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Studies on radical cyclization of 2,3-epoxy alcohols containing a β-(alkoxy)acrylate moiety using Cp_2TiCl☆

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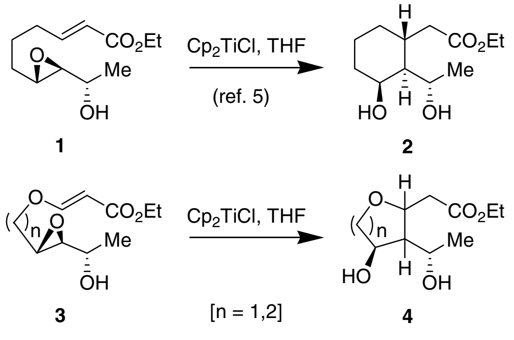
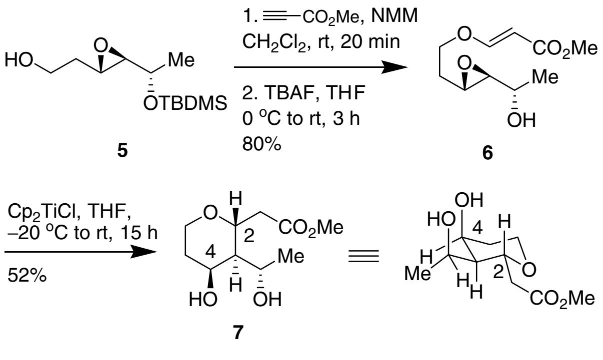
Abstract—Radical-mediated opening of chiral 2,3-epoxy alcohols, containing suitably positioned β-(alkoxy)acrylate moieties, using Cp_2TiCl triggered intramolecular cyclization to give tetrahydrofuran and tetrahydropyran moieties.

Tetrahydrofurans and tetrahydropyrans are the important structural components of a large number of organic natural products.[1] Total syntheses of these natural products generally commence with the construction of these saturated heterocyclic constituents.[2] One of the widely used methods for the synthesis of such tetrahydrofuran and tetrahydropyran rings is based on radical-mediated cyclization of β-(alkoxy)acrylates.[3] Recently, we reported that radicals formed during the opening of 2,3-epoxy alcohols **1** with $Cp_2Ti(III)Cl$[4] could be trapped intramolecularly by a suitably positioned α,β-unsaturated ester moiety in the same molecule giving rise to a cyclohexane ring system **2** (Scheme 1).[5] This encouraged us to investigate similar transformations of the corresponding oxo-analogs, that is, β-(alkoxy)acrylate-containing substrates **3**. Our studies revealed that intramolecular trapping of the radicals formed by Ti(III)-mediated opening of the epoxide rings of **3** led to the formation of highly substituted tetrahydrofurans and tetrahydropyrans **4**.



Scheme 1.

The details of the processes are outlined in Schemes 2 and 3. Scheme 2 describes the synthesis of the tetrahydropyran framework. The starting chiral epoxy alcohol **5** was prepared by us earlier.[6] Treatment of **5** with propynoic acid methyl ester in the presence of *N*-methylmorpholine (NMM) gave the 'β-(alkoxy)acrylate' intermediate[7] which on desilylation furnished the requisite acrylate **6** for the ring opening reaction. Compound **6** on ring opening with $Cp_2Ti(III)Cl$, generated in situ from Cp_2TiCl_2 following the reported



Scheme 2.

Keywords: Epoxy alcohol; Tetrahydrofuran; Tetrahydropyran; Sharpless epoxidation; Epoxide opening; Ti(III).

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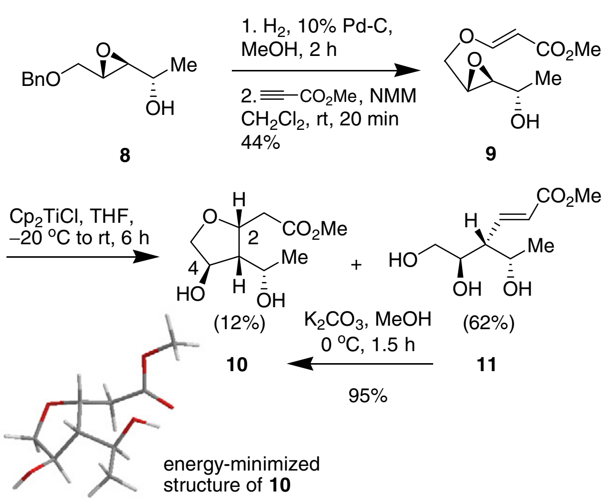

Scheme 3.

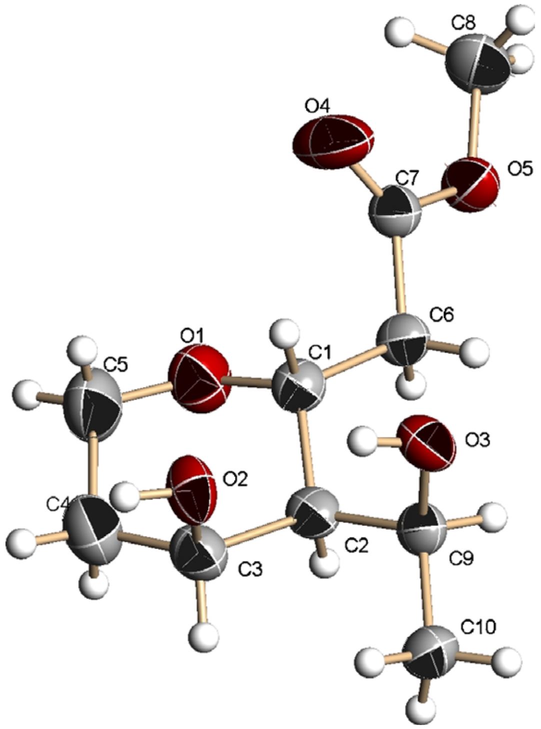

Figure 1. ORTEP plot of compound **7**.

procedure,[8] gave a radical intermediate that underwent facile intramolecular trapping by the acrylate moiety leading to the formation of the six-membered tetrahydropyran **7**[9] as the major product in 52% isolated yield, along with some other unidentified minor compounds.

The stereochemistry of **7** was determined from the ^3J values of the C4–*H* proton, which did not show a large coupling with any of its vicinal protons suggesting its equatorial orientation in a chair-type conformation. The C*H*(OH)Me proton appeared as a dq at δ 4.29 with ~6 Hz couplings to the methyl protons and C3–*H*. The stereochemistry at C3 was *S* as concluded from the fact that diol **7** could be easily converted into its acetonide, which otherwise would have been difficult. Finally, equatorial orientation of the C2-substituent is possibly more stable than axial. The axial orientation would be expected to give rise to a lactone during the formation of **7**. That no lactone was formed in the reaction provides additional support in favor of the proposed *S* stereochemistry for the C2 carbon. The C2*H*–C3*H* proton coupling of ~11 Hz supported the trans relationship between them, as was observed in the carbocyclic congener.[5]

The stereochemistry of **7** was finally established unequivocally from single-crystal X-ray analysis,[10] which clearly showed the assigned structure (Fig. 1).

For the synthesis of the tetrahydrofuran ring, the starting material was the known chiral epoxy alcohol **8**,[11] prepared by Sharpless kinetic resolution[12] of the corresponding racemic allylic alcohol in >92% ee as determined using the Mosher ester method.[13] Hydrogenation of **8** gave a diol intermediate which on treatment with 1 equiv of propynoic acid methyl ester in the presence of *N*-methylmorpholine (NMM) furnished, selectively, the required 'β-(alkoxy)acrylate' **9**. Compound **9** on ring opening with $Cp_2Ti(III)Cl$ gave the five-membered tetrahydrofuran **10**[14] as the minor product in 12% isolated yield only. The major product obtained in 62% yield was the acyclic compound **11**,[15] which was probably formed by in situ opening of the cyclic ether **10** during the reaction. Compound **11** could be transformed to cyclic ether **10** in 95% yield, on treatment with anhydrous K_2CO_3 in methanol, taking the overall yield of **10** to 71%.

The stereochemistry of cyclic product **10** was determined by ^{1}H NMR analysis. The C2–*H* signal appeared as a dt at 4.50 ppm with coupling constants of 6.0 and 9.1 Hz. While the former was for the coupling with –CH_2CO$_2$Me resonating at 2.59 ppm, the larger ^3J value was for the C2*H*–C3*H* vicinal coupling confirming their cis relationship. The C4–*H* signal appeared as a ddd at δ 4.62 with ^3J values of 4.5, 3.8, and 1.5 Hz. The smaller couplings were with C5–H_2 whilst that of 4.5 Hz was for the C3*H*–C4*H* coupling which were trans. The –C*H*(OH)Me proton appeared as a dq at δ 4.07 with ~6 Hz couplings with the methyl protons and C3–*H*. The energy-minimized structure of **10** (Chem3D, MOPAC) showed the H–C2–C3–H dihedral angle as 24.2 ° and the H–C3–C4–H angle as 142.4° supporting the observed ^3J values of 9.1 and 4.5 Hz, respectively.[3i]

In conclusion, we have demonstrated the radical cyclizations of β-(alkoxy)acrylate-containing 2,3-epoxy alcohols using $Cp_2Ti(III)Cl$. Although the yields of the cyclized products in these reactions were not very good, the ring-opened acyclic product **11** could be cyclized to give a moderate yield of the desired product **10**. Additionally, this chemistry should be amenable to extension for the synthesis of natural products containing similar structural frameworks.

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9. Selected physical data for **7**: $R_f = 0.5$ (silica gel, 80% EtOAc in hexane); IR (KBr): ν_{max} 3421, 2924, 1736 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.51–4.44 (m, 1H), 4.29 (dq, $J = 6.0$, 6.0 Hz, 1H), 3.99 (dd, $J = 5.9$, 2.5 Hz, 1H), 3.90 (dd, $J = 11.0$, 4.2 Hz, 1H), 3.73 (s, 3H), 3.71–3.64 (m, 1H), 2.67 (dd, $J = 16.1$, 5.9 Hz, 1H), 2.52 (dd, $J = 16.1$, 5.1 Hz, 1H), 1.75–1.64 (m, 2H), 1.34 (d, $J = 6.8$ Hz, 3H), 1.27–1.23 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.3, 70.5, 67.4, 64.5, 62.6, 52.1, 49.1, 38.9, 33.6, 20.5; MS (ESI): m/z (%) 241 (100) $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$ calcd for $C_{10}H_{18}O_5Na$, 241.1051; found, 241.1061.
10. X-ray crystal data for compound **7**: Crystal data, $C_{10}H_{18}O_5$, $M = 218.24$, monoclinic, space group $P2_1$, $a = 5.7441(8)$ Å, $b = 9.6774(13)$ Å, 10.1662(14) Å, $\beta = 99.141(2)$, $V = 557.94(13)$ $Å^3$, $d_{calc} = 1.299$ Mg m^{-3}. Data were collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite monochromated MoKα radiation ($\lambda = 0.71073$ Å) with ω-scan method.[16] Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Unit cell dimensions were determined from the setting angles of 2107 reflections for compound **7**. Integration and scaling of intensity data were accomplished using the SAINT program.[16] The structure was solved by direct methods using SHELXS97[17] and refinement was carried out by full-matrix least-squares technique using SHELXL97.[17] All the hydrogen atoms were positioned geometrically and were treated as riding on their parent carbon atoms, with C–H distance of 0.93–0.98 Å and an O–H = 0.82 Å, with $U_{iso}(H) = 1.2\ U_{eq}$ (C) or 1.5 U_{eq} (methyl C and O). The structure was refined with $R_1 = 0.0343$, $wR_2 = 0.0864$ for 986 reflections with $I > 2\sigma(I)$. In the structure shown in Figure 1, displacement ellipsoids are drawn at 30% probability level and H atoms are shown as small spheres of arbitrary radii. Intramolecular O–H···O hydrogen bond involving O3 and O2 dimensions: H3A···O2 2.055 Å, O3–H3A···O2 137°, and O3···O2 2.710 Å. Intermolecular O–H···O hydrogen bond connecting O2 with O3 ($-x$, $y - 1/2$, $-z + 1$) dimensions: H2A···O3 1.918 Å, O2–H2A···O3 165, and O2···O3 2.719 Å.
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14. Selected physical data for **10**: $R_f = 0.4$ (silica gel, 90% EtOAc in hexane); IR (KBr): ν_{max} 3416, 2923, 2856, 1727 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.62 (ddd, $J = 4.5$, 3.8, 1.5 Hz, 1H), 4.50 (dt, $J = 9.1$, 6.0 Hz, 1H), 4.07 (dq, $J = 6.0$, 6.0 Hz, 1H), 3.95 (dd, $J = 9.8$, 3.8 Hz, 1H), 3.83 (d, $J = 9.8$ Hz, 1H), 3.71 (s, 3H), 2.59 (d, $J = 6.0$ Hz, 2H), 1.83 (ddd, $J = 9.1$, 6.0, 4.5 Hz, 1H), 1.39 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

171.8, 75.1, 75.0, 73.8, 65.9, 55.1, 51.9, 39.2, 22.4; MS (FAB): m/z (%) 244 (10) $[M+K+H]^+$; HRMS (ESI): $[M+Na]^+$ calcd for $C_9H_{16}O_5Na$, 227.0895; found, 227.0898.

15. Selected physical data for **11**: $R_f = 0.3$ (silica gel, 90% EtOAc in hexane); IR (KBr): ν_{max} 3394 (b), 2924, 2854, 1709, 1653 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (dd, $J = 16.1$, 10.2 Hz, 1H), 5.90 (d, $J = 15.4$ Hz, 1H), 4.24–4.14 (m, 1H), 4.06–3.96 (m, 1H), 3.78 (s, 3H), 3.58–3.42 (m, 2H), 2.26–2.16 (m, 1H), 1.18 (d, $J = 5.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 145.8, 124.0, 70.9, 67.5, 65.3, 52.6, 51.7, 22.1; MS (ESI): m/z (%) 205 (30) $[M+H]^+$, 222 (50) $[M+NH_4]^+$; HRMS (ESI): $[M+Na]^+$ calcd for $C_9H_{16}O_5Na$, 227.0895; found, 227.0893.
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