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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 5819–5822

The furan approach to carbocyclic systems. Synthesis of cyclohexane derivatives from butenolides through an intramolecular Michael addition

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Received 31 May 2005; revised 22 June 2005; accepted 27 June 2005
Available online 14 July 2005

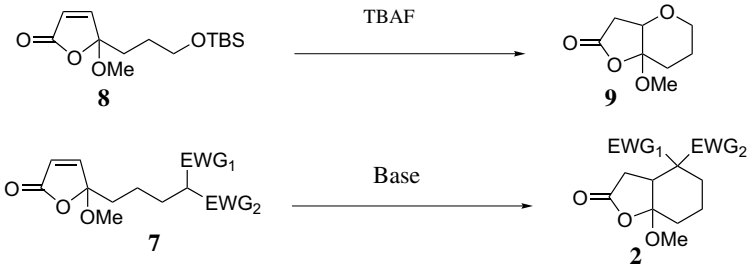
Abstract—We describe an efficient new approach for the synthesis of highly substituted cyclohexane derivatives that is based on the oxidation of a furan ring with singlet oxygen followed by an intramolecular Michael addition of the resulting butenolide containing an acidic methine group.

The construction of carbocyclic systems is of paramount importance in organic synthesis. Intramolecular Michael-type conjugate addition of carbanionic species to activated alkenes and alkynes with an electron-withdrawing group is one of the most frequently used methods.[1] Radical cyclizations have also proved to be a powerful and versatile method for the construction of mono and polycyclic systems.[2] We recently described a new methodology for the synthesis of oxacyclic compounds using either methoxyallene[3a,e] or furan[3b–d] as starting material. Both routes lead to a common intermediate: butenolide **8**, which affords bicyclic lactone **9** on removal of its silyl protecting group through an intramolecular hetero Michael addition (Scheme 1). The scope and limitations of this very powerful methodology are being determined and its application to the synthesis of cyclic as well as polycyclic natural products is currently underway in our laboratories.

We now decided to further enlarge the scope of our methodology by targeting carbocyclic compounds. It was anticipated that butenolide **7** possessing an acidic methine group would lead to carbocyclic compound **2** on reaction with a base (Scheme 1).

The synthesis of butenolide **7** can be accomplished according to the reaction sequence shown in Scheme 2.

Commercially available furan **3** reacted with LAH in ether to give alcohol **4**[4] in 96% yield. Alcohol **4** was



Scheme 1.

Keywords: Butenolide; Furan; Singlet oxygen; Michael addition; Carbocyclization.
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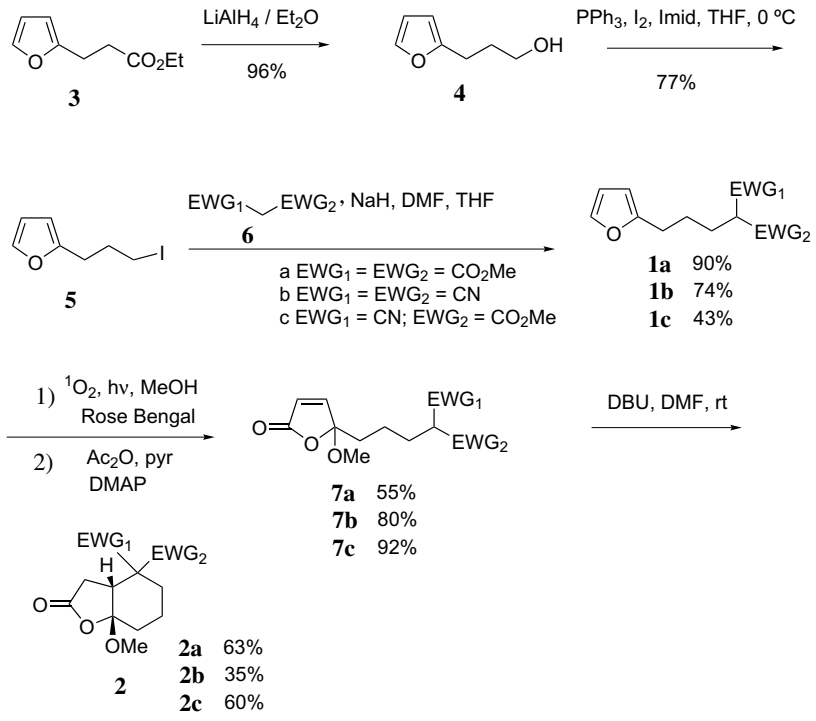
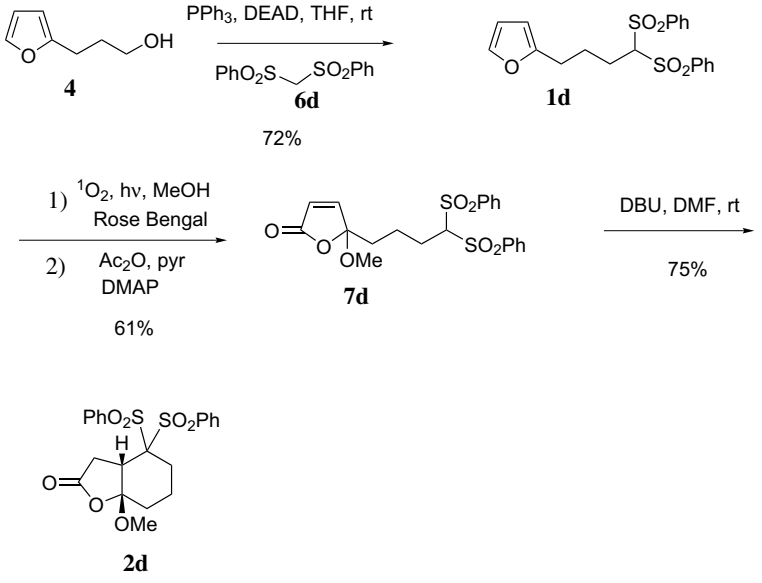
doi:10.1016/j.tetlet.2005.06.137



Scheme 2.



Scheme 3.

easily converted into iodide **5**[4,5] in 77% yield. The condensation of a methylene active compound **6** with iodide **5** afforded furan **1a**–**c**.[4] Oxidation of **1** with singlet oxygen followed by treatment with acetic anhydride in pyridine, afforded butenolide **7**.[4] We were delighted to see that treatment of **7** with 0.5 equiv of DBU in DMF at room temperature,[1d] afforded bicyclic compounds **2a**–**c**[4,6] through an intramolecular Michael addition. The synthesis of bicyclic lactone **2d**[4,6] was carried out according to Scheme 3. Noteworthy is the straightforward synthesis of furan **1d** from alcohol **4** using the Mitsunobu conditions.[7]

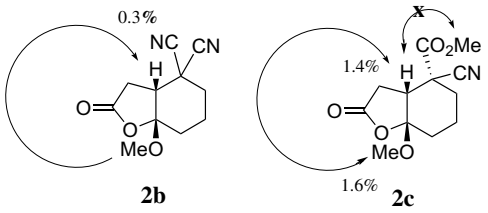
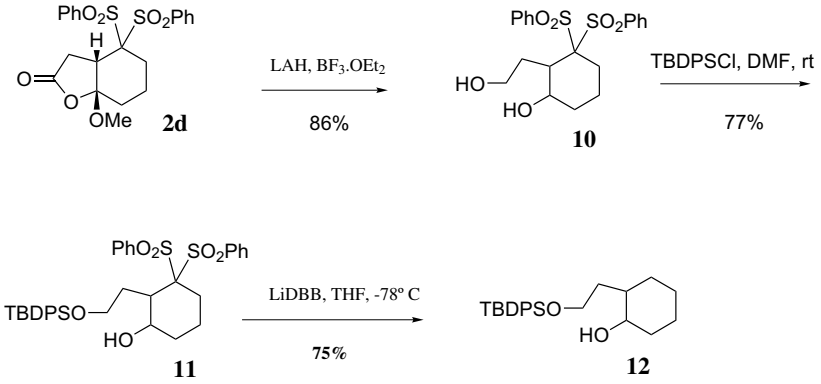


Figure 1. NOE correlations for **2b** and **2c**.



Scheme 4.

Bicyclic lactones **2a–d** were obtained as a single diastereoisomer as confirmed by their ^{1}H and ^{13}C NMR data. Presumably the cyclization of **7a–d** occurs to give **2a–d** with the thermodynamically preferred cis ring-junction. This hypothesis was confirmed in the cases of **2b** and **2c** where carrying out NOE correlations was possible (Fig. 1).

Surprisingly, **2c** with two different EWG (CO_2Me and CN) was formed as a single diastereoisomer.

The transformations in Scheme 4 illustrate, in part, the potential utility of bicyclic lactone **2d**. The latter was opened with LAH.[3b–d] leading to diol **10** in good yield. Selective protection of the primary alcohol of **10** afforded **11** in 77% yield. Alcohol **11** may be desulfonylated[8] to afford 2-substituted cyclohexanol **12** in 75% yield. Compounds **10**, **11**, and **12** are diastereoisomeric mixtures, which can be stereoselectively transformed into the cis derivatives.[3d]

In conclusion, a new and efficient method for the synthesis of highly substituted cyclohexanes from commercially available furan has been developed. Work is now in progress toward the optimization of the yields and large scale synthesis of bicyclic lactones **2** and their use as building blocks for the synthesis of biologically interesting natural products. The application of this new methodology to the synthesis of smaller and larger carbocyclic systems is also currently underway in our laboratories.

Acknowledgments

This work was supported by a grant from the Xunta de Galicia (PGIDIT04BTF301031PR). We also thank the NMR service of the CACTI, University of Vigo, for NMR studies.

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6. General procedure for the cyclization of **7a–d** to **2a–d**: To a solution of **7a–d** (0.38 mmol) in DMF (3 mL) was added DBU (0.19 mol, 0.5 equiv) and the mixture was stirred at rt. At the end of the reaction (TLC), EtOAc (20 mL) was added and the organic layers washed with water (3×20 mL), dried (Na_2SO_4), filtered, and concentrated to afford a residue, which was chromatographed on silica gel giving **2a–d**. Compound **2a**: ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.75 (3H, s, CO_2Me), 3.70 (3H, s, CO_2Me), 3.39 (3H, s, OMe), 2.74 (1H, dd, $J = 8.73$, 17.53), 2.57 (1H, dd, $J = 10.68$, 17.53), 2.35–2.29 (1H, m), 2.10–2.06 (1H, m), 1.83–1.90 (1H, m), 1.70–1.51 (3H, m); ^{13}C NMR ($CDCl_3$), δ: 172.67 (CO), 169.99 (CO), 169.96 (CO), 109.00 (C), 55.84 (C), 53.68 (OCH_3), 53.00 (OCH_3), 50.28 (OCH_3), 40.96 (CH), 33.24 (CH_2), 31.11 (CH_2), 26.17 (CH_2), 17.8 (CH_2); HRMS: calcd for $C_{13}H_{19}O_7$ $[M+1H]^+$ 287.1131, found 287.1088. Compound **2b**: mp 175–177 °C; IR (neat): 2248, 1800, 1744 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.38 (3H, s, OMe), 3.21 (1H, dd, $J = 7.60$, 17.78), 2.86 (1H, dd, $J = 3.53$, 7.60), 2.70 (1H, dd, $J = 3.53$, 17.78), 2.39–2.33 (2H, m), 2.16–1.80 (4H, m); ^{13}C NMR ($CDCl_3$), δ: 171.69 (CO), 114.67 (CN), 112.89 (CN), 105.51 (C), 50.05 (OCH_3),

45.74 (CH), 35.79 (C), 33.59 (CH_2), 31.89 (CH_2), 28.56 (CH_2), 17.68 (CH_2); HRMS: calcd for $C_{11}H_{13}N_2O_3$ $[M+1H]^+$ 221.0926, found 221.0583. Compound **2c**: mp 116–118 °C; IR (neat): 2247, 1786, 1746 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ: 3.86 (3H, s, CO_2Me), 3.50 (3H, s, OMe), 3.17 (1H, t, $J = 10.32$), 2.59–2.53 (2H, m), 2.49–2.46 (1H, m), 2.40–2.36 (1H, m), 2.25–1.82 (4H, m); ^{13}C NMR ($CDCl_3$), δ: 170.14 (CO), 166.97 (CO), 117.74 (CN), 108.02 (C), 54.11 (CO_2Me), 51.00 (OCH_3), 44.27 (C), 42.46 (CH), 32.22 (CH_2), 30.64 (CH_2), 26.85 (CH_2), 17.89 (CH_2); HRMS: calcd for $C_{11}H_{15}O_5$ $[M-CN]^+$ 227.0919, found 227.0910. Compound **2d**: ^1H NMR (300 MHz, $CDCl_3$), δ: 8.16–8.12 (4H, m),7.78–7.70 (2H, m), 7.69–7.58 (4H, m), 3.36 (1H, m), 3.34 (3H, s, OMe), 2.80 (1H, dd, $J = 1.53$, 18.35), 2.57–2.50 (3H, m), 2.44–2.40 (1H, m), 2.03–1.99 (1H, m), 1.81–1.74 (2H, m); ^{13}C NMR ($CDCl_3$), δ: 174.83 (CO), 136.51 (C), 135.34 (C), 135.12 (CH), 134.97 (CH), 132.19 (CH), 131.26 (CH), 128.83 (CH), 128.77 (CH), 106.75 (C), 91.33 (C), 49.67 (OCH_3), 44.62 (CH), 31.74 (CH_2), 29.13 (CH_2), 25.57 (CH_2), 16.52 (CH_2).

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