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SYNTHESIS OF OPTICALLY PURE 1-(3-FURYL)-1,2-DIHYDROXYETHANE DERIVATIVES

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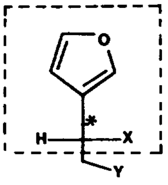
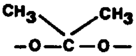
Abstract: *The synthesis of the enantiomerically pure 1-(3-furyl)-1,2-dihydroxyethane derivatives* **1**-*(R),* **2**-*(R),* **3**-*(S) and* **3**-*(R) is described.*

While a number of methods have been described for the synthesis of β-substituted furans,[1] scarce attention has received the synthesis of simple "furochirons" of type A (X = OH, O-protecting group; Y = OH, good leaving group), critical intermediates in any chiral synthesis of some natural products containing this structural unit (dotted lines in A).[2] In this letter we report the synthesis of the enantiomerically pure 1-(3-furyl)-1,2-dihydroxyethane derivatives **1**-(R), **2**-(R), **2**-(S) and **3**-(R).



A

1 X = Y = 
$-O-C(CH_3)_2-O-$

2 X = Y = OH

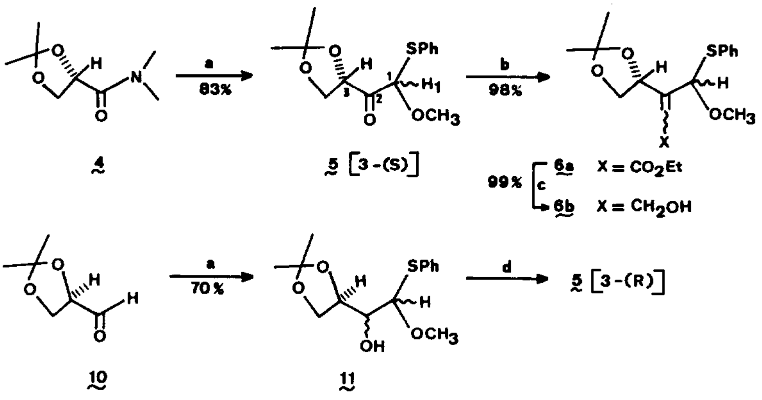
3 X = OH , Y = OTs

7 X = SPh , Y = OH

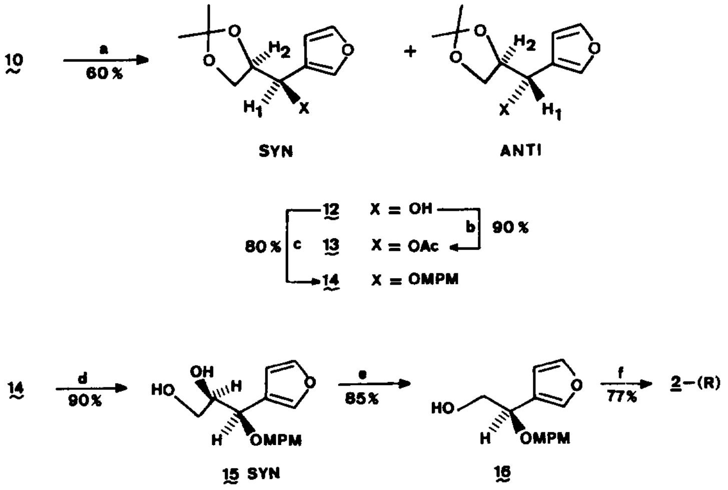
8 X = H , Y = OH

9 X = SPh , Y = OAc

In the first route (Scheme 1) **4**[3] was treated with the anion of methoxymethyl phenyl sulfide[4] yielding **5** [3-(S)].[5] With this simple and promising C_4 chiral building block we approached our objective following the method described by Otera[6] for the synthesis of β-substituted furans. Thus, **6a**[7] [obtained as a mixture (1:1.1) of the *Z* and *E* isomers] and **6b**[7] were cleanly synthesized in almost quantitative yield from **5** [3-(S)]. Treatment of **6b** in benzene at room temperature with a catalytic amount of *p*-toluenesulphonic acid gave **1**-(R)[7] (≈ 20 %) and **7** (65 %).[8] Treatment of **6b** in toluene at reflux in the presence of silica gel[9] gave **1**-(R) (≈ 20 %) [(≈ 26 %) based on recovered starting material] and **7** (18 %) [(21 %)]. Compound **1**-(R), which was unfortunately unseparable from an aromatic impurity (<4 %), was transformed into **2**-(R)[10] by simple hydrolysis (CF_3CO_2H, CH_3CN, H_2O, room temperature, overnight, 90 %). Tosylation of **2**-(R) gave **3**-(R)[7] (89 %) [oil, $[\alpha]_D^{25}$ -22° (*c* 1.5, $CHCl_3$)]. The structure of **7**



Scheme 1. a: *n*-BuLi, $PhSCH_2OCH_3$, THF, -78°, 1 h. b: $(EtO)_2POCH_2CO_2Et$, HNa, THF, r.t., overnight. c: DIBAL, Et_2O, -30°, 1 h. d: $(CrO_3)_2py$, CH_2Cl_2, r.t., 5 h.



Scheme 2. a: *n*-BuLi, 3-bromofuran, -78°, 1 h, b: Ac_2O, py, r.t. c: NaH, THF, *p*-methoxybenyl chloride, r.t. d: CF_3CC_2H, CH_3CN, H_2O, r.t. e: $NaIO_4$, MeOH; then $NaBH_4$. f: DDQ, CH_2Cl_2, H_2O).

was firmly established through its transformation into 8[11] by Raney nickel reaction and 9[11] by acetylation.

By the same method, using 5[3-(R)][7] obtained from 10[12] as described in the Scheme 1, we could obtain 2-(S) [m.p. 79-81°, $[\alpha]_D^{25}$ +21° (c 0.2, $CHCl_3$)] identical to 2-(R) in its spectroscopic data.

In view of these results, being the stereochemistry at C-1 unambigously established, the previously reported physical data for 2-(R) should be corrected.

The formation of **7** as the major and unexpected product[13] moved us to investigate other method in order to obtain the desired compounds with better yields. This was successfully accomplished reacting **10** with 3-furyllithium (Scheme 2) giving an unseparable mixture of *syn* and *anti* adducts **12** in a 6:4 ratio[14]. This is in accordance with the results reported by Mukaiyama[15] for the analogous α-furan derivatives. The compound **15** was synthesized from **12** and the major *syn* epimer was obtained in pure form by flash-chromatography. Finally, by simple manipulations 2-(R)[15] was again cleanly obtained with good yields.

The use of these compounds in the total synthesis of some natural products is now in progress and will be reported in due course.

Acknowledgements. We are pleased to acknowledge Dr. Rodríguez for the correction of the manuscript and his continuous support and interest during the course of this work.

REFERENCES AND NOTES

1. S. P. Tanis, *Tetrahedron Lett.*, (1982), **23**, 3115 and references cited therein.
2. S. Jarosz and A. Zamojski [*Tetrahedron*, (1982), **38**,1447] obtained 2-(R) [m.p. 55°C, $[\alpha]_D^{18}$ +15° (c 1.6, EtOH)] by resolution and, in a very low e.e., by asymmetric synthesis. The absolute configuration was established correlating the total diastereoisomeric mixture (≃7% d.e.) with (S)-(-)-dimethyl malate [[α] -0.6° (c 5.7, MeOH); lit. $[\alpha]_D$ -6.85°].
3. M. Larcheveque and J. Petit, *Synthesis*, (1986), 60.
4. T. Mandai, K. Hara, T. Nakajima and J. Otera, *Tetrahedron Lett.*, (1983), **24**, 4943.
5. 5 [3-(S)]: Oil, IR (film) $\bar{\nu}$ (cm^{-1}): 3060, 2990, 1735, 1220, 850, MS (70 eV) m/e: 282 (M^+, 1.3), 267 (0.6), 231 (5), 153 (100). (Found: C, 59.46; H, 6.40; S, 11.50. Calcd. for $C_{14}H_{18}SO_4$: C, 59.56; H, 6.43; S, 11.33). This compound appears in t.l.c. as two diastereoisomers in a 1:1.75 ratio as could be determined integrating the areas corresponding to H_1 (*s*,δ 5.37 and 5.45 ppm).
6. T. Mandai, M. Takeshita, K. Mori, M. Kawada and J. Otera, *Chem. Lett.*, (1983), 1909.
7. All new compounds gave satisfactory analytical and spectroscopic data.
8. 7: Oil, IR (film) $\bar{\nu}$ (cm^{-1}): 3600-3200, 1590, 1070, 1030, 870. ^1H-NMR (90 MHz, $CDCl_3$) δ: 7.60-7.20 (*m*, 7H), 6.40 (*m*, 1H), 4.25 (*t*, 1H, $J = 6$ Hz), 3.85 (*d*, 2H, $J = 6$ Hz), 2.10 (*s*, 1H). MS (70 eV) m/e: 220 (M^+, 25), 189 (16), 111 (100). (Found: C, 65.64; H, 5.55; S, 14.34. Calcd. for $C_{12}H_{12}SO_2$: C, 65.44; H, 5.49; S, 14.53). **7** shows $[\alpha]_D^{25}$ -5.1° (c 0.8, $CHCl_3$).
9. T. Mandai, T. Moriyama, Y. Nakayama, K. Angino, M. Kawada and J. Otera, *Tetrahedron Lett.*, (1984), **25**, 5913.
10. 2-(R): Needles (hexane), m.p.: 82-84°C, $[\alpha]_D^{25}$ -19.0°(c 0.55, $CHCl_3$). ^1H-NMR (200 MHz, $CDCl_3$) δ: 7.45 (*m*, 1H), 7.40 (*m*, 1H), 6.40 (*m*, 1H), 4.77 (*dd*, $J = 7.3$ and 3.9 Hz, 1H), 3.79 (*dd*, $J = 12$ and

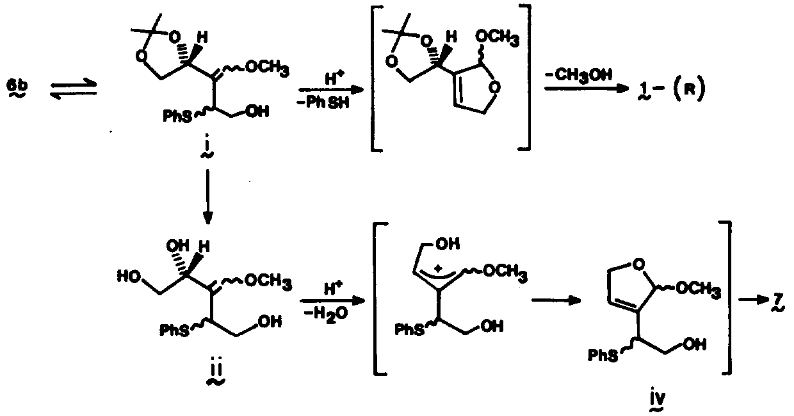
3.9 Hz, 1H), 3.70 (*dd*, $J = 12$ and 7.3 Hz, 1H), 2.09 (*br s*, 2H). (Found: C, 56.43; H, 6.59. Calcd. for $C_6H_8O_3$: C, 56.24; H, 6.29).

11. 8: Oil, IR (film) ν (cm^{-1}): 3600-3100, 2940, 1510, 1030, 880. ^1H-NMR (200 MHz, $CDCl_3$) δ: 7.32 (*m*, 1H), 7.25 (*m*, 1H), 6.25 (*m*, 1H), 3.72 (*m*, 2H), 2.61 (*t*, 2H, $J = 6.5$ Hz), 1.39 (*br s*, 1H).

    9: Oil, IR (film) ν (cm^{-1}): 2930, 1745, 1585, 1510, 1240, 1030, 875. ^1H-NMR (90 MHz, $CDCl_3$) δ: 7.50-7.25 (*m*, 7H), 6.40 (*m*, 1H), 4.35 (*m*, 3H), 2.00 (*s*, 3H). MS (70 eV) m/e: 262 (M^+, 2), 202 (8), 153 (40), 111 (60), 43 (100).

12. J. Jurzak, S. Pikul and T. Bauer, *Tetrahedron*, (1986), **42**, 447.

13. We suggest the following mechanism for the formation of **7**:



In the acidic medium compound **6b** is in equilibrium with **i** (for an example of the acid-catalyzed thioallylic rearrangement, see P. Brownbridge and S. Warren, *J. Chem. Soc., Perkin 1*, **1976**, 2125 and reference 9) and transformed into **ii**. Facile acid elimination of water gives **iv**, direct precursor of **7** (see reference 6).

14. Determined by ^1H-NMR in **13** (*syn*: δ_1 5.80 ppm, $J_{1,2} = 7.5$ Hz; *anti*: δ_1 5.85 ppm, $J_{1,2} = 6$ Hz).

15. K. Suzuki, Y. Yuki and T. Mukaiyama, *Chem. Lett.*, (1981), 1529.

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