An Unexpected Access to a New Sphingoid Base Containing a Vinyl Sulfide Unit

Ingrid Nieves,[a] María Garrido,[a] José Luis Abad,[a] Antonio Delgado*[a,b]

[a] Spanish National Research Council (CSIC); Institute for Advanced Chemistry of Catalonia (IQAC), Department of Biomedicinal Chemistry; Research Unit on BioActive Molecules (RUBAM), Jordi Girona 18–26, 08034 Barcelona, Spain
Fax +34(93)2045904; E-mail: adelgado@cid.csic.es

[b] University of Barcelona, Faculty of Pharmacy, Medicinal Chemistry Unit (Associated to CSIC), Avgda. Juan XXIII, s/n, 08028 Barcelona, Spain

Received 24 June 2010

Dedicated to Prof. Pelayo Camps on the occasion of his 65th birthday

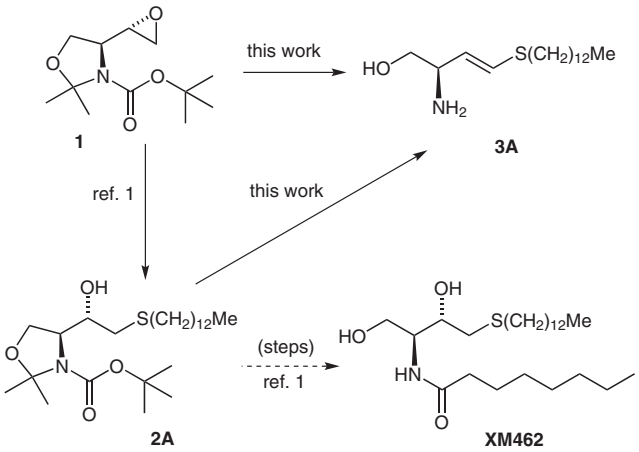
Abstract: An unexpected access to a new sphingoid base containing a vinyl sulfide unit is described. The process involves the 'one-pot' regioselective opening of an epoxide with a thiolate, followed by intramolecular acyl transfer, base-promoted elimination, and final hydrolysis. Excess sodium hydride and high dilution conditions are required for optimal yields. The process is amenable to a variety of thiolates. The resulting compounds can be regarded as new hybrid sphingoid bases that combine some structural motifs present in other reported sphingolipid analogues.

Key words: amino alcohol, epoxide, thiolate, elimination, olefin, sphingolipids

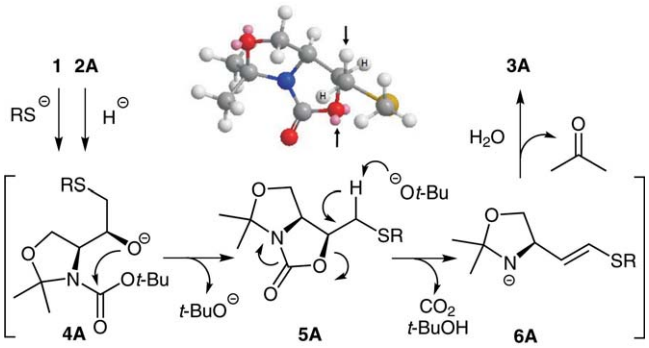
In the course of our current research on new modulators of sphingolipid metabolism, we required the preparation of several batches of the novel dihydroceramide desaturase inhibitor **XM462**.[1] The synthesis relies on the regiocontrolled nucleophilic opening of epoxide **1**, in DMF, with *n*-tridecylthiolate (**A**) to afford the required β-alkylthio alcohol **2A** for its subsequent transformation into **XM462** (Scheme 1). Compound **2A** was obtained in acceptable yields in all cases. However, a careful TLC analysis of the crude reaction mixtures revealed the presence of a hitherto unnoticed, more polar compound in variable yields, which could be isolated and characterized as the vinyl sulfide **3A** (around a 40:1 *E*/*Z* mixture, based on NMR data; Scheme 1 and Table 1, entry 1).[2] Although, at first glance, formation of **3A** seemed detrimental for our purposes, we recognized it as an interesting new hybrid sphingoid base that combines the presence of a sulfur atom at C5 position (as in **XM462**) with the C3 unsaturation present in a series of related ceramidase inhibitors containing a 2-aminoethanol amide framework.[3]

A plausible mechanism to account for the formation of **3A** from epoxide **1** is depicted in Scheme 2.

Thus, intramolecular acyl transfer[4] of the initially formed alkoxide **4A** leads to the bicyclic oxazolidinone **5A**. Subsequent E2 elimination (with loss of CO_2) and final hydrolysis of the intermediate hemiaminal **6A** during the aqueous workup affords vinyl sulfide **3A**. The *E* stereochemistry observed for the major isomer is in agreement with the *anti* disposition between the acidic OC(H)SR proton and the carbamate leaving group in the most stable conformation, as illustrated in the ball and stick representation shown in Scheme 2.[5] The stereochemistry of the starting epoxide seems crucial for the outcome of the process, since no elimination products were observed from the corresponding epoxide epimeric at the C–O carbon.[6] Although the base-promoted formation of oxazolidinones structurally related to **5A** has been reported in the litera-



Scheme 1 Formation of vinylsulfide **3a** and alcohol **2a** from epoxide **1**. For reaction conditions, see text and Table 1.



Scheme 2 Proposed mechanism leading to **3a** from **1** and **2A**. Arrows indicate the *anti* relationship among the atoms involved in the elimination step from **5A**. In the ball and stick model, the hydrogen atoms leading ultimately to the major *E*-olefin are also shown.

SYNLETT 2010, No. 19, pp 2950–2952
Advanced online publication: 11.11.2010
DOI: 10.1055/s-0030-1259047; Art ID: D16210ST

ture,[7] no ensuing elimination products are usually found, as illustrated in our previous work involving a similar process from an aryloxy derivative structurally related to **2A**.[8] We rationalize the unexpected reaction outcome from **2A** as a result of the higher acidity of the vicinal methylene protons α to the sulfur atom in intermediate **5A**, thus triggering the observed elimination process.

In an attempt to exploit the synthetic usefulness of this unexpected process, we carried out a systematic survey of the optimal reaction conditions leading to **3A**, as shown in Table 1. Interestingly, the stoichiometry of NaH seemed crucial, since an, at first sight irrelevant, slight increase in the excess NaH (2.0 equiv/mol epoxide vs. our previously reported[1] 1.6 equiv/mol) led to a roughly 1:1 mixture of **2A** and **3A** (entry 1). Furthermore, by increasing the NaH/**1** molar ratio to 5:1, no trace of **2A** was observed in the crude reaction mixture and compound **3A** (*E*/*Z* isomeric ratio around 40:1) was obtained in 49% yield (entry 2). In agreement with these observations and the above mechanistic proposal, the independent treatment of **2A** under the same conditions cleanly afforded **3A** in comparable yields (entry 5). In all cases, the use of THF as solvent led to slow conversion rates (entries 4 and 6). Moreover, since the process leading to **2A** is formally catalytic in base,[9] the use of substoichiometric NaH led exclusively to **2A** in excellent yield (Table 1, entry 3).[10]

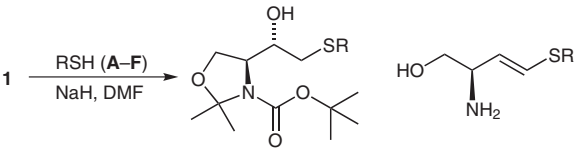
Table 1 Synthesis of **3a** from Reaction of **1** with *n*-Tridecylthiolate or **2a** with NaH

Entry[a]	Starting material	Base[b]	Solvent	Time (h)	Products (%)[c]
1	**1**	2.0	DMF	4	**2A/3A** (1:1)
2	**1**	5.0	DMF	4	**3A** 49 (40:1)[d]
3	**1**	0.5	DMF	4	**2A** 91
4	**1**	1.5	THF	48	**1/2A** (1:3)
5	**2a**	5.0	DMF	4	**3A** 50 (40:1)[d]
6	**2a**	5.0	THF	18[e]	**3A** 72 (40:1)[d]

[a] Reactions were carried out at 0.1 M concentration (based on epoxide **1**) at 40 °C, unless otherwise noted.
[b] Molar ratio of NaH relative to starting epoxide **1**.
[c] Relative ratio or isolated yield.
[d] Approximate *E*/*Z* ratio (based on ^{1}H NMR).
[e] Reaction at 25 °C

In an attempt to widen the scope of this process, thiols **B**–**F** were also evaluated as reaction partners for epoxide **1** (Table 2). However, the reaction conditions shown above for **3A** (Table 1, entry 2) failed to give the expected vinyl sulfides **3**, since epoxide-opening adducts **2B**–**E** were obtained as the major reaction products (Table 2, entries 1–4). The only exception was 2-naphthylthiol **F** (entry 5), which afforded olefin **3F** (9:1 *E*/*Z* mixture) together with the opening adduct **2F**. After much experimentation with cyclohexanethiol **B**, which was chosen as model, optimized reaction conditions for the exclusive formation of olefin **3B** were found. Thus, an excess base (NaH/**1** molar ratio 15:1) and high dilution conditions (0.02 M relative to **1**) turned out to be crucial for this unprecedented addition–elimination reaction (Table 2, entry 7).[11] These optimized conditions led also to **3A** in a slightly higher yield (entry 6) than that reported above and, most importantly, they also proved successful for the remaining thiols **C**–**F** used in this study (entries 8–11), although formation of minor amounts of epoxide-opening adducts **2E** and **2F** was still observed in some cases (entries 10 and 11).[12]

Table 2 Optimized Reaction of Epoxide **1** with Thiols **A**–**F**



2A–F **3A–F**

Entry[a]	Thiol	R	Base[b]	Concn[c]	Product, yield (%)	Other, yield (%)
1	**B**	cyclohexyl	5	0.09	**2B** 58[d]	
2	**C**	*t*-Bu	5	0.09	**2C** 61[d]	**3C** 6[d]
3	**D**	Bn	5	0.09	**2D** 74[d]	
4	**E**	Ph	5	0.08	**2E** 47[d]	
5	**F**	2-naphthyl	5	0.08	**3F** 42[d] (9:1)[e]	**2F** 18[d]
6	**A**	*n*-tridecyl	15	0.02	**3A** 61[f] (40:1)[e]	
7	**B**	cyclohexyl	15	0.02	**3B** 79[f] (10:1)[e]	
8	**C**	*t*-Bu	15	0.02	**3C** 78[f] (6:1)[e]	
9	**D**	Bn	15	0.02	**3D** 76[f] (13:1)[e]	
10	**E**	Ph	15	0.02	**3E** 67[f] (9:1)[e]	**2E** 9[f]
11	**F**	2-naphthyl	15	0.02	**3F** 59[f] (9:1)[e]	**2F** 18[f]

[a] Reactions were carried out in DMF at 40 °C for 4 h (see ref. 12 for details).
[b] Molar ratio of NaH relative to starting epoxide **1**.
[c] Molar concentration of epoxide **1** in DMF.
[d] Calculated by NMR with dimethyl terephthalate as external standard.
[e] Aprox *E*/*Z* ratio (based on ^{1}H NMR).
[f] Isolated yield.

The vinyl sulfides herein reported were obtained as mixtures of *E*/*Z* isomers in ratios ranging from 6:1 (for the bulky *tert*-butyl derivative **3C**, entry 8) to 40:1 (for **3A**). In general, the acceptable overall yields obtained with the selected thiols (entries 6–11), together with their straightforward chromatographic separation from the corresponding adducts **2**, whenever formed, and the possibility to carry out the separation of the minor *Z* olefin stereoisomer at a later synthetic stage,[13] makes this process synthetically useful. As far as vinyl sulfide **3A** is concerned, acceptable yields are also obtained using the more practical

reaction conditions shown in Table 1 (entry 2), in which the use of high dilution conditions and a large excess NaH can be avoided.

In summary, a new protocol for the synthesis of β-amino alcohols containing a vinyl sulfide unit is reported. This represents an addition to other methods based on radical chemistry,[14] as well a potential new entry into the vinyl sulfone framework, a well-established motif found in several families of Cys-protesase inhibitors.[15] In addition, our interest in vinyl sulfides **3** as a new, hybrid sphingoid backbone opens new possibilities for the design of sphingolipid analogues with potential biological properties. Efforts along this line are currently in progress in our group, and results will be reported in due course.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

Partial financial support from the 'Ministerio de Ciencia e Innovación', Spain (Project SAF2008-00706), CSIC (PIE 200880I034) and 'Generalitat de Catalunya' (Grant 2009SGR-1072) is acknowledged. MG is grateful to CSIC for predoctoral research training support within the JAE-Predoc program. The authors are grateful to Mrs. Eva Dalmau for technical assistance with HRMS.

References and Notes

(1) Munoz-Olaya, J. M.; Matabosch, X.; Bedia, C.; Egido-Gabas, M.; Casas, J.; Llebaria, A.; Delgado, A.; Fabrias, G. *ChemMedChem* **2008**, *3*, 946.

(2) The higher ^3J value found for C4–H in the major isomer was indicative of the *E*-stereochemistry. Compound **3A** (major isomer): δ = 6.32, (d, *J* = 14.9 Hz, 1 H), minor isomer: δ = 6.11, (d, *J* = 9.5 Hz, 1 H).

(3) Bedia, C.; Canals, D.; Matabosch, X.; Harrak, Y.; Casas, J.; Llebaria, A.; Delgado, A.; Fabrias, G. *Chem. Phys. Lipids* **2008**, *156*, 33.

(4) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.

(5) Minimizations were carried out with the MM2 package found in Chem3D ultra (version 9.0) from Cambridge Soft.

(6) Koviach, J. L.; Chappell, M. D.; Halcomb, R. L. *J. Org. Chem.* **2001**, *66*, 2318.

(7) Triola, G.; Fabrias, G.; Casas, J.; Llebaria, A. *J. Org. Chem.* **2003**, *68*, 9924.

(8) Grijalvo, S.; Matabosch, X.; Llebaria, A.; Delgado, A. *Eur. J. Org. Chem.* **2008**, 150.

(9) The nucleophilic thiolate required for the opening of epoxide **1** can arise from deprotonation of the starting thiol by the transient alkoxide **4A** (see Scheme 2).

(10) In light of these results, we cannot rule out at this point the possibility that the excess NaH reported in our previous work (ref. 1) was lower than assumed, probably due to adventitious reagent hydrolysis over prolonged storage.

(11) Reactions carried out at higher concentration (0.05 M relative to epoxide **1**) failed to give **3B**, even in the presence of excess base (NaH/**1** molar ratio 15:1). Concentrations between 0.05 and 0.02 M afforded variable mixtures of **2B** and **3B**.

(12) **Typical Procedure**
A solution of 0.60 mmol of the required thiol in DMF (5 mL) was added dropwise over an ice-cooled suspension of NaH (250 mg of a 60% dispersion in mineral oil, 6.0 mmol) in DMF (10 mL) under Ar. Once the addition was complete, the reaction mixture was allowed to warm to r.t. and stirred for an additional 30 min until a suspension formed. A solution of epoxide **1** (100 mg, 0.4 mmol) in DMF (5 mL) was next added dropwise to the above suspension, and the reaction mixture was heated to 40 °C. After stirring for 4 h, the reaction was cooled to r.t. and quenched with H_2O (2.5 mL), dried with anhyd $MgSO_4$, and filtered. The solids were washed with Et_2O (3 × 5 mL) and the combined filtrates were evaporated to dryness to afford a crude residue, which was purified by flash chromatography. Data for compounds reported in Table 2 are collected in the Supporting Information.

(13) For example, the major *E*-isomers of a series of amides of **3A** could be easily purified by conventional chromatographic methods. Unpublished results.

(14) Friestad, G. K.; Jiang, T.; Fioroni, G. M. *Tetrahedron* **2008**, *64*, 11549.

(15) Santos, M. A.; Moreira, R. *Mini-Rev. Med. Chem.* **2007**, *7*, 1040.