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Stereoselective synthesis of side chain-functionalized tetrahydropyrans from 5-hexenols

Patrick Fries, Melanie Kim Müller, Jens Hartung *

Fachbereich Chemie, Organische Chemie, Technische Universität Kaiserslautern, Erwin-Schrödinger-Straße, D-67663 Kaiserslautern, Germany

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ABSTRACT

Molecular oxygen stereoselectively converts 5-hexenols into 2,6-trans-, 2,5-trans-, and 2,4-cis-derivatives of 2-methyltetrahydropyran via oxidative cyclization/radical functionalization cascades, when activated by fluoro-substituted cobalt(II) bis-(β-diketonate) complexes in solutions of cyclohexa-1,4-diene (CHD). Aerobic 5-hexenol oxidations in solutions of bromotrichloromethane and CHD furnish products of 6-*exo*-bromocyclization, as exemplified by synthesis of diastereomerically pure 2,4,6-substituted tetrahydropyrans. The cobalt method extends to intermolecular alkene/alkanol cross-coupling and to multi-component reactions between dimethyl fumarate, CHD, a 5-hexenol, and dioxygen, providing α-tetrahydropyranyl-2-methyl succinates in synthetically useful yields.

1. Introduction

Constitutionally dissymmetric tetrahydropyrans are secondary metabolites, biosynthetically formed from terpenols,[1,2] acetogenins,[3] polyketides, and oxidative enzymes.[4,5] Terminal oxidants to bring about the alkenol ring closure in biosynthesis are dioxygen and hydrogen peroxide, being activated by metalloproteins.[6,7] The protein coordinating the metal co-factor controls electronic properties of the oxidant and folding of the alkenol chain at the active site for attaining stereospecific oxidative tetrahydropyran ring closure.[8,9]

In organic synthesis, as in biosynthesis, the important method for constructing constitutionally dissymmetric tetrahydropyrans (cf. Fig. 1) is the 5-hexenol ring closure.[10,11] Since the oxygen and the carbon–carbon double bond in non-Michael-type alkenols are nucleophiles, one of the functional groups has to be converted into an electrophile for accomplishing the alkenol cyclization.

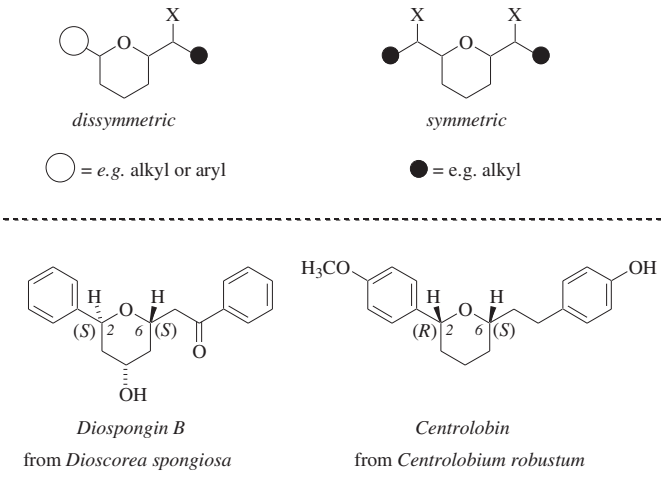

Fig. 1. General structure formulas for constitutionally dissymmetric and symmetric 2,6-substituted tetrahydropyran nuclei (X=e.g., OH), and examples for tetrahydropyran natural products showing (2*S*,6*S*)- (i.e. 2,6-*like*)[27]-configuration (cf. diospongin B)[28] and (2*R*,6*S*)- (i.e. 2,6-*unlike*)[27]-configuration (cf. centrolobin).[29]

* Corresponding author. Tel.: +49 631 205 2431; fax: +49 631 205 3921; e-mail address: hartung@chemie.uni-kl.de (J. Hartung).

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Changing polarity at the alkenol oxygen is feasible by abstracting the hydroxyl hydrogen, to give an alkenoxyl radical.[12] 5-Hexenoxyl radicals add 6-*exo*-selectively to non-activated carbon–carbon double bonds with rate constants of 10^7 s^{-1} and above, to furnish 2,4-cis, 2,5-trans-, and 2,6-cis-isomers of sidechain-functionalized tetrahydropyrans as major products, when trapped by a suitable heteroatom donor.[13]

Changing polarity at the alkenol π-bond is feasible by activating the alkene subunit using soft Lewis acids, such as gold(III)- or mercury (II) compounds,[14] or alternatively by oxidants such as bromine,[15–17] high-valent transition metal oxo compounds,[18,19] or transition metal peroxido complexes.[20] Electrophile-induced 5-hexenol cyclizations furnish in most instances ~70:30 mixtures of stereoisomers, containing the 2,3-trans-, 2,4-cis-, 2,5-trans-, and 2,6-cis-stereoisomer in excess. This stereochemical sequence and the degree of diastereoselection reflect conformational preferences associated with transition structures of C,O-cyclization, hereafter referred to as substrate control.[21]

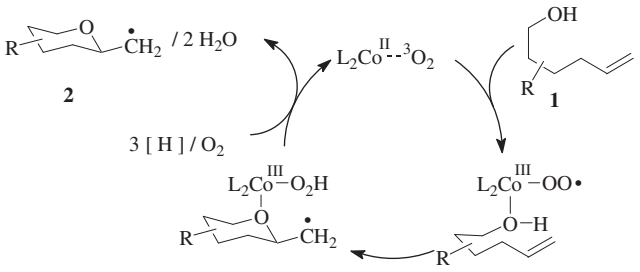
Successful concepts for improving stereoselectivity in substrate-controlled alkenol cyclizations use specially designed auxiliaries for sterically blocking the unwanted mode of cyclization, for example, in transition metal-catalyzed oxidations.[20] Approaches for reversing stereoselectivity in substrate-controlled 5-hexenol ring closures commonly change the mechanism for intramolecular carbon–oxygen bond formation, as successfully put into practice by dichloroacetylperrhenate/dichloroacetic anhydride-mediated cyclizations,[22] and oxidations of 1,6-dienes[23,24] or hept-6-ene-1,2-diols by high-valent transition metal oxo compounds.[25,26] 1,6-Dienes and hept-6-ene-1,2-diols under such conditions furnish derivatives of *trans*-2,6-bis(hydroxymethyl)-tetrahydropyran in notable diastereomeric excess. Both methods are for structural reasons not the method of choice for finalizing synthesis of constitutionally dissymmetric 2,6-substituted tetrahydropyrans, such as diospongin B or centrolobin (Fig. 1).

For stereoselectively preparing constitutionally dissymmetric tetrahydropyrans by a new approach (Scheme 1), we chose to oxidize 5-hexenols by molecular oxygen in cobalt(II)-catalyzed reactions. The method extends the Mukaiyama oxidation of 4-pentenols, which uses dioxygen and *tert*-butyl hydroperoxide as terminal oxidants.[30] Shi[31] and Pagenkopf[32,33] and their collaborators applied the Mukaiyama method for landmark contributions on stereoselective synthesis of tetrahydrofuran natural products. Changing the original Mukaiyama-auxiliary to fluorinated diketones allowed us to use air as exclusive terminal oxidant without the need to add *tert*-butyl hydroperoxide.[34] The true potential of the cobalt method for synthesis of cyclic ethers became apparent from mechanistic studies,[35,36] uncovering that the aerobic 4-pentenol oxidation furnishes (tetrahydrofuran-2-yl)-methyl radicals, which enable to prepare a variety of new, side chain-functionalized tetrahydrofurans by heteroatom-trapping or addition to Michael-type alkenes (for a related mechanism devised as concept for the present study on tetrahydropyran synthesis, see Scheme 1).

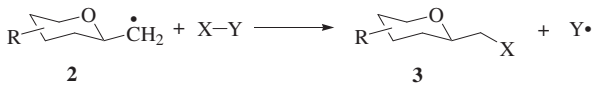
In a project on alkenol methylsulfanyl cyclization, we discovered that a 1,2-disubstituted 5-hexenol furnishes a diastereomerically pure 2,3,6-substituted tetrahydropyran, when oxidized by air in the presence of a cobalt(II)-diketonate complex.[37] In the present study we systematically investigated stereodirecting effects exerted by one substituent in position 1 or 2, and by two substituents in 5-hexenol positions 1,2 or 1,3. We furthermore explored (tetrahydropyran-2-yl)-methyl radical trapping by heteroatom donors and alkenes, for diversifying the methods used for carbon radical functionalization.

The major results from the study show that 5-hexenols yield 2,6-trans-, 2,5-trans-, and 2,4-cis-substituted tetrahydropyrans as major products, when exposed at elevated temperatures to air and cyclohexa-1,4-diene in solutions of toluene, containing a fluorinated cobalt bis-(β-diketonate) complex. Oxidizing 5-hexenols in solutions of bromotrichloromethane chemoselectively gives 6-*exo*-bromocyclized products in up to 89% yield, as exemplified by synthesis of diastereomerically pure 2,4,6-substituted tetrahydropyrans. Multi-component reactions between 5-hexenols, dioxygen, dimethyl fumarate, and cyclohexa-1,4-diene (CHD), catalyzed by cobalt complexes furnish α-tetrahydropyranyl-2-methyl succinates in synthetically useful yields.

(i) *aerobic 5-hexenol oxidation*



(ii) *(tetrahydropyran-2-yl)methyl radical functionalization*



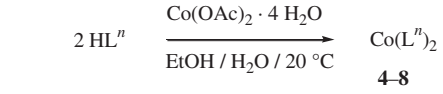
Scheme 1. Concept for tetrahydropyran formation from aerobic 5-hexenol oxidation (step i) and radical trapping (step ii); [H]=hydrogen atom from, e.g., cyclohexa-1,4-diene (CHD); R=aryl or alkyl; L^-=1-arylbutane-1,3-dione monoanion (Table 1); X–Y=e.g. CHD or $BrCCl_3$; the dashed line indicates triplet-dioxygen ($^3O_2$)-binding to cobalt(II) bis-(β-diketonate) complex CoL_2 (for structure formula of CoL_2, refer to Section 2.1).

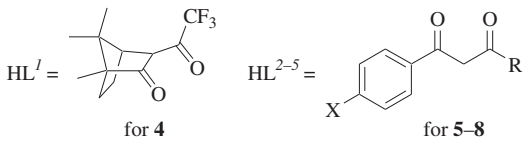
2. Results and discussion

2.1. Cobalt complexes

From a screening of catalysts, we selected fluoro-substituted cobalt(II) bis(β-diketonate)-complexes of the general formula

Table 1
Preparation and spectroscopic characteristics of fluorinated bis-[butane-1,3-dionato(−1)]-cobalt(II) complexes





Entry	HL^n	X	R	**4**–**8**[a]/%	λ_{max} (log $\varepsilon/\varepsilon^*$)[b]/nm	$\nu_{C=O}$[c]/cm^{-1}
1	HL^1	—	—	**4**: 89	309 (3.25)	1560, 1654
2	HL^2	H	CF_3	**5**: 99	319 (3.55)	1576, 1609
3	HL^3	F	CH_3	**6**: 84	316 (3.01)	1575, 1603
4	HL^4	F	CF_3	**7**: 89	319 (3.04)	1586, 1616
5	HL^5	F	C_7F_{15}	**8**: 96	323 (2.93)	1593, 1617

[a] Dihydrate.
[b] ε in m^2 mol^{-1}; ε^*=1 m^2 mol^{-1}.
[c] From samples pelletized in potassium bromide.