Pergamon

Tetrahedron Letters 43 (2002) 8795–8796

TETRAHEDRON LETTERS

An efficient synthesis of δ-amino[3-^{13}C]levulinic acid

Yasuhiro Kajiwara and A. Ian Scott*

Center for Biological NMR, Department of Chemistry, Texas A&M University, College Station, TX 77843-3255, USA

Received 26 July 2002; accepted 12 September 2002

Abstract—A new convenient synthesis of [3-^{13}C]ALA, using ^{13}C-methyl phenyl sulfone, with 62% overall yield in six steps, is described. The overall yield of this synthesis exceeds that of previously reported methods. © 2002 Elsevier Science Ltd. All rights reserved.

δ-Aminolevulinic acid (ALA, **1a**) which is known as an insecticide and herbicide,[1] is an intermediate in the biosynthesis of tetrapyrrolic compounds such as vitamin B_{12}, chlorophyll and heme.[2a,b] As shown in Fig. 1, vitamin B_{12} and other tetrapyrrolic compounds are biosynthesized from uroporphyrinogen III (uro'gen III, **3**), which is derived in turn from eight molecules of ALA via 'tetramerization' of the monopyrrolic precursor porphobilinogen (PBG, **2**).[3a,b]

Isotopomers of ALA regioselectively labeled with ^{13}C have been systematically used for the structural elucidation of the intermediates in the biosynthesis and metabolism of these tetrapyrrolic compounds in combination with the widely available high-field FT NMR technique. Especially for the vitamin B_{12} biosynthetic pathways, the availability of not only [4-^{13}C]ALA and [5-^{13}C]ALA but also [3-^{13}C]ALA (**1b**) has proved extremely useful as **1b** leads to the labeling of positions C-2, C-7, C-12 and C-18 of the porphyrinoid ring.[4a,b] There have been several reports concerning the synthesis of ALA[5a–l] including two regioselective synthesis of [3-^{13}C]ALA (**1b**).[5a,b] However, the synthetic methods for **1b**, which is now commercially available (but extremely expensive), suffer from low yields resulting in high costs. Therefore more efficient synthetic methods for **1b** were required and we now report on a new synthetic method which is of lower cost, easy handling and convenient for large scale preparations, as illustrated in Scheme 1.

The target product **1b** was synthesized starting from ^{13}C-methyl phenyl sulfone **4**, which is easily made from ^{13}C-iodomethane.[6] Sulfone **4** was treated with ^{n}BuLi and to the resulting yellow solution, ethyl *tert*-butyldimethylsiloxy-acetate was added to give ketone **5** in 86% yield.[7] Coupling of ketone **5** with ethyl bromoacetate using NaH in THF, gave sulfone **6** in 83%

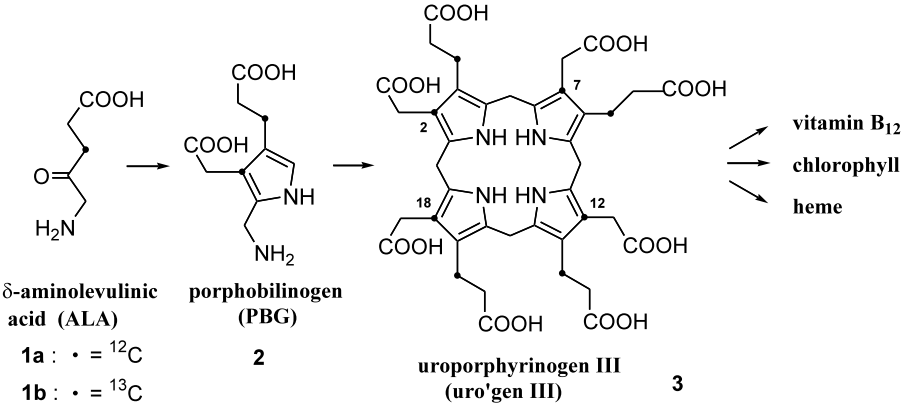
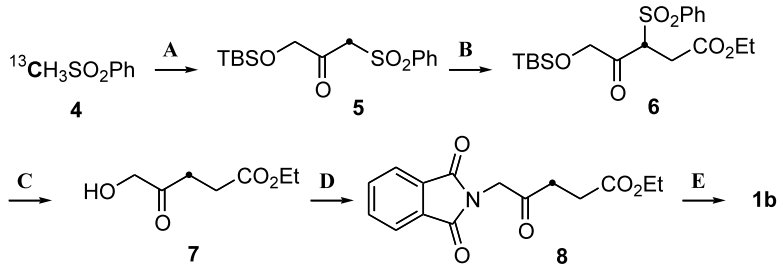


Figure 1. Overview of the early stages in the biosynthesis of some porphyrinoids.

* Corresponding author. Fax: +1-979-845-5992; e-mail: scott@mail.chem.tamu.edu

0040-4039/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(02)01970-6



Scheme 1. *Reagents and conditions*: (A) ^{n}BuLi, THF, 0°C then $TBSOCH_2CO_2Et$, 86%; (B) NaH, THF, 0°C then $BrCH_2CO_2Et$, 83 and 15% recovered **5**; (C) (i) Al(Hg), THF–H_2O, rt, 97%, (ii) AcOH, THF–H_2O, rt, 99%; (D) phthalimide, DEAD, Ph_3P, PhH, rt, 81%; (E) 6N HCl, reflux, 95%.

yield and recovered **5** (which can be recycled; 15%). Removal of the benzensulfonyl group of **6** with Al(Hg)[8] in 97% yield followed by removal of TBS group with excess AcOH in THF–H_2O provided alcohol **7** (99%). Compound **7** was converted to phthalimido **8** via the Mitsunobu reaction[9] using phthalimide, DEAD and Ph_3P in 81% yield. Hydrolysis of the phthalyl and ethyl ester groups with 6N HCl of phthalimido **8** followed by recrystallization from H_2O–^{i}PrOH–Et_2O yielded the desired product **1b** in 95% yield. The spectral data (mp, IR, ^{1}H, ^{13}C NMR) for synthetic **1b**[10] are in full agreement with those reported previously.[5a,b]

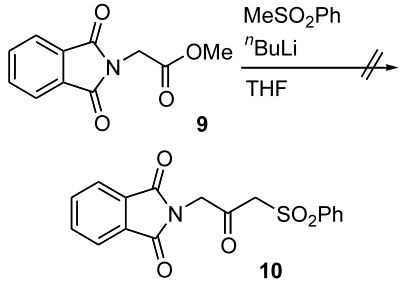
The above methodology was achieved in six steps and 62% overall yield (from **4**). The overall yield of the present synthesis and the better costs exceed that of any other method reported to date.

Acknowledgements

We would like to thank the NIH and the Robert A. Welch Foundation for financial support of this work.

References

1. Duke, S. O.; Rebeiz, C. A. *Porphyric Pesticides: Chemistry, Toxicology, and Pharmaceutical Applications*. ACS Symposium Series 559, 1994.
2. (a) Bogorad, L. *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1979; Vol. VI, Part A, pp. 125–178; (b) Leeper, F. J. *Nat. Prod. Rep.* **1985**, *2*, 561–580.
3. (a) Battersby, A. R.; Fookes, C. J. R.; Matcham, G. W. J.; McDonald, E. *Nature* **1980**, *285*, 17–21; (b) Roessner, C. A.; Santander, P. J.; Scott, A. I. *Vitamins Hormones* **2001**, *61*, 267–297.
4. (a) Scott, A. I. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1223–1243; (b) Blanche, F.; Cameron, B.; Crozet, J.; Debussche, L.; Thibaut, D.; Vuilhorgne, M.; Leeper, F. J.; Battersby, A. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 383–411.
5. (a) Pfaltz, A.; Jaun, B.; Fassler, A.; Eschenmoser, A.; Jaenchen, R.; Gilles, H. H.; Diekert, G.; Thauer, R. K. *Helv. Chim. Acta* **1982**, *65*, 828–865; (b) Kurumaya, K.; Okazaki, T.; Seido, N.; Akasaka, Y.; Kawajiri, Y.; Kajiwara, M. *J. Label. Compd. Radiopharm.* **1989**, *27*, 217–235; (c) Battersby, A. R.; Hunt, E.; McDonald, E.; Moron, J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2917–2922; (d) Herdeis, C.; Dimnerling, A. *Arch. Pharm.* **1984**, *317*, 304–306; (e) Benedikt, E.; Kost, H.-P. *Z. Naturforsch.* **1986**, *41b*, 1593–1594; (f) Pfaltz, A.; Anwar, S. *Tetrahedron Lett.* **1984**, *25*, 2977–2980; (g) Cambell, J. B.; Johnston, J. S. *J. Label. Compd. Radiopharm.* **1989**, *27*, 1353–1358; (h) Kawakami, H.; Ebata, T.; Matsushita, H. *Agric. Biol. Chem.* **1991**, *55*, 1687–1688; (i) Vishwakarma, R. A.; Balachandran, S.; Alanine, A. I. D.; Stamford, N. P. J.; Kiuchi, F.; Leeper, F. J.; Battersby, A. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2893–2899; (j) Ha, H.-J.; Lee, S.-K.; Ha, Y.-J.; Park, J.-W. *Synth. Commun.* **1994**, *24*, 2557–2562; (k) Wang, J.; Scott, A. I. *Tetrahedron Lett.* **1997**, *38*, 739–740; (l) Iida, K.; Tokiwa, S.; Ishii, T.; Kajiwara, M. *J. Label. Compd. Radiopharm.* **2002**, *45*, 569–576.
6. Choudhry, S. C.; Serico, L.; Cupano, J. *J. Org. Chem.* **1989**, *54*, 3755–3757.
7. Initially we considered protection in the nitrogen form **10** instead of the oxygen form **5**. However, this approach led to a complex mixture of products, which did not include sulfone **10**.



8. Corey, E. J.; Chavkovsky, M. *J. Am. Chem. Soc.* **1964**, *86*, 1639–1640.
9. Mitsunobu, O. *Synthesis* **1981**, 1–28.
10. **δ-Amino[3-^{13}C]levulinic acid hydrochloride (1b)**. Mp 144–147°C. IR (KBr): 3461, 3042, 1725, 1692, 1419, 1403, 1178, 1146 cm^{-1}. ^{1}H NMR (500 MHz, D_2O) δ: 2.57–2.60 (2H, m), 2.64 (1H, t, J=6.2 Hz), 2.90 (1H, t, J=6.2 Hz), 4.00 (2H, s). ^{13}C NMR (125 MHz, D_2O) δ: 27.5 (d, J=37.8 Hz), 34.4 (^{13}C, m), 47.1 (d, J=17.0 Hz), 176.9, 204.2 (d, J=41.9 Hz). ESIMS m/z: 133 (M^+–Cl, 71), 115 (100).