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Synthesis of chiral 2,3-*cis*-fused butan-4-olides from levoglucosenone–1,3-diene Diels–Alder adducts

Anna N. Davydova,* Alexey A. Pershin, Bulat T. Sharipov and Farid A. Valeev

Ufa Institute of Chemistry, Russian Academy of Sciences, 450054 Ufa, Russian Federation.
E-mail: sinvmet@anrb.ru

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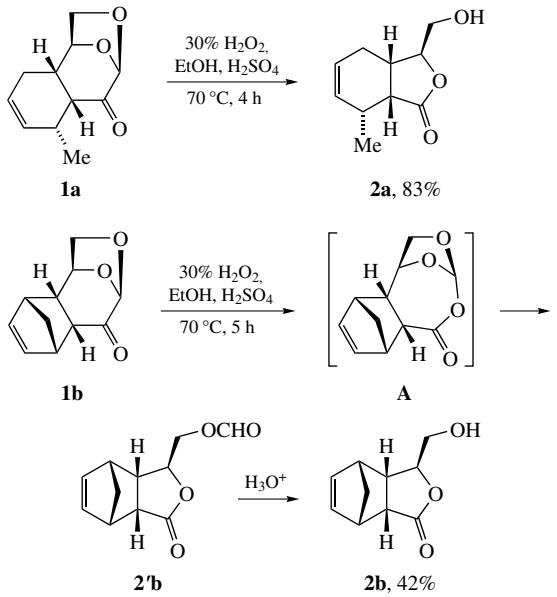
Acid-catalyzed Baeyer–Villiger oxidation of levoglucosenone–1,3-diene Diels–Alder adducts affords chiral 2,3-*cis*-fused (2*R*,3*S*,4*S*)-4-hydroxymethylbutan-4-olides.

Levoglucosenone and its derivatives are the promising starting materials for the synthesis of chiral butanolides.[1] Their Baeyer–Villiger oxidation is a good tool to access (+)-*trans*-whisky lactone, (+)-*trans*-cognac lactone,[2] 9,11-ethano analogues of prostaglandin endoperoxide (PGH_2)[3] and building blocks for eleuthesides.[4]

In view of this, similar oxidation of Diels–Alder adducts of levoglucosenone with 1,3-dienes seems topical. Previously, the Baeyer–Villiger oxidation with peroxyacetic acid was effective only for the levoglucosenone–butadiene adduct and brought about 4-formyloxymethylbutanolides.[1(*b*)] Apparently, the intermediate species of the process was polycyclic orthoformate of type **A** (Scheme 1) which on rearrangement gave formyloxy derivative. In the case of other adducts the yields were poor since the double bond in cyclohexene moiety was oxidized too.[4,5] On the other hand, oxidation of levoglucosenone–piperylene adduct **1a** using 30% H_2O_2–H_2SO_4–EtOH system at 70 °C gives hydroxy lactone **2a** lacking formyl group.[4] Under the same conditions, cyclopentadiene adduct **1b**[6] is transformed into hydroxy lactone **2b** in 42% yield, while its precursor formate **2′b** was not detected among the products (see Scheme 1).

More tolerant catalyst used in the Baeyer–Villiger oxidation is TsOH.[7] In the current study we have found that treatment of adduct **2b** with 30% H_2O_2 in EtOH in the presence of 10 mol% TsOH for 9 h gives 69% of product **2b**, while in isopropanol 70% yield was reached within 21 h (Table 1, entries 1 and 2).† Lowering amount of TsOH to 3 mol% extends the reaction time to 35 h with a slight decrease in yield (entry 3). In ethanol the reaction duration is shorter in most cases, but the yields sometimes drop sharply in comparison with the reaction in isopropanol. As shown previously,[8] an increase in the solvent polarity may lead to an increase in the rate constant in which the addition step is rate determining. This may account for the quicker reaction in ethanol.



Scheme 1

Table 1 The Baeyer–Villiger oxidation of adduct **1b**.[a]

Entry	Acid	Solvent	*T*/°C	Time/h	Yield of **2b** (%)
1	TsOH (10 mol%)	EtOH	70	9	69
2	TsOH (10 mol%)	Pr^{i}OH	80	21	70
3	TsOH (3 mol%)	Pr^{i}OH	80	35	67
4	H_3PO_4 (1.2 mmol)	Pr^{i}OH	80	22	77
5	H_2SO_4 (10 mol%)	Pr^{i}OH	80	20	66
6	H_2SO_4 (10 mol%)	EtOH	70	5	42

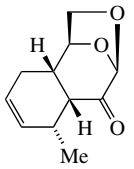
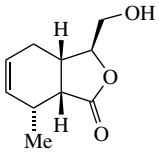
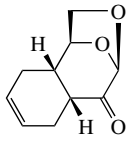
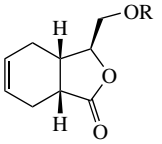
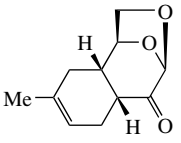
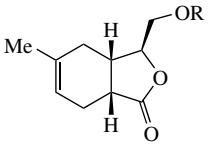
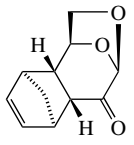
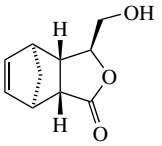
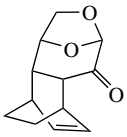
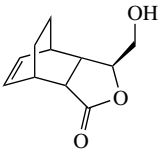
[a] Conditions: **1b** (1 mmol), 30% H_2O_2 (5 mmol), acid, solvent.

It is known that the Baeyer–Villiger oxidation can be processed using equimolar quantities of peroxyphosphoric acid[9] which is prepared from 90% H_2O_2. Our attempts to carry it out using 30% H_2O_2 with catalytic amounts of H_3PO_4 were unsuccessful. However, application of excess H_3PO_4 made the oxidation to proceed giving product **2b** in 77% yield, although the reaction time was longer than in cases of H_2SO_4 or TsOH (see Table 1, entry 4). Thus, the system H_3PO_4–30% H_2O_2 proved to be more efficient.

As the nature of the acid catalyst can affect the yield of the product, in oxidation of other substrates **1a**,[10] **1c**,[6(*a*)] **1d**,[11] **1e** and **1f**[6(*a*)] we have tested the three acids (Table 2).† In general, relatively close yields were achieved for all the substrates and catalysts in isopropanol. Longer reaction times were required on

† *Synthesis of compounds* **2a–f** *(general procedure)*. 30% H_2O_2 (0.51 ml, 5 mmol) and H_2SO_4 (0.005 ml, 0.1 mmol, method A); or TsOH·H_2O (19 mg, 0.1 mmol, method B); or 85% H_3PO_4 (0.08 ml, 1.2 mmol, method C) were added to a solution of adduct **1a–f** (1 mmol) in Pr^{i}OH (5 ml). The resulting solution was stirred at 80 °C. After completion of the reaction (TLC), the mixture was cooled to room temperature and treated with a saturated solution of Na_2SO_3 until peroxide compounds disappeared. The solvent was removed under reduced pressure, and the aqueous phase was extracted with EtOAc, dried over anhydrous $MgSO_4$, concentrated *in vacuo* and purified by silica gel column chromatography. For characteristics of products **2a–f**, see Online Supplementary Materials.

Table 2 The Baeyer–Villiger oxidation of levoglucosenone–1,3-diene Diels–Alder adducts.

Starting compound	Products	Method[a]	Time/h	Yield (%)
 **1a**	 **2a**	A	5	**2a**, 70
		B	6	**2a**, 73
		C	10	**2a**, 75
 **1c**	 **2c** R = H **2′c** R = CHO	A	1	**2c**, 88
		B	1	**2c**, 87
		C	1	**2c**, 47
				2′c, 37
			3.5	**2c**, 84
 **1d**	 **2d** R = H **2′d** R = CHO	A	1	**2d**, 86
		B	1.5	**2d**, 85
		C	1	**2d**, 34
				2′d, 56
			3	**2d**, 81
 **1e**	 **2e**	A	7	**2e**, 59
		B	18	**2e**, 68
		C	32	**2e**, 67
 **1f**	 **2f**	A	70	**2f**, 64
		B	70	**2f**, 60
		C	100	**2f**, 64

[a] Method A: 30% H_2O_2 (5 mol/mol), H_2SO_4 (10 mol%), Pr^iOH, 80 °C. Method B: 30% H_2O_2 (5 mol/mol), TsOH (10 mol%), Pr^iOH, 80 °C. Method C: 30% H_2O_2 (5 mol/mol), H_3PO_4 (1.2 mol/mol), Pr^iOH, 80 °C.

using phosphoric acid, meanwhile the intermediate formates **2′c** and **2′d** were detected when the reactions were not complete. Evidently, these formates are hydrolyzed to final hydroxy lactones without loss in the yields on further processing.

In support of hypothesis that the rate determining step is an addition of peroxide at the keto group we indicate that more sterically hindered substrates would oxidize slower. In the case of unhindered adducts **1c** and **1d** the oxidation is faster, and hydrolysis of the intermediate formates **2′c**,**d** becomes the rate determining factor.

In summary, we have prepared a series of chiral 2,3-*cis*-fused 4-(hydroxymethyl)butan-4-olides from available levoglucosenone–1,3-diene Diels–Alder adducts using a simple and scalable Baeyer–Villiger procedure. The products obtained seem promising as biologically active compounds.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.07.013.

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