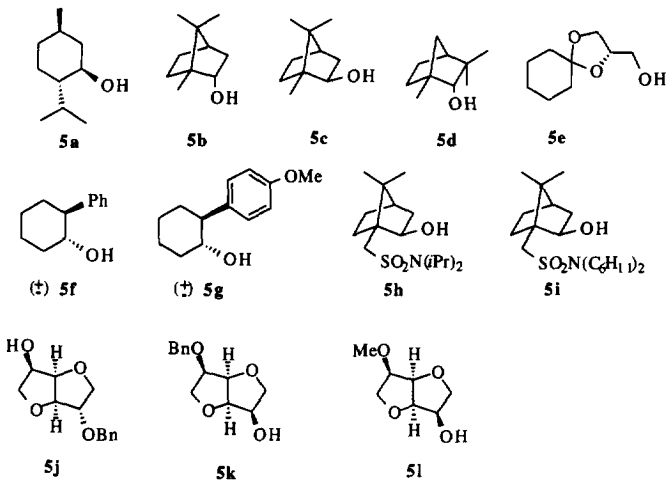


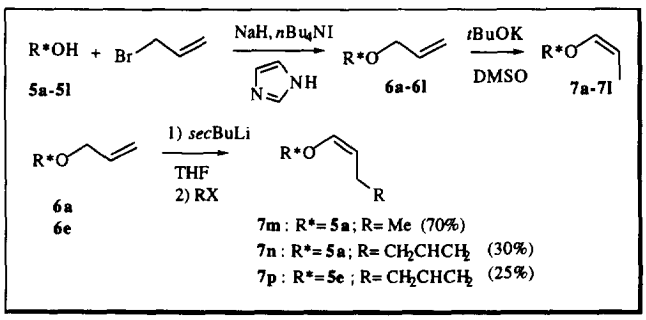
Scheme 1

Asymmetric Bradsher cycloadditions between unsubstituted enol ethers and an isoquinolinium salt have already been reported in literature[4]. In the present communication, we describe a versatile preparation of enantiomerically pure (*Z*)-enol ethers from the corresponding allylic ethers and their use in asymmetric Bradsher cycloaddition with 2,7-naphthyridinium salt **4b** as diene.

Chiral (*Z*)-1,2-disubstituted enol ethers were prepared in two steps starting from alcohols **5a-5l**. Classical *O*-alkylation with allyl bromide gave rise to the corresponding allylic ethers **6a-6l** (Scheme 2, table

1). Isomerisation of the double bond in the presence of potassium *ter*-butylate in DMSO[5] at 60°C afforded geometrically pure (*Z*)-enol ethers **7a-7l** generally in good yields[6]. However, deprotonation of allylic ether **6f** induced a β-elimination producing phenyl cyclohexene. This side reaction was partially supressed by using THF and *sec*-butyl lithium as the base at -78°C[7]. Under these conditions, (*Z*)-enol ether **7f** was obtained in 20% yield, with 21% of starting allylic alcohol **6f**, and 10% of phenyl cyclohexene. Moreover, this inconvenience has been overcome using the 4-methoxyphenyl cycohexanol **5g**. For further synthetic elaborations, a tandem isomerisation-alkylation sequence of reactions has also been studied with the *sec*-BuLi-THF system and methyl iodide or allyl bromide as electrophiles. Alkylated (*Z*)-enol ethers **7m-7p** were thus obtained in moderate to good yields.



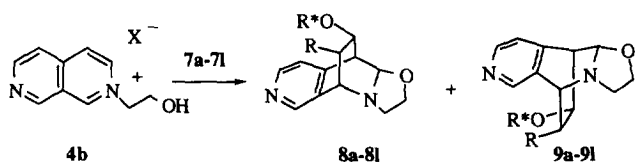


Scheme 2

Entry	1	2	3	4	5	6	7	8	9	10	11	12
Starting material	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**	**5i**	**5j**	**5k**	**5l**
Alkylation Yield %	95	68	40	60	99	90	85	54	68	93	98	90
Isomerisation Yield %	90	46	75	90	70	20	90	96	70	95	98	65

Table 1

Bradsher cycloadditions between enol ethers **7a-7n** and naphthyridinium salt **4b** were studied, the most significant results are reported in table 2. The use of the Bradsher cycloaddition conditions developed in our preliminary study[2] (dichloromethane-methanol 9:1, $CaCO_3$) gave rather poor results with dienophile **7a** and naphthyridinium salt **4b**. Adduct **8a** as a mixture of diastereomers was isolated in 15% yield after 48 hours at room temperature. Only starting materials were recovered with other solvents such as *ter*-butanol, *N,N*-dimethylformamide or 1,4-dioxan. Fortunately, when the reaction was performed in water[8], a faster cycloaddition was observed and adduct **8a** was isolated in 55% yield after 9 hours at room temperature with a diastereoselectivity of 20% (Table 2, entry 1). Other cycloadditions with dienophiles **7b-7i** were performed under the same conditions with or whithout cobalt (II) nitrate as an additive[9]. Finally the best results were obtained with isosorbide enol ether derivative **7j** and isomannide derivatives **7k** and **7l**[10] in a mixture of *ter*-butanol-water as solvent (entries 8, 9 and 10). These compounds gave interesting results for both yield and diastereoselectivity[11]. As previously observed with Bradsher cycloadditions[3], these reactions were highly *exo* selective[12]. Diastereoselectivities were measured by ^1H NMR[12]. However, the direction of the asymmetric induction could not be easily deduced from the examination of the NMR spectra and a crystal of adduct **8l** (or **9l**) has been submitted to an X-ray analysis[13]. As shown in figure 1, the absolute configuration does agree with structure **8l** which fit well for further use of such adduct in asymmetric synthesis of Manzamine A **1**.



Scheme 3

Entry	1	2	3	4	5	6	7	8	9	10
Dienophile	**7a**	**7a**	**7b**	**7b**	**7c**	**7f**	**7g**	**7j**	**7k**	**7l**
Solvent + Additive	a	b	a	c	c	c	c	b	b	b
Time (Hour or day)	9 h	5 d	4 h	5 h	5 h	6 h	5 h	4 d	2 d	3 d
Yield %	55	62	40	70	58	52	48	90	90	63
d. e. %	20	20	37		20	69	80	80	80	80

Table 2 : Reaction condition : **4b** (1 equiv.), 20°C, $CaCO_3$ (1.5 equiv.), **7a-7f** (10 equiv.), **7j-7l:** (5 equiv.). a: H_2O. b: H_2O-*tert* butanol = 2:1. c: H_2O, $Co(NO_3)_2$ (0.025 equiv.)

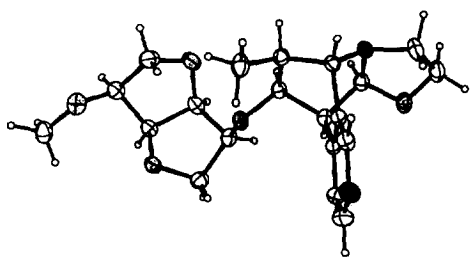


Figure 1 X-Ray structure of **8l**

Acknowledgements: We are grateful to the Association pour la Recherche sur le Cancer (ARC), Université de Paris-sud and CNRS for a financial support, to MESR for a grant (O.S.), to Miss D. Monteux for a generous gift of isosorbide and isomannide derivatives **5j**, **5k** and **5l**, Dr.C. Merienne for nOe experiments and to Dr. A.E. Greene for stimulating discussion.

References and notes:

1) a) Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.*, **1986**, *108*, 6404-6405. b) Sakai, R.; Kohmoto, S.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *Tetrahedron Lett.*, **1987**, *28*, 5493-5496. c) Nakamura, H.; Deng, S.; Kobayachi, J.; Ohizumi, Y.; Tomotake, Y.; Matsuzaki, T. *Tetrahedron Lett.*, **1987**, *28*, 621-624. d) Ichiba, T.; Sakai, R.; Kotmoto, S.; Saucy, G.; Higa, T. *Tetrahedron Lett.*, **1988**, *29*, 3083-3086. e) Kondo, K.; Shigemori, H.; Kikuchi, Y.; Ishibashi, M.; Sakai, T ; Kobayashi, J; *J. Org. Chem.*, **1992**, *57*, 2480-2483. f) Ichiba, I.; Corgiat, J. M.; Scheuer, P. J.; Borges, M. K. *J. Nat. Prod.*, **1994**, *57*, 168-170. g) Tsuda, M.; Kawasaki, N.; Kobayashi, J. *Tetrahedron Lett.*, **1994**, *35*, 4387-4388. h) Kobayashi,M.; Chen Y.-J.; Aoki, S.; In, Y.; Ishida, T.; Kitagawa, I. *Tetrahedron*, **1995**, 51, 3727-3736.

2) Magnier, E.; Langlois, Y.; Merienne, C. *Tetrahedron Lett.*, **1995**, *36*, 9475-9478.

3) Chen, T.-K.; Bradsher, C. K. *J. Org. Chem.*, **1979**, *44*, 4680-4683. b) Manna, S.; Falk, J. R.; Mioskowski; C. *J. Org. Chem.*, **1982**, *47*, 5021-5023. C) Falk, J. R.; Manna, S.; Mioskowski, C. *J. Am. Chem. Soc.*, **1982**, *105*, 631-633. d) Gupta, R. B.; Frank, R. W. *J. Am. Chem. Soc.*, **1987**, *109*, 5393-5403. e) Gupta, R. B.; Franck, R. W.; Onan, K. D.; Soll, C. E. *J. Org. Chem.*, **1989**, *54*, 1097-1101. f) Bolitt, V.; Mioskowski, C.; Kollah, R. O.; Manna, S.; Rajapaksa, D.; Falk, J. R. *J. Am. Chem. Soc.*, **1991**, *113*, 6320-6321. g) Yin, H.; Frank, R. W.; Chen, S.-L.; Quigley, G. J.; Todaro, L. *J. Org. Chem.*, **1992**, *57*, 644-651.

4) Choudury, A.; Frank, R. W.; Gupta, R. B. *Tetrahedron Lett.*, **1989**, *37*, 4921-4924.

5) Taskinen, E. *Tetrahedron*, **1993**, *49*, 11389-11394 and references there in.

6) For alternative methods for preparation of enantiomerically pure enol ethers, see *inter alia* : a) Denmark, S. E.; Schnute, M. E.; Marcin, L; R.; Thorarensen, A. *J. Org. Chem.*, **1995**, *60*, 3205-3220. b) Solà, L.; Castro, J.; Moyano, A.; Pericàs, M.A.; Riera, A. *Tetrahedron Lett.*, **1992**, *33*, 2863-2866. c) Charbonnier, F.; Moyano, A.; Greene, A. E. *J. Org. Chem.*, **1987**, *52*, 2303-2306. d) Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.*, **1987**, *52*, 2919-2922 and references there in.

7) a) Clark Still, W.; Macdonald, T. L. *J. Org. Chem.*, **1976**, *41*, 3620-3622. b) Evans, D. A.; Andrews, G. C.; Buckwalter, B. *J. Org. Chem.*, **1974**, *96*, 5560-5561. c) Clark Still, W.; Macdonald, T. L. *J. Org. Chem.*, **1974**, *96*, 5561-5563.

8) For recent reviews concerning the water promoted organic reactions, see: a) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis*, **1994**, 741-760. b) Li, C. *Chem. Rev.* **1993**, *93*, 2023-2035.

9) The role of this salt is not well understood.

10) For the preparation of isosorbide-isomannide derivatives **5j-5l**, see: Abenhaim, D.; Loupy; A.; Munnier, L.; Tamion, R.; Marsais, F.; Queguiner, G. *Carbohydrate Res.*, **1994**, *261*, 255-266.

11) For the use of isomannide-isosorbide derivatives in normal electron demand asymmetric Diels-Alder reactions, see the following paper, Loupy, A.; Monteux, D.

12) The *exo* selectivity of these cycloadditions was deduced from nOe experiments showing the spatial proximity between N-C<u>H</u>-O and R*O-C<u>H</u>. Moreover, a cycloaddition performed with (*E*) **7f** afforded a mixture of diastereomeric *endo-exo* adducts. For further discussion, see ref. 3d. The diastereoselectivity of these cycloadditions was measured by integration of the signal attributed to N-C<u>H</u>-O which appeared as a doublet between 4.8 and 5 ppm.

13) Crystal data: $C_{20}\,H_{26}\,N_2\,O_5$, M_w = 374.44, crystal of 0.33 x 0.37 x 0.46 mm, monoclinic, space group P 2_1 , Z = 2, a = 7.938(5), b = 8.129(7) , c = 14.287(8) Å, β = 98.95(2)°, V = 910 (1) Å^3, d_{calc} = 1.37 g cm^{-3}, F(000) = 400, λ (Cu Kα) = 1.5418 Å, μ = 0.76mm^{-1}. Enraf-Nonius CAD-4 diffractometer, (θ-2θ) scan technique up to θ = 65°; 6296 collected reflexions (h: -9 to 9, k: -9 to 9, l: -16 to 16), 3099 unique reflexions (R_{int} = 0.023), 3063 observed having I ≥ 3 σ(I). R = 0.037 and R_w = 0.051 (with R_w = {Σw(Fo-|Fc|)^2 / ΣwFo^2}$^{1/2}$ and w = 1/[σ^2(Fo)+ 0.0034 Fo^2]. Residual electron density: -0.32 and 0.49 e Å^{-3}. The structure was solved by direct methods using *SHELXS86* and refined by full matrix least squares with *SHELX76*, minimizing the function Sw(Fo-|Fc|)^2. The coordinates of the hydrogen atoms were refined with an isotropic thermal factor equivalent to that of the bonded carbon atom, plus 10%. Atomic coordinates, bond lengths, bond and torsion angles, and thermal parameters at the Cambridge Crystallographic Data Centre, UK.

(*Received in France* 2 *July* 1996; *accepted* 6 *August* 1996)