ORGANIC LETTERS

2003
Vol. 5, No. 23
4321−4323

Aziridines as a Protecting and Directing Group. Stereoselective Synthesis of (+)-Bromoxone

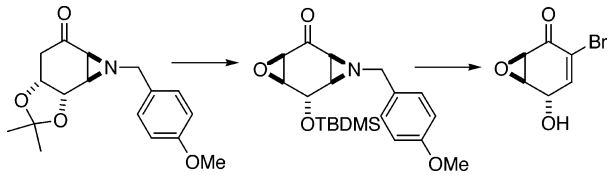
M. Teresa Barros,[†] Pedro M. Matias,[‡] Christopher D. Maycock,*[,‡] and M. Rita Ventura[‡]

Departamento de Química, Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa, 2825 Monte da Caparica, and Instituto de Tecnologia Química e Biológica, Universidade Nova de Lisboa, Apartado 127, 2780 Oeiras, Portugal

maycock@itqb.unl.pt

Received August 21, 2003

ABSTRACT



The directing ability of an aziridine group for the epoxidation of adjacent double bonds is demonstrated. The aziridine group is also used to effectively protect a double bond in a cycloenone system for a short synthesis of the title compound.

(+)-Bromoxone **1** and its acetate were isolated in 1987 from a species of acorn worm belonging to the genus *Ptychodera* found in deep underwater caves on the island of Maui.[1] The acetate of bromoxone shows potent antitumor activity against P388 cells in vitro. These compounds belong to the bioactive polyoxygenated cyclohexenone family. Bromoxone also provides an entry to more complex members of this family such as Manumycin A and Asukamycin via cross-coupling reactions. Several syntheses of **1** have been developed. Racemic syntheses of **1** have been reported by the groups of Taylor[2] and enantioselective syntheses by Altenbach,[3] Johnson,[4] and Kitahara.[5]

The chiral enone **3** derived from (−)-quinic acid **2**[6] was used as the starting material, having the required cyclohexane skeleton, a 1,4-oxygen functionality suitable for synthesis of the necessary hydroxyl, and carbonyl groups in these positions of the target compound. In fact, it has already been used to synthesize several members of the polyoxygenated cyclohexane metabolite family.[6−8] α-Iodocycloenone **4** was

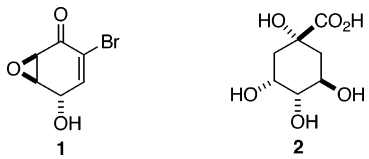


Figure 1.

obtained from enone **3**, which in turn was obtained from quinic acid in five steps.[6] We have recently described a general method to prepare aziridines from α-iodocycloenones in very good yield, by a Michael addition/cyclization

[†] Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa.
[‡] Instituto de Tecnologia Química e Biológica.

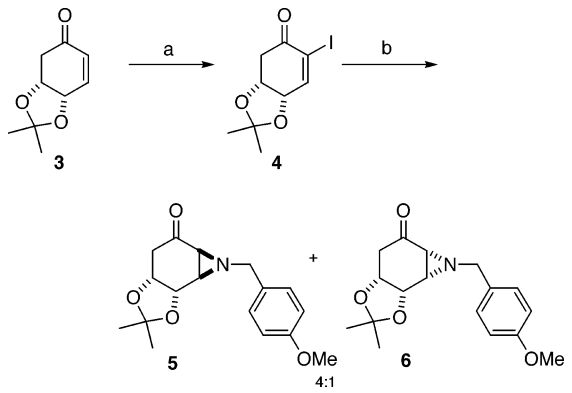
(1) Higa, T.; Okuda, R. K.; Severns, R. M.; Scheur, P. J.; He, C.-H.; Changfu, X.; Clardy, J. *Tetrahedron* **1987**, *43*, 1063.
(2) Gautier, E. C. L.; Lewis, N.; McKillop, A.; Taylor, R. J. K. *Tetrahedron Lett.* **1994**, *35*, 8759.
(3) (a) Adelt, S.; Plettenburg, O.; Stricker, R.; Reiser, G.; Altenbach, H.-J.; Vogel, G. *J. Med. Chem.* **1999**, *42*, 1262. (b) Altenbach, H.-J. In *Antibiotics and Antiviral Compounds;* Krohn, K., Kirst, H., Maas, H., Eds.; VCH: Weinheim, 1993, 359−372. (c) Block, O.; Klein, G.; Altenbach, H.-J.; Brauer, D. *J. Org. Chem.* **2000**, *65*, 716.
(4) Johnson, C. R.; Miller, M. W. *J. Org. Chem.* **1995**, *60*, 6674.
(5) Tachihara, T.; Kitahara, T. *Tetrahedron* **2003**, *59*, 1773.

10.1021/ol035576i CCC: $25.00 © 2003 American Chemical Society
Published on Web 10/11/2003

(Gabriel−Cromwell) process using only a slight excess of primary amine and Cs_2CO_3 as a base at 95 °C.[9]

α-Iodocycloenone **4** was employed as the substrate for aziridination, and we postulated that the presence of an adjacent asymmetric center on a cyclohexane nucleus should induce stereoselectivity to the process.[9] The aziridination reaction with 4-methoxybenzylamine afforded, however, two diastereoisomers **5** and **6** in a 4:1 ratio (84% yield, Scheme 1), accompanied by an aromatic byproduct **7**. The configuration of aziridine **5** was confirmed by X-ray crystallographic studies. We also attempted this reaction with other amines, with differing results. For benzylamine, only one diastereoisomer was obtained, with the aziridine below the plane of the molecule (60%), along with an aromatic byproduct, which contaminated the aziridine. When *n*-butylamine was used, the two diastereoisomers of the aziridine were obtained in a 1:1 ratio (70%). As before, aromatic byproduct was also formed.

Scheme 1[a]



[a] Reaction conditions: (a) I_2, DMAP, Pyr/CC_4I, rt, 80%. (b) 4-Methoxybenzylamine, Cs_2CO_3, 1,10-phenanthroline, xylene, 95 °C, 84%.

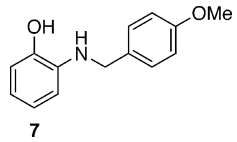
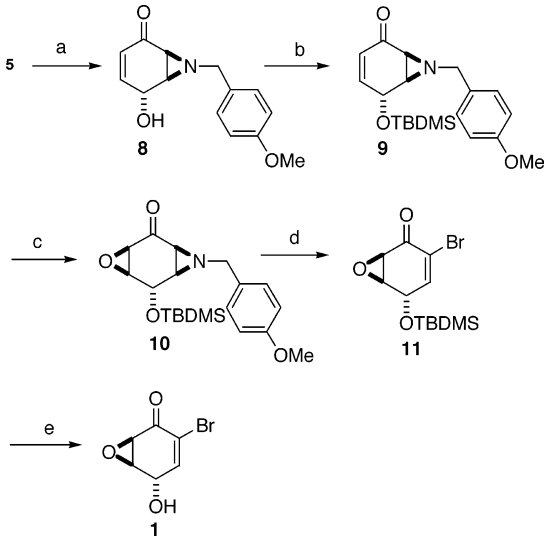


Figure 2.

Treatment of aziridine **5** with catalytic NaOH 0.5 N afforded the alcohol **8** (Scheme 2) in good yield (88%). Once more, care was needed to avoid aromatization and the degree of purity of the aziridine was very important for the successful outcome of this reaction. To induce the formation of the epoxide with the correct stereochemistry, the free hydroxyl group in **8**, which in previous syntheses[8] had been shown to have a strong influence in directing the cis epoxide formation, was protected with TBDMSCl, a bulky group, to afford **9**. Epoxidation of the enone system of **9** with hydrogen peroxide and catalytic Triton B afforded exclusively the epoxide **10** (80%). Surprisingly the epoxidation of **8**, and silylation of the resulting epoxide, afforded the same compound **10**. It was thus concluded that in this case, it was not the hydroxyl group that exerted the strongest orientating effect but the nitrogen atom of the aziridine group. This was also confirmed by performing the same sequence of reactions on the minor diastereoisomer **6**; in this case, the epoxide formed was syn with respect to the adjacent bulky TBDMS ether group.

Scheme 2[a]



[a] Reaction conditions: (a) NaOH 0.5 N, THF, 0 °C, 88%. (b) TBDMSCl, DMAP, (*i*-Pr)$_2$NEt, CH_2Cl_2, rt, 80%. (c) H_2O_2, Triton B, THF 0 °C, 90%. (d) HBr, MeOH, rt, 80%. (e) HF 40%, MeCN, rt, 89%.

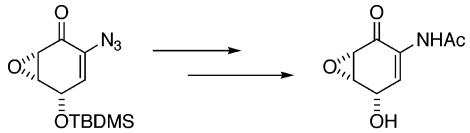
Resuming the synthesis, at this stage, we had a molecule with five asymmetric centers and two three-membered rings on opposite sides of the cyclohexane ring, a highly strained molecule.

The next step was critically important, since we were dependent upon the exclusive opening of the benzylaziridine in the presence of the epoxide. This proved to be rather easy to accomplish employing 0.1 M HBr in MeOH at rt, and TBDMS-protected bromoxone **11** was efficiently obtained in 80% yield (Scheme 2), $[\alpha]^{20}_D$ +99.3 (*c* 1.03, $CHCl_3$) (lit. $[\alpha]^{20}_D$ +98.9 (*c* 0.79, $CHCl_3$),[5] mp 46−47 °C (lit. 49−50 °C).[5]

Hydrolysis of the silyl protecting group afforded (+)-bromoxone **1** (89%), $[\alpha]^{20}_D$ +205.7 (*c* 0.32, acetone) (lit. $[\alpha]^{20}_D$ +204.0 (c 0.21, acetone),[5] $[\alpha]^{22}_D$ +220 (*c* 0.09,

(6) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Org. Chem.* **1997**, *62*, 3984.
(7) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Tetrahedron* **1999**, *55*, 3233.
(8) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Chem. Eur. J.* **2000**, *6*, 3991.
(9) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Tetrahedron Lett.* **2002**, *43*, 4329.

Scheme 3



$CHCl_3$),[1] $[\alpha]^{25}_D$ +203 (*c* 2.5, acetone)[3c], mp 125−126 °C (lit. 123−127 °C,[1] 124−125 °C,[5] 138−139 °C,[4] 131−132 °C[3c]). This is an efficient asymmetric synthesis of (+)-bromoxone, with an overall yield of 24%, starting from enone **3**. It is the only asymmetric synthesis of bromoxone that does not rely on an enzymatic resolution.

The aziridine ring could also be opened with HN_3 in the presence of the epoxide ring to afford α-azido enone **12** (Scheme 3), which represents a novel and short route to (−)-LL-C10037 α **13**. These studies are currently being carried out.

Acknowledgment. We thank Fundação para a Ciência e a Tecnologia for a grant conceded to M.R.V.

Supporting Information Available: Experimental procedures and spectrosocopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035576I