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Addition of Dimethyl Phosphite to Imines Bearing the L-Methionine Moiety and Its Surprisingly Poor Chiral Assistance

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ABSTRACT: *The preparation of methyl 2-{[(dimethoxyphosphoryl)-methyl]-amino}-4-methylsulfanylbutyrates (**3a–e**) by the addition of dimethyl phosphite to 2-(methylidenamino)-4-methylsulfanylbutyric acid methyl esters (**2a–e**) is described. The nearly nonexisting diastereoselectivity, which was observed in all cases, is unexpected and astonishing in light of the fact that some other amino acid esters, e.g., leucine, demonstrated very high stereoselectivity in similar reactions. The separation of formed diastereoisomers occurred.* © 2012 Wiley Periodicals, Inc. Heteroatom Chem 00:1–4, 2012; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21029

INTRODUCTION

The addition of dialkyl and diaryl phosphites to an azomethine bond of chiral Schiff bases, such as *N*-α-methylbenzylimines, has been described in several papers [1–5]. Diastereoselectivity of reported reactions varied from 2:1 to 9:1 of a diastereoisomeric ratio.

Mikołajczyk and co-workers invented an interesting method for highly stereoselective synthesis of aminophosphonic acids using the addition of dialkyl phosphite anions to chiral sulfimines [6], which achieved promising results.

We have reported the formation of *N*-(1-methoxycarbonyl-3-methylbutyl)- aminomethylphosphonic acids, i.e., aminophosphonic systems derived from l-leucine, where the diastereoselectivity varied from *de* = 14% up to *de* = 100% [7]. Moreover, we observed the self-separation of predominant diastereoisomers of studied leucine-derived aminophosphonic acids.

Therefore, we wished to extend our studies on some other amino acid derivatives and we have chosen methionine in hope of obtaining similar or even better results. To our surprise, methionine did not turn out to be a good chiral auxiliary and we would like to report our observations and reflections about it.

RESULTS AND DISCUSSION

Imines **2a–d** [8–11] have been prepared using a previously published method [7] by simple mixing of an aldehyde **1a–d** with methionine methyl ester hydrochloride in dichloromethane in the presence of triethylamine. They were isolated and used for further conversions without previous purification (Scheme 1).

Methyl 2-{[(dimethoxyphosphoryl)-methyl]-amino}-4-methyl-sulfanylbutyrates (**3a–d**) were synthesized by the reaction of 2-(methylidenamino)-4-methyl-sulfanylbutyric acid methyl esters (**2a–d**) with dimethyl phosphite in acetonitrile for 10 days, where the mixture was refluxed during the day and stirred at room temperature at night (Scheme 1). Chromatography on silica gel with ethyl acetate: hexane (4:1) obtained pure aminophosphonates **3a** and **3c** as a mixture of diastereoisomers, whereas for

Dedicated to Professor Henri-Jean Cristau on the occasion of his 70th birthday.

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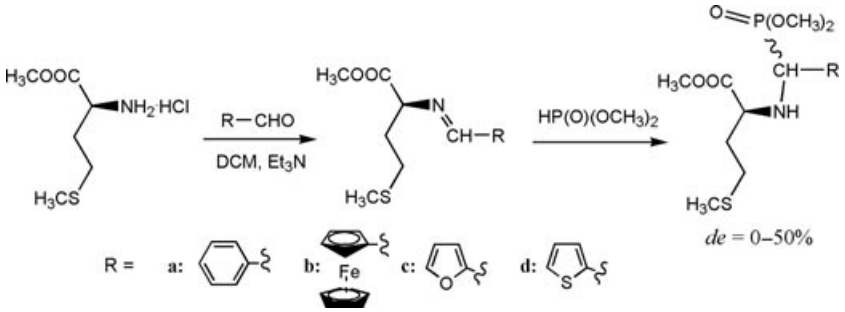


SCHEME 1

TABLE 1 Results of Addition of Dimethyl Phosphite to 2-(Methylidenamino)-4-methylsulfanylbutyric Acid Methyl Esters (**2a–d**)

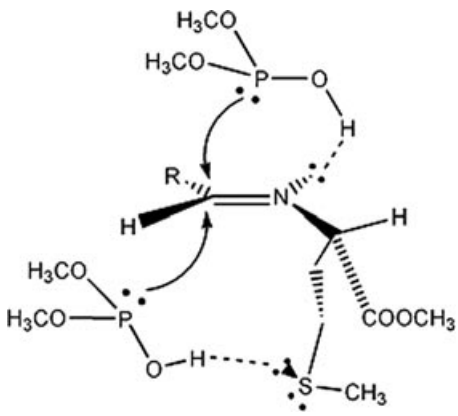
					A Single Isomer[a]	
Compound	*R*	*Y (%)*	*dr (de%)*	^{31}*P NMR*	^{31}*P NMR*	α_D^{20}
3a	Ph	62	5:4 (11)	25.01, 24.99	–	–
3b	Ferrocenyl	63	2:6 (50)	24.11, 24.00	24.00	+164.5 ($c = 0.1$, $CHCl_3$)
3c	2-Furyl	53	2:3 (20)	22.46, 22.42	–	–
3d	2-Thienyl	61	1:1 (0)	23.27, 23.02	23.27	−0.82 ($c = 1.14$, $CHCl_3$)

[a]Spectral data of separated diastereoisomer.

3b and **3d** obtained separation of one of two diastereoisomers. Results are presented in Table 1.

Unfortunately, the addition of dimethyl phosphite to an azomethine bond of methionine-derived imines turned out not to be significantly diastereoselective: the highest one, which occurred in a case of a ferrocenyl derivative **3b** ($de = 50\%$), and the lowest, practically null in a case of a thiophene derivative **3d**. Results are presented in Table 1. It is highly astonishing, first because amino acids, i.e., proline, is a well-known chiral auxiliary and catalyst in asymmetric synthesis [12,13]. Moreover, valine is largely used as a chiral auxiliary in the Schoellkopf reagent, the precursor for amino acid synthesis [14]. Studying a case of phosphite addition to leucine analogues, diastereoselectivity was much higher, from $de = 14\%$ for the thienyl derivative until $de = 100\%$ for the ferrocene one [7]. Certainly, the tendency remained the same; we noticed that in both cases, the highest stereoselectivity occurred for ferrocene derivatives (vide supra), less selectivity occurred for 2-furyl ones ($de = 67\%$ for the leucine analogue [7] vs. $de = 20\%$ for the methionine one), and dramatically less for 2-thienyl derivatives (vide supra). Higher diastereoselectivity of ferrocene derivatives has been discussed in light of the Houk model [15], which provided the explanation suggesting that "diastereoselection is reinforced due to the stabilizing interaction between the phosphorus atom orbital and the ferrocenyl substituent" [7, p. 328].

Such a low diastereoselectivity could also be explained on the basis of the Houk model [15]. The "normal" Houk action causes the formation of the hydrogen bond between the hydrogen of dimethyl phosphite and the nitrogen of the azomethine bond from the side opposite to the methoxycarbonyl substituent. The diastereoselection is weakened by the formation of the hydrogen bond between the hydrogen of dimethyl phosphite and sulfur of the methionine ethylthiomethyl group from the side of the methoxycarbonyl substituent, as it is depicted in Scheme 2, which results in a very low diastereoselectivity. This reaction will be



SCHEME 2

investigated in the future for some other amino acids, such as valine or *tert*-leucine.

EXPERIMENTAL

All solvents were routinely distilled and dried prior to use. Aldehydes, methionine methyl ester hydrochloride, and dimethyl phosphite (Aldrich, Poznań, Poland) were used as received. For column chromatography, silica gel (Kiesegel 60 0.063–0.200 nm/70–230 mesh) from Aldrich was used. NMR spectra were recorded on a Bruker Avance III apparatus (Bruker Biospin, Poznań, Poland) working at 600 MHz for ^{1}H NMR, 150 MHz for ^{13}C NMR (with TMS as an internal standard), and 243 MHz for ^{31}P NMR (with 85% H_3PO_4 as an external standard).

*2-(Methylidenamino)-4-methylsulfanylbutyric Acid Methyl Esters (**2a–d**)*

General procedure. To a solution of aldehyde (2 mmol) in dichloromethane (30 mL), OMe-methionine hydrochloride (2 mmol) in triethylamine (2 mmol) was added and the solution was refluxed for 5 days. Then the content of a flask was concentrated in vacuo up to/one third of the volume; hexane was added and precipitated. $Et_3N{\cdot}HCl$ was filtered off to obtain dense oil of an imine.

*2-(Benzenylideneamino)-4-methylsulfanylbutyric acid methyl ester (**2a**) [12].* Yield: 90%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.33 (s, —CH=N, 1H); 7.80–7.76 (m, ArH, 2H); 7.45–7.41 (m, ArH, 3H); 4.21 (dd, ^{3}J = 7.8 Hz and ^{2}J = 5.6 Hz, —CH_{met}, 1H); 3.75 (s, —C(O)—OCH_3, 3H); 2.66–2.35 (m, —$CH_2C\underline{H}_2SCH_3$, 2H); 2.32–2.20 (m, —$C\underline{H}_2CH_2SCH_3$, 2H); 2.09 (s, —$SCH_3$, 3H).

*2-(Ferrocenylideneamino)-4-methylsulfanylbutyric acid methyl ester (**2b**) [13].* Yield: 95%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.20 (s, —CH=N, 1H); 4.73–4.72 (m, C_pH, 1H); 4.67–4.66 (m, C_pH, 1H); 4.41–4.39 (m, C_pH, 2H); 4.21 (s, C_pH, 5H); 4.06 (dd, ^{3}J = 9.0 Hz and ^{2}J = 4.8 Hz, —CH_{met}, 1H); 3.75 (s, —C(O)—OCH_3, 3H); 2.61–2.57 (m, —$CH_2\underline{H}CHSCH_3$, 1H); 2.49–2.44 (m, —$CH_2HC\underline{H}SCH_3$, 1H); 2.28–2.16 (m, —$C\underline{H}_2CH_2SCH_3$, 2H); 2.10 (s, —$SCH_3$, 3H).

*2-(2-Furylideneamino)-4-methylsulfanylbutyric acid methyl ester (**2c**) [14].* Yield: 96%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.13 (s, CH=N, 1H); 7.55 (dd, ^{3}J = 1.8 Hz and ^{4}J = 0.6 Hz, $^{5}H_{fur}$, 1H); 6.85 (dd, ^{3}J = 3.6 Hz and ^{4}J = 0.6 Hz, $^{3}H_{fur}$, 1H); 6.50 (dd, ^{3}J = 3.6 Hz and ^{3}J = 1.8 Hz, $^{4}H_{fur}$, 1H); 4.16 (dd, ^{2}J = 8.4 Hz and ^{3}J = 4.8 Hz, CH_{met}, 1H); 3.48 (s, —C(O)—OCH_3, 3H); 2.62–2.57 (m, —$CH_2\underline{H}CHSCH_3$, 1H); 2.46–2.42 (m, —$CH_2HC\underline{H}SCH_3$, 1H); 2.32–2.19 (m, —$C\underline{H}_2CH_2SCH_3$, 2H); 2.16 (s, —$SCH_3$, 3H).

*2-(2-Thienylideneamino)-4-methylsulfanylbutyric acid methyl ester (**2d**) [15].* Yield: 77%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.45 (s, —CH=N, 1H); 7.47 (dd, ^{3}J = 4.8 Hz and ^{4}J = 1.2 Hz, $^{5}H_{thio}$, 1H); 7.41 (dd, ^{3}J = 3.6 Hz and ^{4}J = 1.2 Hz, $^{3}H_{thio}$, 1H); 7.11 (dd, ^{3}J = 4.8 Hz and ^{3}J = 3.6 Hz, $^{4}H_{thio}$, 1H); 4.20 (dd, ^{3}J = 8.4 Hz and ^{2}J = 4.8 Hz, —CH_{met}, 1H); 3.77 (s, —C(O)—OCH_3, 3H); 2.64–2.6 (m, —$CH_2\underline{H}CHSCH_3$, 1H); 2.5–2.45 (m, —$CH_2HC\underline{H}SCH_3$, 1H); 2.31–2.23 (m, —$C\underline{H}_2CH_2SCH_3$, 2H); 2.12 (s, —$SCH_3$, 3H).

*Methyl 2-{[(dimethoxyphosphoryl)-methyl]-amino}-4-methyl-sulfanylbutyrates (**3a–d**)*

General method. Imine (**2a–d**) (2 mmol) was dissolved in acetonitrile (30 mL), and dimethyl phosphite (2 mmol) was added. A mixture was refluxed for 10 days, and then the solvent was evaporated in vacuo; residue was dissolved in a small amount of dichloromethane and washed three times with saturated aqueous $NaHCO_3$ (3 × 20 ml). An organic layer was separated, dried, and filtered, and the solvent was evaporated. Obtained crude aminophosphonate was then chromatographed on silica gel with ethyl acetate: hexane (4:1).

Predominant diastereoisomers in the mixture are denoted with an asterisk.

*Methyl 2-{[phenyl(dimethoxyphosphoryl)-methyl]-amino}-4-methyl-sulfanylbutyrate (**3a**).* Calcd for $C_{15}H_{24}NO_5SP$: C, 49.85; H, 6.69; N, 3.88. Found: C, 49.59; H, 6.51; N, 3.85.

Yield: 62%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43–7.29 (m, ArH, 5H); 4.15* (d, $^{2}J_{PH}$ = 18,6 Hz, —P—CH—N, 1H); 4.01 (d, $^{2}J_{PH}$ = 20.4 Hz, —P—CH—N, 1H); 3.78 and 3.51 (2d, $^{3}J_{PH}$ = 10.8 Hz, —P(O)—OCH_3, 3H); 3.69* and 3.46 (2s, —C(O)—OCH_3, 3H); 3.67* and 3.64* (2d, ^{2}J = 10.8 Hz, —P(O)—OCH_3, 3H); 3.49–3.45* (m, —CH_{met}, 1H); 3.25–3.20 (m, —CH_{met}, 1H); 2.67–2.62* (m, —$CH_2C\underline{H}_2SCH_{3met}$, 2H); 2.60–2.50 (m, —$CH_2C\underline{H}_2SCH_{3met}$, 2H); 2.09* and 2.04 (2s, —SCH_3, 3H); 1.93–1.80* (m, —$C\underline{H}_2CH_2SCH_{3met}$, 2H). ^{31}P NMR (243 MHz, $CDCl_3$): δ 25.01*, 24.99.

*Methyl 2-{[ferrocenyl(dimethoxyphosphoryl)-methyl]-amino}-4-methyl-sulfanyl-butyrate (**3b**).* Yield: 63%.

Isolated predominant diastereoisomer: Calcd for $C_{19}H_{28}NO_5SPFe$: C, 48.62; H, 6.01; N, 2.98. Found: C, 48.29; H, 6.08; N, 2.75.

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.30 (s, C_pH, 5H); 4.27–4.25 (m, C_pH, 1H); 4.21–4.19 (m, C_pH, 2H); 4.18–4.16 (m, C_pH, 1H); 3.79 (s, −C(O)−OCH_3, 3H); 3.74 (d, $^2J_{HP}$ = 18.4 Hz, −P−CH−N, 1H); 3.67 (d, $^3J_{PH}$ = 10.8 Hz, −P(O)−OCH_3, 3H); 3.60 (d, $^3J_{PH}$ = 10,8 Hz, −P(O)−OCH_3, 3H); 3.50–3.47 (m, −CHN_{met}, 1H); 2.74–2.67 (m, −$CH_2C\underline{H}_2SCH_3$, 2H); 2.15 (s, −$SCH_3$, 3H); 1.27–1.23 (m, −$C\underline{H}_2CH_2SCH_3$, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 175.39 (C=O); 70.64 (d, $^2J_{PC}$ = 10.5 Hz, C^{ferr}_{quat}); 69.81 ($C^{ferr}_{4,5}$); 68.79 (C_5H_5); 67.72 (d, $^3J_{PC}$ = 10.9 Hz, $C^{ferr}_{2,3}$); 58.68 (C(O)O$\underline{C}H_3$); 53.56 (d, $^1J_{PC}$ = 160.7 Hz, PCN); 53.80 (d, $^2J_{PC}$ = 7.1 Hz, POC); 52.76 (d, $^2J_{PC}$ = 7.4 Hz, POC); 51.87 (CHC(O)); 34.06, 30.58 (CH_2CH_2); 15.49 (SCH_3). ^{31}P NMR (243 MHz, $CDCl_3$): δ 24.00.

Second diastereoisomer: ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.29 (m, C_pH, 5H); 4.25–4.24 (m, C_pH, 1H); 4.22–4.21 (m, C_pH, 1H); 4.19–4.18 (m, C_pH, 2H); 3.80 (s, −C(O)−OCH_3, 3H); 3.73 (d, $^2J_{HP}$ = 15.6 Hz, −P−CH−N, 1H); 3.59 (d, $^3J_{PH}$ = 10.8 Hz, −P(O)−OCH_3, 3H); 3.49 (d, $^3J_{PH}$ = 10.2 Hz, −P(O)−OCH_3, 3H); 3.53–3.50 (m, −CHN_{met}, 1H); 2.73–2.64 (m, −$CH_2C\underline{H}_2SCH_3$, 2H); 2.17 (s, −$SCH_3$, 3H); 2.09–2.02 (m, −$C\underline{H}_2CH_2SCH_3$, 2H). ^{31}P NMR (243 MHz, $CDCl_3$): δ 24.11.

*Methyl 2-{[2-furyl(dimethoxyphosphoryl)-methyl]-amino}-4-methyl-sulfanylbutyrate (***3c***).* Calcd for $C_{13}H_{22}NO_6SP$: C, 44.44; H, 6.31; N, 3.99. Found: C, 44.23; H, 6.21; N, 4.02.

Yield: 53%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43–7,42* and 7.41–7.40 (2m, $^5H_{fur}$, 1H); 6.41–6.40* and 6.38–6.37 (2m, $^3H_{fur}$, 1H); 6.36–6.35* and 6.35–6.34 (2m, $^4H_{fur}$, 1H); 4.32 (d, $^2J_{PH}$ = 19.8 Hz, −P−CH−N, 1H); 4.11* (d, $^2J_{PH}$ = 22.8 Hz, −P−CH−N, 1H); 3.83* and 3.73* (2d, $^3J_{PH}$ = 10.2 Hz, −P(O)−OCH_3, 3H); 3.79 and 3.66 (2d, $^3J_{PH}$ = 10.8 Hz, −P(O)−OCH_3, 3H); 3.70* and 3.55 (2s, −C(O)−OCH_3, 3H); 3.47* (dd, ^3J = 7.2 Hz and ^2J = 5.4 Hz, CH_{met}, 1H); 3.35 (dd, ^3J = 7.8 Hz and ^2J = 4.8 Hz, CH_{met}, 1H); 2.67–2.51 (m, −$CH_2C\underline{H}_2SCH_3$, 2H); 2.09 and 2.05* (2s, −SCH_3, 3H); 1.96–1.79 (m, −$C\underline{H}_2CH_2SCH_3$, 2H);. ^{31}P NMR (243 MHz, $CDCl_3$): δ 22.46; 22.42*.

*Methyl 2-{[2-thienyl-(dimethoxyphosphoryl)-methyl]-amino}-4-methyl-sulfanylbutyrate (***3d***).* Yield: 61%.

Isolated diastereoisomer: Calcd for $C_{13}H_{22}NO_5S_2P\bullet^1/_2H_2O$: C, 41.48; H, 6.61; N, 3.72. Found: C, 41.21; H, 6.47; N, 4.01.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (dd, $^3J_{HH}$ = 6.6 Hz and $^4J_{HH}$ = 1.8 Hz, $^5H_{thi}$, 1H); 7.12–7.11 (m, $^3H_{thi}$, 1H); 6.98 (dd, $^3J_{HH}$ = 6.6 Hz and $^3J_{HH}$ = 3,6 Hz, $^4H_{thi}$, 1H); 4,30 (d, $^2J_{PH}$ = 20,4 Hz, −P−CH−N, 1H); 3,81 (d, $^3J_{PH}$ = 10,2 Hz, −P(O)−OCH_3, 3H); 3,63 (d, $^3J_{PH}$ = 10,2 Hz, −P(O)−OCH_3, 3H); 3.61 (dd, J = 6.0 and 7.2 Hz, CH–N, 1H); 3,57 (s, −C(O)−OCH_3, 3H); 2,66–2.52 (m, $CH_2C\underline{H}_2SCH_3$, 2H); 2,11 (s, SCH_3, 3H); 1.95–1.86 (m, $CH_2C\underline{H}_2SCH_3$, 2H). ^{31}P NMR (243 MHz, $CDCl_3$): δ 23.27.

Second diastereoisomer: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34–7.32 (m, $^5H_{thi}$, 1H); 7.15–7.14 (m, $^3H_{thi}$, 1H); 6.98 (dd, ^3J = 4.8 Hz and ^3J = 3,6 Hz, $^4H_{thi}$, 1H); 4,51 (d, $^2J_{PH}$ = 18.6 Hz, −P−CH−N, 1H); 3,84 (d, $^3J_{PH}$ = 10.8 Hz, −P(O)−OCH_3, 3H); 3,75 (d, $^3J_{PH}$ = 10.8 Hz, −P(O)−OCH_3, 3H); 3.75 (s, −C(O)−OCH_3, 3H); 3.34 (dd, J = 4.2 and 8.4 Hz, CH–N, 1H); 2,66–2.52 (m, $CH_2C\underline{H}_2SCH_3$, 2H); 2,01 (s, SCH_3, 3H); 1.95–1.86 (m, $CH_2C\underline{H}_2SCH_3$, 2H). ^{31}P NMR (243 MHz, $CDCl_3$): δ 23.02.

REFERENCES

[1] Yuan, C.; Cui, S. Phosphorus Sulfur Silicon 1991, 55, 159–164.

[2] Głowiak, T.; Sawka-Dobrowolska, W.; Kowalik, J.; Mastalerz, P.; Soroka, M.; ZoÒ, J. Tetrahedron Lett 1977, 45, 3965–3968.

[3] Skwarczyński, M.; Kafarski, P. Synth Commun 1995, 25, 3565–3572.

[4] Sheiko, S.; Guliaiko, I.; Grushkun, E.; Kolodiazhnyi, O. I. Phosphorus Sulfur Silicon 2002, 177, 2269–2270.

[5] (a) Kachkovskii, G. A.; Andrushko, N. V.; Sheiko, S. Yu.; Kolodiazhnyi, O. I. Russ J Gen Chem 2006, 75, 1735–1746; (b) Zh Obshch Khim 2006, 75, 1818–1826.

[6] Mikołajczyk, M.; Łyźwa, P.; Drabowicz, J. Tetrahedron: Asymmetry 1997, 8, 3991–3996.

[7] Lewkowski, J.; Karpowicz, R. Heteroatom Chem 2010, 21, 326–331.

[8] Riera, X.; Lopez, C.; Caubet, A.; Moreno, V.; Solans, X.; Font-Bardia, M. Eur J Inorg Chem 2001, 2135–2141.

[9] Hess, A.; Sehnert, J.; Weyhermueller, T.; Metzler-Nolte, N. Inorg Chem 2000, 39, 5437–5443.

[10] Grigg, R.; Sridharan, V.; Wang, J.; Xu, J. Tetrahedron 2000, 56, 8967–8976.

[11] Ankersmit, H. A.; Witte, P. T.; Kooijman, H.; Lakin, M. T.; Spek, A. L.; Goubitz, K.; Vrieze, K.; van Koten, G. Inorg Chem 1996, 35, 6053–6063.

[12] List, B. Tetrahedron 2002, 58, 5573–5587.

[13] List, B. Chem Commun 2006, 8, 819–824.

[14] Bull, S. D.; Davies, S. G.; Moss, W. O. Tetrahedron: Asymmetry 1998, 9, 321–328.

[15] Houk, K. N.; Duh, H.-Y; Wu, Y.-D.; Moses, S. R. J Am Chem Soc 1986, 108, 2154–2755.