Pergamon

Tetrahedron Letters, Vol. 38, No. 47, pp. 8141-8144, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10186-1

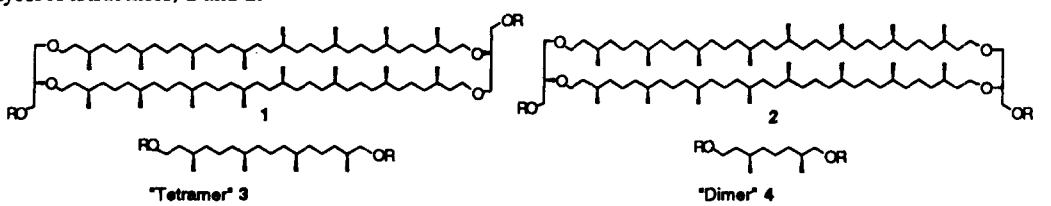
Synthesis of Archaebacterial Lipid C_{20} Chirons

William F. Berkowitz* and Yanzhong Wu

Department of Chemistry and Biochemistry, Queens College of the City University of New York, 65-30 Kissena Blvd., Flushing, NY 11367

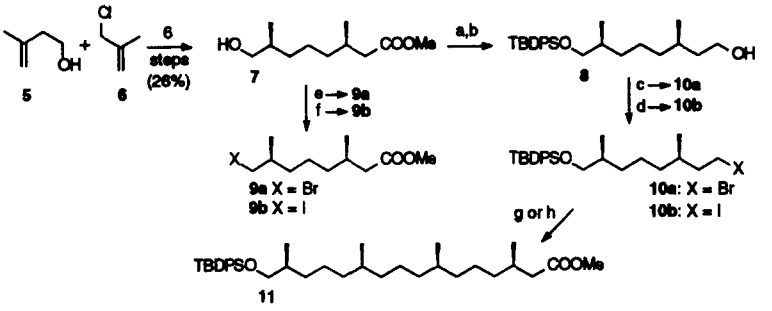
Abstract: Archaebacterial lipid C_{20} chirons were synthesized by cross-coupling optically active C_{10} "dimer" units prepared from hydroxyester **7**. Vitamin E (C_{15}) side chain was similarly constructed. © 1997 Elsevier Science Ltd.

Archaebacteria,[1] a third, new, taxon evolutionarily distinct from the well-known domains *Bacteria* and *Eukarya*, are single cell organisms which can survive in extremely harsh environments - temperatures up to 120°C, pH 0.5 to 12, and high (20+%) salt concentrations.[2c] The unusual membrane lipids of the archaebacteria are an important contributor to the remarkable adaptation of these organisms to such extremes.[2] Two major constituents of the membrane lipids isolated from these prokaryotes are the remarkable C_2-symmetric, *sn*-2,3-bisbiphytanyl-glycerol tetraethers, **1** and **2**.[3]



Considerable effort has been devoted to the synthesis of precursors of **1** and **2**.[4] In addition, Kakinuma has recently constructed a model, 72-membered cyclic, bis-glycerol tetraether,[4b] by sequentially coupling appropriately functionalized C_{16} straight chain units to protected glycerol molecules. We intend to use the same ring-forming strategy[5] with isopranyl "tetramers," e.g. **3**. To this end, we recently developed methods for the synthesis of enantiomerically pure C_{10} "dimer" units,[6] e.g. **4**, using asymmetric enolization of *meso*-3,7-dimethylcyclooctanone as a key step. Here we report procedures for coupling two C_{10} dimer units to form an optically active C_{20} tetramer unit (Scheme 1), and its further conversion to the well-known C_{15} side-chain of α-tocopherol (Scheme 3).[7]

Scheme 1.

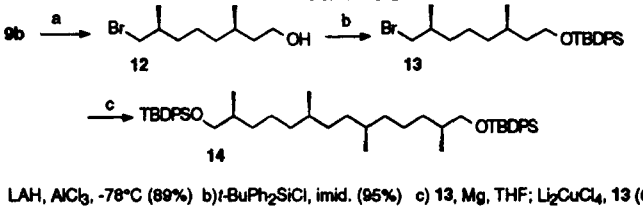


a) *t*-BuPh$_2$ SiCl, Imid. (91%) b) LAH, Et$_2$O (94%) c) Ph$_3$P, NBS (87%) d) PH$_3$P, I$_2$, Imid. (86%)
e) Ph$_3$P, NIS (75%) f) Ph$_3$P, NBS g) (93%) **10a**, Mg, THF; Li$_2$CuCl$_4$; **9** (71%)
h) **10b**, SmI$_2$, HMPA, THF; cat. CuBr; **9b** (81%)

Hydroxy ester **7** (98+%ee), prepared from 3-methyl-3-butenol and methallyl chloride in 6 steps in 26% overall yield,[6] was protected by *tert*-butyldiphenylsilyl chloride,[8] then reduced with LAH to give **8** in 94% yield. This was converted to both the bromide **10a**, with Ph$_3$P/NBS[9] in 87% yield, and iodide **10b**, with Ph$_3$P/I$_2$[10] in 86% yield. In parallel, hydroxy ester **7** was converted to bromoester **9a**, using Ph$_3$P/ NBS in 93% yield, and iodoester **9b**, with Ph$_3$P/NIS[9a] in 72% yield. The desired C_{20} synthon **11** was prepared *via* the copper catalyzed coupling[11] of the Grignard reagent of bromide **10a** with iodide **9b** in 71% yield. In comparison, the samarium diiodide initiated coupling[12] between iodide **10b** and **9b** gave **11**[13] ($[\alpha]_D^{25}$ 1.50, *c* 1.70, CHCl$_3$) in 81% yield.

In addition, we prepared alternative C_{20} unit **14** ($[\alpha]_D^{25}$ -1.21, *c* 0.99, CHCl$_3$) which corresponds to the middle of the C_{40} lipid chain. Alane[14] reduction of bromo ester **9a**, protection, and *homo*-coupling of bromide **13**, gave **14**, as shown in Scheme 2.

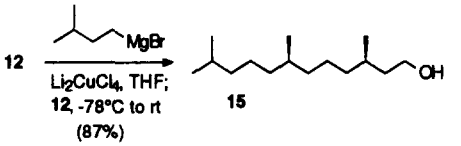
Scheme 2



a) LAH, AlCl$_3$, -78°C (89%) b)*t*-BuPh$_2$SiCl, imid. (95%) c) **13**, Mg, THF; Li$_2$CuCl$_4$, **13** (68%

Finally, the Vitamin E side chain **15** ($[a]_D^{25}$ +3.53 (*c* 1.205, CHCl$_3$; Lit:$[a]_D^{25}$ +3.55 (c 1.075, CHCl$_3$);[7p] $[a]_D^{18}$ +3.49 (c 0.98, CHCl$_3$);[7n] $[a]_D^{23}$+3.35 (c 0.955, CHCl$_3$)[7m] was quickly assembled by copper catalyzed coupling of the Grignard reagent of isoamyl bromide with bromo-alcohol **12** in 87% yield.

Scheme 3.



Acknowledgment. This work was supported by PSC-CUNY Faculty Research Award 666291. We are especially grateful to our colleague Prof. David C. Locke for the GC-MS spectra, and the New York State Urban Development Corp., under the Higher Education Applied Technology Program, for purchase of the GC-MS instrument. We also gratefully acknowledge support from the National Science Foundation (CHE-9408535) for funds used for the purchase of the 400 MHz NMR spectrometer.

REFERENCES AND NOTES

1. Woese, C.R.; Kandler, O.; Wheelis, M.L. "Towards a natural system of organisms: Proposal for the domains Archaea, Bacteria, and Eucarya," *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 4576-4759.
2. *(a) The Biochemistry of Archaea (Archaebacteria); New Comprehensive Biochemistry, Vol. 26;* Kates, M.; Kushner, D.J.; Matheson, A.T. Eds.; Elsevier: Amsterdam, **1993**; (b) Langworthy, T.A. *Lipids of Archaebacteria* in *The Bacteria* Vol. 8, Woese, C.R.; Wolfe, R.S., Eds.; Academic Press, N.Y. **1985**, 459-497. (c) De Rosa, M.; Morana, A.; Riccio, A.; Gambacorta, A.; Trincone, A.; Incani, O. *Biosensors & Bioelectronics* **1994**, *9*, 669-675.
3. Grather, O.; Arigoni, D. *J. Chem. Soc., Chem. Commun.* **1995**, 406.
4. (a) Eguchi, T; Kana, H.; Kakinuma, K., *J. Org. Chem.* **1997**, 62, 1924-1933. (b) Eguchi, T; Kana, H.; Kakinuma, K., *Chem.Commun.* **1996**, 365-366. (c) Eguchi, T; Kana, H.; Kakinuma, K., *J. Chem. Soc. Chem. Commun.* **1994**, 137. (d) Eguchi, T; Kana, H.; Kakinuma, K., *Tetrahedron Lett.*. **1993**, 34, 2175. (e) Heathcock, C.H.; Finkelstein, B.L.; Jarvi, E.T.; Radel. P.A.; Hadley, C.R. *J. Org. Chem.* **1988**, *53*, 1922. (f) Heathcock, C.H.; Radel, P.A., *J. Org. Chem.* **1986**, *51*, 4323. (g) Heathcock, C.H.; Finkelstein, B.L.; Poulter, C.D. *Science* **1985**, 862. (h) Czeskis, B.A.; Alexeev, I.G.; Moiseenkov, A.M., *Russian Chemical Bulletin* **1993**, *42*, 1246. (i) Czeskis, B.A.; Alexeev, I.G.; Moiseenkov, A.M. *Mendeleev Commun.* **1993**, 93.
5. We had developed substantially the same chemistry, except for the all-important final 72-membered ring-forming step, prior to Kakinuma's publication: Thesis of Mengxiao Shi, Ph.D. Program in Chemistry, The City University of New York; completed 7/97. See also: Berkowitz, W.F.; Pan, D.; Bittman, R., *Tetrahedron Lett.* **1993**, *34*, 4297.
6. Berkowitz, W. F.; Wu, Y., *J. Org. Chem.* **1997**, 62, 1536-1539.
7. A. Syntheses of the **3*R*, 7*R*-C_{15}** side chain: (a) Mayer, H.; Schudel, P.; Rüegg, R.; Isler, O. *Helv. Chim. Acta* **1963**, *46*, 650. (b) Burrell, J.W.K.; Garwood, R.F.; Jackman, L.M.; Oskay, E.; Weedon, B.C.L. *J. Chem. Soc., Chem. Commun.* **1966**, 2144. (c) Chan, K.K.; Cohen, N.; De Noble, J.P.; Specian, Jr., A.C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497. (d) Schmid, M.; Barner, R., *Helv. Chim. Acta* **1979**, *62*, 464. (e) Zell, R., *Helv. Chim Acta* **1979**, *62*, 474. (f) Cohen, N; Lopresti, R. J.; Saucy, G., *J. Am Chem. Soc.* **1979**, *101*, 6710. (g) Fuganti, C.; Grasseli, P. *J. Chem. Soc., Chem. Commun.* **1979**, 995. (h) Takahashi, J.; Mori, K.; Matsui, M. *Agric. Biol. Chem.* **1979**, *43*, 1605. (i) Trost, B.M.; Klun, T.P. *J. Am. Chem. Soc.* **1979**, *101*, 6756. (j) Trost, B.M.; Klun, T.P. *J. Org. Chem.* **1980**, *45*, 4256 (k) Fujisawa, T.; Sato, T.; Kawara, T.; Ohashi, K., *Tetrahedron Lett.* **1981**, *2*, 4823. (l) Trost, B.M.; Klum, T.P., *J. Am. Chem. Soc.* **1981**, *103*, 1864. (m) Koreeda, M.; Brown, L., *J. Org. Chem.* **1983**, *48*, 2122, (n) Fujiwara, J.; Fukutani, Y.; Hasegawa, M.; Muruoka, K.; Yamamoto, H., *J. Am. Chem. Soc.* **1984**, *106*, 5004. (o) Takabe, K.;

Uchiyama, Y.; Okisaka, K.; Yamada, T.; Katagiri, T.; Okazaki, T.; Oketa, Y.; Kumobayashi, H.; Akutagawa, S. *Tetrahedron Lett.* **1985**, *26*, 5153. (p) Gramatica, P.; Manitto, P.; Monti, D.; Speranza, G., *Tetrahedron* **1986**, *24*, 6687. (q) Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, A.; Akutagawa, S.; Inoue, S.; Kasahara, O.; Noyori, R., *J. Am. Chem. Soc.* **1987**, *109*, 1596. (r) Gould, T. J.; Balestra, M.; Wirrman, M. D.; Gary, T. A.; Rossano, L. T.; Kallmerten, J., *J. Org. Chem.* **1987**, *52*, 3889. (s) Schmid, R.; Hansen, H. *Helv. Chim. Acta* **1990**, *73*, 1258. (t) Schmid, R.; Antoulas, S.; Rüttimann, Schmid, M.; Vecchi, M.; Weiser, H. *Helv. Chim. Acta* **1990**, *73*, 1276. (u) Takaya, H.; Ohta, T.; Mashima, K.; Noyori, R. *Pure Appl. Chem.* **1990**, *62*, 1135. (v) Heiser, B.; Broger, E. A.; Crameri, Y., *Tetrahedron Asymmetry* **1991**, *2*, 51. (w) Takano, s.; Sugihara, T.; Ogasawara, K., *Synlett.* **1991**, 279. (x) Cohen, N.; Sachaer, G.; Scalone, M., *J. Org. Chem.* **1992**, *57*, 5783.

B. Syntheses of the **2*R*, 6*R*-C_{14}** side chain: (a) Scott, J.W.; Bizzaro, F.T.; Parrish, D.R.; Saucy, G. *Helv. Chim. Acta* **1976**, *59*, 290. (b) Cohen, N.; Eichel, W.F.; Lopresti, R.J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505. (c) Cohen, N.; N.; Eichel, W.F.; Lopresti, R.J.; Neukom, C.; Saucy, G *ibid.* **1976**, *41*, 3512. (d) Chan, K.K.; Saucy, G. *J. Org. Chem.* **1977**, *42*, 3828. (e) Ref. 8Ag (f) Ref. 8Ah (g) Cohen, N.; Scott, C.G.; Neukom, C.; Lopresti, R.J.; Weber, G.; Saucy, G. *Helv. Chim. Acta* **1981**, *64*, 1158. (h) Heathcock, C.H.; Jarvi, E.T. *Tetrahedron Lett.* **1982**, *23*, 2825. (i) Helmchen, G.; Schmierer, R. *Tetrahedron Lett.* **1983**, *24*, 1235. (j) Harada, T.; Hayashiya, T.; Wada, I.; Iwa-ake, N.; Oku, A. *J. Am. Chem. Soc.* **1987**, *109*, 527. (k) Takano, S.; Shimazaki, Y.; Iwabuchi, Y.; Ogasawara, K. *Tetrahedron Lett.* **1990**, *31*, 3619. (l) Naoshima, Y.; Munakata, Y.; Yoshida, S.; Funai, A. *J. Chem. Soc. Perkin Trans. I* **1991**, 549. (m) Mori, K.; Harada, H.; Zagatti, P.; Cork, A.; Hall, D.R. *Liebigs Ann. Chem.* **1991**, 259. (n) Chenevert, R.; Desjardins, M. *J. Org. Chem.* **1996**, *61*, 1219.

8 Hanessian, S.; Lavallee, P., *Can. J. Chem.* **1975**, 53, 2975-77.

9 a) Bose, A. K.; Lal, B., *Tetrahedron Lett.* **1973**, 39397-3940. (b) Hanessian, S.; Ponpipom, M.M.; Lavallee, P. *Carbohydrate Res.* **1972**, *24*, 45.

10 (a) Lange, G.; Gottardo, C. *Synthetic Commun* **1990**, *20*, 1473-1479. (b) Garegg, P.J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans, 1* **1980**, 2866-2869.

11 Tamura, M.; Kochi, J.K. *Synthesis* **1971**, 303.

12 Berkowitz, W. F.; Wu, Y., *Tetrahedron Lett.* **1997**, 38, 3171-3173.

13 All compounds reported were identified by ^1H and ^{13}C NMR, IR, and elemental analysis or high resolution MS.

11, IR ($CDCl_3$) 1739.4, cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 0.83 (d, J=6.0Hz, 6H,), 0.91 (d, J=4.5Hz, 3H), 0.93 (d, J=4.4Hz, 3H), 0.95-1.42 (m, 29H), 1.62 (m, 1H), 1.92 (m, 1H), 2.10 (q, J=14.6, 8.2Hz, 1H), 2.31 (q, J=14.6, 5.9Hz, 1H), 3.43 (q, J=9.6, 6.3Hz, 1H), 3.51 (q, J=10.5, 6.3Hz, 1H), 3.66 (s, 3H), 7.40 (m, 6H), 7.67 (m, 4H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 16.99, 19.32, 19.73, 19.75, 19.80, 24.35, 24.40, 24.47, 26.88, 30.40, 32.77, 33.49, 35.74, 37.08, 37.12, 37.36, 37.40, 41.67, 51.34, 68.91, 127.54, 129.45, 134.14, 135.63, 173.85. ESI-MS 581.3 $(M+H)^+$; MS/MS (Tandem Mass Spectrum, Parent Ion $(M+H)^+$ 581.3, Major peaks) 503.3 $[(M+H)^+-C_6H_6]$, 471.1 $[(M+H)^+-C_6H_6-HOCH_3]$, 425.3 $[(M+H)^+-2C_6H_6]$, 393.3 $[(M+H)^+-2C_6H_6-HOCH_3]$, 325.1 $[(M+H)^+-{}^tBuPh_2SiO]$, 293.3 $[(M+H)^+-{}^tBuPh_2SiO-HOCH_3]$, 239.3 $({}^tBuPh_2Si^+)$. Anal. Calcd. for $C_{37}H_{60}O_3Si$: C, 76.49; H, 10.41. Found: C, 76.72; H, 10.29. HRMS calcd. for $C_{37}H_{60}O_3Si$: 580.4312, found 580.4292.

14. Nystrom, R.F. *J. Am. Chem. Soc.* **1959**, *81*, 610.

(*Received in USA* 18 *August* 1997; *accepted* 15 *September* 1997)