Химический журнал Армении, т. 49, № 1—3, стр. 94—104 (1996 г.)

THE DIASTEREOSELECTIVITY OF VARIOUS ROUTES TO ISOFLAVAN-4-OLS(3-PHENYL-CHROMAN-4-OLS)

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Abstract—The reduction of isoflavan-4-ones (3-phenyl-chroman-4-ones) by nucleophilic hydrides (sodium borohydride, lithium aluminum tri-tert-butoxyhydride, lithium tri-sec-butylborohydride), leads to mixtures of *cis*- and *trans*-diastereoisomers of isoflavan-4-ols. Their reduction with electrophilic hydrides (borane-tetrahydrofuran, bis-tert-butylthioethane diborane (BTED) or 9-borabicyclo[3,3,1]-nonane (9-BBN) is stereoselective and forms *cis* diastereisomers with excellent yields. The hydroboration followed by alkaline hydroperoxide oxidation of 3-phenyl-4-hydroxy-coumarins is also a stereoselective route to *trans* diastereoisomers of isoflavan-4-ols.

Introduction

Isoflavonoids constitute an homogenous group of naturally occuring oxygen heterocyclic compounds and their biosynthesis is elaborated from a $C_6C_3C_6$ common precursor to flavonoids [1]. They behave as Phytoalexins and are capable to inhibit the growth of parasites and the enzymes involved in parasitic reactions [2—9]. Furthermore, isoflavones present hormonal receptor binding affinity [10—14] and isoflavanes or isoflavenes anti-rhinovirus activity [15].

During the course of an ongoing program in relation with the study of the potential biological properties of isoflavan-4-ols, we were looking for convenient preparation routes of these derivatives. An extensive survey of the literature showed the lack of interesting stereoselective methods for their preparation. The reduction of isoflavones with sodium borohydride [16—18], the catalytic hydrogenation or the application of the MEERWEIN-PONDORF-VERLEY method to isoflavan-4-ones showed the lack of their stereoselectivity and the formation of mixtures of *cis* and *trans* derivatives [19, 20]. Although the preparation of *trans* isoflavan-4-ols is reported, it involves a number of steps and give low overall yields (20).

Our needs for large amounts of *cis* and *trans* isoflavan-4-ols and the lack of availability of simple and easy stereoselective methods led us to the systematic investigations of the following routes:

—reduction of isoflavan-4-ones by nucleophilic hydrides: sodium borohydride and further lithium aluminum tri-tert-butoxyhydride and lithium tri-sec-butylborohydride, in order to study the influence of the steric hindrance of these reducing agents,

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—reduction of isoflavan-4-ones with electrophilic hydrides with the same objectives: borane-tetrahydrofuran complex, bis-tert-butylthioethane diborane (BTED) and 9-bora-bicyclo-[3,3,1]-nonane (9-BBN).

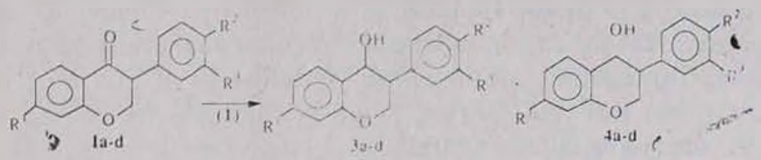
—hydroboration followed by hydroperoxide oxidation [22, 23] of 3-phenyl-4-hydroxy-coumarins according to previous known results in his field [27—33].

The stereochemistry of isoflavan-4-ols was already established. The *cis* diastereoisomers present an equatorial 3-phenyl and an axial 4-hydroxyl groups: JH3 (ax), H4 (eq) = 2.9—3.0 Hz, while the *trans* isoflavan-4-ols present a 3-phenyl equatorial and a 4-hydroxyl equatorial groups: JH3 (ax), H4 (ax) = 7.9—8.0 Hz [18—20].

Results

1. Reduction of isoflavan-4-ones by nucleophilic hydrides

The reduction of the isoflavan-4-ones 1a-d performed with sodium borohydride led in all cases to mixtures of *cis* and *trans* diastereoisomers of isoflavan-4-ols: a set of *cis* 3a-d and another major *trans* 4a-d derivatives (scheme 1) and confirmed the previously obtained results with this reducing agent [18]. The use of the sterically hindered hydrides lithium aluminum tri-tert-butoxyhydride and lithium tri-sec-butylborohydride improved the stereoselectivity and higher amounts of *trans* diastereoisomers were obtained (table 1).



(1) $NaBH_4$, $Li(t\text{-}BuO)_3AlH$, $Li[CH(CH_3)C_2H_5]_3BH$

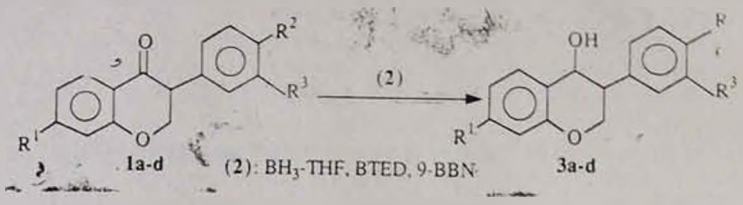
Table 1

Isoflavan-4-ones	Reducing agent	% *cis*-isoflavan-4-ols		% *trans* isoflavan-4-ols	
isoflavan-4-one	$NaBH_4$	3a	42	4a	58
	$Li(t\text{-}BuO)_3AlH$	3a	34	4a	66
7-methoxyisoflavan-4-one	$NaBH_4$	3b	44	4b	56
	$Li(t\text{-}BuO)_3AlH$	3b	33	4b	67
	$Li[CH(CH_3)C_2H_5]_3BH$	3b	37	4b	63
7,4'-dimethoxyisoflavan-4-one	$NaBH_4$	3c	43	4c	57
	$Li(t\text{-}BuO)_3AlH$	3c	34	4c	66
7,3',4'-trimethoxyisoflavan-4-one	$NaBH_4$	3d	36	4d	64
	$Li(t\text{-}BuO)_3AlH$	3d	32	4d	68

2. Reduction of isoflavan-4-ones by electrophilic hydrides

The lack of stereoselectivity of the reduction of isoflavan-4-ones by nucleophilic hydrides led us to the investigation of their reduction with electrophilic hydrides: borane-tetrahydrofuran complex, bis-tert-butylthioethane diborane (BTED) and the sterically hindered 9-bora-bicyclo-[3,3,1]-nonane (9-BBN).

The reactions performed in anhydrous tetrahydrofuran led to the corresponding *cis* diastereoisomers of isoflavan-4-ols 3a-d with excellent yields (scheme 2).



Discussion

Various transition state models and rules have been already reported in order to explain and predict the reduction of chiral carbonyl compounds by nucleophilic and electrophilic hydrides [34—41].

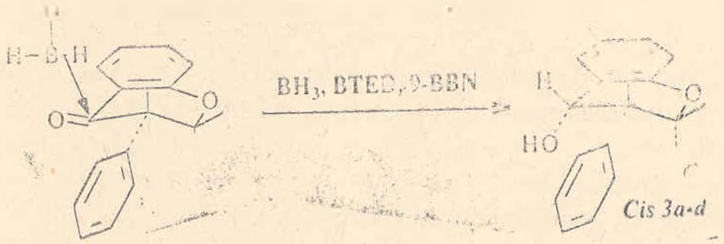
Reductions of isoflavanones by nucleophilic hydrides

In the case of isoflavan-4-ones (3-phenyl-chroman-4-ones) the phenyl group is most probably in the equatorial thermodynamically more stable conformation. Taking into consideration the influence of the steric effects of the middle (M) and the large (L) phenyl groups thd attack of the carbonyl by the nucleophilic hydride H^- should be done from the less hindered and antiparallel face to the phenyl group (L) [35—40]. These conditions would be in favour of an attack from the face (1) instead of the face (2), leading to higher proportions of *cis* diastereoisomers (scheme 3). Examination of Table 1 shows however different results from those expected and suggest that the transition state of the reacting isoflavan-4-one is an equilibrium of two conformers with the phenyl group in axial or equatorial position with different reduction rates for each conformer, leading to the formation of the diastereomeric mixture.

Reductions of isoflavan-4-ones by electrophilic hydrides

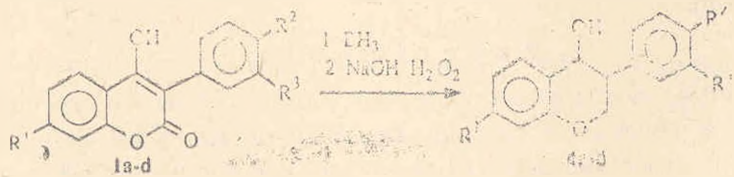
In the case of electrophilic hydrides a model applicable to ethylenic compounds was already proposed [40].

It is important to note that reductions performed with any of the electrophilic hydrides borane-tetrahydrofuran complex, BTED, which generates BH_3- and 9-BBN are stereoselective and lead only to *cis* diastereoisomers. The scheme 4 gives an interpretation to these reductions of isoflavanones with an anti-CRAM already proposed reduction scheme [40] (scheme 4).



3-Hydroboration-oxidation of 3-phenyl-4-hydroxy-coumarins

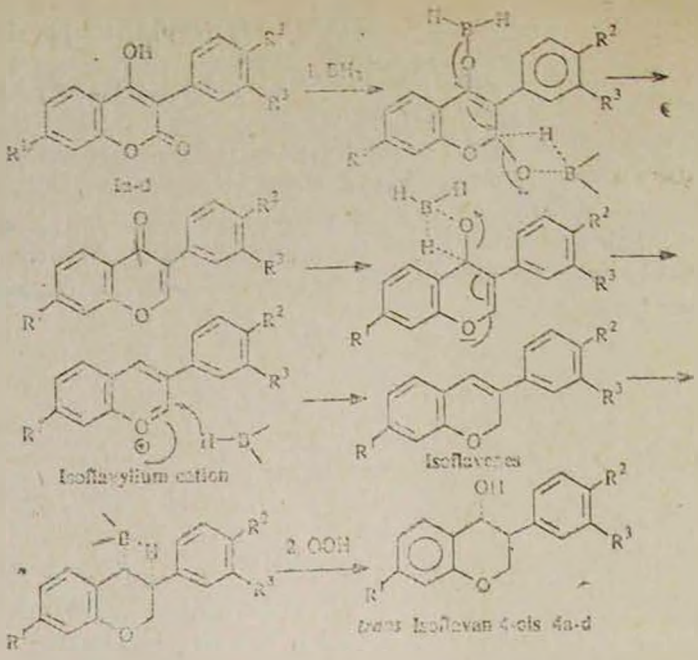
The hydroboration followed by alkaline hydroperoxide oxidation [22, 23] of coumarins and 4-hydroxycoumarins either substituted or not on positions 3 constitutes a previously developed general synthetic route [27—32] to the corresponding chroman-3-ols or 4-ols. It was therefore interesting to know the stereoselectivity of this reaction in the case of a set of substituted 3-phenyl-4-hydroxy-coumarins which are more easily available derivatives than isoflavan-4-ones [24—26]. Indeed, the application of this reaction to the 4-hydroxycoumarins 2a-d led to the corresponding expected isoflavanols and only the *trans*-diasterecisomers 4a-d were isolated (scheme 5).



This reaction is therefore a facile diastereoselective route to *trans*-isoflavan-4-ols.

The stereoselectivity of this reaction can be interpreted according to the scheme 6 with the formation of 3-phenyl-2H-1-benzopyran intermediate during the last step.

The steric hindrance brought by the 3-phenyl group is important and explains the stereoselectivity of the preparation of *trans*-isoflavan-4-ols.



Conclusion

This study leads to the following conceusions:

—the reduction of substituted isoflavan-4-ones by various nucleophilic hydrides shows the absence of stereoselectivity of these reactions. However the sterically hindered hydrides improve this stereoselectivity,

—the reduction of isoflavanones by electrophilic hydrides are always stereoselective and lead exclusively to the formation of the *cis*-diastereoisomers with excellent yields,

—finally, the hydroboration followed by oxidation of 3-phenyl-4-hydroxy-caumarins offers an excellent diastereoselective route to *trans*-isoflavan-4-ols.

Experimental

Infrared spectra are recorded on a Perkin—Elmer 117 spectrometer. The ^1H NMR spectra are recorded in $CDCl_3$ solutions on Varian T60 or Bruker AC200 spectrometers. Chemical shifts δ (ppm) are taken in comparison to TMS used as internal standard. Melting points are uncorrected.

The isoflavan-4-ones (3 phenyl-chroman-4-ones) are prepared according to described methods [42—43].

The determination of the percentages of the diastereoisomers is achieved by high pressure liquid chromatography (HPLC) using a Waters chromatograph, UV detection and a silica C18 grafted column.

The diastereoisomers were always separated by column chromatography over silica gel. Their structure was established by elemental analysis, Infrared and ^1H NMR spectroscopy.

The borane-THF complex and 9-bora-bicyclo-[3,3,1]-nonane (9-BBN) are commercially available from Aldrich. The bis-tert-butylthioethane diborane (BTED) is a gift from EXPANSIA.

For hydroborations all glass equipement is dryed at 100° in an oven prior to their use. Anhydrous tetrahydrofuran is obtained by distillation over benzophenone ketyl.

1. Reduction of isoflavan-4-ones (3-phenyl-chroman-4-ones) by nucleophilic hydrides

1.1. Reductions with sodium borohydride

**Isoflavan-4-ols cis 3a and trans 3b* (general method). In a 100 *ml* double necked round bottom flask provided by a magnetic stirring bar isoflavan-4-one (0,224 *g*, 1,0 *mmol*) is dissolved in a 10 *ml* of methanol-THF (8/2) mixture. To this solution sodium borohydride (0,076 *g*, 2,0 *mmol*) is added in small portions at room temperature under stirring (the progress of the reaction is monitored by TLC). After 3 hours 5 *ml* of cold water are added and the solvent evaporated. The residue is then extracted by Et_2O (3×50 *ml* portions). The etheral extracts are washed with water untill neutrality, dried over sodium sulfate, filtered and evaporated. The residue (0,226 *g*) is dissolved in acetonitrile (5 *ml*) and the percentage of *cis* and *trans*-diastereoisomers was determined by injection of 10 *µl* by HPLC. The remaining solution was evaporated and the residue was used for the separation of the diastereoisomers by column chromatography over silica gel (solvent chloroform-methanol : 9/1). Two compounds are separated for each reaction: (% yield for each diastereoisomer by HPLC, weight after separation by column chromatography, m. p.°, ^1H NMR spectroscopy).

Isoflavan-4-ol cis 3a: (42%, 0,92 *g*), 75°; (0,091 *g*); ^1H RMN: 1,85 (d, 1H, OH), 3,18 (sex, 1H, H-3), 4,35 (m, 2H, H-2), 4,6 (d, 1H, H-4, J 3,4=2.9 Hz), 6.9—7.6 (m, 9H, arom.) and

Isoflavan-4-ol trans 4a: (58%, 0,126 *g*), 98°, ^1H RMN: 1.97 (d, 1H, OH), 3.2 (sex, 1H, H-3), 4.32 (m, 2H, H-2), 4.92 (d, 1H, H-4, J 3.4=8.1 Hz), 6.85—7.5 (m, 9H, arom.).

The application of the general method to the other isoflavan-4-ones using the same molar ratio of reacting agents led to the following derivatives:

**7-Methoxy-Isoflavan-4-ol cis 3b*: (43%, 0.101 *g*) 144°, ^1H RMN: .7 (d, 1H, OH), 3.26 (sex, 1H, H-3), 3.79 (s, 3H, OCH_3), 4,46 (m, 2H, 1-2), 4.64 (d, 1H, H-4), J 3.4=3.0 Hz) 6.4—7.4 (m, 8H, arom.) and

7-Methoxy-Isoflavan-4-ol trans 4b: (56%, 0.137 *g*), 135°, ^1H RMN: .78 (d, 1H, OH), 3.09 (sex; 1H, H-3), 3.78 (s, 3H, OCH_3), 4.23 (m, H, H-2), 4.88 (d, 1H, H-4, J 3.4=7.4 Hz), 6.4—7.45 (m, 8H, arom.).

7,4'-Dimethoxy Isoflavan-4-ol cis 3c: (43%, 0.12 g), 144°, ^{1}H RMN: 1.83 (d, 1H, OH), 3.28 (sex, 1H, H-3), 3.80 (s, 6H, $(OCH_3)_2$, 4.47 (m, 2H, H-2), 4.60 (d, 1H, H-4, J 3,4=2.9 Hz), 6.5—7.45 (m, 7H, arom.) and

7,4'-Dimethoxy Isoflavan-4-ol trans 4c: (57%, 0.155 g), 123° ^{1}H RMN: 1.83 (d, 1H, OH), 3.28 (sex, 1H, H-3), 3.80 (s, 6H, $(OCH_3)_2$), 4.47 (m, 2H, H-2), 4.60 (d, 1H, H-4, J 3,4=2.9 Hz), 6.5—7.45 (m, 7H, arom.).

7,3',4'-trimethoxy-Isoflavan-4-ol cis 3d: (35%, 0.103 g), 130°, ^{1}H RMN: 1,68 (d, 1H, OH), 3.24 (sex, 1H, H-3), 3.85 (s, 9H, $(OCH_3)_3$), 4.45 (m, 2H, H-2). 4.62 (d, 1H, H-4; J 3,4=3,0 Hz), 6.4—7.3 (m, 6H, arom.) and

7,3',4'-trimethoxy-Isoflavan-4-ol trans 4d: F 150° (64% 0,202 g); ^{1}H RMN: 1,80 (d, 1H, OH), 3.17 (sex, 1H, H-3), 3.83 (s, 6H, $(OCH_3)_2$), 4.29 (m, 2H, H-2), 4.87 (d, 1H, H-4, J 3,4= 2,9Hz), 6.48—7.42 (m, 6H, arom.),

1.2. Reductions with Lithium aluminum tri-tert-butoxyhydride

**Isoflavan-4-ols cis 3a and trans 4a* (general method). In a 250 *ml* double necked round bottom flask, provided by a magnetic stirring bar and a calcium chloride drying tube, 3-phenyl-chroman-4-one (0.224 *g*, 1.0 *mmol*) is dissolved in dry THF (100 *ml*) and the solution cooled in an ice-water bath. A solution of lithium aluminum tri-tert-butoxyhydride (10 *ml*, 10 *mmol*) is added dropwise under stirring (1H). After the end of the reaction (controled by TLC), a 5% hydrochloric acid solution (10 *ml*) is added in small portions. The two phases are separated in a funnel and the aqueous layer extracted with Et_2O (3×50 *ml* portions). The mixed organic extracts are then washed with sat. aq. NaCl to neutrality and dried (Na_2SO_4), filtered and evaporated. The residue is treated by the usual manner by HPLC and column chromatography. Two diastereoisomers are separated: Isoflavan-4-ols *cis* (3-phenyl-chroman 4-ol) 3a (35%, 0.071 *g*) and Isoflavan-4-ol *trans* (3-phenyl-chroman-4-ol) 4a (66% 0.14 *g*).

The application of the general method to the other isoflavan-4-ones 2b, 2c and 2d using the same molar ratio of reacting agents led to the following derivatives:

*3-phenyl-7-methoxy-chroman-4-ol *cis* 3b (33% 0.08 *g*) and 3-phenyl-7-methoxy-chroman-4-ol *trans* 4b (67% 0.165 *g*);

*3-(4-methoxyphenyl)-7-methoxy-chroman-4-ol *cis* 3c: 144°; (34%, 0.09 *g*) 3-(4-methoxyphenyl)-7-methoxy-chroman-4-ol *trans* 4c: 123°; (66%, 0.179 *g*);

*3-(3,4-dimethoxyphenyl)-7-methoxy-chroman-4-ol *cis* 3d (32%, 0.90 *g*) and 3-(3,4-dimethoxyphenyl)-7 methoxy-chroman-4-ol *trans* 4d (68%, 0.191 *g*).

2. Reduction of isoflavan-4-ones (3-phenyl-chroman-4-ones) by electrophilic hydrides

2.1. Borane-tetrahydrofurane

**Izoflavan-4-ol cis 3a* (general method). To a nitrogen flushed 100 *ml* three necked round-bottom flask, fitted with a magnetic stirring bar and a reflux condenser topped with a connecting tube leading to a mercury bubbler, a borane-tetrahydrofuran solution (40 *ml*, 40 *mmol*) is added dropwise with a syringe via a septum ineet. ta a cooled solution (0—5°C) of 3-phenyl-chroman-4-one (0,5 *mmol*, 0.112 *g*) dissolved in dry THF (100 *ml*). The reaction is left to come to r. t. while stirring is continued till the end of the reaction (1H). The excess of hydride is destroyed by careful addition of cold water drops followed by a 5% aqueous hydrochloric acid (10 *ml*).

The two phases are separated in a funnel and the aqueous layer extracted with Et_2O (3 × 50 *ml* portions).

The mixed organic extracts are then washed with sat. aq. NaCl to neutrality and dried (Na_2SO_4), filtered and evaporated. The remaining product is pure 3-phenyl-chroman-4-ol *cis* 3a: yield 0,106 *g* (98%).

The application of the general method to the other isoflavan-4-ones 1b, 1c and 1d using the same molar ratio of reacting agents led to the following derivatives:

*7-methoxy-3-phenyl-chroman 4-ols *cis* 3b 0,129 *g* (100%);

*3-(4-methoxyphenyl)-7-methoxy-chroman-4-ol *cis* 3c, 0,142 *g* (97%);

*3-(3,4-dimethoxyphenyl)-7-methoxy-chroman-4-ol *cis* 3d, 0,132 *g* (98%).

2.2. Bis-tert-butylthioethane diborane (BTED)

**7-methoxy-isoflavan-4-ol cis 3b* (general method). To a nitrogen flushed 100 *ml* three necked round-bottom flask, fitted with a magnetic stirring bar and a reflux condenser topped with a connecting tube leading to a mercury bubbler, 7-methoxy-isoflavan-4-one (0.254 *g*, 1,0 *mmol*) is dissolved in anhydrous THF (10) *ml*) and the mixture cooled (0—5°). Bis-tert-butylthio-ethane diborane (0,154 *g*, 0.658 *mmol*) is added in small portions. The reaction is left to come to r. t., while stirring is continued till the end of the reaction (8H). The excess of hydride is destroyed by careful addition of cold water drops followed by a 5% aqueous hydrochloric acid (10 *ml*).

The two phases are separated in funnel and the aqueous layer extracted with Et_2O (3 × 50 *ml* portions).

The mixed organic extracts are then washed with sat. aq. NaCl to neutrality and dried (Na_2SO_4), filtered and evaporated. The remaining product is pure 7-methoxy-3-phenyl-chroman-4-ol *cis* 3b.

The application of the general method to the other isoflavan-4-ones 1b, 1c and 1d using the same molar ratio of reacting agents led to the following *cis* derivatives:

Isoflavan-4-ols *cis* 3a, 7,4′-dimethoxy-isoflavan-4-ol *cis* 3c and 3-(3,4-dimethoxyphenyl)-7-methoxy-chroman-4-ol *cis*, (7,3,4′-trimetoxy-isoflavan-4-ol *cis* (7,3,4′-trimethoxy-isoflavan-4-ol *cis*) 3d, with yields up to 97—98%.

2.3. 9-Bora-bicyclo-[3,3,1]-nonane (9-BBN)

These reactions were performed according to a standard procedure (44). The yields in *cis* isoflavanols are also within the range of 95—96%.

3. Hydroboration of 3-phenyl-4-hydroxy-coumarins 2a-d

**Isoflavan--4-ol trans 4a* (general method). To a nitrogen flushed 250 *ml* double necked round-bottom flask, fitted with a magnetic stirring bar and a reflux condenser topped with a connecting tube leading to a mercury bubbler 3-phenyl-4-hydroxy-coumarine 2a (38 *g*, 10.0 *mmol*) is dissolved in anhydrous THF (100 *ml*) and the mixture cooled (0—5°). A borane—THF solution (36.6 *ml*, 44 *mmol*) is added dropwise, with a syringe via a septum inlet. The reaction is heated overnight (35°) while stirring is continued. The next day, the reaction mixture is cooled (0—5°) and the excess of hydride is destroyed by careful addition of cold water drops. The oxidation is performed by the slow addition of a 10% sodium hydroxide solution (24 *ml*) and of a 10% hydrogen peroxide solution (24 *ml*). The stirring is continued during (2H) after which the mixture is saturated by addition of potassium carbonate. The organic phase is separated and the aqueous phase extracted with Et_2O (4 × 50 *ml* portions). The mixed organic extracts are then washed with sat aq. NaCl to neutrality and dried (Na_2SO_4), filtered and evaporated. The remaining product is purified by column chromatography over silica gel and gave Isoflavanol *trans* 4a, 1.11 *g* (54%), mp: 98° (benzene—hexane).

The application of the general method to the other 3-phenyl-4-hydroxy-coumarins 2b, 2c and 2d using the same reaction conditions and molar ratios of reacting agents led to the following *trans* derivatives:

7-methoxy-isoflavan-4-ol *trans* 5a, 1.33 *g* (52%), m. p. 135 (benzene-hexane).

7,4′-dimethoxy-Isoflavan-4-ol *trans* 4c, 1.60 *g* (56%), m. p. 129—131 (benzene-hexane).

7,3′,4′-trimethoxy-isoflavan-4-ol *trans* 4d, 1.32 *g* (42%), m. p. 150—152 (benzene-hexane).

ԻԶՈՖԼԱՎԱՆ-4-ՕԼԵՐԻ (3-ՖԵՆԻԼԽՈՐՄԱՆ-4-ՕԼԵՐԻ) ՍՏԱՑՄԱՆ ՏԱՐԲԵՐ ԵՂԱՆԱԿՆԵՐԻ ԴԻԱՍՏԵՐԵՈԸՆՏՐՈՂԱԿԱՆՈՒԹՅՈՒՆԸ

ՀԵՆՐԻ ՁԻՊԱՆ և Բ. ՍԵՐԹ ԿԻԲՈՒԱՇԱՐՅԱՆ

Իզոֆլավան-4-օլերի (3-ֆենիլխորման-4-օլերի) վիրակաղնումը նատրիումի հիդրիդներով (նատրիումի բորհիդրիդ, լիթիում-ալյումինիում հա-

երրորդային-բուտոքսիհիդրիդ, լիթիումի նա-երկրորդային բուտիլբորհիդրիդ) բերում է իզոֆլավաններ-4-օլերի ցիս- և տրանս-դիաստերեոիզոմերների խառնուրդի առաջացմանը: Նրանց վերականգնումը էլեկտրոֆիլ հիդրիդներով (բորան-տետրահիդրոֆուրան, բիս-երրորդային բուտիլէթիլդիբորան կամ 9-բորաբիցիկլո [3,3,1] նոնան) տարածականորեն ընտրողական է և բարձր ելքերով բերում է ցիս-դիաստերեոիզոմերների առաջացմանը: 3-ֆենիլ-4-օքսիկումարինների հիդրոբորացումը և դրան հաջորդող հիմնային հիդրոպերօքսիդներով օքսիդացումը նույնպես դիաստերեոսիզոմեր-իզոֆլավան-4-օլների տարածընտրողական ստացման եղանակ է:

ДИАСТЕРЕОИЗБИРАТЕЛЬНОСТЬ РАЗЛИЧНЫХ СПОСОБОВ ПОЛУЧЕНИЯ ИЗОФЛАВАН-4-ОЛОВ (3-ФЕНИЛХРОМАН-4-ОЛОВ)

ГЕНРИ ЧИДИАК и Б. СЕРЖ КИРКИАШАРЯН

Восстановление изофлаван-4-олов-(3-фенилхроман-4-олов) нуклеофильными гидридами (натрия боргидрид, литий-алюминий-тритрет-бутоксигидрид, литий три-вторич.-бутилборгидрид) приводит к смеси цис- и транс-диастереоизомеров изофлаван-4-олов. Их восстановление электрофильными гидридами (боран—ТГФ, бис-трет-бутилоэтан диборан или 9-борабицикло[3,3,1]нонан) стереоизбирательно и приводит к образованию цис-диастереоизомеров с хорошими выходами.

Гидроборирование с последующим окислением щелочной гидроокисью 3-фенил-4-оксикумаринов также является стереоселективным методом синтеза диастереоизомеров изофлаван-4-олов.

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