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Fused Oxacycle Synthesis via Radical Cyclization of β-Alkoxyacrylates

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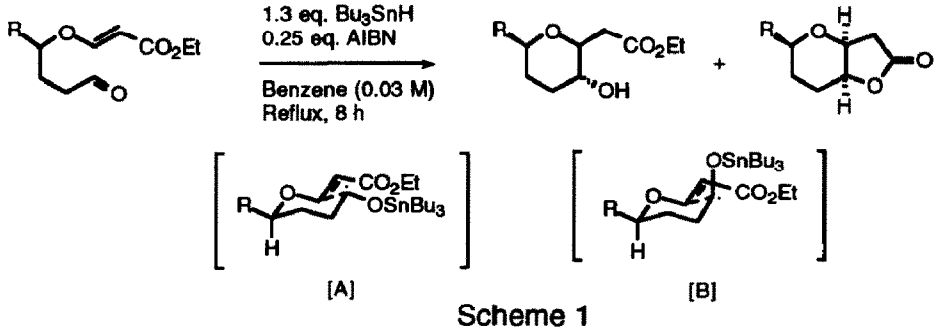
Abstract : β-Alkoxyacrylates are efficient radical acceptors in intramolecular addition of O-stannyl ketyls. This cyclization reaction can be applied reiteratively to form fused oxacycles.

Radical-mediated cyclizations are extensively used for the construction of oxygen-containing ring systems. For example, α-haloacetal cyclization has now become one of the classic methods in synthesis and various α-alkoxy alkyl, vinyl and aryl radicals were also used in oxacycle synthesis. Alkoxy radicals were also used for cyclizations. Cyclization reactions of a variety of oxygen-substituted alkyl radicals were reported recently. Vinyl ethers were used as radical acceptors in cyclic ether synthesis.[1]

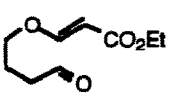
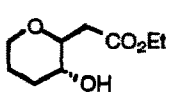
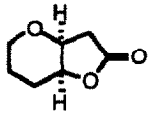
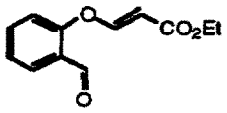
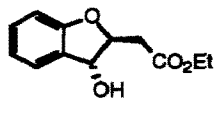
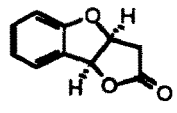
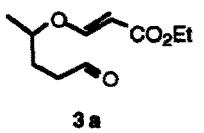
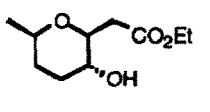
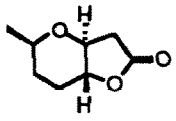
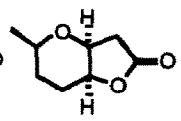
Recently we reported that β-alkoxyacrylates were exceptionally efficient radical acceptors in radical-mediated intramolecular cyclizations and that highly stereoselective synthesis of tetrahydrofurans and tetrahydropyrans was possible in many cases.[2]



Scheme 1

We now wish to report that oxacyclic ring products with secondary hydroxyl groups are formed when O-stannyl ketyls (stannyloxyalkyl radicals)[3] are employed in the cyclization reaction of β-alkoxyacrylates (Scheme 1). The substrate aldehydes **1a** and **3a** were synthesized from corresponding diol monoacetates via addition to ethyl propiolate,[4] hydrolysis of the acetate protecting group, and PCC oxidation.[5] Under the

Table 1

Substrates	Products		Yield (%)
 1a	 1b	 1c	91 (46:54)
 2a	 2b	 2c	92 (60:40)
 3a	 3b	 3c  3d	97 (43:11:46)

standard radical generating conditions,[3b] uniformly high yield conversion to hydroxy tetrahydrofurans and tetrahydropyrans was achieved(Table 1). In each case, two diastereomeric isomers were formed, and the *cis*-3-hydroxytetrahydrofuran-2-yl and *cis*-3-hydroxytetrahydropyran-2-yl derivatives were isolated as the corresponding lactones.[6] Diastereomeric transition states [A] and [B] appear to have similar energies[7] (Scheme 1). Formation of **3b**, **3c**, **3d**[8] and no other diastereomers from **3a** is noteworthy: the result conforms with previous examples where only *cis*-2,5-disubstituted tetrahydrofuranyl and *cis*-2,6-disubstituted tetrahydropyranyl products were formed.[2]

The need to develope conditions for more selective addition reactions of O-stannyl ketyls is obvious,[9] but the above reaction sequence should prove valuable because of its brevity and efficiency in providing oxacycles with defined stereochemistry. Particularly, the sequence can easily be adopted in a reiterative manner for the synthesis of polyoxacycles as shown in Scheme 2. Thus *trans*-3-hydroxytetrahydropyran-2-yl derivative **1b** was converted into the diol monoacetate **1d** which was converted into the substrate **4a** via **1e**. As expected, the reaction of **4a** afforded products **4b** and **4c** almost quantitatively.[10,11] Similarly the *cis*-lactone **1c** was converted to an alternative substrate **5a** via intermediates **1f** and **1g**. An excellent yield of fused bistetrahydropyran **5b** was obtained.[12] The structures of **4c** and **5b** were confirmed through X-ray analysis.[13] In all cases involved, *"2,6-cis"* principle was not violated.

Above schemes appear to be extremely useful in the synthesis of many complex natural products and further results in that direction will be the subjects of our next communications.

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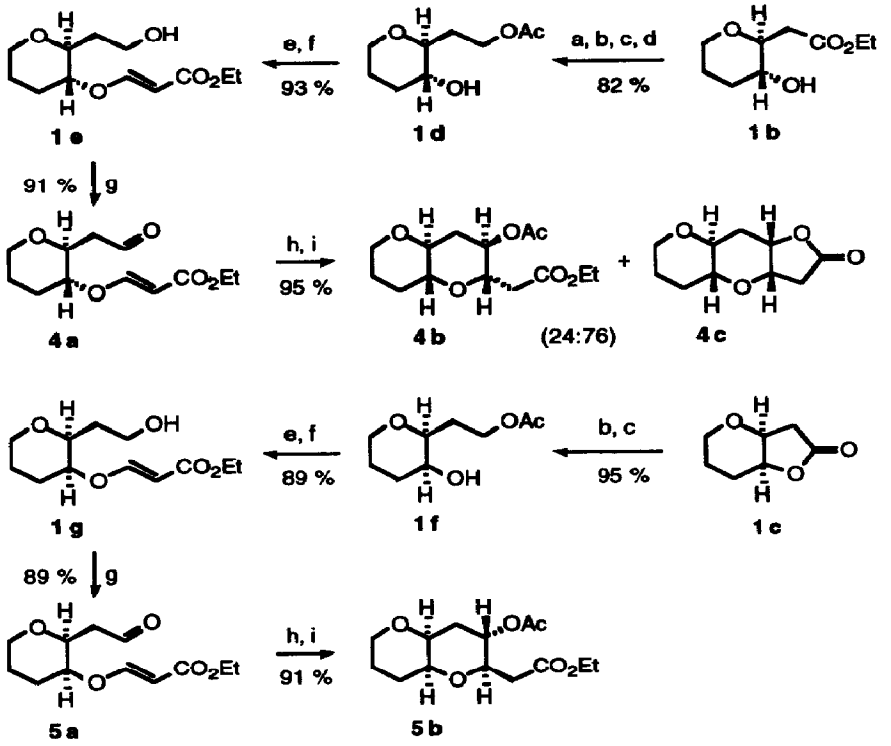
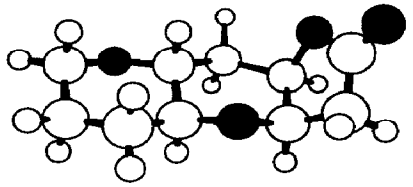


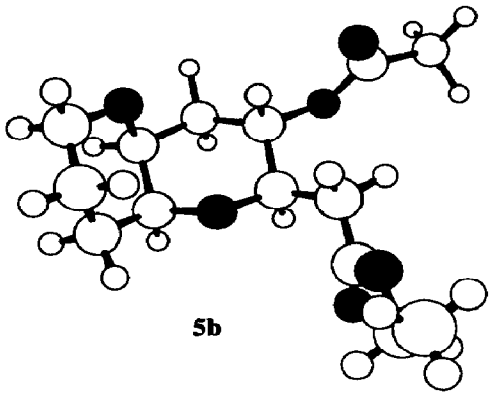
a) DHP, cat. p-TsOH, DCM
b) LAH, Ether
c) Ac_2O, cat. DMAP, Pyridine
d) cat. p-TsOH, MeOH
e) $HCCCO_2Et$, N-Methylmorpholine, DCM
f) K_2CO_3, MeOH
g) PCC, NaOAc, 4Å MS, DCM
h) Bu_3SnH, cat. AIBN, Benzene, Reflux, 7 h
i) Ac_2O, Pyridine, cat. DMAP

Scheme 2

X-ray Crystal Structures



4c



5b

REFERENCES

1. Representative examples are listed in reference 2.
2. Lee, E.; Tae, J. S.; Lee, C.; Park, C. M. *Tetrahedron Lett.* **1993**, *34*, 4831-4834.
3. a) Beckwith, A. L. J.; Roberts, D. H. *J.Am.Chem.Soc.* **1986**, *108*, 5893.
   b) Enholm, E. J.; Prasad, G. *Tetrahedron Lett.* **1989**, *30*, 4939.
4. Winterfeldt, E.; Preuss, H. *Chem.Ber.* **1966**, *99*, 450.
5. The substrate **2a** was directly synthesized from salicylaldehyde.
6. The complete lactonization of the *cis* isomers reflects large increase of the nucleophilic character of the oxygen atom upon transformation of hydroxy groups into stannyloxy groups. See: Pereyre, M.; Quintard, J-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworth: London, **1987**; pp 261-265. *cis*-Lactones were separated from *trans* hydroxy isomers after acetylation by column chromatography.
7. The recent ab initio calculations reveal that the *inside* and *anti* methyl conformers of the hydroxypropyl radical both have gauche O-C-C-C arrangements and have similar energies. The *outside* methyl conformation of the hydroxypropyl radical is less stable by 0.3 kcal/mol. In this case, the transition state leading to **3b**, although initially more appealing, corresponds in fact to the *outside* methyl conformer of hydroxypropyl radical. The alternative one leading to **3d** corresponds to the *inside* methyl conformer of hydroxypropyl radical. See: Wu, Y-D.; Houk, K. N. *J.Am.Chem.Soc.* **1992**, *114*, 1656.
8. The structural assignment of products **3b** and **3d** was confirmed by chemical correlation: LAH reduction, TBDMS protection of the primary hydroxyl group, and Barton deoxygenation of the secondary hydroxyl group led to the formation of *cis*-2-(2'-t-butyldimethylsilyloxyethyl)-6-methyltetrahydropyran from both **3b** and **3d**.
9. Other stannanes were tested for possible improvement in stereoselectivity. Use of triphenylstannane led to the isolation of 6% **1b** and 39% **1c** (69% conversion) from **1a**, and reaction of **1a** with tricyclohexylstannane yielded 24% **1b** and 44% **1c**.
10. **4b**: ^{1}H-nmr (300MHz, $CDCl_3$); δ 1.26(t, 3H, CH_3), 1.34-1.80(m, 4H), 2.04(m, 1H), 2.05(s, 3H, OAc), 2.38-2.58(m, 3H), 3.05(m, 2H), 3.38(m, 1H), 3.88(m, 2H), 4.17(q, 2H, OCH_2), 4.65(m, 1H).
    4c: ^{1}H-nmr (300MHz, $CDCl_3$); δ 1.45(m, 1H), 1.75(m, 3H), 1.21(m, 1H), 2.56(m, 1H), 2.68 and 2.57(A and B part of ABX system, J_{AB}=17.4Hz, J_{AX}=4.2Hz, J_{BX}=0.0Hz, 2H, CH_2COO), 3.08(m, 1H), 3.27(m, 1H), 3.42(m, 1H), 3.91(m, 1H), 4.29(m, 1H), 4.57(m, 1H).
11. The structural assignment of **4b** was confirmed by chemical correlation with **4c**: the same reaction sequence as in reference 8 was used to obtain the identical deoxy derivative from both **4b** and **4c**.
12. **5b**: ^{1}H-nmr (300MHz, $CDCl_3$); δ 1.27(t, 3H), 1.58(m, 2H), 1.63(m, 1H), 1.92(m, 2H), 2.02(s, 3H), 2.31(m, 1H), 2.56 and 2.50(A and B part of ABX system, J_{AB}=15.6Hz, J_{AX}=4.2Hz, J_{BX}=7.8Hz, 2H, CH_2COO), 3.39(m, 1H), 3.51(m, 2H), 3.82(m, 1H), 3.98(m, 1H), 4.16(q, 2H), 4.88(m, 1H).
13. Crystallographic data for **4c**: $C_{10}H_{14}O_4$, FW=198.22, monoclinic $P2_1/c$, a=6.505(3), b=15.199(2), c=10.129(4)Å, β=105.74(2)°, V=964.0Å^3, Z=4, ρ_{calc}=1.37 g/cm^3, μ=1.0 cm^{-1}, R=0.040 for 1653 observed data [Fo≥1.0σ(Fo)]. The diffraction data were collected on Enraf-Nonius CAD4 diffractometer at 23°C in the ω-2θ scan mode using Mo-Kα radiation to a maximum 2θ value of 50° and corrected for Lorentz-polarization and secondary extinction (coefficient=2.8x10^{-6}) effects. The structure was solved by direct method and full-matrix least-squares procedures using the MolEN software package (Enraf-Nonius).
    Crystallographic data for **5b**: $C_{14}H_{22}O_6$, FW=286.33, monoclinic C2/c, a=14.351(5), b=8.573(2), c=24.690(9)Å, β=98.59(2)°, V=3003(3)Å^3, Z=8, ρ_{calc}=1.266 g/cm^3, μ=0.9 cm^{-1}, R=0.049 for 2300 observed data [Fo>1.0σ(Fo)].
    The atomic coordinates and data for the X-ray work are available from the Cambridge Crystallographic Data Center, Lensfield Road, Cambridge CB2 1EU, England.

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