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Diastereoselective addition of alkenylchromium(III) reagents to Garner's aldehyde. The Nozaki–Hiyama–Kishi coupling approach to sphingosines and ceramides

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Abstract: Intermolecular Nozaki–Hiyama–Kishi coupling between alkenylchromium(III) reagents, derived from either (*E*)-(2-bromoethenyl)benzene or (*E*)-1-iodo-1-pentadecene, and the conformationally rigid Garner's aldehyde resulted in the stereoselective formation of Felkin-type allylic alcohols in good yields, thus providing an easy access to sphingosines. In addition, when the protecting group in the Garner's aldehyde was changed (from Boc to *N*-octanoyl), a reversal of stereoselectivity was observed in the reaction with (*E*)--1-pentadecenylchromium(III), probably as the result of hydrophobic interactions between the long carbon chains of the reaction partners.

Keywords: Nozaki–Hiyama–Kishi reaction; sphingosine; Garner's aldehyde; organochromium reagent.

INTRODUCTION

Nozaki–Hiyama–Kishi (NHK) coupling is a versatile carbon–carbon bond forming reaction that involves nucleophilic addition of organochromium(III) species to carbonyl compounds under very mild conditions.[1,2] The NHK reaction showed good tolerance to a range of functional groups in both reaction partners. The great synthetic potential of the nickel-catalyzed addition of alkenylchromium reagents to aldehydes was demonstrated in the syntheses of various natural products,[3] including palytoxin,[4] halichondrin,[5] epothilone B and D,[6] pestalotiopsin A[7] and abyssomicin C.[8]

As alkenylchromium species are less basic than other organometallic reagents, their addition to chiral aldehydes proceed without epimerization at the α carbon atom.[2c] While the stereochemical outcome of intermolecular NHK reactions was thoroughly investigated with allylchromium species,[2,9] less attention has been paid to the stereoselectivity of the addition of alkenylchromium nuc-

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leophiles. Intermolecular additions, as well as intramolecular reactions on conformationally more flexible substrates, often result in mixtures of diastereoisomers, sometimes even with a complete lack of diastereoselectivity.[8,10]

Garner's aldehyde (*tert*-butyl (4*S*)-4-formyl-2,2-dimethyloxazolidine-3-carboxylate) (**1**)[11] is a conformationally restricted *α*-nitrogen-substituted aldehyde, which represents a good substrate for probing the stereochemical outcome of alkenylchromium(III) addition. Nucleophilic additions of various organometallic species to Garner's aldehyde (**1**) are well studied.[12,13] Curiously, there is no report on alkenylchromium addition, although the addition of vinyl metals to Garner's aldehyde (**1**) represents a straightforward entry to sphingosines and ceramides (Fig. 1),[13c,d] sphingolipid key metabolites.[14] These compounds constitute a novel family of lipid second messengers[15] that play important roles in cell regulation and apoptosis,[16] as well as in higher-order physiological processes.[17]

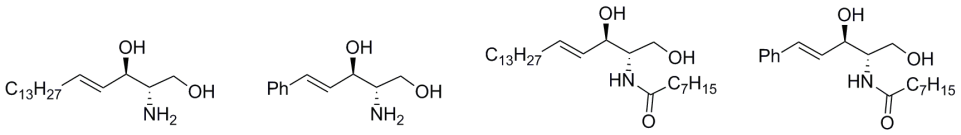


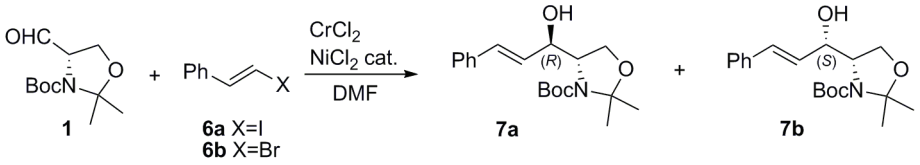
Fig. 1. Biologically important sphingosines and ceramides.

RESULTS AND DISCUSSION

Before exploring the diastereoselectivity of the addition of (*E*)-styrylchromium(III) to Garner's aldehyde (**1**),[18] the focus was initially directed to optimizing the reaction conditions. Attempts to use (*E*)-(2-iodoethenyl)benzene (**6a**) as a precursor of alkenylchromium(III) species had limited success, as the coupling products **7a** and **7b** were isolated in only 20 % yield (Scheme 1, Entry 1). However, the yield was improved by using (*E*)-(2-bromoethenyl)benzene (**6b**) as an (*E*)-styrylchromium(III) precursor (Scheme 1, Entry 2). Additionally, the reaction yield was shown to be highly dependent on chromium(II) concentration (Scheme 1, Entries 3 and 4) and tenfold excess of $CrCl_2$ was found to be the optimal loading. It is well known that, in practice, the NHK reaction requires the use of a large excess of $CrCl_2$.[2a]

Based on the available literature data,[19] it was anticipated that the stereochemistry of the addition would be in accordance with the non-chelated Felkin–Ahn Model (re-attack), thus favoring the formation of the *anti* product, due to the pronounced voluminosity of the *tert*-butoxycarbonyl group. Indeed, when performed at room temperature, the reaction stereoselectively provided allylic alcohol **7a** (*anti*:*syn* = 5:1).[20] This selectivity could be improved to 8.5:1 by performing the reaction at 0 °C, albeit with a drop in the reaction yield (Scheme 1,

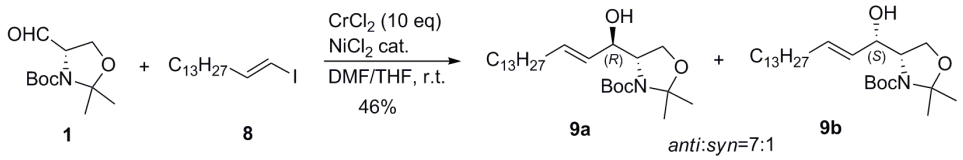
Entry 5). The observed diastereoselectivity of the addition of (*E*)-styrylchromium(III) to Garner's aldehyde (**1**) was significantly higher than expected for an intermolecular NHK reaction (usually up to 3:1).[2c]



Entry	X	$CrCl_2$ eq.	Temp.	Yield **7a**,**b** %	dr(**7a** : **7b**)
1	I	4	r.t.	20	5 : 1
2	Br	4	r.t.	32	-
3	Br	6	r.t.	56	-
4	Br	10	r.t.	69	5 : 1
5	Br	10	0 °C	22	8.5 : 1

Scheme 1. Addition of (*E*)-styrylchromium(III) to Garner's aldehyde (**1**).

Next, attention was turned toward the most abundant sphingosine **2** in nature, which could be obtained through the addition of (*E*)-1-iodo-1-pentadecene (**8**)[21] to Garner's aldehyde (**1**, Scheme 2). With the previously optimized chromium(II) loading, N,O-protected sphingosines **9a** and **9b** were obtained with an even higher diastereoselectivity (*anti*:*syn* = 7:1).[20,22] Although the yield of this product was moderate (46 %), the straightforwardness of the NHK approach, coupled with its experimental simplicity, qualified it for synthetic application.

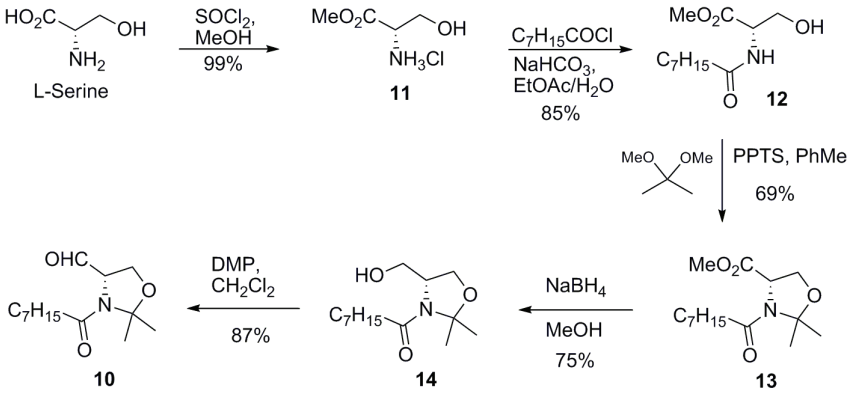


Scheme 2. Addition of (*E*)-1-pentadecenylchromium(III) to Garner's aldehyde (**1**).

Diastereoselectivity in the addition of (*E*)-1-pentadecenylchromium(III) to Garner's aldehyde (**1**) was somewhat higher, as compared to other approaches to sphingosines based on the addition of other vinylmetals (Li, Mg, Zn, Al; *anti*:*syn* ratio from 5:1 to 1:6).[19,23] Fürstner *et al*. showed that rhodium-catalyzed addition of 1-octenylboronic acid to Garner's aldehyde proceeded with a moderate diastereoselectivity (4:1).[13a] The diastereoselectivity in the addition of 1-(*E*)-alkenylzirconocene-zinc reagents, according to Murakami *et al*., is superior to other alkenylmetals (*anti*:*syn* ratio from 20:1 to 1:15). However in this method, different additives were required ($ZnBr_2$ for *syn*; Et_2Zn for *anti*).[13c]

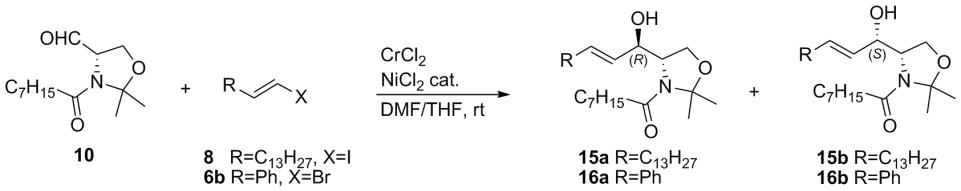
Due to sensitivity of *N*-Boc-*N*,*O*-acetal moiety, aldehyde **10** (Scheme 3) was subjected to further research, by supstituing the octanoyl group for Boc. This

substrate is also expected to be conformationally restricted and, additionally, it would allow for a direct synthesis of protected ceramides. Aldehyde **10** was prepared from L-serine, according to Scheme 3. L-Serine was transformed into its methyl ester **11**,[24] which was then acylated with octanoyl chloride, and the resulting amide **12** was protected as *N*,*O*-acetal.[25] After subsequent reduction of ester moiety in **13**, aldehyde **10** was finally obtained by the oxidation of the intermediary alcohol **14** with Dess–Martin periodinane (DMP).



Scheme 3. Synthesis of aldehyde **10** from L-serine.

First, the reaction of the optically pure aldehyde **10** with (*E*)-1-pentadecenylchromium(III) (Scheme 4, Entry 1) was examined. This time, unfortunately, neither the yield (18 %) nor the diastereoselectivity (*anti*:*syn* = 1:2)[26] reached synthetically useful levels.



Entry	X	R	$CrCl_2$ eq.	Yield **15a,b** %	Yield **16a,b** %
1	I	$C_{13}H_{27}$	12	18	-
2	Br	Ph	7	-	55
3	Br	Ph	12	-	75

Scheme 4. Addition of alkenylchromium(III) to aldehyde **10**.

It is interesting to note that this reaction proceeded with a reversal of diastereoselectivity, with the predominant formation of the *syn*-product. The anti-Felkin stereochemical outcome could be the result of a stabilizing hydrophobic

interaction between the two long, aliphatic chains of the reaction partners. Due to this interaction, favored in polar media, alkenylchromium(III) species attack the carbonyl group from the opposite, *si*-face (Fig. 2).

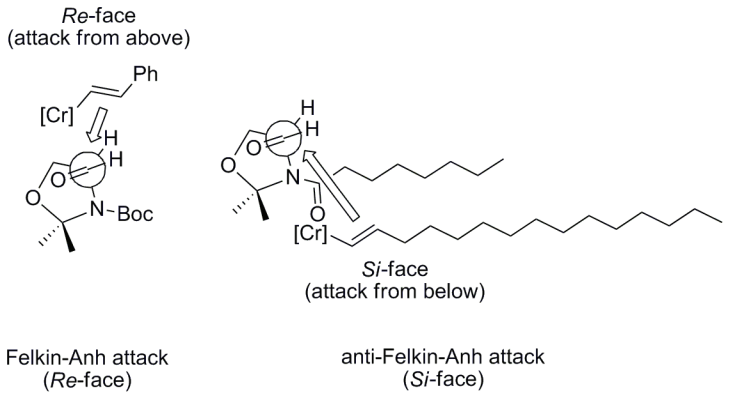
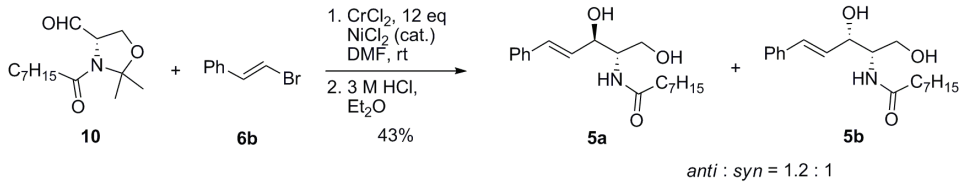


Fig. 2. *si*-Attack of (*E*)-1-pentadecenylchromium(III) on **10**, which is favored by hydrophobic interactions.

However, the treatment of aldehyde **10** with (*E*)-styrylchromium(III), prepared *in situ* from (*E*)-(2-bromoethenyl)benzene (**6b**), resulted in a smooth conversion, affording the desired products **16a** and **16b** in a good yield (Scheme 4, Entries 2 and 3). Contrary to the ^{1}H-NMR spectra of the diastereomeric mixtures **7a** and **b** or **9a** and **b**, it was difficult to determine directly the diastereomeric ratio (dr) of **16a** and **b** from the ^{1}H-NMR spectrum, as it consisted of broad and overlapping signals of rotamers, even at a higher temperature (60 °C). Therefore, it was decided to modify the work-up procedure by *in situ* hydrolysis, consequently leading to the formation of ceramides from aldehyde **10** in a single step (Scheme 5). Once the reaction was completed, the reaction mixture was treated with hydrochloric acid instead of sodium serinate,[25] and the thus-obtained free ceramides **5a** and 5**b** were analyzed by ^{1}H-NMR. Surprisingly, the ^{1}H-NMR analysis showed that the addition proceeded with almost complete lack of diastereoselectivity (*anti*:*syn* = 1.2:1), possibly as a result of the smaller steric hindrance of the *n*-octanoyl group, as compared to that of the *tert*-butoxycarbonyl group.



Scheme 5. Direct synthesis of ceramides **5a** and **5b** from aldehyde **10**.

EXPERIMENTAL

General experimental

All chromatographic separations[26] were performed on Silica 10–18, 60 Å, ICN Biomedicals, using petroleum ether (b. p. 65–70 °C). Standard techniques were used for the purification of the reagents and solvents.[27] The NMR spectra were recorded on a Bruker Avance III 500 (^{1}H-NMR at 500 MHz, ^{13}C-NMR at 125 MHz). The chemical shifts are expressed in ppm (δ) using tetramethylsilane as an internal standard, coupling constants (J) are in Hz. The IR spectra were recorded on a Nicolet 6700 FT instrument, and are expressed in cm^{-1}. The mass spectra were obtained on Agilent technologies 6210 TOF LC/MS instrument (LC: series 1200). The optical rotations were measured on Rudolph Research Analytical AUTOPOL IV automatic polarimeter.

Nozaki–Hiyama–Kishi couplings

*Addition of (*E*)-styrylchromium(III) to Garner's aldehyde **1***. Commercial chromium(II) chloride (113 mg; 0.924 mmol; 10 eq; 99.9 % purity) and anhydrous nickel(II) chloride (0.6 mg; 5 mol %) were suspended in freshly distilled and degassed dry DMF (0.4 mL), in a glovebox, under an argon atmosphere. A solution of **1** (21 mg; 0.0924 mmol) and **6b** (50 mg; 0.277 mmol; 3 eq) in DMF (0.4 mL) was added dropwise to the suspension, and the mixture was stirred at room temperature for 1 h. The reaction mixture was treated with 1 M sodium serinate (3 mL) and diethyl ether (10 mL) and vigorous stirring was continued for 1 h. The layers were separated, the aqueous layer was extracted with diethyl ether (2×10 mL), and the combined organic extract was washed with brine (2×5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (eluent, petroleum ether:ethyl acetate:triethylamine = 80:20:1) afforded 21 mg (69 %) of mixture of allylic alcohols **7a** and **7b** (**7a**:**7b** = 5:1), as a colorless oil. The diastereoisomeric ratio was determined by integrating signals in ^{1}H-NMR spectrum (500 MHz, C_6D_6 at 60 °C, δ / ppm): δ (isomer **7a**) = 6.74 (1H, *d*, J = 16.0 Hz); δ (isomer **7b**) = 6.62 (1H, *d*, J = 15.5 Hz). The spectroscopic data were fully consistent with those previously reported.[13c]

*Addition of (*E*)-1-pentadecenylchromium(III) to Garner's aldehyde (**1**)*. Commercial chromium(II) chloride (80 mg; 0.654 mmol; 10 eq; 99.9 % purity) and anhydrous nickel(II) chloride (0.4 mg; 5 mol %) were suspended in freshly distilled and degassed dry DMF (0.4 mL), in a glovebox, under an argon atmosphere. A solution of **1** (15.0 mg; 0.0654 mmol) and **8** (66 mg; 0.196 mmol; 3 eq) in DMF/THF (V/V = 1/1; 0.4 mL) was added dropwise to the suspension, and the mixture was stirred at room temperature for 1 h. The reaction mixture was treated with 1 M sodium serinate (3 mL) and diethyl ether (10 mL) and vigorous stirring was continued for 1 h. The layers were separated, the aqueous layer was extracted with diethyl ether (2×10 mL), and the combined organic extract was washed with brine (2×5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (eluent, petroleum ether:ethyl acetate:triethylamine = 90:10:1) afforded 13.3 mg (46 %) of a mixture of allylic alcohols **9a** and 9**b** (**9a**:**9b** = 7:1), as a colorless oil. The diastereoisomeric ratio was determined by integrating signals in the ^{1}H-NMR spectrum (500 MHz, C_6D_6 at 60 °C, δ / ppm): δ (isomer **9a**) = 5.79 (1H, *dt*, J = 6.5 and 15.5 Hz); δ (isomer **9b**) = 5.71 (1H, *dt*, J = 6.5 and 15.5 Hz). The spectroscopic data were fully consistent with those previously reported.[13c,19a]

*Addition of (*E*)-1-pentadecenylchromium(III) to aldehyde **10***. Commercial chromium(II) chloride (122 mg; 0.993 mmol; 12 eq; 99.9 % purity) and anhydrous nickel(II) chloride (0.5 mg; 5 mol %) were suspended in freshly distilled and degassed dry DMF (0.5 mL), in a

glovebox, under an argon atmosphere. A solution of **10** (21.0 mg; 0.0827 mmol) and **8** (83 mg; 0.248 mmol) in DMF/THF (*V*/*V* = 1/1; 0.6 mL) was added dropwise to the suspension, and the mixture was stirred at room temperature for 1 h. The reaction mixture was treated with 1 M sodium serinate (2.1 mL) and diethyl ether (10 mL) and vigorous stirring was continued for 1 h. The layers were separated, the aqueous layer was extracted with diethyl ether (2×10 mL), and the combined organic extract was washed with brine (2×5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (eluent, petroleum ether:ethyl acetate:triethylamine = 90:10:1) afforded 7.1 mg (18 %) of a mixture of allylic alcohols **15a** and **15b**, as a colorless oil.

The thus-obtained alcohols **15a** and **15b** (7.1 mg; 0.0152 mmol) were dissolved in 70 % acetic acid (0.5 mL) and the mixture was stirred overnight. The mixture was diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (eluent, petroleum ether:ethyl acetate = 1:4) afforded 4.8 mg (73 %) of mixture of allylic alcohols **4a** and **4b** (**4a**:**4b** = 1:2), as a white wax. The diastereoisomeric ratio was determined by integrating signals in the ^{1}H--NMR spectrum (500 MHz, $CDCl_3$, δ / ppm): δ (isomer **4a**) = 6.26 (1H, *d*, *J* = 7.5 Hz); δ (isomer **4b**) = 6.13 (1H, *d*, *J* = 8.0 Hz). The spectroscopic data were fully consistent with those previously reported.[30]

*Addition of (*E*)-styrylchromium(III) to aldehyde **10***. Commercial chromium(II) chloride (173 mg; 1.41 mmol; 12 eq; 99.9 % purity) and anhydrous nickel(II) chloride (0.7 mg; 5 mol %) were suspended in freshly distilled and degassed dry DMF (0.8 mL), in a glovebox, under an argon atmosphere. A solution of **10** (30 mg; 0.117 mmol) and **6b** (64 mg; 0.352 mmol; 3 eq) in DMF (0.4 mL) was added dropwise to the suspension, and the mixture was stirred at room temperature for 1 h. Hydrochloric acid (3 M; 0.6 mL) was added to the reaction mixture and stirring was continued for 1 h, before the resulting mixture was diluted with ethyl acetate, and the layers were separated. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (eluent, petroleum ether:ethyl acetate = 1:2) afforded 16.3 mg (43 %) of a mixture of allylic alcohols **5a** and **5b** (**5a**:**5b** = 1.2:1), as a white wax. The diastereo-isomeric ratio was determined by integrating signals in the ^{1}H-NMR spectrum (500 MHz, $CDCl_3$, δ / ppm): δ (isomer **5a**) = 6.48 (1H, *d*, *J* = 8.0 Hz); δ (isomer **5b**) = 6.34 (1H, *d*, *J* = 8.0 Hz). The spectroscopic data were fully consistent with those previously reported.[31]

*Preparation of aldehyde **10***

*Synthesis of (*S*)-methyl 3-hydroxy-2-octanamidopropanoate (**12**)*. To a cold solution (–15 °C) of L-serine (1.0 g, 9.6 mmol) in anhydrous methanol (20 mL), thionyl chloride (1.37 g, 11.52 mmol) was added slowly using a syringe. The solution was stirred at –15 °C for 30 min and then at room temperature overnight. The reaction mixture was concentrated under reduced pressure to afford 1.47 g (99 %) of crude L-serine methyl ester hydrochloride (**11**), as a white powder, which was further used without purification.

L-Serine methyl ester hydrochloride (**11**, 1.47 g, 8.75 mmol) was added to a solution of sodium bicarbonate (1.08 g, 17.49 mmol) in water (27 mL), followed by the addition of ethyl acetate (27 mL). Octanoyl chloride (1.78 g, 10.94 mmol) was added to the vigorously stirred reaction mixture and stirring was continued for 1 h. The reaction mixture was extracted with ethyl acetate (3×20 mL) and the combined organic extract was washed with brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by dry-flash chromatography (eluent, petroleum ether:ethyl acetate = 1:1), to afford 1.81 g (85 %) of **12** as a colorless, viscous oil.

*Synthesis of (*S*)-methyl 2,2-dimethyl-3-octanoyloxazolidine-4-carboxylate (**13**)*. A solution of 2,2-dimethoxypropane (8.9 g; 85.7 mmol), pyridinium *p*-toluenesulfonate (122 mg; 0.48 mmol) and the amide alcohol **12** (660 mg; 2.69 mmol) in toluene (11 mL) was heated at 90 °C for 20 h. The reaction mixture was diluted with dichloromethane, washed with saturated $NaHCO_3$ and water. The organic extract was dried over anh. $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by dry-flash chromatography (eluent, petroleum ether:ethyl acetate = 85:15) afforded 530 mg (69 %) of compound **13**, as a colorless oil.

*Synthesis of (*R*)-1-(4-(hydroxymethyl)-2,2-dimethyloxazolidin-3-yl)-1-octanone (**14**)*. A solution of **13** (720 mg; 2.52 mmol) in methanol (5 mL) was treated with sodium borohydride (429 mg; 11.34 mmol) for 1 h at room temperature. The reaction was quenched with saturated NH_4Cl and the resulting mixture was stirred for 5 min. After dilution with water, the reaction mixture was extracted twice with dichloromethane and the extract was dried over anh. $MgSO_4$. Concentration under reduced pressure, followed by purification of the residue by dry-flash chromatography (eluent, petroleum ether:ethyl acetate = 1:1) gave alcohol **14** (490 mg; 75%), as a colorless, viscous oil.

*Synthesis of (*S*)-2,2-dimethyl-3-octanoyloxazolidine-4-carboxaldehyde (**10**)*. Dess–Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one, 372 mg; 0.87 mmol) was added to a solution of alcohol **14** (30 mg; 0.19 mmol) in dichloromethane (3 mL) and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was diluted with dichloromethane and washed with 10% $Na_2S_2O_3$ and saturated $NaHCO_3$. The organic extract was dried over anh. $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by dry-flash chromatography (eluent, petroleum ether:ethyl acetate = 1:1) afforded 26 mg (87 %) of the title compound, as a colorless oil.

The physical and spectral data for aldehyde **10** and the isolated intermediates in its preparation **12**–**14** are given in the Supplementary material to this paper.

CONCLUSIONS

In conclusion, it was shown that alkenylchromium(III) species add to conformationally rigid Garner's aldehyde (**1**) in a stereoselective manner. The predominant formation of Felkin-type products is in accordance with non-chelation control in the transition state. In addition, it was shown that a nonpolar interaction between two long, aliphatic chains of the reaction partners may play an important role in diastereofacial selectivity, thus favoring the formation of the anti-Felkin product. Therefore, Nozaki–Hiyama–Kishi reaction with Garner's aldehyde (**1**) offers an alternative synthetic route toward sphingosines. This coupling approach also allows for a direct, but non-stereoselective preparation of aromatic ceramide analogue **5**, in a good yield.

SUPPLEMENTARY MATERIAL

The physical and spectral data for aldehyde **10** and the isolated intermediates **12**–**14** are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

ДИЈАСТЕРЕОСЕЛЕКТИВНЕ АДИЦИЈЕ АЛКЕНИЛХРОМ(III) РЕАГЕНАСА НА ГАРНЕРОВ АЛДЕХИД. СИНТЕЗА СФИНГОЗИНА И ЦЕРАМИДА НОЗАКИ–ХИЈАМА–КИШИЈЕВИМ КУПЛОВАЊЕМ

ЗОРАНА ФЕРЈАНЧИЋ[1], РАДОМИР МАТОВИЋ[2] и ФИЛИП БИХЕЛОВИЋ[1]

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У интермолекулском Нозаки–Хијама–Кишијевом куповању алкенилхром(III) реагенаса, изведених из (*E*)-2-бромстирена или (*E*)-1-јод-1-пентадецена, и конформационо ригидног Гарнеровог (*Garner*) алдехида стереоселективно се добијају алилни алкохоли Фелкиновог (*Felkin*) типа у добрим приносима, што омогућује лак приступ сфингозинима. Такође, промена заштитне групе у Гарнеровом алдехиду (из *терц*-бутоксикарбонил- у октаноил-), резултује обрнутом дијастереоселективношћу у случају (*E*)-1-пентадеценилхрома(III), вероватно као последица хидрофобних интеракција између дугих угљоводоничних ланаца реакционих партнера.

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REFERENCES

1. a) Y. Okude, S. Hirano, T. Hiyama, H. Nozaki, *J. Am. Chem. Soc.* **99** (1977) 3179; b) T. Hiyama, K. Kimura, H. Nozaki, *Tetrahedron Lett.* **22** (1981) 1037; c) T. Hiyama, Y. Okude, K. Kimura, H. Nozaki, *Bull. Chem. Soc. Jpn.* **55** (1982) 561; d) K. Takai, K. Kimura, T. Kuroda, T. Hiyama, H. Nozaki, *Tetrahedron Lett.* **24** (1983) 5281
2. For recent reviews on Cr-mediated reactions, see: a) A. Fürstner, *Chem. Rev*. **99** (1999) 991; b) L. A. Wessjohann, G. Scheid, *Synthesis* (1999) 1; c) K. Takai, *Org. React.* **64** (2004) 253 and references cited therein
3. For review on the application of the Nozaki–Hiyama–Kishi reaction in the syntheses of complex natural products see: E. M. Daly, R. E. Taylor, *Chemtracts* **20** (2007) 1
4. R. W. Armstrong, J.-M. Beau, S. H. Cheon, W. J. Christ, H. Fujioka, W.-H. Ham, L. D. Hawkins, H. Jin, S. H. Kang, Y. Kishi, M. J. Martinelli, W. W. McWhorter, M. Mizuno, M. Nakata, A. E. Stutz, F. X. Talamas, M. Taniguchi, J. A. Tino, K. Ueda, J.-I. Uenishi, J. B. White, M. Yonaga, *J. Am. Chem. Soc.* **111** (1989) 7525
5. T. D. Aicher, K. R. Buszek, F. G. Fang, C. J. Forsyth, S. H. Jung, Y. Kishi, M. C. Matelich, P. M. Scola, D. M. Spero, S. K. Yoon, *J. Am. Chem. Soc*. **114** (1992) 3162
6. R. E. Taylor, Y. Chen, *Org. Lett.* **3** (2001) 2221
7. a) K.-I. Takao, N. Hayakawa, R. Yamada, T. Yamaguchi, U. Morita, S. Kawasaki, K.-I. Tadano, *Angew. Chem. Int. Ed.* **47** (2008) 3426; b) T. M. Baker, D. J. Edmonds, D. Hamilton, C. J. O'Brien, D. J. Procter, *Angew. Chem. Int. Ed.* **47** (2008) 5631
8. F. Bihelovic, R.N. Saicic, *Angew. Chem. Int. Ed.* **51** (2012) 5687
9. a) M. D. Lewis, Y. Kishi, *Tetrahedron Lett.* **23** (1982) 2343; b) J. Mulzer, T. Schulze, A. Strecker, W. Denzer, *J. Org. Chem.* **53** (1988) 4098; c) Y. Aoyagi, H. Inaba, Y. Hiraiwa, A. Kuroda, A. Ohta, *J. Chem. Soc., Perkin Trans. 1* (1998) 3975; d) T. Nagamitsu, T. Sunazuka, H. Tanaka, S. Omura, P. A. Sprengeler, A. B. Smith, *J. Am. Chem. Soc.* **118** (1996) 3584; e) P. Ciapetti, M. Falorni, M. Taddei, *Tetrahedron* **52** (1996) 7379; f) W. R. Roush, D. S. Coffey, D. Madar, A. D. Palkowitz, *J. Braz. Chem. Soc*. **7** (1996) 327
10. a) E. Piers, A. M. Kaller, *Tetrahedron Lett.* **37** (1996) 5857; b) A. Lubineau, I. Billault, *J. Org. Chem.* **63** (1998) 5668; c) K. M. Foote, M. John, G. Pattenden, *Synlett* (2002) 365

11. a) P. Garner, *Tetrahedron Lett.* **25** (1984) 5855; b) P. Garner, J. M. Park, *J. Org. Chem.* **52** (1987) 2361; c) P. Garner, J. M. Park, *Org. Synth.* **70** (1991) 18
12. For review article on the Garner's aldehyde, see: X. Liang, J. Andersch, M. Bols, *J. Chem. Soc., Perkin Trans. 1* (2001) 2136
13. a) A. Fürstner, H. Krause, *Adv. Synth. Catal.* **343** (2001) 343; b) K. Sa-Ei, J. Montgomery, *Tetrahedron* **65** (2009) 6707; c) T. Murakami, K. Furusawa, *Tetrahedron* **58** (2002) 9257; d) T. Murakami, R. Hirono, K. Furusawa, *Tetrahedron* **61** (2005) 9233
14. For recent review on the syntheses of sphingosines, see: J. A. Morales-Serna, J. Llaveria, Y. Diaz, M. I. Matheu, S. Castillón, *Curr. Org. Chem.* **14** (2010) 2483
15. a) Y. A. Hannun, *Science* **274** (1996) 1855; b) Y. A. Hannun, *Sphingolipid-Mediated Signal Transduction*, Chapman and Hall, New York, 1997
16. a) Y. A. Hannun, L. M. Obeid, *Trends Biochem. Sci.* **20** (1995) 73; b) S. Mathias, L. A. Pena, R. N. Kolesnick, *Biochem. J.* **335** (1998) 465; c) H. Birbes, S. E. Bawab, L. M. Obeid, Y. A. Hannun, *Adv. Enzyme Regul.* **42** (2002) 113
17. a) M. El Alwani, B. X. Wu, L. M. Obeid, Y. A. Hannun, *Pharmacol. Ther.* **112** (2006) 171; b) K. M. Argraves, B. A. Wilkerson, W. S. Argraves, P. A. Fleming, L. M. Obeid, C. J. Drake, *J. Biol. Chem.* **279** (2004) 50580
18. Garner's aldehyde (**1**) was prepared according to a previously published procedure: M. Trajkovic, Z. Ferjancic, R. N. Saicic, *Tetrahedron Asymmetr.* **23** (2012) 602
19. a) P. Garner, J. M. Park, E. Malecki, *J. Org. Chem.* **53** (1988) 4395; b) X. Liang, J. Andersch, M. Bols, *J. Chem. Soc., Perkin Trans. 1* (2001) 2136
20. This pair of diastereomeric products exists as mixture of rotamers, and its ^{1}H-NMR spectrum shows broad and overlapping signals at room temperature. The *anti*/*syn* ratio was determined by ^{1}H-NMR at 60 °C
21. J. Llaveria, A. Beltran, M. M. Diaz-Requejo, M. I. Matheu, S. Castillon, P. J. Perez, *Angew. Chem. Int. Ed.* **49** (2010) 7092
22. THF was used as a cosolvent, in order to overcome the problem of a poor solubility of (*E*)-1-iodo-1-pentadecene in DMF
23. a) R. S. Coleman, A. J. Carpenter, *Tetrahedron Lett.* **33** (1992) 1697; b) K. Soai, K. Takahashi, *J. Chem. Soc., Perkin Trans. 1* (1994) 1257; c) K. Suzuki, T. Hasegawa, T. Imai, H. Maeta, S. Ohba, *Tetrahedron* **51** (1995) 4483
24. K. Gu, L. Bi, M. Zhao, C. Wang, J. Ju, S. Peng, *Bioorg. Med. Chem.* **15** (2007) 6273
25. W. Wu, R. Li, S. S. Malladi, H. J. Warshakoon, M. R. Kimbrell, M. W. Amolins, R. Ukani, A. Datta, S. A. David, *J. Med. Chem.* **53** (2010) 3198
26. The *anti*/*syn* ratio was determined by ^{1}H-NMR of the unprotected (3*R*)- and (3*S*)-epimers of ceramide **4**, obtained after acidic hydrolysis (70 % acetic acid) of the acetal moiety in **15a** and 15**b**
27. D. P. Stamos, X. C. Sheng, S. S. Chen, Y. Kishi, *Tetrahedron Lett.* **38** (1997) 6355
28. For a description of the technique of dry-flash chromatography, see: a) L. M. Harwood, *Aldrichim. Acta* **18** (1985) 25; b) A. I. Vogel, A. R. Tatchell, B. S. Furnis, A. J. Hannaford, P. W. G. Smith, *Vogel's Textbook of Practical Organic Chemistry*, Longman Scientific & Technical, 5th ed., London, 1989, p. 220; c) An account which includes some improvements of the separation technique: D. S. Pedersen, C. Rosenbohm, *Synthesis* (2001) 2431
29. D. D. Perrin, W. L. F. Armarego, *Purification of Laboratory Chemicals*, 3rd ed., Pergamon Press, Oxford, 1988
30. N. Karasavvas, R. K. Erukulla, R. Bittman R. Lockshin, Z. Zakeri, *Eur. J. Biochem.* **236** (1996) 729
31. M. Moreno, C. Murruzzu, A. Riera, *Org. Lett.* **13** (2011) 5184.