Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 1161–1166

TETRAHEDRON: *ASYMMETRY*

Asymmetric addition of titanium and sodium alkoxides to chiral imines

Anna Kulesza,[a] Adam Mieczkowski,[a] Jan Romański[a] and Janusz Jurczak[a,b,*]

[a]*Department of Chemistry, Warsaw University, Pasteura 1, PL-02-093 Warsaw, Poland*
[b]*Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, PL-01-224 Warsaw, Poland*

Received 6 January 2003; accepted 27 January 2003

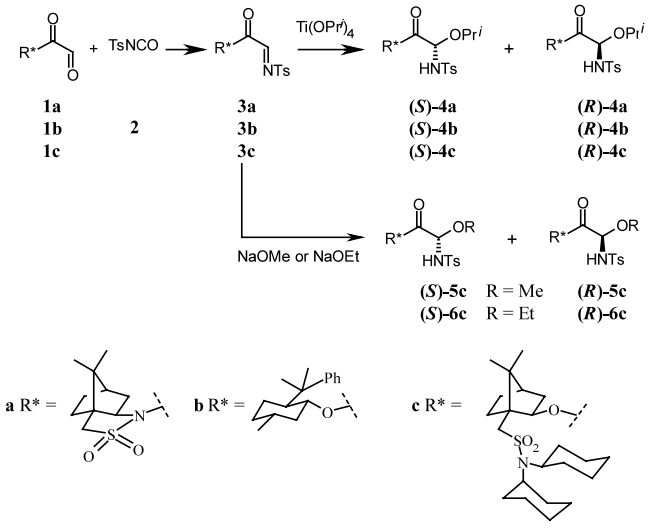
Abstract—A novel method for the alkoxylation of imines was developed using alkoxytitanium(IV) derivatives as the alkoxy nucleophile donors. A rationale of the results obtained using stereochemical models is proposed. The differences in the stereochemical outcome of the reaction with the titanium species and sodium alkoxides were studied as well as the influence of chiral auxiliaries such as (2*R*)-bornano-10,2-sultam, (*R*)-8-phenylmenthol and 10-*N*,*N*-dicyclohexylsulphamoyl-(*R*)-isoborneol.

1. Introduction

In our previous reports on the asymmetric induction properties of *N*-glyoxyloyl-(2*R*)-bornano-10,2-sultam in nucleophilic addition[1] and hetero-Diels–Alder reactions,[2,3] we described a stereochemical rationalisation of the asymmetric induction and the advantages of (2*R*)-bornano-10,2-sultam as a chiral auxiliary. The 10-*N*,*N*-dicyclohexylsulphamoyl-(*R*)-isobornyl glyoxylate was found to be less beneficial in terms of diastereoselectivity in the nucleophilic addition of allyltrimethylsilane to carbonyl compounds.[4] Recently, we have reported on the diastereoselective hetero-Diels–Alder reactions of *N*-tosylimines of *N*-glyoxyloyl-(2*R*)-bornano-10,2-sultam that have shown a very good diastereofacial differentiation.[5] Our initial study on asymmetric nucleophilic additions to imines bearing different chiral auxiliaries was focused on the addition of allyl-type reagents such allyltrimethylsilane[6,7] or Barbier reagents[8] to *N*-tosylimines derived from *N*-glyoxyloyl-(2*R*)-bornano-10,2-sultam and glyoxylates of (*R*)-8-phenylmenthyl and 10-*N*,*N*-dicyclohexylsulphamoyl-(*R*)-isobornyl. In the course of studying the addition of allyltrimethylsilane, we examined various Lewis acids in an atempt to optimise the reaction conditions. Among them, we tested titanium(IV) isopropoxide, which has been used successfully as a catalyst for additions to carbonyl compounds and unexpectedly, we found that instead of the appropriate allyl addition product we obtained the isopropoxy derivative. At this point, we decided to investigate this type of nucleophilic addition.

2. Results and discussion

The *N*-tosylimines were obtained from the corresponding derivatives of glyoxylic acid by the method introduced recently by Holmes et al.[9] The reaction of compounds **1a–c** with *p*-toluenesulphonyl isocyanate **2** in refluxing toluene afforded the expected imines **3a–c**, respectively (Scheme 1).



Scheme 1.

* Corresponding author. Tel.: +48-(22)-823-0944; fax: +48-(22)-822-5996; e-mail: jjurczak@chem.uw.edu.pl

0957-4166/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0957-4166(03)00121-6

2.1. Addition of titanium alkoxides to chiral imines

The addition of isopropoxytitanium to imines was carried out using 1 molar equivalent of the nucleophile and afforded easily separable, crystalline diastereoisomers. The reaction proved the advantage of (2*R*)-bornano-10,2-sultam over other auxiliaries, resulting in excellent diastereoselectivity (d.e. >97%). The less structurally rigid 10-*N*,*N*-dicyclohexylsulphamoyl-(*R*)-isoborneol system gave lower levels of asymmetric induction. In contrast with the previous results, the *N*-tosylimine of (*R*)-8-phenylmenthylglyoxylate displayed moderate stereoselectivity in this reaction. With all of these chiral auxiliaries we obtained the (2′*R*) diastereoisomer in excess (Table 1).

Table 1. Results of addition of tetraisopropoxytitanium to *N*-tosylimines

Imine	Yield (%)	Diastereomeric ratio *R*:*S*
2a	50	100:0
2b	55	77:23
2c	56	84:16

In order to provide a thorough rationalisation for alkoxylation with tetraisopropoxytitanium we have to mention the results of addition of allyltrimethylsilane to the corresponding *N*-tosylimines of *N*-glyoxyloyl-(2*R*)-bornano-10,2-sultam that afforded the (2′*S*) diastereoisomer as the major product. In the case of the allyl nucleophile, we proposed that the SO_2/CO *syn*-periplanar, CO/CHNTs *s–cis* planar conformer **A** was most likely to take part in the transition state due to its high reactivity reinforced by the cooperative stereoelectronic effect, as recently formulated by Chapuis et al.[2,3] for *N*-glyoxyloyl-(2*R*)-bornano-10,2-sultam **1a** (Fig. 1).

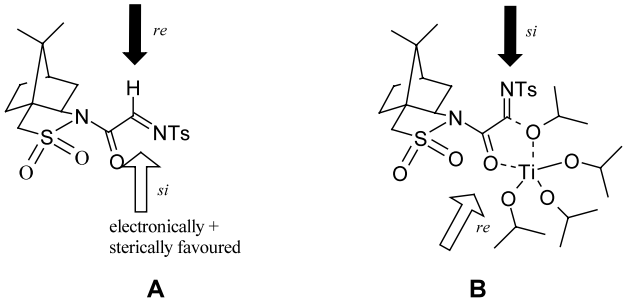


Figure 1.

Based on that rationale, the opposite absolute configuration (2′*R*) of the major isomer obtained from the addition of tetraisopropoxytitanium is a consequence of chelation of the carbonyl group and the oxygen atom of the nucleophile by titanium (Fig. 1, **B**).

Another stereodifferentiating effect has its origin in the π–π stacking of the (*R*)-8-phenylmenthyl moiety of **1b**. It provides excellent asymmetric induction in the reactions of its various derivatives such as acrylates, acetamidoacrylates, glyoxylates and many others.[10] In addition, the stereoselectivity is believed to benefit from face-to-face π–π interactions between the aryl moiety and the unsaturated reacting site in the *s–trans* conformation due to chelation by the titanium species as shown in Fig. 2.

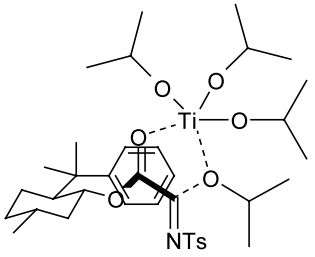


Figure 2.

62.2. Addition of sodium alkoxides to chiral imines

The above stereochemical model is supported by the results from the addition of simple sodium alkoxides to *N*-tosylimines. These reactions provide the opposite diastereoisomer (2′*S*) as the predominant one for all chiral auxiliaries (Table 2). Introduction of a non-chelating nucleophile releases the *s–trans* conformation of CO/CNTs imposed by titanium (Fig. 1, conformer **B**, and Fig. 2) and leads to the preferred *s–cis* conformation being the one (Fig. 3).

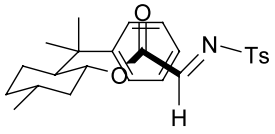


Figure 3.

Table 2. Results of addition of sodium alkoxides to *N*-tosylimines

Imine	Nucleophile	Yield (%)	Diastereomeric ratio *R*:*S*
2b	$Pr^iO^-Na^+$/10% $Ti(O\text{-}^iPr)_4$	65	23:77
2b	$Pr^iO^-Na^+$	70	25:75
2c	$Pr^iO^-Na^+$	38	18:82
2c	MeO^-Na^+	54	35:65
2c	EtO^-Na^+	46	27:73

As Oppolzer has proposed,[11] the most favourable conformation is reached when the alkoxy C–H bond is *syn*-periplanar to the C=O moiety of the ester (as supported by recent X-ray analysis).[12] As a consequence, these prosthetic groups possess an identical sterically-induced C_{α}-*si* topicity, where the (*E*)C=N bond is *s–cis* to the C=O bond (Fig. 3). PM3 calculations confirmed the thermodynamic stability and higher reactivity of *s–cis* conformers over the *s–trans* forms.[13]

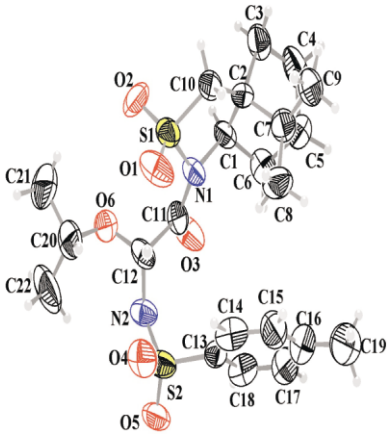


Figure 4. Crystal structure of *N*-((2′*R*)-*N*′-*p*-toluenesulphonylisopropoxyglycinoyl)-(2*R*)-bornano-10,2-sultam imide (*R*)-**4a**.

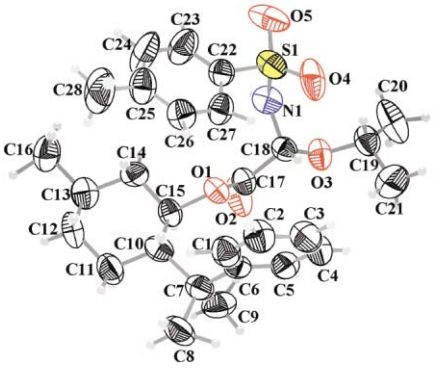


Figure 5. Crystal structure of *N*-((2′*R*)-*N*′-*p*-toluenesulphonylisopropoxyglycine)-8-(*R*)-phenylmenthyl ester (*R*)-**4b**.

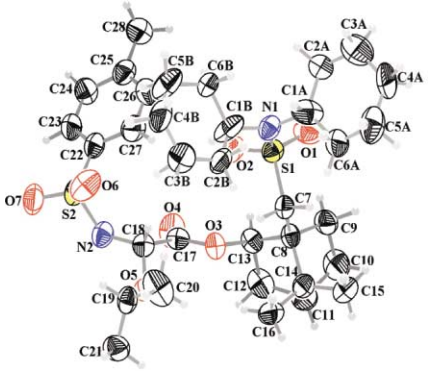


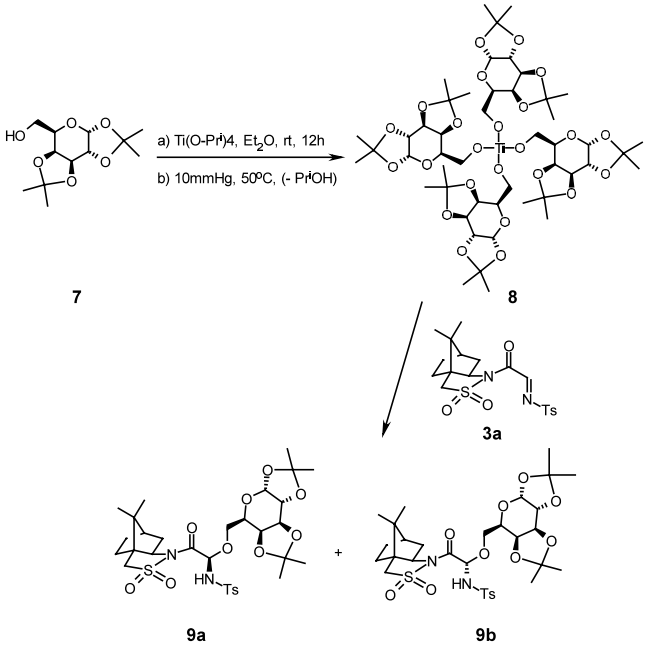
Figure 6. Crystal structure of *N*-((2′*R*)-*N*′-*p*-toluenesulphonylisopropoxyglycine)-10-*N*,*N*-dicyclohexylsulphamoyl-(2*R*)-isoborneyl ester (*R*)-**4c**.

The influence of the steric bulk of the nucleophilic species was also investigated. The diastereoselectivity rises for more sterically demanding alkoxides such as isopropoxide and it drops to the lowest value for the methoxy derivative. Due to the high basicity of the nucleophiles, during the reactions with (2*R*)-bornano-10,2-sultam as the chiral auxiliary, hydrolysis of the imide bond was observed and no product was recovered from the reaction mixture.

The 2′*R* absolute configurations were determined for **4a–c** by X-ray analysis (Figs. 4–6, respectively).

2.3. Addition of tetra-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranosyltitanium to 3a

In the course of our studies, we decided to investigate the outcome of addition of chiral titanium nucleophiles to imines. Transition metals have already been used to assemble sugars in novel architectures[14] and the titanium–carbohydrate complexes were applied as the chiral catalysts eg. in enantioselective allylation of carbonyl compounds[15] and aldol reaction.[16] The molecules so formed take advantage of the inherent properties of both sugar and metal. The formation of chiral complex **8** involved reaction of tetra-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose with $Ti(O\text{-}Pr^{i})_4$ in Et_2O to afford titanium complex **8** (Scheme 2), which was used in situ in the alkoxylation reaction with *N*-tosylimine of *N*-glyoxyloyl-(2*R*)-bornano-10,2-sultam. Such double stereocontrol resulted in >95% asymmetric induction. More detailed analysis was unmanageable due to the instability of the product.



Scheme 2.

3. Conclusions

The 1,2-nucleophilic addition of different titanium and sodium alkoxides to three *N*-tosylimines bearing different chiral auxiliaries has been described. Excellent stereoselectivities were obtained with (2*R*)-bornano-10,2-sultam. The application of the titanium-complexed nucleophile leads to an excess of the opposite diastereoisomer to that obtained in predominance with sodium alkoxides, which suggests the chelation of both substrates by the metal. Finally, we have introduced the chiral complex tetra-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranosyl titanium(IV) as a nucleophile for such addition reactions.

4. Experimental

Reagent grade solvents (CH_2Cl_2, hexanes, EtOAc, THF) were distilled prior use. All reported NMR spectra were recorded on a Varian Gemini spectrometer operating at 200 MHz (^{1}H NMR) or 50 MHz (^{13}C NMR). Chemical shifts are reported as δ values relative to TMS pas internal standard ($\delta=0$). IR spectra were recorded on a Perkin–Elmer 1640 FTIR. Mass spectra were obtained on an AMD-604 Intectra instrument using the electron impact (EI) mode. Column chromatography was performed on silica (Kieselgel 60, 200–400 mesh). Optical rotations were recorded using a JASCO DIP-360 polarimeter with a thermally jacketed 10 cm cell. All air- or moisture-sensitive reactions were carried out in a flame-dried glassware under argon.

4.1. General procedure of preparation of *N*-toluenesulphonylimines 3a–c

Tosyl isocyanate (1.5 mmol, 0.23 ml) was added under Ar to a solution of the corresponding glyoxylic acid derivative (1.5 mmol) in toluene (10 ml) and the reaction mixture was heated under reflux for 24 h. The obtained imines were used without purification for the alkoxylation reactions.

4.2. General procedure for addition of tetraisopropoxytitanium to *N*-toluenesulphonylimines 3a–c

Tetraisopropoxytitanium (0.048 ml, 0.32 mmol) was added to a solution of the *N*-tosylimine of 10-*N*,*N*-dicyclohexylsulphamoyl-(*R*)-isobornyl glyoxylate **2c** obtained from 10-*N*,*N*-dicyclohexylsulphamoyl-(2*R*)-isobornyl glyoxylate (**1c**; 146 mg, 0.32 mmol) in toluene (5 ml). The reaction mixture was stirred at room temperature overnight, then worked up with $NaHCO_3$, and extracted several times with EtOAc. The organic extracts were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The product was purified by flash chromatography using 10% Et_2O–toluene as an eluent to afford the separated diastereoisomers. In the case of the product derived from (2*R*)-bornano-10,2-sultam and (*R*)-8-phenylmenthol, 20% EtOAc–toluene was used as an eluent.

4.2.1. *N*-((2′*R*)-*N*′-*p*-Toluenesulphonylisopropoxyglycinoyl)-(2*R*)-bornano-10,2-sultam imide, (*R*)-4a. Mp = 155–158°C; $[\alpha]_D^{20}=-68.3$ (*c* 1, $CHCl_3$); IR 3276, 2970, 1942, 1697, 1345, 1169 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.74 (d1/2AB, $J=8.4$, 2H), 7.25 (d1/2AB, $J=8.4$, 2H), 5.94 (d, $J=9.8$, 2H), 4.13 (septet, $J=6.0$, 1H), 3.71 (t, $J=6.3$, 1H), 3.42 (qAB, 2H), 2.40 (s, 3H), 2.00–1.80 (m, 4H), 1.53–1.22 (m, 3H), 1.19 (d, $J=6.2$, 3H), 1.17 (d, $J=6.4$, 3H), 1.08 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 165.7, 143.6, 137.8, 129.7, 127.1, 79.0, 71.0, 65.0, 52.8, 49.0, 47.8, 44.3, 37.6, 32.7, 26.4, 23.1, 21.6, 21.0, 20.4, 19.9; ESIMS *m*/*e* (%) 991 $(2M+Na)^+$ (15), 507 (M+Na) (100); HRMS (EI) calcd for $C_{22}H_{32}N_2NaO_6S_2$ (M+Na): 507.1617. Found: 507.1594. Anal. calcd for $C_{22}H_{30}N_2O_6S_2$: C, 54.5; H, 6.7; N, 5.8; S, 13.7. Found: C, 54.4; H, 7.0; N, 5.7; S, 13.2%.

4.2.2. *N*-((2′*R*)-*N*′-*p*-Toluenesulphonylisopropoxyglycine)-8-(*R*)-phenylmenthyl ester, (*R*)-4b. Mp = 85–88°C; $[\alpha]_D^{20}=+5.0$ (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.79 (d1/2AB, $J=8.4$, 2H), 7.34–7.12 (m, 5H), 5.49 (d, $J=10$, 1H), 4.74 (d, $J=10$, 1H), 4.60 (td, $J_1=4.4$, $J_2=10.6$, 1H), 3.99 (septet, $J=6.2$, 1H), 2.40 (s, 3H), 1.87–1.70 (m, 1H), 1.56–1.34 (m, 3H), 1.28 (s, 3H), 1.21 (s, 3H), 1.17–1.12 (m, 6H), 1.06–0.84 (m, 3H), 0.77 (d, $J=6.4$, 3H), 0.59–0.42 (m, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 166.7, 150.1, 143.5, 129.7, 128.7, 128.1, 127.0, 125.7, 125.5, 79.7, 77.1, 69.9, 50.2, 40.8, 40.1, 34.3, 31.1, 28.6, 26.9, 25.5, 22.8, 21.7, 21.6, 21.0.

4.2.3. *N*-((2′*S*)-*N*′-*p*-Toluenesulphonylisopropoxyglycine)-8-(*R*)-phenylmenthyl ester, (*S*)-4b. Oil; $[\alpha]_D^{20}=+31.7$ (*c* 1, $CHCl_3$); IR (KBr): 3285, 2968, 2926, 1735, 1344, 1167 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.70 (d1/2AB, $J=8.4$, 2H), 7.37–7.14 (m, 7H), 5.00 (d, $J=9.2$, 1H), 4.68 (td, $J_1=4.2$, $J_2=10.8$, 1H), 4.42 ($J=9.4$, 1H), 3.71 (septet, $J=6.2$, 1H), 2.41 (s, 3H), 2.04–1.20 (m, 7H), 1.14 (d, $J=7.4$, 6H), 1.02–0.97 (m, 6H), 0.82 (d, $J=6.6$, 3H), 0.67–0.49 (m, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 166.5, 151.8, 143.4, 138.6, 129.7, 129.5, 128.3, 126.9, 125.8, 79.5, 70.8, 50.2, 40.7, 39.3, 34.4, 31.1, 29.2, 28.8, 26.3, 23.1, 22.4, 21.7, 21.5, 21.3; MS (EI) *m*/*e* (%) 442 $(M+H)^+$(23), 242 (12), 215 (31), 119 (70), 105 (100); HRMS (EI) calcd for $C_{28}H_{39}NNaO_5S$ (M+Na): 524.2447. Found: 524.2451.

4.2.4. *N*-((2′*R*)-*N*′-*p*-Toluenesulphonylisopropoxyglycine)-10-*N*,*N*-dicyclohexylsulphamoyl-(2*R*)-isoborneyl ester, (*R*)-4c. Mp = 135–137°C; $[\alpha]_D^{20}=-10.9$ (*c* 1, $CHCl_3$); IR: 3270, 2932, 2856, 1746, 1598 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.80–7.66 (m, 2H), 7.33–7.22 (m, 2H), 5.86 (d, $J=9.4$, 1H), 5.22 (d, $J=9.0$, 1H), 4.90–4.80 (m, 1H), 4.00 (m, 1H), 3.39–3.18 (m, 3H), 2.75 (d, 1H), 2.40 (s, 3H), 1.98–1.08 (m, 33H), 0.99 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 166.0, 143.3, 138.0, 129.5, 127.0, 80.4, 80.0, 69.2, 57.8, 54.7, 49.9, 49.3, 44.4, 39.2, 32.9, 32.6, 30.9, 27.0, 26.4, 25.1, 22.5, 21.6, 21.4, 20.3, 19.8; MS (EI) *m*/*e* (%): 666 M^+ (10), 606 (12), 451 (100), 387 (20), 244 (35), 228 (40), 200 (35); HRMS (EI) calcd for $C_{34}H_{54}N_2NaO_7S_2$ (M+Na): 689.3265. Found: 689.3322. Anal. calcd for $C_{34}H_{54}N_2O_7S_2$: C, 61.2; H, 8.2; N, 4.2; S, 9.6. Found: C, 61.4; H, 8.3; N, 4.3; S, 9.5%.

4.2.5. *N*-((2′*S*)-*N*′-*p*-Toluenesulphonylisopropoxyglycine)-10-*N*,*N*-dicyclohexylsulphamoyl-(2*R*)-isoborneyl ester, (*S*)-4c. Mp = 171–173°C; $[\alpha]_D^{20} = -3.5$ (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.81–7.65 (m, 2H), 7.33–7.22 (m, 2H), 6.49 (d, $J = 9.2$, 1H), 4.96 (d, $J = 9.4$, 1H), 4.70–4.59 (m, 1H), 4.00 (m, 1H), 3.40–3.17 (m, 3H), 2.65 (d, $J = 13.4$, 1H), 2.40 (s, 3H), 1.98–1.08 (m, 33H), 0.99 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 166.4, 143.7, 138.1, 129.4, 127.0, 80.4, 80.1, 69.5, 57.8, 54.4, 49.8, 49.2, 44.4, 39.3, 32.8, 32.6, 30.9, 27.1, 26.5, 25.1, 22.5, 21.3, 21.4, 20.4, 19.8.

4.3. General procedure for addition of sodium alkoxides to *N*-toluenesulphonylimine, 3c

Sodium ethoxide (1.6 ml, 0.4 mmol) was added to a solution of the *N*-tosylimine of 10-*N*,*N*-dicyclohexylsulphamoyl-(*R*)-isobornyl glyoxylate **2c** obtained from 10-*N*,*N*-dicyclohexylsulphamoyl-(2*R*)-isobornyl glyoxylate (**1c**; 167 mg, 0.4 mmol) in toluene (5 ml). The reaction mixture was stirred at room temperature for 1 hour and then neutralised with NH_4Cl, extracted with EtOAc, dried over $MgSO_4$ and evaporated under reduced pressure. The product was purified by flash chromatography using 30% Et_2O–hexane as eluent. The separation of isomers was unfeasible due to instability of products except for compound (*S*)-**5c**.

4.3.1. *N*-((2′*S*)-*N*′-*p*-Toluenesulphonylmethoxyglycine)-10-*N*,*N*-dicyclohexylsulphamoyl-(2*R*)-isoborneyl ester, (*S*)-5c. Oil; $[\alpha]_D^{20} = -16.1$ (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.75–7.69 (m, 2H), 7.34–7.26 (m, 2H), 6.39 (d, $J = 9.2$, 1H), 4.97 (d, $J = 9.4$, 1H), 4.82–4.73 (m, 3H), 3.35–3.15 (m, 4H), 2.61–2.11 (m, 6H), 2.46–1.0 (m, 25H), 0.98 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 165.6, 143.5, 129.6, 127.3, 82.9, 80.5, 57.6, 54.1, 54.0, 49.7, 49.3, 44.4, 39.2, 33.1, 32.4, 31.6, 30.7, 29.7, 27.0, 26.4, 25.1, 22.7, 21.6, 20.3, 20.0.

4.3.2. *N*-((2′*S*/*R*)-*N*′-*p*-Toluenesulphonylmethoxyglycine)-10-*N*,*N*-dicyclohexylsulphamoyl-(2*R*)-isoborneyl ester (*S*/*R*)-5c. IR: 3276, 2933, 2856, 1745, 1598 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.76–7.69 (m, 2H), 7.33–7.25 (m, 2H), 6.43 (d, $J = 9.2$, 0.65H), 6.24 (d, $J = 8.4$, 0.35H), 5.24 (d, $J = 8.2$, 0.35H), 4.97 (d, $J = 9.2$, 0.65H), 4.83–4.74 (m), 2.18–2.25 (m), 2.02–0.98 (m); ^{13}C NMR (200 MHz, $CDCl_3$): δ 165.9, 165.5, 143.5, 138.4, 138.1, 129.6, 129.5, 128.3, 127.0, 126.7, 125.3, 82.8, 82.3, 80.5, 57.7, 57.5, 54.5, 54.3, 54.1, 54.0, 49.9, 49.7, 49.3, 49.2, 44.4, 39.2, 33.1, 33.0, 32.6, 32.4, 30.7, 30.6, 27.0, 26.4, 25.1, 21.6, 21.5, 20.3, 19.9, 19.8; MS (EI) *m*/*e* (%): 638 M^+(2), 606 (30), 451 (100), 387 (12), 298 (30), 254 (10), 244 (40), 180 (12); HRMS (EI) calcd for $C_{32}H_{50}N_2NaO_7S_2$ (M+Na): 661.2652. Found: 661.2932.

4.3.3. *N*-((2′*S*/*R*)-*N*′-*p*-Toluenesulphonylethoxyglycine)-10-*N*,*N*-dicyclohexylsulphamoyl-(2*R*)-isoborneyl ester (*S*/*R*)-6c. Oil; IR: 3274, 2933, 2856, 1745, 1598 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.79–67 (m, 2H), 7.36–7.22 (m 2H), 6.43 (d, $J = 9.2$, 0.37H); 6.12 (d, $J = 7.8$, 0.63H), 5.29 (d, $J = 7.8$, 0.63H), 4.90 (m, 2H), 4.80–4.70 (m, 1H), 3.82–3.62 (m, 2H), 3.61–3.40 (m, 2H), 3.38–3.17 (m, 3H), 2.63 (m, 1H), 2.40 (s, 3H), 1.46–1.10 (m, 30H), 0.99 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 166.2, 165.8, 143.4, 138.4, 138.0, 129.6, 129.5, 129.0, 128.2, 127.0, 126.7, 126.4, 82.0, 81.2, 80.5, 80.2, 63.0, 57.7, 54.4, 48.8, 49.3, 49.4, 39.2, 33.0, 3.27, 32.5, 30.8, 30.6, 27.0, 26.0, 26.5, 26.4, 25.2, 25.1, 21.6, 20.3, 19.8; MS (EI) *m*/*e* (%): 606 (52), 562 (12), 525 (15), 451 (100), 387 (11), 298 (75), 254 (22), 180 (38); HRMS (EI) calcd for $C_{33}H_{52}N_2NaO_7S_2$ (M+Na): 675.3108. Found: 675.3149.

4.4. Preparation of complex 8

$Ti(O\text{-}^iPr)_4$ (0.5 mmol, 0.15 ml) was added dropwise to a stirred solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactose (1.9 mmol, 500 mg) in dry diethyl ether (10 ml) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The volatiles were evaporated under reduced pressure at 50°C and the complex was used without purification for the addition to imine **3a**.

4.5. Addition of tetra-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranosyltitanium to 3a

To a stirred solution of imine **3a** (1 mmol) in dry toluene (5 ml) the solution of **8** in toluene (5 ml) was added. The reaction mixture was quenched with NH_4Cl, extracted with CH_2Cl_2, dried over $MgSO_4$, and evaporated. The product was purified by flash chromatography using as eluent 10% EtO_2 in toluene to give the product in 30% yield (200 mg).

4.5.1. *N*-((2′*R*)-*N*′-*p*-Toluenesulphonyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranosylglycinoyl)-(2*R*)-bornano-10,2-sultam imide, 9a. Oil; $[\alpha]_D^{20} = -37.1$ (*c* 1.0, $CHCl_3$); IR: 3267, 2989, 2961, 2941, 1700, 1346, 1167 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d1/2AB, $J = 8.3$, 2H), 7.36–7.30 (m, 2H), 6.06 (d, $J = 9.8$, 1H), 5.49 (d, $J = 4.99$, 1H), 5.38 (d, 9.8, 1H), 4.55 (dd, $J_1 = 2.3$, $J_2 = 7.9$, 1H), 4.36 (m, 1H), 4.20 (dd, $J_1 = 1.8$, $J_2 = 7.9$, 1H), 4.08–4.00 (m, 1H), 3.87 (m, 1H), 3.74 (m, 1H), 3.68 (m, 1H), 3.11 (qAB, 2H), 2.43 (s, 3H), 2.021.80 (m, 5H), 1.52 (s, 3H), 1.43 (s, 3H), 1.32 (s, 6H), 1.23–1.40 (m, 2H), 1.05 (s, 3H), 0.95 (s, 3H); ESI *m*/*e* (%) 1391 $(2M+Na)^+$(100), 706 (M+Na) (15); HRMS (EI) calcd for $C_{31}H_{44}N_2NaO_{11}S_2$ (M+Na): 707.2242. Found: 707.2279.

4.6. X-Ray data

X-Ray single-crystal diffraction experiments were carried out on a Kuma KM4CCD κ-axis diffractometer using Mo Kα radiation (0.7107 Å). The program used to solve and refine was SHELX-97.[17]

$C_{22}H_{32}N_2O_6S_2$ (*R*-**4a**), $M = 484.61$, monoclinic, $a = 11.550(2)$, $b = 12.211(2)$, $c = 17.882(4)$, $\alpha = 90$, $\beta = 103.31(3)$, $\gamma = 90°$, space group $P2_1$, $Z = 4$, $D_{calcd} = 1.311$ Mg/m^3, μ(Mo Kα) = 0.256 mm^{-1}, 23243 reflections measured, 23243 [$R_{int} = 0.0568$] unique reflections, which were used in all calculations. Data/restraints/parameters 23243/1/587. The final $R_1 = 0.0954$ (all

data), 0.04(10). Residual electron density 0.304 and –0.200 e Å^{-3}.

$C_{56}H_{78}N_2O_{10}S_2$ (*R*-**4b**), $M=501.66$, Monoclinic, $a=24.643(5)$, $b=11.741(2)$, $c=19.761(4)$, $\alpha=90$, $\beta=102.24(3)$, $\gamma=90°$, space group C_2, $Z=4$, $D_{calcd}=1.193$ Mg/m^3, μ(Mo Kα) = 0.152 mm^{-1}, 9879 reflections measured, 4897 ($R_{int}=0.0448$) unique reflections, which were used in all calculations. Data/restraints/parameters 4897/1/819. The final $R_1=0.0718$ (all data), $s=0.2(2)$. Residual electron density 0.314 and –0.217 Å^{-3}.

$C_{34}H_{54}N_2O_7S_2$ (*R*-**4c**), $M=666.91$, orthorhombic, $a=10.089$ (2), $b=14.267(3)$, $c=25.303(5)$, space group $P2_12_12_1$, $Z=4$, $D_{calcd}=1.216$ Mg/m^3, 47355 reflections measured, 4752 ($R_{int}=0.0688$) unique reflections, which were used in all calculations. Data/restraints/parameters 4752/0/534. The final $R_1=0.0622$ (all data), $s=0.0(1)$. Residual electron density 0.168 and –0.163 Å^{-3}.

The crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 199881–199883 for compounds *R*-**4a**, *R*-**4b** and *R*-**4c**, repectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax (+44) 1223336033; e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

This work was supported by Polish State Commitee for Scientific Research, Grant PBZ 6.05/T09/1999. The X-ray measurements were undertaken in the Crystallographic Unit of the Physical Chemistry Laboratory at the Chemistry Department of the University of Warsaw.

References

1. Kiegiel, K.; Jurczak, J. *Tetrahedron Lett*. **1999**, *40*, 1009.
2. Bauer, T.; Chapuis, C.; Jezewski, A.; Kozak, J.; Jurczak, J. *Tetrahedron: Asymmetry* **1996**, *7*, 1391.
3. Chapuis, C.; Laumer, J.-V. S.; Marty, M. *Helv. Chim. Acta* **1997**, *80*, 146–172.
4. Czapla, A.; Chajewski, A.; Bauer, T.; Wielogórski, Z.; Urbanczyk-Lipkowska, Z.; Jurczak, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2101.
5. Bauer, T.; Szymanski, S.; Jezewski, A.; Gluzinski, P.; Jurczak, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2619.
6. Kulesza, A.; Jurczak, J. *Chirality* **2001**, *13*, 634.
7. Kulesza, A.; Mieczkowski, A.; Jurczak, J. *Tetrahedron: Asymmetry* **2002**, *13*, 2061.
8. Kulesza, A.; Jurczak, J. *Synthesis* **2003**, in press.
9. Hamley, P.; Holmes, A. B.; Kee, A.; Ladduwahetty, T.; Smith, D. F. *Synlett* **1991**, 29.
10. Kober, R.; Papadopoulos, K.; Miltz, W.; Enders, D.; Steglich, W.; Reuter, H.; Puff, H. *Tetrahedron* **1985**, *41*, 1693.
11. Oppolzer, W.; Chapuis, C.; Mao Dao, G.; Rechlin, D.; Godel, T. *Tetrahedron Lett*. **1982**, *23*, 4781.
12. Blanco, J. M.; Caamano, O.; Fernandez, F.; Garcia-Mera, X.; Lopez, C.; Rodriguez, G.; Rodriguez-Borges, J. E.; Rodriguez-Hergueta, A. *Tetrahedron Lett*. **1998**, *39*, 5663.
13. Szymanski, S.; Chapuis, C.; Jurczak, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1939.
14. Williams, D. N.; Piarulli, U.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *J. Chem. Soc., Dalton Trans*. **1994**, 1243.
15. Riediker, M.; Duthaler, R. *Angew. Chem*. **1989**, *28*, 494.
16. Duthaler, R.; Herold, P.; Lottenbach, W.; Oertle, K.; Riediker, M. *Angew. Chem*. **1989**, *28*, 495.
17. Sheldrick, G. M. *SHELXL-93: Program for the Refinement of Crystal Structures*; University of Göttingen: Germany, 1993.