Asymmetric Synthesis of 2*H*-Azirines: First Enantioselective Synthesis of the Cytotoxic Antibiotic (*R*)-(−)-Dysidazirine

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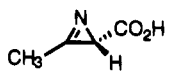
The chemistry of 2*H*-azirines, the smallest of the nitrogen-unsaturated heterocycles, has been extensively explored because of the high reactivity of this ring system toward nucleophilic and electrophilic reagents.[1] Methods for the synthesis of azirines include the modified Neber reaction,[2,3] thermolysis and photolysis of vinyl azides[4] and isoxazoles,[5] and thermolysis of oxazaphospholines.[6] Because these procedures are not readily adaptable, there is only one example of the asymmetric synthesis of this class of compounds where a diastereoselective Neber rearrangement was used to prepare a 3-amino-2*H*-azirine.[7] The only other known optically active azirines are the antibiotics azirinomycin (**1**),[8] isolated from *Streptomyces aureus*, and (*R*)-(−)-dysidazirine (**2**), obtained from *Dysidea fragilis*, a marine sponge.[9] Dysidazirine (**2**) is cytotoxic to L1210 cells and inhibits the growth of Gram negative bacteria and yeast.[9] In this communication we report methodology for the asymmetric synthesis of 2*H*-azirine 2-carboxylic acids and the first enantioselective synthesis of (*R*)-(−)-**2**. The latter confirms both the structure and absolute configuration of **2**.



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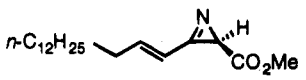
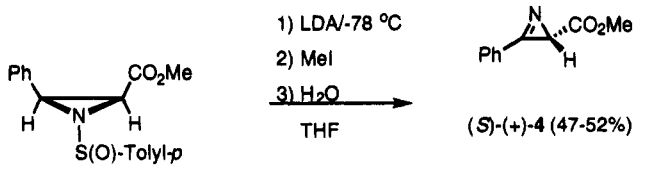


(*R*)-(-)-**2**

A potentially useful route to enantiomerically enriched azirines is β-elimination of the sulfinyl group in chiral nonracemic *N*-sulfinylaziridines.[10] Indeed thermolysis of sulfoxides,[11] sulfinamides,[12] and sulfinimines[13] with cycloelimination of the sulfenic acid (RSOH) is a well-established procedure for the synthesis of alkenes, imines, and nitriles, respectively. However, heating racemic *N*-(*p*-tolylsulfinyl)-2-carbomethoxy-3-phenylaziridine (**3**)[14] at reflux in benzene for 18 h produced no reaction; in xylene at reflux decomposition occurred.



(2*S*,3*S*)-(+)-**3**

(*S*)-(+)-**4** (47-52%)

+

p-TolylS(O)-Me

5 (79-80%)

Remarkably, treatment of (2*S*,3*S*)-(+)-**3** with 1.3−1.5 equiv of lithium diisopropylamide (LDA) at −78 °C in THF for 20 min and quenching with H_2O afforded (*S*)-(+)-2-carbomethoxy-3-phenyl-2*H*-azirine (**4**), $[\alpha]^{20}_D$ +289.3° (*c*, 1.8, $CHCl_3$), in 47% yield following purification by preparative TLC. In addition to azirine **4**, polar residues were isolated along with products resulting from disproportionation of *p*-toluenesulfenic acid (ArSOH)[11] [e.g.: *p*-tolyl *p*-toluenethiosulfonate ($ArSSO_2Ar$) and *p*-tolyl disulfide (ArSSAr)].[15] When the reaction was carried out in the presence of 2 equiv of iodomethane, the yield of (+)-**4** improved to 52% and a better than 80% yield of methyl *p*-tolyl sulfoxide (**5**) was obtained. The addition of iodomethane traps the intermediate sulfenate ion improving product isolation and may be responsible for the small but reproducible improvement in the yield. Additional attempts to improve the yields by variation of base and solvent were unsuccessful. None of the known isomeric 3-carbomethoxy-2-phenyl-2*H*-azirine, identified by the C-2 proton absorption at δ 3.4 ppm[16] compared to δ 2.87 ppm in **4**,[17] was detected in the reaction mixtures. The enantiomeric purity of (+)-**4** was estimated to be >95% ee using the chiral shift reagent Eu(hfc)$_3$. The other enantiomer was not detected. Making the reasonable assumption that the stereocenter at C-2 in (+)-**3** is unaffected by deprotonation at C-3, (+)-**4** would therefore have the *S* configuration.

Since α-deprotonation of aziridyl ketones[18] and *S*-phenyl aziridinecarbothioates,[19] with C-alkylation of the latter, has been reported, formation of (+)-**4** via removal of the seemingly less acidic C-3 proton was unexpected.[20] However, the generation of aziridine enolates may be hampered by ring strain (I-strain) and stereoelectronic effects such that deprotonation of the two aziridine ring protons may be competitive.[21] While removal of the C-3 proton leads to **4**, we speculate that proton elimination at C-2 results in an unstable lithio species that decomposes to polar material and thus accounts for the modest yields. That both protons can be lost in the deprotonation step is suggested by the 80% isolated yield of **5**. Furthermore, treatment of *N*-tosylaziridine (±)-**6**[14] with LDA, under the reaction conditions, affords methyl *trans*-2-(*N*-(*p*-tolylsulfonyl)amino)cinnamate (**7**) in 61% yield. Hydrogenation (H_2/Pd) of **7** gave the known phenylalanine derivative **8** in quantitative yield.[14] This result is consistent with C-2 deprotonation followed by stereospecific ring-opening and is similar to results reported by Padwa et al. for 1,3-dibenzoyl-2-phenylaziridine.[22]

(1) For reviews on the chemistry of azirines, see: (a) Padwa, A.; Woolhouse, A. D. In *Comprehensive Heterocyclic Chemistry*; Lowowski, W., Ed.; Pergamon Press: 1984; Vol. 7, Chapter 5, p 47. (b) Nair, V. In *Heterocyclic Compounds*; Hassner, A., Ed.; John Wiley & Sons: New York, 1983; Chapter 2, p 215. (c) Fowler, F. W. In *Advance in Heterocyclic Chemistry*; Academic Press: New York, 1971; p 45.

(2) Nair, V. *J. Org. Chem.* **1968**, *33*, 2121.

(3) Padwa, A.; Carlsen, P. H. J. *J. Am. Chem. Soc.* **1977**, *99*, 1514. Padwa, A.; Carlsen, P. H. J. *J. Org. Chem.* **1978**, *43*, 2029.

(4) Hassner, A.; Levy, L. A. *J. Am. Chem. Soc.* **1965**, *87*, 4203. Fowler, F. W.; Hassner, A.; Levy, L. A. *J. Am. Chem. Soc.* **1967**, *89*, 2077. Hassner, A.; Fowler, F. A. *J. Org. Chem.* **1968**, *33*, 2686.

(5) Nishiwaki, T.; Kitamura, T.; Nakano, A. *Tetrahedron* **1970**, *26*, 453.

(6) Huisgen, R.; Wulff, J. *Tetrahedron Lett.* **1967**, 917. Bestmann, H. J.; Kunstmann, R. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 1039.

(7) Piskunova, I. P.; Eremeev, A. V.; Mishnev, A. F.; Vosekalna, I. A. *Tetrahedron* **1993**, *49*, 4671.

(8) Miller, T. W.; Tristram, E. W.; Wolf, F. J. *J. Antibiot.* **1971**, *24*, 48.

(9) Molinski, T. F.; Ireland, C. M. *J. Org. Chem.* **1988**, *53*, 2103.

(10) The synthesis of racemic 2*H*-azirine-3-carboxylic esters in low yield from the dehydrohalogenation of *N*-haloaziridines has been described. Legters, J.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chem. Pays-Bas* **1992**, *111*, 75.

(11) Davis, F. A.; Jenkins, L. A.; Billmers, R. L. *J. Org. Chem.* **1986**, *51*, 1033 and references cited therein.

(12) Trost, B. M.; Liu, G.-J. *J. Org. Chem.* **1981**, *46*, 4617.

(13) Davis, F. A.; Friedman, A. J.; Nadir, U. K. *J. Am. Chem. Soc.* **1978**, *100*, 2844.

(14) Davis, F. A.; Zhou, P. Reddy, G. V. *J. Org. Chem.* **1994**, *59*, 3243.

(15) Kice, J. L.; Rogers, T. E. *J. Am. Chem. Soc.* **1974**, *96*, 8009. Freeman, F.; Bartosik, L. G.; Bui, N. B.; Keindl, M. C.; Nelson, E. L. *Phosphorus, Sulfur, Silicon* **1988**, *53*, 375.

(16) Knittel, D. *Synthesis* **1985**, 186.

(17) Hassner, A.; Fowler, F. W. *J. Am. Chem. Soc.* **1968**, *90*, 2869.

(18) Lutz, R. E.; Turner, A. B. *J. Org. Chem.* **1968**, *33*, 516. Tarburton, P.; Chung, A.; Badger, R. C.; Cromwell, N. H. *J. Heterocycl. Chem.* **1976**, *13*, 295. Tarburton, P.; Wall, D. K.; Cromwell, N. H. *J. Heterocycl. Chem.* **1978**, *15*, 1281.

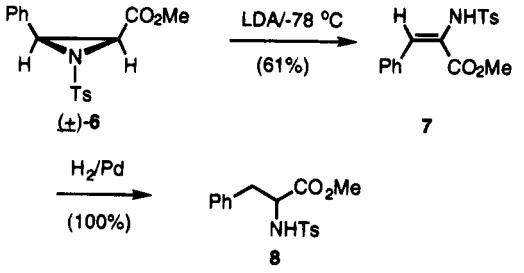
(19) Haner, R.; Olano, B.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1676.

(20) Stereospecific proton transfer from the 3-position to a 2-lithio species in **3** cannot be ruled out at this time, but seems most unlikely because of the high enantiomeric purity of (+)-**4**.

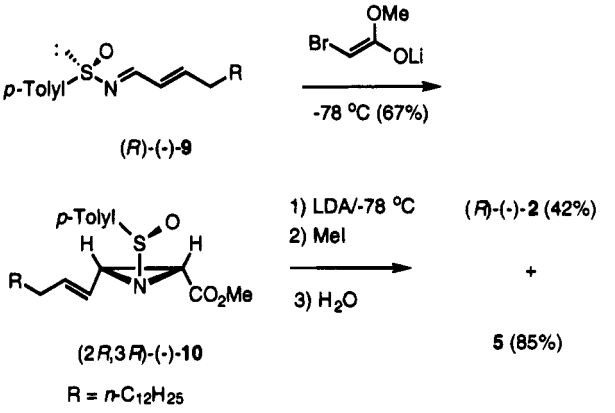
(21) For a discussion of the factors affecting the stability and structure of aziridine enolates, see ref 18.

(22) Padwa, A.; Eisenhardt, W. *J. Org. Chem.* **1970**, *35*, 2472. See also: Nakajima, K.; Oda, H. Okawa, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3232.

0002-7863/95/1517-3651$09.00/0



We next turned our attention to the enantioselective synthesis of the marine cytotoxic antibiotic (*R*)-(−)-dysidazirine (**2**). The requisite aziridine (2*R*,3*R*)-(−)-**10** [mp 40−42 °C, $[\alpha]^{20}_D$ −86.9° (*c* 1.6, $CHCl_3$)] was prepared by treatment of sulfinimine (*R*)-(−)-**9** [mp 38−40 °C, $[\alpha]^{20}_D$ −393.3° (*c* 1.87, $CHCl_3$)][23] with the lithium enolate of methyl bromoacetate according to our recently reported Darzens-type synthesis of *cis*-*N*-sulfinylaziridine carboxylic acids.[14] The product was isolated by flash chromatography in 67% yield along with ca. 3% of the (2*R*,3*S*)-**10** isomer. Treatment of (−)-**10** with LDA/MeI, as before, gave (*R*)-(−)-**2** in 42% isolated yield in addition to an 85% yield of **5**, following flash chromatography. The spectral properties of synthetic (−)-**2** were identical in all respects with values reported for the naturally occurring material.[9] However, the specific rotation for synthetic (*R*)-(−)-**2** [$[\alpha]^{20}_D$ −186.3° (*c* 2.53, MeOH)], determined to be >95% ee by the chiral shift reagent $Eu(hfc)_3$, was higher than that reported for the natural product [$[\alpha]^{20}_D$ −165°],[9] suggesting that the latter is less than 89% optically pure. The antipodal dysidazirine, (*S*)-(+)-**2** [$[\alpha]^{20}_D$ +183.7° (*c* 2.23, MeOH)], was prepared in a similar manner.[25] Since the absolute stereochemistry of aziridine (2*R*,3*R*)-**10** is known from earlier studies,[14] these results confirm the structure and absolute configuration of (*R*)-(−)-**2** established by Ireland et al.[9] based on chemical correlation and circular dichroism studies.



Attempts to prepare the methyl ester of azirnomycin (**1**) in a similar fashion gave only highly polar materials in addition to good isolated yields of **5**. In the corresponding aziridine (**3**, Ph = Me) the acidity of the C-3 proton is expected to be considerably less than that in (+)-**3** or (−)-**10**; deprotonation at the two positions would therefore no longer be competitive.

The enantioselective synthesis of azirine-2*H*-carboxylic acids opens the rich chemistry of this class of heterocyclic compounds to asymmetric transformations; work is underway to exploit this discovery.

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Supplementary Material Available: Experimental procedures and analytical data for all new compounds (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(23) Sulfinimine (*R*)-(−)-**9** was prepared in 79−80% yield from (+)-menthyl (*R*)-*p*-toluenesulfinate, lithium bis(trimethylsilyl)amide and 2(*E*)-hexadecenal as describe earlier.[24]

(24) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Portonovo, P. *Tetrahedron Lett.* **1993**, *34*, 6229.

(25) (*S*)-(+)-**9**: mp 38−40 °C, $[\alpha]^{20}_D$ +394.1° (*c* 2.23, $CHCl_3$). (2*S*,3*S*)-(+)-**10**: mp 40−42 °C; $[\alpha]^{20}_D$ +86.3° (*c* 1.8, $CHCl_3$).