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ARTICLE

Formation of steroidal C-25 chiral center *via* asymmetric alkylation methodology

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Yu. V. Ermolovich, V. N. Zhabinskii* and V. A. Khripach

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A novel approach for the preparation of steroids containing a chiral center at C-25 is reported. The key stereochemistry inducing step was asymmetric alkylation of pseudoephenamine amides of steroidal C-26 acids. The reaction proceeded with high diastereoselectivity (dr > 99:1). The developed methodology was successfully applied to the synthesis of (25*R*)- and (25*S*)-cholestenoic acids as well as (25*R*)- and (25*S*)-26-hydroxy brassinolides.

Introduction

The C-26 hydroxylation is an important enzymatic reaction involved in the biosynthesis and metabolism of many natural steroids (26-hydroxycholesterol,[1] cholic acids,[2] dafachronic acids,[3] cholestenoic acids,[4] brassinosteroids,[5] polyhydroxylated marine steroids[6]). The reaction may occur at either of the two terminal methyl groups. Due to their non-equivalence, this process results in the creation of a new asymmetric centre at C-25. As a rule, the C-26 hydroxylation in living organisms proceeds stereoselectively to give directly or in a few biosynthetic steps the corresponding natural steroids as either (25*R*)- or (25*S*)-isomers.[7] Apart from a functional group instead of one of the methyl group, such compounds may possess additional functionalities at C-22, C-23, and C-24. Figure 1 provides only a few examples out of a large variety of possible structural types for side chains of these steroids.

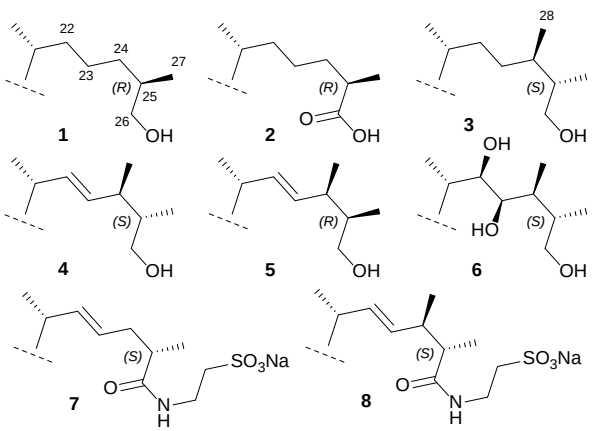
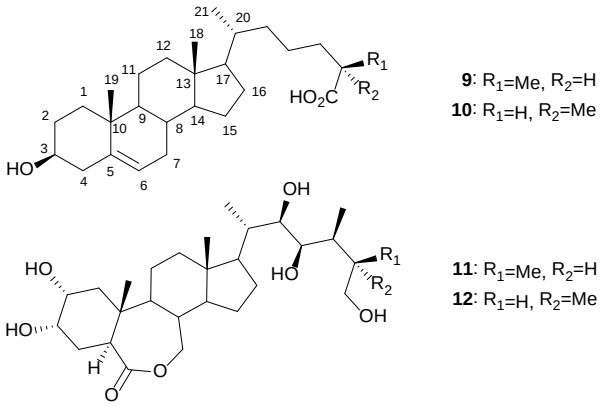


Fig. 1 Selected structural types of steroidal side chains bearing a chiral center at C-25.



9: R_1=Me, R_2=H
10: R_1=H, R_2=Me
11: R_1=Me, R_2=H
12: R_1=H, R_2=Me

Fig. 2 Structure of (25*R*)-cholestenoic acid **9**, (25*S*)-cholestenoic acid **10**, (25*R*)-26-hydroxybrassinolide **11**, (25*S*)-26-hydroxybrassinolide **12**.

Despite the impressive number of publications devoted to the synthesis of certain steroids ((25*R*)-26-alcohols **1**,[8] (25*S*)-26-alcohols,[8b, 8d, 8l, 8o, 9] (25*R*)-26-acids **2**,[10] (25*S*)-26-acid,[10b-f, 11] 24-methyl-26-alcohols **3**-**5**,[12] 26-hydroxybrassinosteroids **6**[13]), the problem of their accessibility is still occurring. In most cases, these syntheses are limited in yield and scope and cannot be applied for the preparation of the whole set of the required structures.

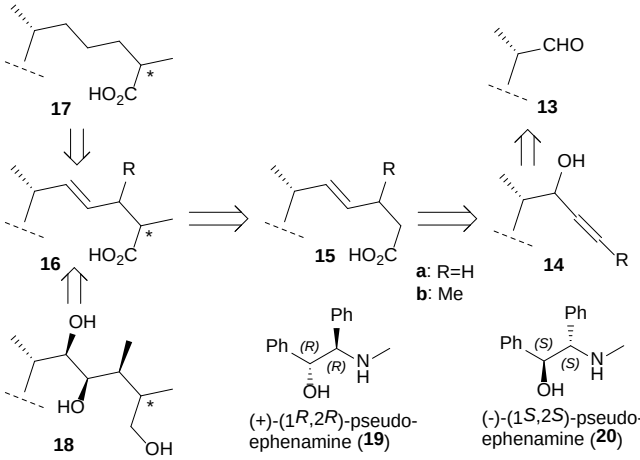
In this paper, we describe a new approach potentially suitable for the synthesis of any type of steroidal side chains shown at Fig. 1. To fulfil the objective of the study, an attempt was made to explore asymmetric alkylation of pseudoephenamine amides. The developed methodology was verified by applying it to the synthesis of (25*R*)- and (25*S*)-cholestenoic acids **9** and **10** as well as (25*R*)- and (25*S*)-26-hydroxybrassinolides **11** and **12** (Fig. 2).

Results and discussion

Retrosynthetically, the target steroidal side chains **17,18** could be prepared *via* γ,δ-unsaturated acid **16** (Scheme 1). The key stereochemistry-determining step was supposed to be asymmetric alkylation at C-25 of appropriate derivatives of acids **15**.

Among various general methods available for achieving the required transformation, asymmetric alkylation of enolates derived from chiral amides has been recognized as one of the best.[14] The latest achievement in this field is the use of pseudoephenamine as a chiral auxiliary.[15] This directing group affords the alkylation products with equal or better diastereoselectivities in comparison with commonly used for this purpose pseudoephedrine. In contrast with the latter, pseudoephenamine is free from regulatory restrictions as it cannot be transformed into illicit substances.

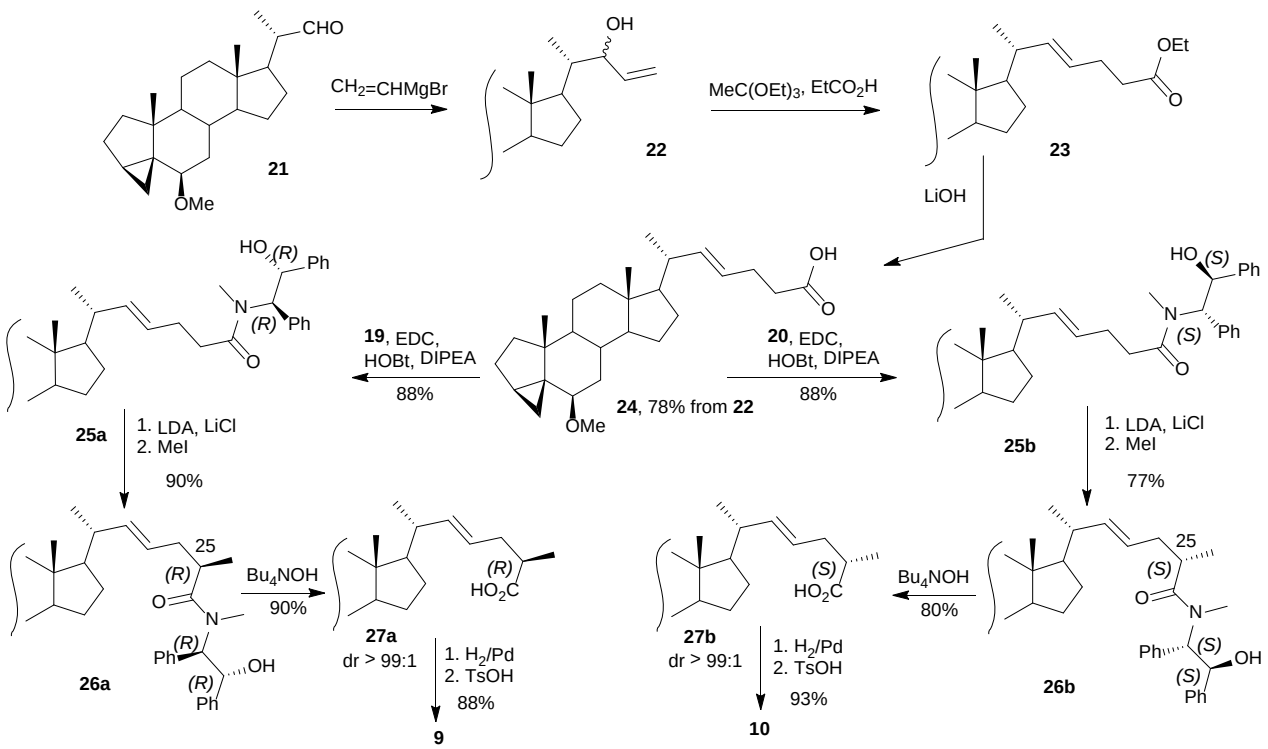
Further retrosynthetic analysis led us to consider the allylic alcohols **14** as possible precursors of the acids **15** in a synthetic procedure using the Claisen rearrangement. This reaction is widely used for the stereoselective construction of 24-alkyl sterols *via* a 1,3-chirality transfer process.[16] The stereochemistry at the newly formed chiral center at C-24 depends on stereochemistry at C-22 and geometry of Δ^{23}-double bond. Since compounds **15a** have no chiral center at C-24, both C-22 isomers of **14a** can be equally used for their preparation. Allylic alcohols **14** are available in one or two steps from the steroidal C-22 aldehyde **13**.



Scheme 1 Retrosynthetic analysis of the target acids **17** and triols **18** and structure of pseudoephenamines **19,20**.

Both isomeric cholestenoic acids **9** and **10** are natural compounds. (25*R*)-Cholestenoic acid **9** was shown to be present in human plasma.[4a] It plays a significant role in biosynthesis of bile acids[17] and lipoprotein-independent reverse cholesterol transport.[18] (25*S*)-Cholestenoic acid **10** was reported[19] as a ligand for the orphan nuclear receptor DAF-12 which is pivotal for the control of dauer formation and lifespan regulation of the *Caenorhabditis elegans* larva, a model organism for aging studies. There are a number of synthetic routes to cholestenoic acids **9**[8o, 10d, 20] and **10**[8o, 10d, 11d, 20a, 20e, 21]. However, the published methods suffer from low yields, lack of generality

Synthesis of cholestenoic acids 9 and 10



Scheme 2 Synthesis of (25*R*)-cholestenoic acid **9** and (25*S*)-cholestenoic acid **10**. Abbreviations: EDC, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride; DIPEA, *N*,*N*-diisopropylethylamine; HOBt, 1-hydroxybenzotriazole hydrate.

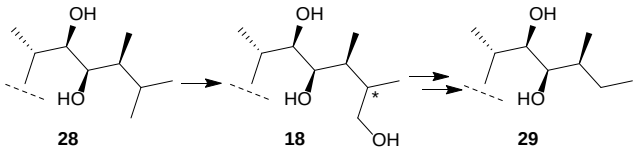
and unsuitability for the preparation of labeled analogs.

Preparation of the title compounds started from aldehyde **21**[22] (Scheme 2) and proceeded through addition of vinylmagnesium bromide to give the allylic alcohol **22** as a mixture of (22*S*)- and (22*R*)-diastereomers.[23] The next step was to build a C-24 – C-26 fragment of the side chain. That was achieved by the Johnson-Claisen rearrangement of the allylic alcohol **22**. The formed ester **23** was hydrolysed and the resulting acid **24** was amidated with pseudoephenamines **19** and **20** to give the corresponding amides **25a** and **25b**. As determined by NMR spectroscopy, these existed as a mixture of rotamers resulting from the hindered rotation of the N-carbonyl bond.

Addition of MeI at - 20°C to enolates of **25a** and **25b**, generated with LDA in THF in the presence of LiCl, and subsequent hydrolysis of alkylated products **26a** and **26b** under basic conditions (proceeded without epimerization at C-25) provided (25*R*)- and (25*S*)-acids **27a** and **27b**. Their transformation into cholestenoic acids **9** and **10** was achieved in two steps in 88-93% yield according to the procedure previously described.[20e]

Synthesis of 26-hydroxybrassinolides 11 and 12

Interest to this pair of compounds comes from the identification of 26-norbrassinolide in cultured cells of *Phaseolus vulgaris*.[5b] Loss of 26-methyl group in brassinolide side chain **28** was supposed to proceed through initial C-26 hydroxylation followed by successive transformation of 26-hydroxy derivative **18** into 26-aldehyde, 26-acid and decarboxylation of the latter (Scheme 3). It is likely that C-26 demethylation is an important catabolic process which serves to maintain a homeostatic level of brassinosteroids.[24] Many details of this process are still to be elucidated, as is the stereochemistry at C-25 in **18**. The accessibility of 26-hydroxybrassinolides **11** and **12** is of much importance for the corresponding studies. Among several syntheses of **18** that have been reported to date,[13] only two attempts were made to prepare compounds **11**[13d, 13e] and **12**[13e].

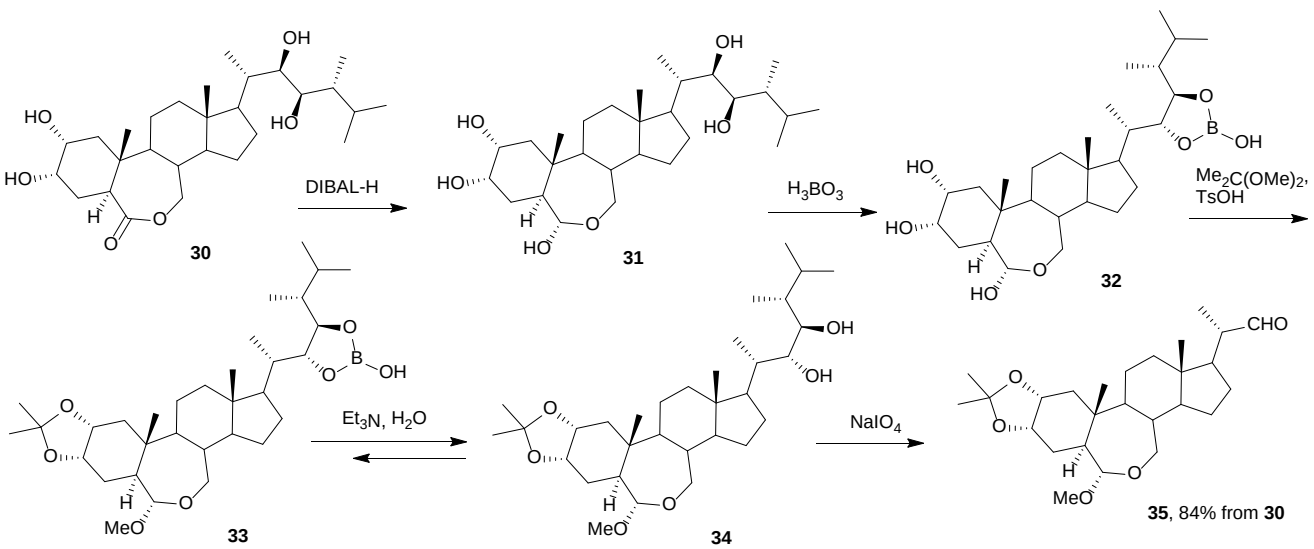


Scheme 3 A proposed biosynthetic pathway to 26-norbrassinolide side chain **29**.

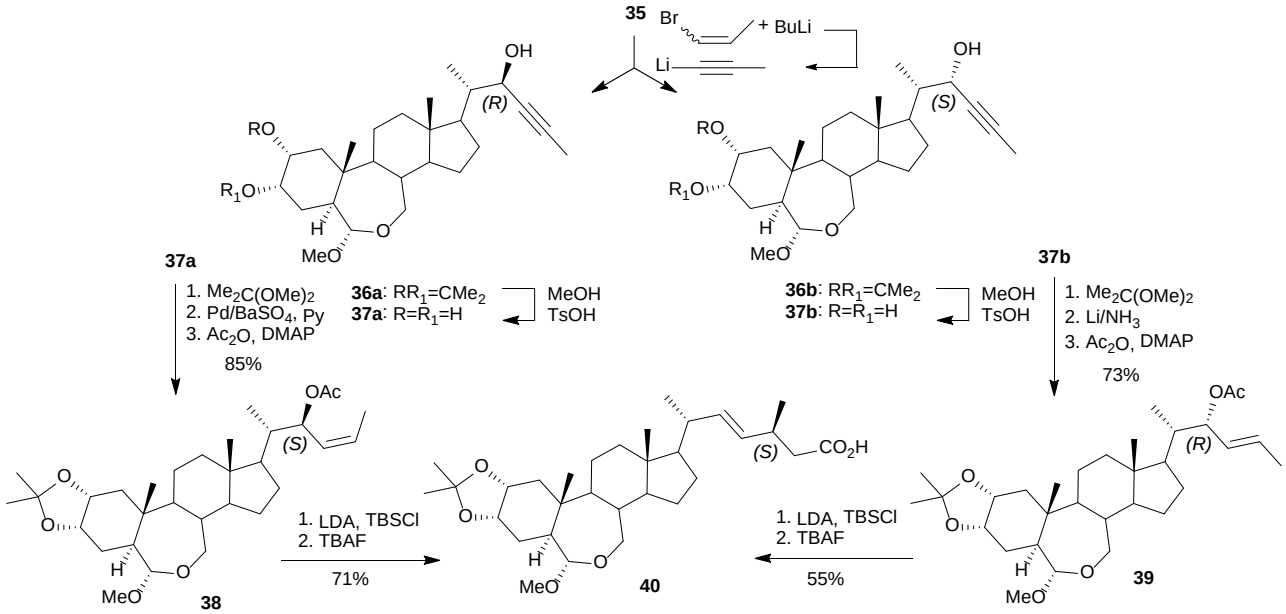
However, these approaches are either tailored to specific isomer[13d] or non-stereoselective[13e].

To reduce the number of synthetic steps, a commercially available 24-epibrassinolide **30**[25] was chosen as a starting material. Its highly functionalized molecule already contains a number of functional groups which are present in the target compounds **11** and **12**. The obvious route to produce C-22 aldehyde from 24-epibrassinolide **30** was oxidative cleavage of its 22,23-diol. Naturally, another diol group needed to be protected prior to the cleavage. A good idea was also to have a B-ring lactone function protected at steps involving reaction with nucleophilic reagents. With this in mind, we have prepared the aldehyde **35** through a five-step transformation in 84% overall yield. The last four steps were carried out as a one-pot procedure. The DIBAL-H reduction of 24-epibrassinolide **30** gave tetrahydroxy lactol **31**. The problem of differentiation between the two diol groups was solved by means of boric acid. Formation of cyclic esters of brassinosteroids with methylboronic[26] or boric[27] acids was shown to proceed preferentially with 22,23-diol. The formed 22,23-cyclic boric acid ester in **32** was stable enough to allow protection of 2α,3α-diol group, but in a mixture of triethylamine and water an equilibrium between **33** and **34** took place. The reaction of the latter with $NaIO_4$ resulted in a shift of the equilibrium towards the aldehyde **35**.

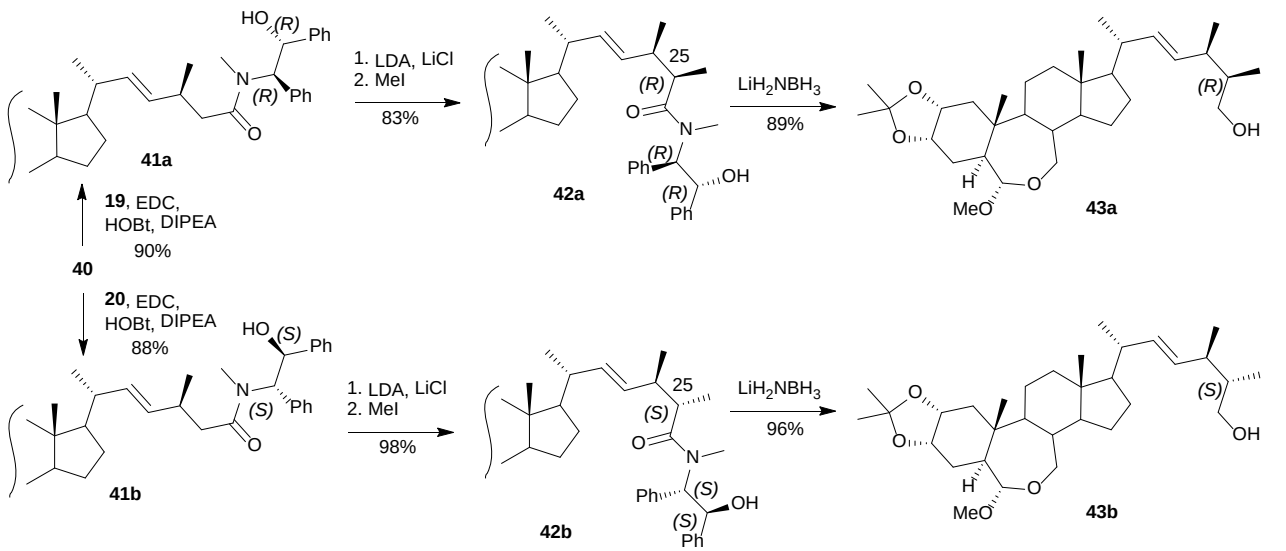
Nucleophilic addition of lithium methylacetylide (generated by reaction of *E*/*Z*-propenyl bromide and BuLi)[28] to the aldehyde **35** gave an inseparable 2.7:1 mixture of 22*R*- and 22*S*-propargyl alcohols **36a** and **36b**. Separation of these two compounds was a critical problem which had to be solved to



Scheme 4 Synthesis of the aldehyde **12**.



Scheme 5 Synthesis of compound **40**.

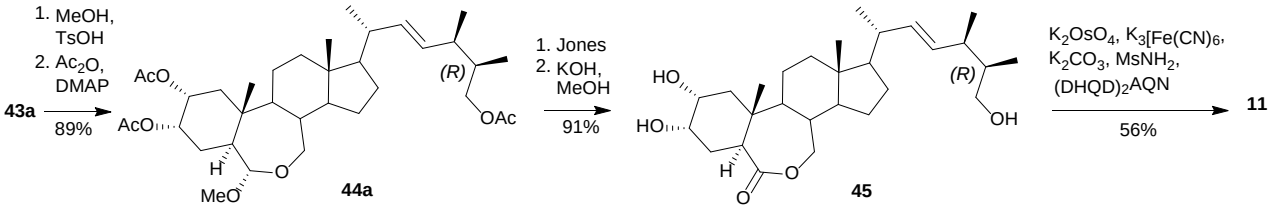


Scheme 6 Synthesis of compounds **43a** and **43b**. Abbreviations: EDC, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride; DIPEA, *N*,*N*-diisopropylethylamine; HOBt, 1-hydroxybenzotriazole hydrate.

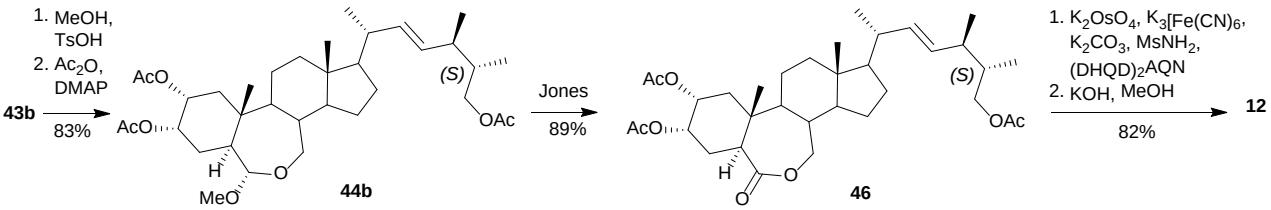
ensure subsequent stereoselective construction of the side chain. Two attempts were made to circumvent this problem. It was reported that addition of terminal acetylenes to aldehydes can proceed in the presence of $Zn(OTf)_2$ and an amine base in the stereoselective manner.[29] However, no reaction at all was observed between the aldehyde **35** and methylacetylene in all cases. Attempt of stereoselective reduction[30] of 23-ketone (obtained by oxidation of a mixture **36a** and **36b**) with Alpine-borane gave only unchanged starting material in our hands. Finally it was found that simple deprotection of acetonide enabled chromatographic separation of isomeric **37a** and **37b**.

Further steroid side chain elongation and formation of C-24 chiral center was performed *via* the Claisen rearrangement. Both isomer **36a** and **36b** were equally suitable for this purpose. At first the Johnson variant of the Claisen rearrangement was tried. The obtained from **36a** by reduction of triple bond allylic alcohol was subjected to heating in toluene with triethylorthoacetate and catalytic amount of propionic acid. However, only a complex mixture of decomposition products was isolated.

Therefore, a more gentle Ireland version[31] of the Claisen rearrangement was tried next. Reprotection of 2,3-diol in **37a** and **37b** followed by reduction of **36a** and **36b** to appropriate allylic alcohols and, finally, acetylation led to compounds **38** and **39**. Both acetates, after subsequent enolization with LDA in THF, treatment with TBSCl in THF-HMPA mixture at -78°C, stirring at room temperature and TBS-ester hydrolysis gave acid **40** as a single diastereomer. It should be noted that the



Scheme 7 Synthesis of (25*R*)-26-hydroxy brassinolide **11**. Abbreviation: DMAP, 4-(dimethylamino)pyridine; $(DHQD)_2AQN$, hydroquinidine anthraquinone-1,4-diyl diether.



Scheme 8 Synthesis of (25*S*)-26-hydroxy brassinolide **12**. Abbreviation: DMAP, 4-(dimethylamino)pyridine; $(DHQD)_2AQN$, hydroquinidine anthraquinone-1,4-diyl diether.

(24*R*)-isomer of **40** could be obtained in the same way by using appropriate alylic alcohols.

Electrophilic addition of MeI to enolates, generated from pseudoephenamine amide derivatives **41a** and **41b** (reaction conditions are similar to alkylation of **25a** and **25b**) provided methylated products **42a** and **42b** (Scheme 6). The diastereoselectivity of the alkylation was determined by ^1H NMR analysis of the primary alcohols **43a** and **43b** (see Supplementary). These compounds were obtained by the reduction of **42a** and **42b** with lithium amidotrihydroborate[32] and exhibited diastereomeric purity greater than 99%.

The further synthetic plan required regeneration of the lactone unit (Scheme 7). Experiments on model compounds to achieve this task with bromine, Fetizon's reagent, peracids[33] or pyridinium chlorochromate[34] gave poor results. The solution of the problem was found to be the use of Jones reagent. The hydroxyl functions had to be properly protected prior to the regeneration step that was achieved by transformation of **43a** into triacetate **44a**. Its reaction with Jones reagent proceeded smoothly and led after deacetylation step to compound **45**. Sharpless dihydroxylation of Δ^{22}-bond in **45** gave (25*R*)-26-hydroxybrassinolide **11**. An unexpected problem occurred at this step. Pentaol **11** and $(DHQD)_2AQN$ exhibited very similar chromatographic behavior that caused difficulties in separating each other. Ultimately the separation was effected by using a mixture of AcOH-EtOAc as eluent, although yield of (25*R*)-26-hydroxy brassinolide **11** was not satisfactory. Therefore, another target compound **12** was prepared according to a slightly modified protocol (Scheme 8). The Sharpless dihydroxylation of Δ^{22}-bond was carried out on the olefin **46**. The intermediate less polar triacetoxy diol was easily separated from the catalyst and subjected to saponification to give (25*S*)-26-hydroxybrassinolide **12**.

Conclusions

In summary, we have developed a novel approach for the preparation of steroids containing a chiral center at C-25. The method provides controlled introduction of an alkyl group at C-24 and Δ^{22}-bond *via* the Claisen rearrangement of the appropriate allylic alcohols. The key stereochemistry inducing step was asymmetric alkylation of pseudoephenamine amides of steroidal C-26 acids. This reaction is potentially interesting for the preparation of labeled analogs by the use of CD_3I instead of CH_3I for the alkylation. The developed methodology was successfully applied to the synthesis of (25*R*)- and (25*S*)-cholestenoic acids as well as (25*R*)- and (25*S*)-26-hydroxybrassinolides.

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Notes

Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Kuprevich st., 5/2, 220141 Minsk, Belarus. E-mail: vz@iboch.bas-net.by; Tel: +375172678647.

† Electronic Supplementary Information (ESI) available: Detailed experimental procedures; characterization data; copies of ^1H and ^{13}C NMR spectra; determination of diastereomeric purity of **43a** and **43b**. See DOI:

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