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

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Abstract

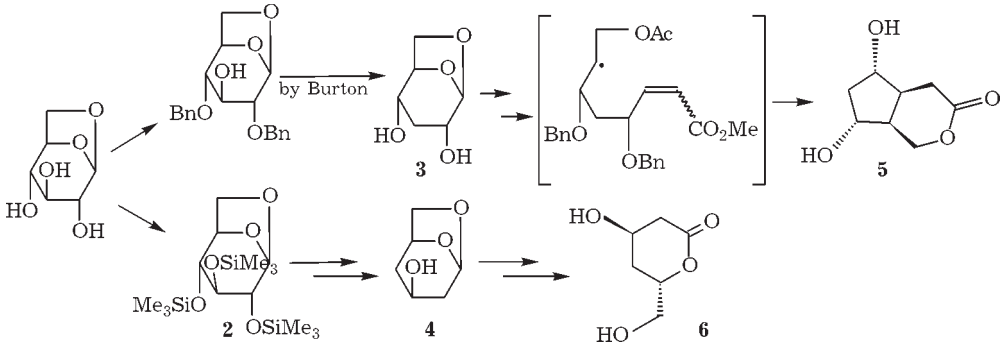
The results of research work concerning the syntheses of prostanoids and eleutesides based on saccarides such as levoglucosan and levoglucosenone, sesquiterpenoid (+)-δ-cadinol and diterpenoid isocembrol are generalized.

Key words: levoglucosan, levoglucosenone, (+)-δ-cadinol, isocembrol, prostanoids, mevinoids, 9,11-carba analog of prostaglandin endoperoxide PGH_2, 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.

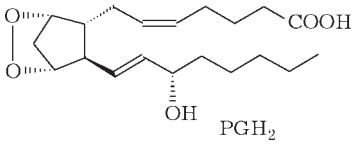
Levoglucosan obtained most often through the pyrolysis of starch or cellulose is well enough understood and it is used in the synthesis of some natural compounds. Nevertheless the potentialities of its use for the synthesis of prostanoids and simvastatins-mivenoids have not been studied till now, which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



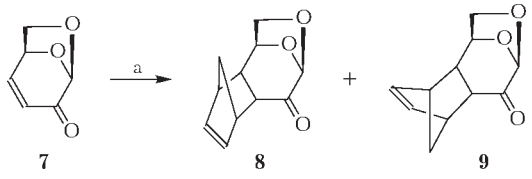
Scheme 1.

1,6-anhydrosaccaride enone levoglucosenone was used in our experiments for the synthesis of prostaglandin endoperoxide PGH_2 [3–7].



PGH_2

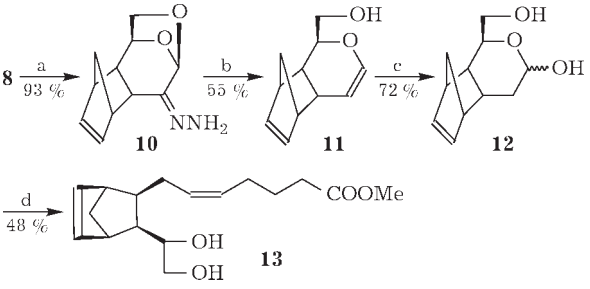
A most suitable for this purpose derivative of levoglucosenone **7** is presented by endo-adduct **8** obtained in the mixture with exo-derivative **9** as the result of the thermal Diels–Alder reaction with cyclopentadiene. We have succeeded in developing a catalytic method for obtaining of the compound required with the formation of endo-adduct **8**.



7 **8** **9**

Reagents and conditions: a – cyclopentadiene, $ZnCl_2$, CH_2Cl_2.

The key intermediate species for 9,11-etheno analog **13** was obtained by means of the deoxygenation of adduct **8** according to Huang–Minlon to produce glycal **11**, its hydrolysis to yield acetal **12** and olefination according to Wittig.

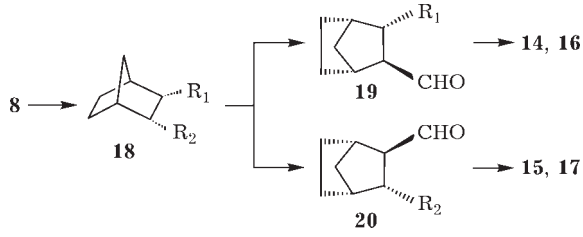


10 **11** **12** **13**

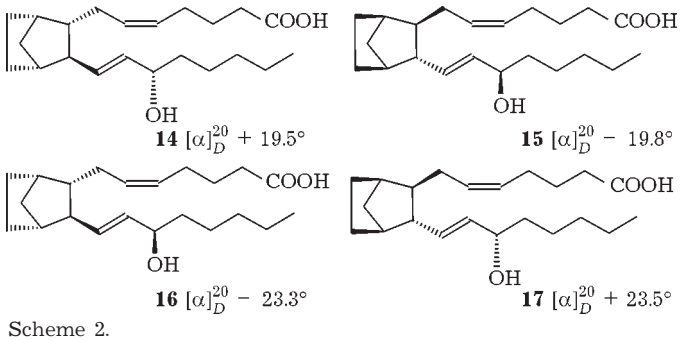
Reagents and conditions: a) $NH_2–NH_2 \cdot H_2O$; b) NaH, DMSO, THF; c) HCl, THF, H_2O; d) $Ph_3P=CH(CH_2)_3CO_2Na$.

Taking into account the practical importance, we have aimed the basic efforts at the creation of PGH_2 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).

For obtaining 9,11-carba analogs PGH_2 **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 R^1 and R^2, and constructing the structures of enantiomers **19**, **20** – the precursors of target compounds **14–17**.



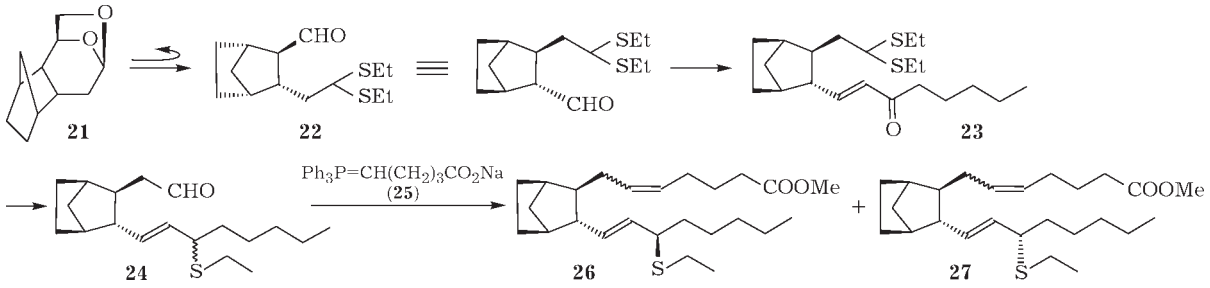
The first approach consisted in performing the deoxygenation of adduct **8** according to Barton to obtain the basic connection **21**. Chiral matrix **22** has been obtained as the result of opening its 1,6-anhydrobridge $EtSH\text{-}BF_3 \cdot Et_2O$, cleaving of *vic*-diol and configuration inversion 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



14 $[\alpha]_D^{20}$ + 19.5° **15** $[\alpha]_D^{20}$ – 19.8°

16 $[\alpha]_D^{20}$ – 23.3° **17** $[\alpha]_D^{20}$ + 23.5°

Scheme 2.



Scheme 3.

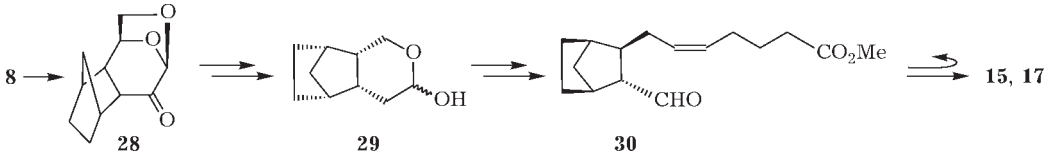
our efforts to be focused on obtaining thio analogs **26** and **27** by means of phosphorane **25** addition (Scheme 3).

In the course of the synthesis we have revealed that with such an order of constructing the lateral chains (*i.e.* ω-chain in the beginning and then α-chain) the Wittig olefination is accompanied by the formation of *Z,E*-isomers in commensurable amounts.

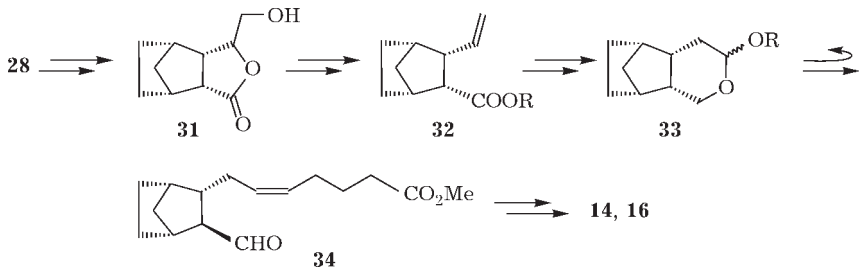
In order to increase the stereoselectivity of this reaction we have had to aim the strategy of the synthesis at first-priority constructing the α-chain. For this purpose, after adduct **8** stereospecific hydrogenation with nickel boride to yield ketone **28**, the Huang–Minlon deoxygenation and a number of transformations already considered above we obtained lactol **29**. This key synton has allowed us to provide smoothly obtaining target enantiomeric carba analogs PGH_2 **15** and **17** basing on the prostaglandin methodology (Scheme 4).

In order to obtain a carba analog containing asymmetric centers corresponding to the configuration of naturally occurring PGH_2, 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).

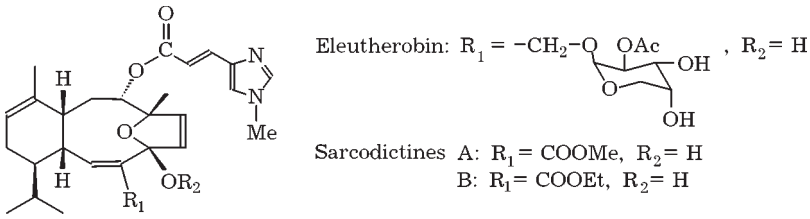
For the synthesis of eleuthesides (sarcodictines A and B, eleutherobin), sea diterpenoids with a cytotoxic taxol-like mechanism of the action [8], we used (+)-carvon and (−)-α-phellandrene [9–12] as initial compounds. In the formal synthesis of eleuthesides we used sesquiterpenoid (+)-δ-cadinol [13–19]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



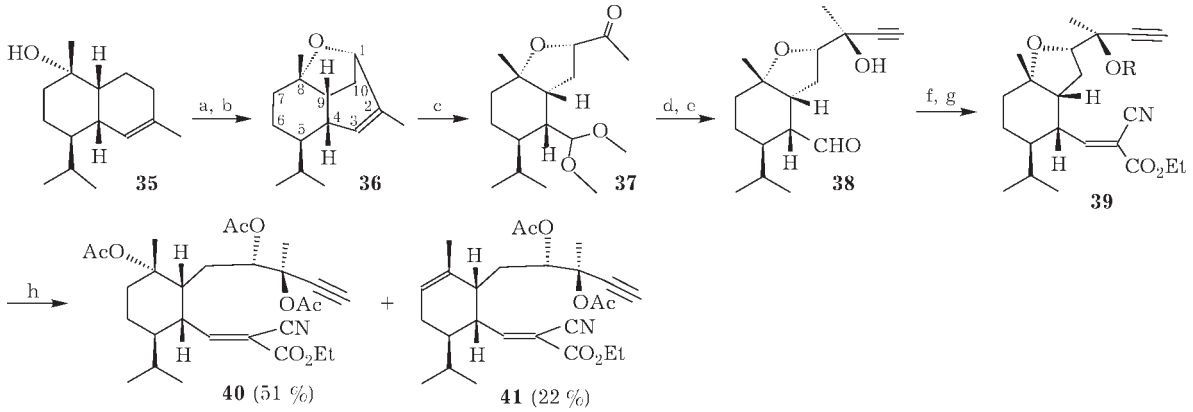
Scheme 4.



Scheme 5.

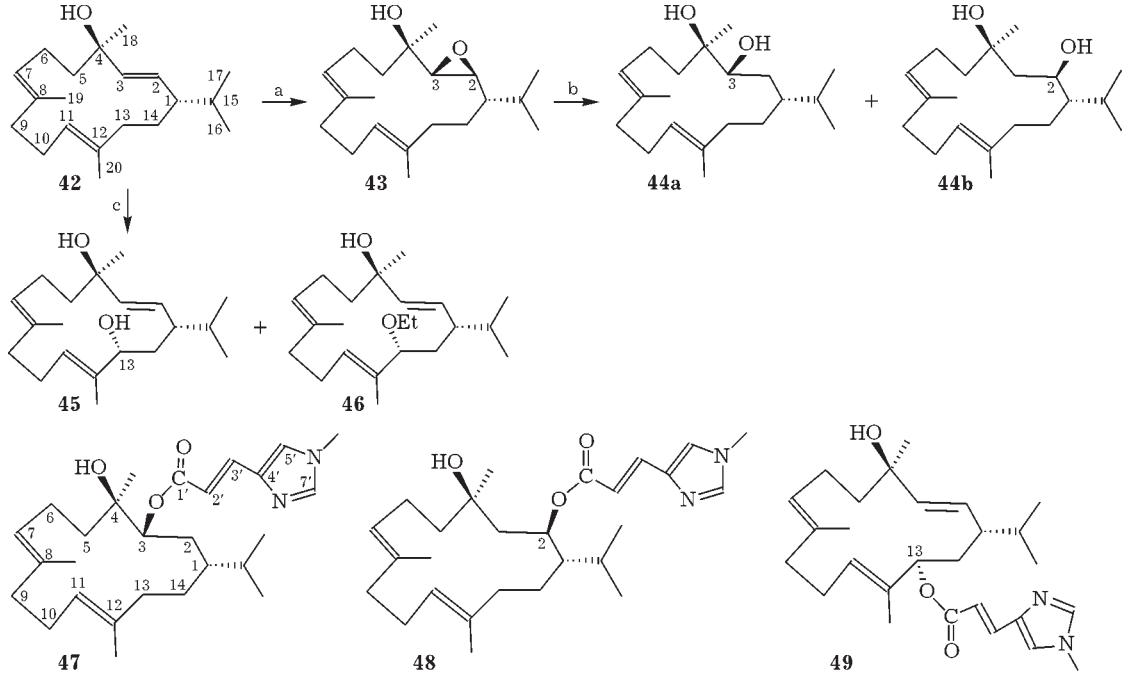


Scheme 6.



Reagents and conditions: a) SeO_2, Ac_2O–AcOH; b) *p*-TsOH, C_6H_6, boiling; c) O_3, MeOH, Me_2S; *p*-TsOH, MeOH; d) CH≡CMgCl, THF, 0 °C; e) CF_3COOH, H_2O, $CHCl_3$; f) $CNCH_2CO_2Et$, EtOH, β-alanine; g) isopropenyl acetate, *p*-TsOH; h) $BF_3 \cdot Et_2O$, Ac_2O, 0 °C.

Scheme 7.



Reagents and conditions: a) HPTB, C_6H_6, $VO(acac)_2$, **43** – 75 %; b) $LiAlH_4$, THF, boiling, **44a** – 84 %, **44b** – 12 %; c) SeO_2, EtOH, boiling, **45** – 30 %, **46** – 35 %.

Scheme 8.

A key transformation is presented by obtaining 1,4-epoxide **36** *via* allylic hydroxylation of SeO_2 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-epohy ring was carried out at final stages under the action of $Ac_2O-BF_3 \cdot Et_2O$ [20] (Scheme 7).

The hypothesis that cembranoids can serve as the precursors of eleuthesides [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 $LiAlH_4$ 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.

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