Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 8227–8228

TETRAHEDRON LETTERS

A furan route to the asymmetric synthesis of *trans*-fused polyether building blocks

Urlam Murali Krishna, G. S. C. Srikanth and Girish K. Trivedi*

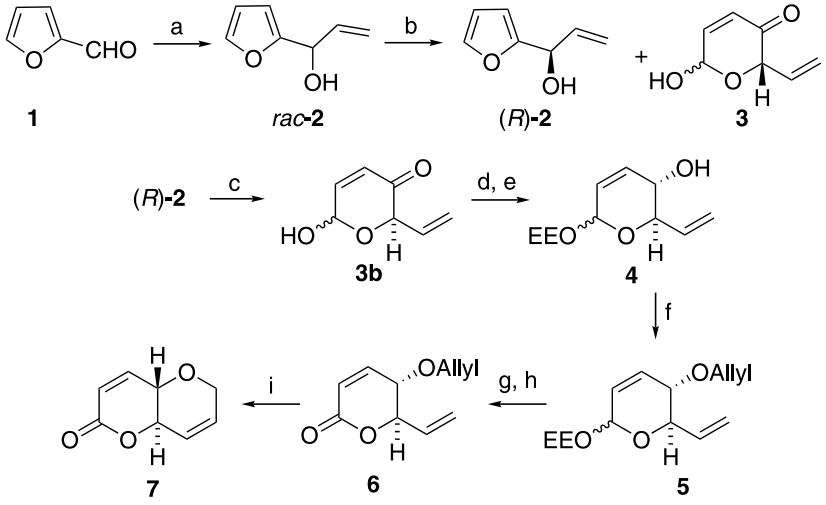
Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400076, India

Received 6 August 2003; revised 3 September 2003; accepted 11 September 2003

Abstract—A novel route towards chiral *trans*-fused polyether lactones **7** and **12** has been developed starting with commercially available furfural. Sharpless kinetic resolution and ring-closing metathesis reactions served as key steps in the strategy.

Recently, synthesis of *trans*-fused polycyclic ethers has received considerable attention due to their presence in a variety of marine natural products with interesting biological activities.[1] After the first characterization of brevetoxin B in 1981,[2] many marine polycyclic ethers of this type as exemplified by brevetoxins, ciguatoxins, yessotoxin, gambierol, gambieric acids and maitotoxins, have been reported. The imposing structural features coupled with the impressive biological properties of these natural products gave impetus for the development of numerous synthetic methods for the construction of cyclic ethers. In this communication we report a flexible and efficient approach to the synthesis of chiral *trans*-fused polyether subunits from racemic 2-furylcarbinols.

Our synthesis commenced with the preparation of furylmethanol *rac*-**2**, by the Grignard reaction of the commercially available furfural with vinylmagnesium bromide (60% yield) (Scheme 1). The chiral furyl-



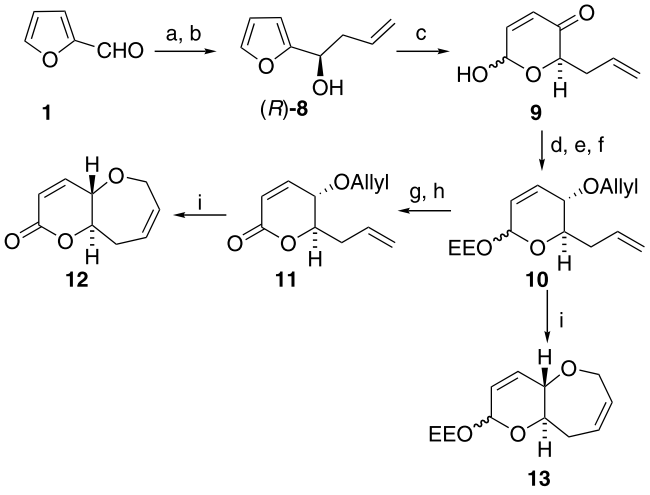
Scheme 1. *Reagents and conditions*: (a) vinylmagnesium bromide (1 M in THF), 60%; (b) Ti(O-*i*-Pr)$_4$, L-(+)-DIPT, *t*-BuOOH, CH_2Cl_2, −21°C, 30 h, 39%; (c) NBS, THF–H_2O (4:1), 0°C, 0.5 h, 97%; (d) EVE, PPTS (cat.), CH_2Cl_2, 0.5 h, 82%; (e) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −60°C, 74%; (f) NaH, allyl bromide, *n*-Bu_4NI, THF–DMF (4:1), 0°C–rt, 90%; (g) PPTS, Me_2CO–H_2O (4:1), 0.5 h; (h) MnO_2, pyridine (cat.), CH_2Cl_2, 1 h, 80% (2 steps); (i) Grubbs' catalyst (6 mol%), benzene, rt, 94%.

Keywords: furfural; kinetic resolution; ring-closing metathesis (RCM); polyether lactones.
* Corresponding author. E-mail: chgktia@chem.iitb.ac.in

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.09.076

methanol (*R*)-**2** was obtained from *rac*-**2**, employing the kinetic resolution of 2-furylcarbinols as developed by Honda[3] and Sato.[4] Oxidative ring expansion of (*R*)-**2** using NBS in THF–H_2O (4:1)[5] afforded the hydroxypyranone **3b** in 97% yield. The anomeric hydroxyl was protected as its ethoxyethyl (EE) ether and the keto group was stereoselectively reduced under Luche's conditions ($NaBH_4$–$CeCl_3$, −60°C) to afford the alcohol **4**.[6] The diastereomeric mixture of alcohols **4** was converted into the allyloxy derivative **5** (quantitative), which was subsequently transformed to the homochiral lactone **6** by deprotection of the anomeric hydroxyl group (PPTS, Me_2CO–H_2O) followed by oxidation with MnO_2. The lactone **6** when treated with Grubbs' catalyst[7] [benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium] (6 mol%) in benzene at room temperature, smoothly underwent ring-closing metathesis to furnish the bicycle **7** in 94% yield.[8]

After preparing the chiral lactone **7**, we attempted to extend this simple protocol for the synthesis of homologous chiral cyclic ether subunits as shown in Scheme 2. Furylmethanol *rac*-**8**, obtained from furfural by treatment with allylmagnesium bromide, was transformed into the optically active furylmethanol (*R*)-**8** ($[\alpha]_D^{25}$ +36.2 (*c* 1.52, $CHCl_3$), lit. $[\alpha]_D^{25}$ +39.9 (*c* 1.54, $CHCl_3$)) by employing kinetic resolution conditions.[4] (*R*)-**8** was oxidatively rearranged to the hemiacetals **9** using $VO(acac)_2$/*t*-BuOOH. The (2*R*)-pyranone **9** was then converted to intermediates **10** and **11** following the reaction conditions given in Scheme 1 (conditions d–f, and g, h). Dienes **10** and **11**, on Grubbs' ring-closure olefin metathesis, gave compounds **12** and **13** in 88% and 80% yields, respectively.[8]



Scheme 2. *Reagents and conditions*: (a) allyl bromide, Mg (excess), Et_2O, 70%; (b) Ti(O-*i*-Pr)$_4$, L-(+)-DIPT, *t*-BuOOH, CH_2Cl_2, −21°C, 36 h, 42%; (c) *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2, rt, 3 h, 91%; (d) EVE, PPTS (cat.), CH_2Cl_2, 0.5 h, 82%; (e) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, −60°C, 76%; (f) NaH, allyl bromide, *n*-Bu_4NI, THF–DMF (4:1), 0°C–rt, 94%; (g) PPTS, Me_2CO–H_2O (4:1), 0.5 h; (h) MnO_2, pyridine (cat.), CH_2Cl_2, 1 h, 80% (2 steps); (i) Grubbs' catalyst (5 mol%), benzene, rt, 88% for **12**, 80% for **13**.

In conclusion, we have developed a facile route to the asymmetric synthesis of polyether intermediates **7** and **12** from commercially available and inexpensive furfural. A particular merit of this approach is that by choosing an appropriate Grignard reagent it may be possible to obtain oxacycles of various ring sizes. We have demonstrated this for six- and seven-membered rings; their enantiomers could be synthesized by using the enantiomeric tartrate ester in the enantioselective step.

Acknowledgements

We thank Department of Science and Technology, New Delhi (India) for the financial support and fellowship to UMK.

References

1. For reviews, see: (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897; (b) Shimizu, Y. *Chem. Rev.* **1993**, *93*, 1685; (c) Scheuer, P. J. *Tetrahedron* **1994**, *50*, 3.
2. Lin, Y. Y.; Risk, M.; Ray, S. M.; VanEngen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773.
3. (a) Kametani, T.; Tsubuki, M.; Tatsuzaki, Y.; Honda, T. *Heterocycles* **1988**, *27*, 2107; (b) Kametani, T.; Tsubuki, M.; Tatsuzaki, Y.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 639; (c) Honda, T.; Kametani, T.; Kanai, K.; Tatsuzaki, Y.; Tsubuki, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1733.
4. (a) Kobayashi, Y.; Kusakabe, M.; Kitano, Y.; Sato, F. *J. Org. Chem.* **1988**, *53*, 1587; (b) Kusakabe, M.; Kitano, Y.; Kobayasho, Y.; Sato, F. *J. Org. Chem.* **1989**, *54*, 2085.
5. Georgiadis, M. P.; Couladoros, E. A. *J. Org. Chem.* **1986**, *51*, 2725.
6. Yonghong, G.; Fangning, Z.; Xinfu, P. *J. Chem. Res. (S)* **1999**, 488.
7. (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18; (b) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 1900.
8. Selected data of compound **7**: $[\alpha]_D^{25}$ +0.42 (*c* 0.48, $CHCl_3$). IR (neat) ν_{max} 1731, 1645 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (d, J=9.6 Hz, 1H), 6.02–5.98 (m, 2H), 5.87–5.83 (m, 1H), 4.71 (m, 1H), 4.4–4.2 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 148.0, 128.5, 124.4, 120.9, 74.9, 70.9, 67.1.
12: $[\alpha]_D^{25}$ −26.1 (*c* 1.57, $CHCl_3$). IR (neat) ν_{max} 1740, 1645 cm^{-1}. ^{1}H NMR (300 10 MHz, $CDCl_3$) δ 6.89 (dd, J=2.2, 4.4 Hz, 1H), 6.0–5.7 (m, 3H), 4.4–4.0 (m, 4H), 2.9–2.6 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7,148.9, 131.4, 125.8, 119.8, 78.6, 78.4, 68.6, 34.0.
13: $[\alpha]_D^{25}$ +5.55 (*c* 0.36, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.0–5.6 (m, 5H), 5.2–4.8 (m, 2H), 4.4–4.3 (m, 1H), 4.1–4.0 (m, 1H), 3.8–3.4 (m, 3H), 2.4–2.2 (m, 2H), 1.2–1.0 (m, 6H). HRMS calculated for $C_{13}H_{20}O_4$: 240.1362, found 240.1403.