Pergamon

Tetrahedron Letters 42 (2001) 3709–3711

TETRAHEDRON LETTERS

Synthesis of 5-(mercaptomethyl)-3(*E*)-undecene-1,11-dioic acid, a non-peptide glutathione analog

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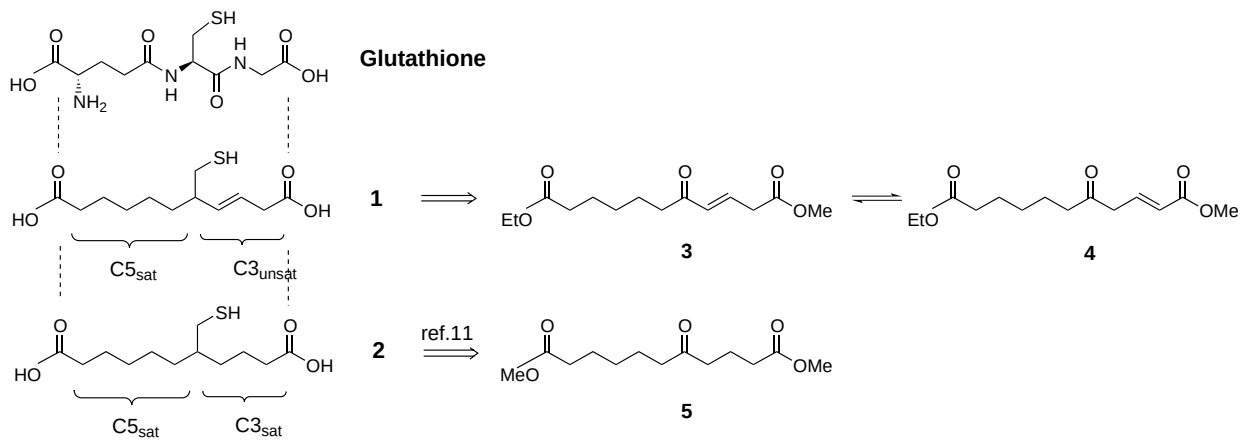
Received 30 March 2001; accepted 3 April 2001

Abstract—The key step in the synthesis of the title compound is a Julia reaction to create the *E*-double bond by introducing a functionalized C3 carbon chain.

Glutathione (GSH) is a widely spread mercapto-containing tripeptide. It is found in nearly all cells playing various physiological and biochemical roles.[1,2] As a result, it is largely involved in human health and diseases.[3–6] Thus, GSH analogs, as mimics or enzymes inhibitors, have often been studied as valuable tools for a better knowledge of the catalytic sites of different GSH-binding enzymes.

We are interested in GSH mimics as precursors for suitable non-peptide leukotriene (LT) C4 probes to further investigate the cys-LT2 receptor, implicated in asthma. Although the literature on GSH derivatives is well documented, few reports concern the synthesis of non-peptide GSH analogs.[7–9] Structure–affinity relationships observed in the literature can be featured as follows: (i) the analog should bear two terminal carboxylic functions;[10] (ii) regardless of the carboxylic acids, the chain lengths are best optimized with C3 atoms at one side of the ethylene thiol group and C5 atoms at the other.[11] According to Toda,[12] we decided not to take into account the amino group of GSH since it is not crucial for the binding to the LTC4 receptor. From peptide literature,[13] the presence of a *trans*-alkene instead of an amide linkage usually provides good bioisosteric mimics due to their close stereochemical resemblance and their inertness to enzymatic hydrolysis.

Thus, on the basis of these observations, we report herein the synthesis of a new GHS analog **1**: we replace the cys–gly amide bond of GSH by a *E*-double bond,



Scheme 1.

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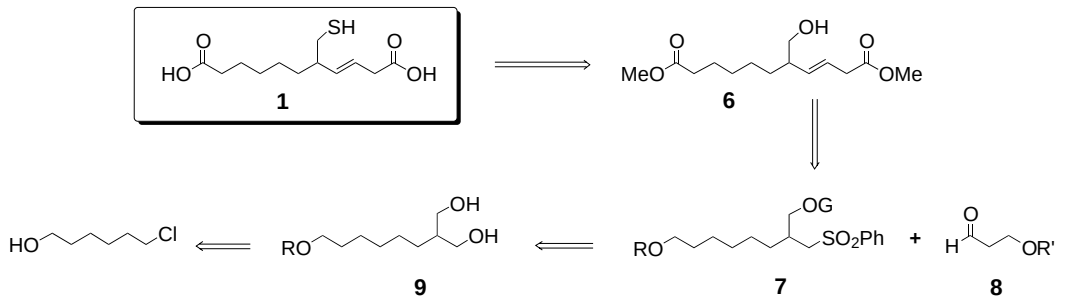
0040-4039/01/$ - see front matter
PII: S0040-4039(01)00554-8

expecting an improvement of the affinity for the cys-LT2 receptor in comparison with the analog containing the completely saturated $C5_{sat}C3_{sat}$ **2** structure.

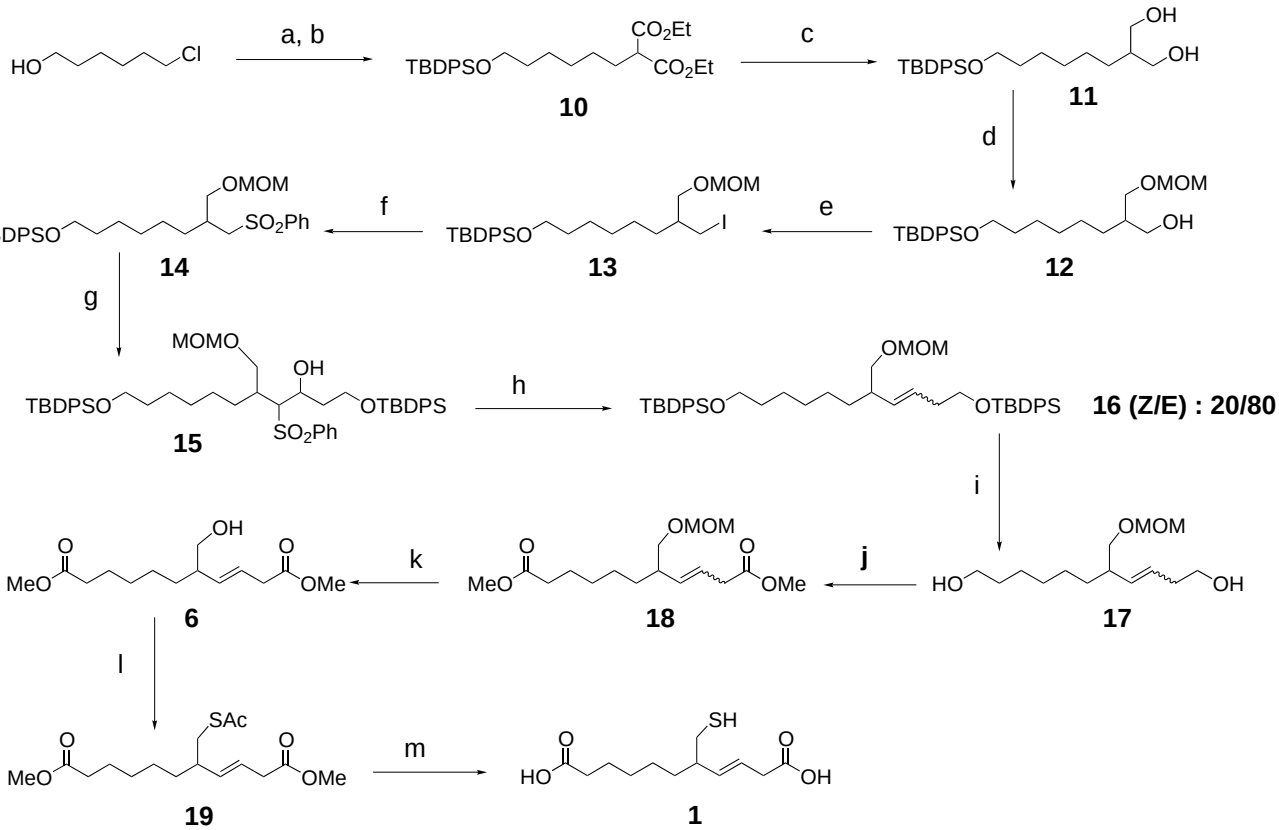
The synthesis of target **1** was first run via functionalization of the corresponding α,β-unsaturated *E*-ketone **3** as previously reported[11] for compound **2** (Scheme 1). However, this strategy failed due to an in situ isomerization of ketone **3** to **4**.

To avoid these difficulties, we applied a new strategy based on the Julia olefination reaction.[14,15] Our approach is summarized in the retrosynthetic Scheme 2, where it was envisioned that the access to the homoallylic thiol **1** could be reached via a Mitsunobu reaction from its hydroxylated analog **6**, which in turn would be obtained from a Julia condensation between a sulfone **7** and an C3 carbon atoms aldehyde **8**. The sulfone **7** could be derived from 1,3-diol **9**, easily prepared in three steps from commercially available 6-chlorohexan-1-ol. The protective group G of the sulfone **7** should be resistant to the reaction conditions used for the deprotection of the R and R′ groups, and compatible with the Julia reaction and Jones oxidation conditions. Following these requirements, G must be a MOM group, whereas R and R′ were chosen as *tert*-butyl diphenylsilyl groups.

The synthetic route to compound **1** is depicted in Scheme 3. Thus, after silylation of 6-chlorohexan-1-ol with *tert*-butyl diphenylsilyl chloride, alkylation with diethyl malonate provides in 61% yield the diester **10**.



Scheme 2.



Scheme 3. (a) TBDPSCl, NEt_3, DMAP, CH_2Cl_2, 97%; (b) diethylmalonate, NaH, THF, 61%; (c) $LiAlH_4$, THF, reflux, 71%; (d) MOMCl (1 equiv.), NaH, THF, 69%; (e) PPh_3, imidazole, I_2, xylene, 80°C, 88%; (f) $PhSO_2Na$, EtOH, reflux, 78%; (g) *n*-BuLi, −78°C then **8**, −78 to −50°C; (h) Na–Hg 5%, THF/MeOH, 0°C, 77% (*E*+*Z*) from **14**; (i) $(n\text{Bu})_4NF$, THF, 88% (*E*+*Z*); (j) Jones reagent, acetone, −10°C then CH_2N_2, Et_2O, 60% (*E*+*Z*); (k) TMSBr, CH_2Cl_2, −30°C, 69% (*E*+*Z*) then preparative HPLC; (l) PPh_3, DIAD, AcSH, THF, 67%; (m) KOH, $EtOH/H_2O$, reflux, 60%.

The later is reduced into 1,3-diol **11** by an excess of lithium aluminium hydride in 71% yield. Selective monoprotection with methoxymethyl chloride (1 equiv., 69%) followed by a modified Garreg reaction afforded the iodide **13**, which was transformated in 78% yield into the corresponding racemic sulfone **14** in the presence of phenylsulfinic acid sodium salt. The lithiated sulfone **14** was condensed with aldehyde **8** (R′ = OTBDPS, derived from propan-1,3-diol)[16] at −78 to −50°C. Reduction of the resulting diastereoisomeric mixture of β-hydroxysulfones **15** with sodium amalgam at 0°C afforded the expected alkenyl compound **16** in 77% yield from **14**. The addition of sulfone anions to aldehydes and the reduction step of the resulting hydroxy sulfones are capricious processes depending on several factors.[15] The Kocienski–Lythgoe modification[17] of the Julia reaction or activation[18] of the aldehyde by complexation with DIBAL–methoxide did not allow us to improve the yield. Different reducting agents (SmI_2-HMPA, Mg power, Na–Hg amalgam) were compared. In all our attempts to perform the Julia olefination sequence, we observed only a moderate stereoselectivity (Z/E: 20/80, measured by ^1H NMR spectroscopy at 360 MHz).

After deprotection of both terminal silyl ethers with fluoride anions in 88% yield, followed by Jones oxidation, the diacid was treated with diazomethane to afford the diester **18** (60% yield from **17**). Selective removal of the MOM group with TMSBr at −30°C then produced free homoallylic alcohol **6** (69% yield), which was functionalized via a Mitsunobu reaction with thioacetic acid in 67% yield. Finally, in the resulting compound **19**, the thioacetate group was cleaved together with ester functions under basic conditions at EtOH–H_2O reflux to give thiol **1**[19] in 60% yield.

Surprisingly, we found no step where the Z/E mixture could be easily separated by flash column chromatography. Using different silica gel phases and eluent conditions, isolation by HPLC of the pure E-isomer **19** or **1** failed since the Z- and E-isomers were co-eluted and the thiol function readily dimerized. Obtention of the pure E-homoallylic thiol **1** was successfully achieved from pure E-homoallylic alcohol **6**, which was separated from its isomers **6**-Z by preparative HPLC on reverse phase (gradient H_2O–MeCN, Lichrospher RP-18, 5 μm).

In conclusion, application of the Julia olefin synthesis provided an efficient access to the required E-double bond on the C3 carbon atom chain. The 13 steps leading to target **1** were achieved in 2.5% overall yield.

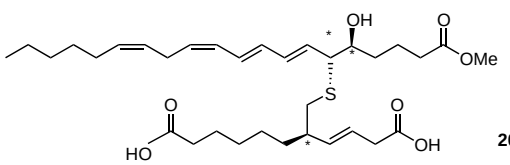
Starting from leukotriene A4, chemical epoxide ring-opening with thiol **1**[20] is underway to provide a protease-resistant leukotriene C4.

Acknowledgements

We wish to thank Professor Marc Julia for strengthening discussion.

References

1. Sies, H. *Free Rad. Biol. Med.* **1999**, *27*, 916–921.
2. Monks, T. J.; Ghersi-Egea, J.-F.; Philbert, M.; Cooper, A. J. L.; Lock, E. A. *Toxicol. Sci.* **1999**, *51*, 161–177.
3. Lomaestro, B. M.; Malone, M. *Ann. Pharmacother.* **1995**, *29*, 1263–1273.
4. Kelly, F. J. *Food Chem. Toxicol.* **1999**, *37*, 963–966.
5. Schröder, C. P.; Godwin, A. K.; O'Dwyer, P. J.; Tew, K. D.; Hamilton, T. C.; Ozols, R. F. *Cancer Invest.* **1996**, *14*, 158–168.
6. Nagasawa, H. T.; Cohen, J. F.; Holleschau, A. M.; Rathbun, W. B. *J. Med. Chem.* **1996**, *39*, 1676–1686.
7. Luisi, G.; Calcagni, A.; Pinnen, F. *Tetrahedron Lett.* **1993**, *34*, 2391–2392.
8. Lucente, G.; Luisi, G.; Pinnen, F. *Il Farmaco* **1998**, *53*, 721–735 and references cited therein.
9. Vince, R.; Brownel, J.; Akella, L. B. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 853–856.
10. Adang, A. E. P.; Brussee, J.; Gen, A. V.d.; Mulder, G. J. *Biochem. J.* **1990**, *269*, 47–54.
11. Klotz, P.; Slaoui-Hasnaoui, A.; Banères, J.-L.; Duckert, J.-F.; Rossi, J.-C. *J. Med. Chem.* **1998**, *41*, 2278–2288.
12. Okuyama, S.; Miyamoto, S.; Shimoji, K.; Konishi, Y.; Fukushima, D.; Niwa, H.; Arai, Y.; Toda, M.; Hayashi, M. *Chem. Pharm. Bull.* **1982**, *30*, 2453–2462.
13. Hann, M. M.; Sammes, P. G.; Kennewell, P. D.; Taylor, J. B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 307–314.
14. Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 4833–4836.
15. Kocienski, P. *Phosphorus Sulfur* **1985**, *24*, 97–127.
16. Breen, A. P.; Murphy, J. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, *23*, 2979–2990.
17. Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829–833.
18. Spaltenstein, A.; Carpino, P. A.; Miyake, F.; Hopkins, P. B. *J. Org. Chem.* **1987**, *52*, 3759–3766.
19. Compound **1**: 5-(Mercaptomethyl)-3(*E*)-undecen-1,11-dioic acid: ^1H NMR (360 MHz, $CDCl_3$) δ ppm: 1.20–1.40 (m, 6H, H6, H7, H8); 1.60–1.72 (m, 2H, H9); 2.17–2.23 (m, 1H, H5); 2.34 (t, 2H, J = 7.7 Hz, H10); 2.51 (dd, 2H, J = 8.4 Hz and 6.4 Hz, CH_2); 3.13 (td, 2H, J_{2-3} = 6.4 Hz, J_{2-4} = 1.70 Hz, H2); 5.32 (ddt, 1H, J_{3-4} = 15.4 Hz, J_{4-5} = 8.8 Hz, J_{4-2} = 1.2 Hz, H4); 5.60 (td, 1H, J_{3-2} = 7.0 Hz, J_{3-4} = 15.4 Hz, H3); 9.50 (s broad, 2H, COOH). ^{13}C NMR (360 MHz, $CDCl_3$) δ ppm: 24.29 (C9); 26.52 (CH_2); 28.70 (CH_2); 29.64 (C12); 33.37 (CH_2); 33.90 (C10); 37.77 (C2); 45.83 (C5); 123.38 (C3); 136.80 (C4); 178.22 (C=O); 180.30 (C=O). LC–MS analysis: t_R = 10.57 min; (ES$^+$) m/z = 260.64 with gradient 100% H_2O to 100% MeCN–0.1% TFA in 20 min; column: symmetry shield RP-18, 4.6×50 mm (3.5 μm); 1 mL/min; at λ = 220 nm.
20. Compound **1** was prepared as a racemic mixture. We failed to separate the enantiomers by chiral HPLC or using a resoluting agent to create diastereomers. Hopefully, after coupling to LTA4, the separation of the different diastereomers of the expected LTC4 analog **20** should be easier.



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