Cobalt-catalysed radical oxygenation with molecular oxygen

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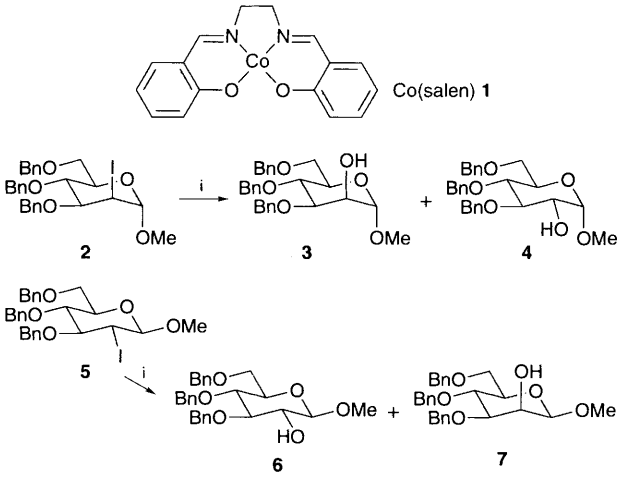
Molecular oxygen is an efficient trap in cobalt-catalysed radical substitution and 5-*exo* radical cyclization reactions.

The mechanism of vitamin B_{12} catalysed biological processes has been the object of considerable investigations and the involvement of carbon-centred radicals is now well established.[1] Numerous synthetic applications have been described with vitamin B_{12} or the model cobaloximes for carbon–carbon bond formation[2,3] and cobalt-catalysed radical cyclizations are valuable tools.[4] The isolable alkylcobalt(III) complexes can also react with various radical trapping agents with the introduction of a useful new sulfur, halogen, selenium, nitrogen or oxygen functionality in the reaction products.[5] However, major drawbacks are associated with these methods: they involve a two step sequence, require a stoichiometric quantity of metal complex and product yields are sometimes low. In particular, the oxygenolysis of the cobalt(III)–carbon bond was only effective after photolysis of the alkylcobalt complexes under oxygen for extended periods of time[3a] although the postulated intermediate radicals[6] should be very reactive towards molecular oxygen.[7] We report that carbon-centred radical oxygenation with molecular oxygen can be achieved with high efficiency by cobalt catalysis. This result is a new and mild system for the one-step radical conversion of unsaturated halogen compounds into cyclic alcohols.[8]

We first examined the radical substitution of methyl 2-deoxy-2-iodo-3,4,6-tri-*O*-benzyl-α-D-*manno*-hexopyranoside **2**[9] and its β-D-*gluco* isomer **5** with molecular oxygen. Treatment of **2** with 3% of Co(salen)[10] **1** and 3 equiv. of sodium borohydride in basic ethanolic solution at 40 °C, dry air being bubbled through the solution, gave after 1.5 h a mixture of isomeric methyl 3,4,6-tri-*O*-benzyl-α-D-*manno*-hexopyranoside **3** and methyl 3,4,6-tri-*O*-benzyl-α-D-*gluco*-hexopyranoside **4**: total yield 60%† and **3**:**4** was 7:4‡ (Scheme 1).

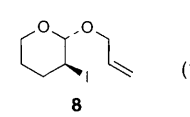
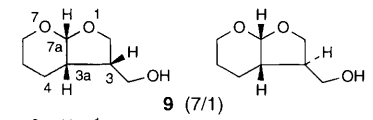
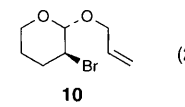
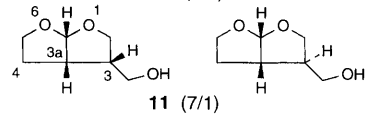
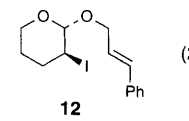
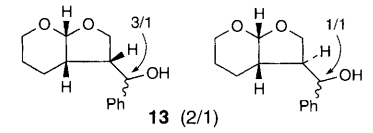
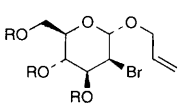
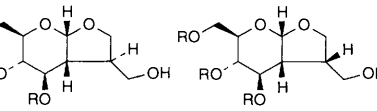
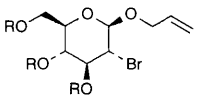
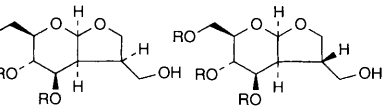
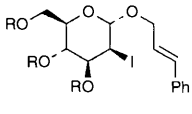
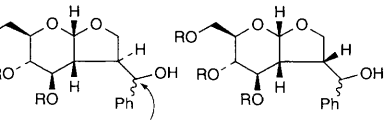
This selectivity is comparable with previous results recently reported by us[11] and others [12] for the radical substitution of 2-iodo-2-deoxyhexopyranoside derivatives with oxygen or nitroxyl radicals. In an analogous manner, **5** was converted in 2 h with 2% Co(salen) into a 1.3/1 mixture of isomeric glycosides **6** and **7** (58%). We turned next to the study of the radical cyclization/oxygenation sequence.[8] When unsaturated iodide **8** was submitted to the reaction, smooth conversion to the bicyclic alcohols **9** (Table 1) was obtained in 1 h under air at room temperature with 3% cobalt catalyst. The yield was 80% and good selectivity was observed (7/1). Bromides reacted equally well and high yields of products were obtained in a few hours provided the reaction temperature was raised to 40 °C. The reaction is general and representative examples are summarized in Table 1.

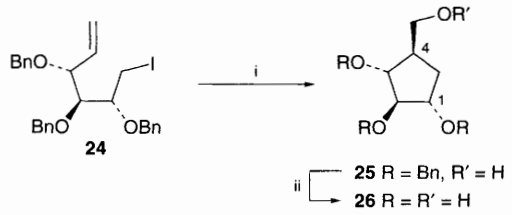
In every case, only the products from 5-*exo* cyclization with a *cis* ring junction were detected;[13] the major by-products were the compounds resulting from H-atom quench of the cyclized radical (5–20%) and very minor amounts of uncyclized



Scheme 1 *Reagents and conditions*: i, 3% **1**, 2 equiv. $NaBH_4$, 1.7 equiv. NaOH, air, ethanol, 40 °C

Table 1 Cobalt-catalysed 5-*exo* radical cyclization/oxygenation of unsaturated halogen compounds

Substrate	Yield (%) (*t*/h, *T*/°C)	Products (selectivity)
 **8**	80 (1, rt)	 **9** (7/1)
 **10**	76 (2, 40)	 **11** (7/1)
 **12**	74 (2, rt)	 **13** (2/1)
 R = Bn **14**	50 (1, 40)	 **15** (7/1)
R = TBDMS **16**	62 (6, 40)	**17** (4/1)
 R = Bn **18**	60 (0.5, 40)	 **19** (3/1)
R = TBDMS **20**	70 (3.5, 40)	**21** (3/1)
 R = TBDMS **22**	84 (0.5, 40)	 **23** (3/1)



Scheme 2 *Reagents and conditions*: i, 3% **1**, 2 equiv. $NaBH_4$, 1.7 equiv. NaOH, air, ethanol, 40 °C, 14 h, 69%; ii, H_2, Pd/C, ethanol, 20 °C, 86%

oxygenated material. Benzyl protective groups were tolerated but better yields were obtained with the more resistant *tert*-butyldimethylsilyl groups (compare **14** and **16**, **18** and **20**, Table 1). Ester groups were not stable in the reaction conditions and unprotected substrates, although reactive, gave polar products which were difficult to purify, low yields of cyclized alcohols were isolated despite complete conversion of the starting material.

Moderate to good selectivity was observed for the induction on the second asymmetric centre.§ In every case, the major diastereoisomers were those predicted by the proposed models for these radical cyclizations[14] with a favoured six-membered *chair* transition state.[15] When a third asymmetric centre was created during the reaction (cyclization of compounds **12** and **22**, Table 1), the observed selectivity for the oxygen quench was moderate (3/1) but significant and shows that some face differentiation occurred onto the cyclized radical. The relative configurations of the major diastereoisomer of **13** were determined to be (3*S'*, 3a*S'*, 7a*R'*, 8*R'*).¶

The mildness of the reaction conditions is striking: molecular oxygen is known to be a good inhibitor of the radical rearrangement of 5-hexenyl ligands on Co^{III} salen complexes[6a] and oxygenolysis of the cobalt(III)–carbon bond with molecular oxygen is not an easy reaction.[3a]

This methodology is not limited to the 3-oxa-5-hexenyl radicals and oxygenated carbocycles could also be made efficiently under Co(salen) catalysis. Thus, iodide **24**, available in three steps from methyl 2,3,4-tri-*O*-benzyl-α-D-*gluco*-hexopyranoside,[16] gave the substituted cyclopentanemethanol **25** in 69% yield and in excellent diastereoisomeric purity (12/1)‖ (Scheme 2). Hydrogenolysis of **25** gave the known pseudo-α-D-arabinofuranose **26**, $[\alpha]_D^{20}$ +45 (MeOH), {lit.,[17] $[\alpha]_D^{20}$ +40 (MeOH), lit.,[18] $[\alpha]_D^{16}$ −40.5 (MeOH) for the enantiomer}. The short synthesis of this compound from D-glucose as well as the availability of other sugar-derived substrates opens a new entry into the synthesis of the biologically important carbocyclic analogues of sugars, nucleosides or deoxynucleosides.[19]

Footnotes

† All yields are for isolated pure products or purified mixtures of diastereoisomers.

‡ Selectivity was obtained from integration of suitable signals in the ^1H NMR spectrum of the mixture and/or separation of the individual isomers when possible.

§ Assignment of the stereochemistry was based on extensive one- and two-dimensional NOE measurements on the purified isomers or on their acetates and by comparison with related known compounds.[20]

¶ Bicyclic alcohols are furo[2,3-*b*]furan **11** or 4 H-furo[2,3-*b*]pyran derivatives (**9**, **13**, **15**, **17**, **19**, **21** and **23**). See Table 1 for numbering.

‖ *Selected data* for **25**: $[\alpha]_D^{20}$ +38 (*c* 0.85, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.03 (m, 1 H, *J* 3.6 Hz), 3.90 (m, 1 H, *J* 6.9, 3.6 Hz), 3.73 (dd, 1 H, *J* 8.2, 5.5 Hz), 3.62 (d, 2 H, *J* 6.0 Hz) 2.39 (m, 1 H), 1.93 (ddd, 1 H, *J* 13.5, 8.0, 3.6 Hz), 1.72 (ddd, 1 H, *J* 13.5, 9.8, 6.9 Hz); NOESY contacts: H-4 ⟷ H-5*S*, H-4 ⟷ H-2, H-5*R* ⟷ H-3.

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