Levoglucosan, Levoglucosenone, (+)-δ-Cadinol and Isocembrol in the Synthesis of Low-Molecular Bioregulators and Cytostatics

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Abstract

The results of research work concerning the syntheses of prostanoids and eleutesides based on saccharides such as levoglucosan and levoglucosenone, sesquiterpenoid (+)-δ-cadinol and diterpenoid isocembrol are generalized.

Key words: levoglucosan, levoglucosenone, (+)-δ-cadinol, isocembrol, prostanoids, mevinoids, 9,11-carba analog of prostaglandin endoperoxide PGH2, enantiodivergent synthesis, eleuthesides, intramolecular 1, 4-oxacyclization, N-methylurocanic acid

One of the ways to solve the problem of optical induction is connected with the use of much more accessible primary metabolites. We have investigated the possibility for using levoglucosan, levoglucosenone, (+)-δ-cadinol, and isocembrol in the syntheses of prostanoids and eleuthesides.

Levoglucosan obtained most often through the pyrolysis of starch or cellulose is well enough understood and it is used in the synthesis of some natural compounds. Nevertheless the potentialities of its use for the synthesis of prostanoids and simvastatins-mivenoids have not been studied till now, which stimulated our works in this filed [1, 2].

The key stage of two our developments consists in the deoxigenation 2,4-dibenzyl or tris-trimethylsilyl derivatives of levoglucosan according to Burton (in the first case at the position 3, in the second case at the positions 2,4) and the subsequent transformation through chiral matrices 3, 4 to produce a key synton for isoprostanes 5 or a lactone fragment of mevinoids/simvastatins 6, respectively (Scheme 1). Another carbohydrate such as highly reactive

![Scheme 1.](image-url)
1,6-anhydroscarcosaccharide enone levoglucosenone was used in our experiments for the synthesis of prostaglandin endoperoxide PGH₂ [3–7].

![Chemical structure of PGH₂](image)

Taking into account the practical importance, we have aimed the basic efforts at the creation of PGH₂ analogues with a saturated norbornane ring system. Earlier these were obtained and tested only in the form racemates, in the best case in the form of diastereomeric mixtures. We have for the first time synthesized individual enantiomeric and diastereomeric compounds 14–17, as well as their thio analogs (Scheme 2).

![Scheme 2](image)

For obtaining 9,11-carba analogs PGH₂ 14–17 we have developed an enantiodivergent approach based on an unified chiral block 8. With reference to chiral asymmetrically substituted meso-norbornane derivative 18 this fact means the realization of a by-turn epimerization in each of the centres with the substituents R₁ and R₂, and constructing the structures of enantiomers 19, 20 – the precursors of target compounds 14–17.

The first approach consisted in performing the deoxygenation of adduct 8 according to Barton to obtain the basic connection 21. Chiral matrix 22 has been obtained as the result of opening its 1,6-anhydrobridge EtSH-BF₃⋅Et₂O, cleaving of vic-diol and configuration inversion at α-carbon atom of the aldehyde formed. The subsequent stages of the Wittig–Emmons–Horner olefination and the keto group reduction proceed smoothly enough. The removal of the thioacetal blockage has unexpectedly completed with a formal substitution of the hydroxyl group by the thioethyl group, which caused

**Reagents and conditions:**
- a) NH₂–NH₂·H₂O;
- b) NaH, DMSO, THF;
- c) HCl, THF, H₂O;
- d) Ph₃P=CH(CH₂)₃CO₂Na.
LEVOGLUCOSAN, LEVOGLUCOSONE, (+)-δ-CADINOL AND ISOCEMBROL IN THE SYNTHESIS

Scheme 3.

In order to obtain a carba analog containing asymmetric centers corresponding to the configuration of naturally occurring PGH₂, as well as its 15-hydroxy epimer we decomposed ketone 28 according to the Baeyer–Villiger reaction, and then carried out a number of stages (hydrolysis, the hydroxyl group substitution by bromine, dehydrobromination and esterification) as a result of which unsaturated ester 32 have been obtained. By means of simple transformations, using compound 32 we obtained lactol 33 and further, with the use of the prostanoid methodology, we have synthesized target carba analogs 14 and 16 (Scheme 5).

For the synthesis of eleuthesides (sarcodictines A and B, eleutherobin), sea diterpenoids with a cytotoxic taxol-like mechanism of the action [8], we used (+)-carvon and (–)-α-phellandrene [9–12] as initial compounds. In the formal synthesis of eleuthesides we used sesquiterpenoid (+)-δ-cadinol [13–19] isolated from turpentine of Pinus Sibirica R. Mayr (Scheme 6).
Scheme 6.

Reagents and conditions: 
a) SeO\textsubscript{2}, Ac\textsubscript{2}O–AcOH; b) p-TsOH, C\textsubscript{6}H\textsubscript{6}, boiling; c) O\textsubscript{3}, MeOH, Me\textsubscript{2}S; p-TsOH, MeOH; d) CH≡CMgCl, THF, 0 °C; e) CF\textsubscript{3}COOH, H\textsubscript{2}O, CHCl\textsubscript{3}; f) CNCH\textsubscript{2}CO\textsubscript{2}Et, EtOH, \(\beta\)-alanine; g) isopropenyl acetate, p-TsOH; h) BF\textsubscript{3}⋅Et\textsubscript{2}O, Ac\textsubscript{2}O, 0 °C.

Scheme 7.

Reagents and conditions: 
a) SeO\textsubscript{2}, Ac\textsubscript{2}O–AcOH; b) p-TsOH, C\textsubscript{6}H\textsubscript{6}, boiling; c) O\textsubscript{3}, MeOH, Me\textsubscript{2}S; p-TsOH, MeOH; d) CH≡CMgCl, THF, 0 °C; e) CF\textsubscript{3}COOH, H\textsubscript{2}O, CHCl\textsubscript{3}; f) CNCH\textsubscript{2}CO\textsubscript{2}Et, EtOH, \(\beta\)-alanine; g) isopropenyl acetate, p-TsOH; h) BF\textsubscript{3}⋅Et\textsubscript{2}O, Ac\textsubscript{2}O, 0 °C.

Scheme 8.
A key transformation is presented by obtaining 1,4-epoxide 36 via allylic hydroxylation of SeO₂ and the subsequent intramolecular 1,4-oxacyclization. This procedure has allowed us to reduce the synthetic sequence due to eliminating the stages of functional groups blocking-unblocking. The cleavage of 1,4-epoxide ring was carried out at final stages under the action of Ac₂O–BF₃⋅Et₂O [20] (Scheme 7).

The hypothesis that cembranoids can serve as the precursors of eleuthersides [21–23], stimulated our studies on the synthesis of esters of N-methylurocanic acid and hydroxyl derivatives of these diterpenoids. As a basic compound we used isocembrol that is contained also in the turpentine of the Siberian cedar. The hydroxylation was carried out via a two-stage process consisting of the epoxidation with tert-butyl hydroperoxide in the presence of vanadyl acetylacetonate and the subsequent boiling of the epoxide obtained with LiAlH₄ in THF. We have obtained the main (84 %) and by-produced (12 %) 3- and 2-hydroxyl derivatives respectively. Moreover, the allylic oxidation of isocembrol has resulted in obtaining 13-hydroxy derivative (30 %) and its ethyl ether (35 %).

The esterification of 2-, 3- and 13-hydroxy derivatives with N-methylurocanic acid has resulted in the formation of esters 47–49, respectively [24, 25] (Scheme 8).

Thus, the use of carbohydrates such as levoglucosan, levoglucosenone, sesquiterpenoid (+)-δ-cadinol and diterpenoid isocembrol for the synthesis prostanoids and eleuthesides has allowed us to perform a high level of stereo control in the transformations of compounds themselves, as well as to provide efficiently carrying out the optical induction in target products.

REFERENCES

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