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Enantioselective synthesis of α,β-diamino ester derivatives: memory of chirality in imino-aldol reactions

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ABSTRACT

A simple strategy for the synthesis of chiral α,β-diamino ester derivatives in good yields and ee (up to 92%) utilizing the 'memory of chirality' concept is reported. This methodology has been extended for the enantioselective synthesis of substituted aziridines with excellent ee (92%).

Optically active α,β-diamino acid derivatives are an important class of compounds found as key structural frameworks in a number of antibiotics and other natural products.[1] Several synthetic routes to α,β-diamino acids and their derivatives are known in the literature,[1a,2] which include direct catalytic asymmetric Mannich reactions,[2a–c] opening of aziridine rings,[2d–f] imino-aldol reactions,[2g] and catalytic asymmetric aza-Henry reactions.[2h] We anticipated that non-racemic α,β-diamino acid derivatives could easily be made from α-amino acid derivatives via a simple intermolecular imino-aldol reaction by using the '*memory of chirality*' (MOC) concept. The MOC concept describes a protocol in which the reactive intermediate is chiral and scalemic with the stereochemical memory of the starting substrate even though the original stereocenter is destroyed during the reaction.[3c] It was first introduced and established by Fuji and Kawabata for the enantioselective α-alkylation of enolates.[3a–g] They utilized this concept for the asymmetric synthesis of various substituted nitrogen heterocycles and cyclic amino acids with tetrasubstituted stereocenters and made a seminal contribution to the field.[4] The MOC concept has added a new dimension[3–8] to asymmetric synthesis involving the α-C substitution reaction of α-amino esters or ketones[3] and different polycyclization processes.[6] For the wider applicability of this novel concept in asymmetric organic synthesis, further exploration with important organic reactions is necessary.

In continuation of our research activities in enolate chemistry exploring the scope of the MOC concept in imino-aldol reactions, we have developed a simple strategy for the enantioselective synthesis of α,β-diamino esters and report herein our preliminary results. Our strategy provides direct access to non-racemic α,β-diamino esters with consecutive quaternary and tertiary stereogenic centers in high enantiopurity. We have designed a new substrate *N*-benzyl-*N*-*tert*-butoxycarbonylamino acid ester **1a** to study asymmetric induction by the MOC concept in imino-aldol reactions. We anticipated that the enolate **A** from **1a** with a chiral C–N axis would be non-racemic and be able to preserve the stereochemical information of starting material **1a** to produce non-racemic products (Fig. 1).[3c]

The substrate **1a** with high enantiopurity (>99% ee) is readily accessible from the (*S*)-phenylalanine ethyl ester through N-benzylation with benzaldehyde and sodium borohydride followed by Boc protection with di-*tert*-butyldicarbonate in the presence of triethyl amine (Scheme 1). Toward the synthesis of chiral α,β-diamino esters initially the ester enolate **A** (M = K) was generated from (*S*)-**1a** by the treatment of KHMDS at −78 °C and was reacted with *N*-tosylphenylaldimine at the same temperature to afford the

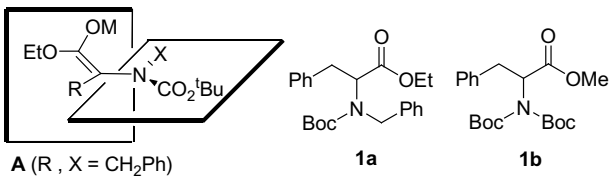

Figure 1. Amino acid ester derivatives and chiral enolate.

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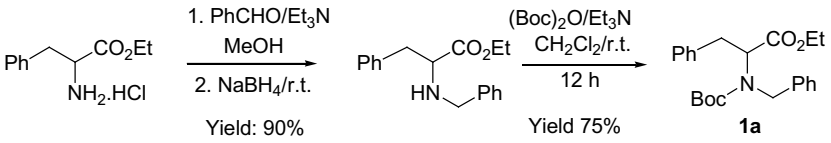


Scheme 1. Synthesis of *N*-benzyl-*N*-*tert*-butoxycarbonylamino acid ester **1a**.

corresponding non-racemic α,β-diamino ester derivative **2a** as an inseparable mixture of diastereomers (Scheme 2). It is worth noting that the corresponding β-lactam could not be formed probably because the negative charge developing on nitrogen was highly delocalized over the sulfonyl group. The ^{1}H NMR spectrum of **2a** contained broad signals probably because of its existence as atropisomers due to restricted rotation along C–N bond although the ^{13}C NMR, DEPT NMR, and mass spectral analyses clearly showed the formation of this product. It was assumed that upon lowering the temperature, one of the atropisomers might be frozen to provide a clean ^{1}H NMR spectrum. The ^{1}H NMR spectrum was found to be better on decreasing the temperature; however, a clean spectrum was not obtained even at −55 °C (in $CDCl_3$). On the other hand, a high temperature ^{1}H NMR study also failed to give a well-resolved spectrum at 60 °C (in DMSO). Other NMR studies, for example, ^{1}H–^{1}H and ^{1}H–^{13}C correlations at low temperature, could not provide further information about the structure of **2a**. At this stage, we anticipated that the ^{1}H NMR spectrum could be simplified if the *N*-Boc group is deprotected. The Boc group of **2a** was deprotected using 1:2 trifluoroacetic acid and dichloromethane to give **3a** in moderate yield with poor ee. As per our expectations, we got a clean ^{1}H NMR spectrum of compound **3a**.

To find out the optimum reaction conditions for better yield and ee, the reaction of **1a** with *N*-tosylphenylaldimine was studied in different solvents with a number of bases. All these results are summarized in Table 1. The best result was obtained with LDA as the base in THF (ee up to 92% for the major diastereomer, entry 1). When toluene served as the solvent, **2a** was formed only in trace amounts (entry 2). Although **2a** was produced in moderate yield using KHMDS as the base, the enantioselectivity was found to be very poor (Table 1, entries 3–6). Other bases, for example, LHMDS or NaHMDS did not work; however, LTMP gave a clean reaction with high yield (80%) and selectivity (ee 80% for the major diastereomer of **3a**) (Table 1, entry 8). Based on the above results, we switched over to LDA as the base and carried out the same reaction. When the reaction was quenched after 2 h, **2a** was obtained in 62% yield but a further improvement in yield and ee was observed when the reaction was continued for 10 h. To generalize this approach, several N-activated imines were reacted under optimized

Table 1
Effect of bases and solvents on imino-aldol reaction

Entry	Base	Solvent	Time (h)	Yield **2a**[a] (%)	Yield **3a**[a] (%)	ee[b,c] (%)
1	LDA	THF	10.0	84	88	92
2	LDA	Toluene	10.0	Trace	—	—
3	KHMDS	THF	6.0	55	89	4
4	KHMDS	THF:toluene 4:1	2.0	71	94	16
5	KHMDS	THF:toluene 1:4	2.5	70	92	26
6	KHMDS	Toluene	2.5	56	87	28
7	LHMDS	THF	14.0	Trace	—	—
8	LTMP	THF	2.0	80	80	80

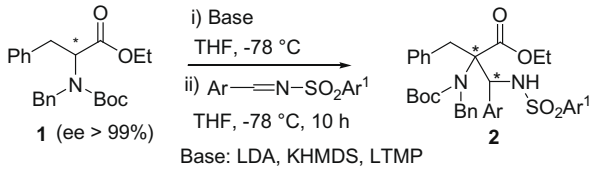
[a] Combined yield of both the diastereomers after purification.
[b] HPLC separation was done using Chiral AD-H column (95:5 hexane/isopropanol as mobile phase and 1.0 mL/min flow rate).
[c] *ee* was determined from HPLC analysis of 3a.

conditions[9] to give non-racemic α,β-diamino acid derivatives **2a–f** (based on optical rotation) in good yields (Scheme 2).

The stereomers of imino-aldol products **2** could not be separated at this stage. The diastereoselectivity as well as the enantioselectivity of **2** could only be determined from its Boc deprotected derivative **3**. To get clear ^{1}H NMR spectra and to determine ee/de, the Boc group was removed from the addition products **2a–f** by the treatment of TFA in dichloromethane to produce **3a–f** in high yields[10] (Scheme 3, Table 2). **3a–f** were fully characterized by ^{1}H NMR, ^{13}C NMR, DEPT NMR, and HRMS analyses.

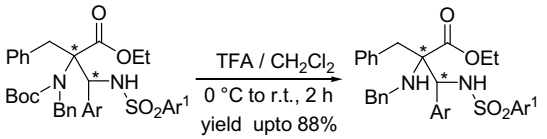
Moderate diastereoselectivity and moderate to high enantioselectivity (for major diastereomer 74–92% and for minor diastereomer 62–88%) were obtained in all the cases (Table 2, entries 1–6). In most of the cases, diastereomers (**3a**, **3d–f**) could be separated after Boc deprotection through flash column chromatography. The relative configuration of the major diastereomers of imino-aldol adducts **2** was determined to be ($2R^*$, $3S^*$) based on X-ray crystallographic analysis of their derivatives **3** (Fig. 2).[11] To provide convincing evidence in support of the MOC effect in imino-aldol reactions, (*S*)-methyl-2-[bis(*tert*-butoxycarbonyl) amino]-3-phenylpropanoate **1b** was reacted with *N*-tosylphenylaldimine under identical reaction conditions where the corresponding addition product **4** was formed as a racemate because the enolate generated from the diBoc ester does not possess any chiral C–N axis (Scheme 4).

This strategy has been extended further for the synthesis of substituted aziridines. To transform **3a** into the corresponding substituted aziridine **7a**, the ester moiety of **3a** was reduced with



a: Ar = Ph, Ar^1 = 4-MeC_6H_4 Yield: 84%
b: Ar = Ph, Ar^1 = Ph Yield: 62%
c: Ar = 3-BrC_6H_4, Ar^1 = 4-MeC_6H_4 Yield: 68%
d: Ar = 2-ClC_6H_4, Ar^1 = 4-MeC_6H_4 Yield: 74%
e: Ar = 2-furyl, Ar^1 = 4-MeC_6H_4 Yield: 74%
f: Ar = Ph, Ar^1 = 4-$NO_2C_6H_4$ Yield: 80%

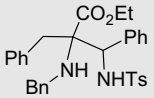
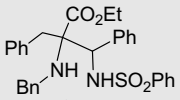
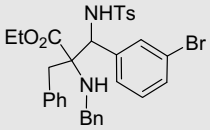
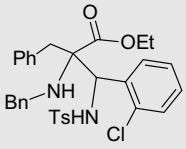
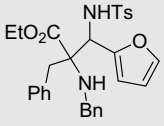
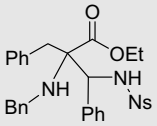
Scheme 2. Synthesis of α,β-diamino acid derivatives **2a–f**.



a: Ar = Ph, Ar^1 = 4-MeC_6H_4; **b**: Ar = Ph, Ar^1 = Ph; **c**: Ar = 3-BrC_6H_4, Ar^1 = 4-MeC_6H_4; **d**: Ar = 2-ClC_6H_4, Ar^1 = 4-MeC_6H_4; **e**: Ar = 2-furyl, Ar^1 = 4-MeC_6H_4; **f**: Ar = Ph, Ar^1 = 4-$NO_2C_6H_4$

Scheme 3. Boc deprotection of compounds **2a–f**.

Table 2
Asymmetric imino-aldol adducts **3a**–**f** generated from Boc deprotection of **2a**–**f**

Entry	Product (**3**)[a]	Yield (**3**)[b] (%)	dr[c] (%)	ee major diastereomer (%)	ee minor diastereomer (%)
1	 **3a**	88	83:17	92	80
2	 **3b**	70	71:29	80	80
3	 **3c**	87	71:29	84	62
4	 **3d**[d]	80	79:21	74	—
5	 **3e**	87	67:33	80	88
6	 **3f**[d]	84	83:17	88	—

[a] Corresponding imino-aldol adducts (**3a**–**f**) obtained after 10 h.
[b] Overall yield of both the diastereomers after purification.
[c] dr based on crude ^{1}H NMR analysis.
[d] Minor isomer could not be separated in chiral HPLC columns (chiralpak AD-H, OD-H).

lithium borohydride in THF at room temperature followed by cyclization in the presence of mesyl chloride and triethyl amine to give **7a** in good yield and high enantioselectivity (ee 92%) (Scheme 5).[12]

In summary, we have developed a straightforward route to optically active α,β-diamino acid derivatives and chiral aziridine with contiguous quaternary and tertiary stereocenters with moderate to high enantiopurity by a base-promoted imino-aldol reaction of

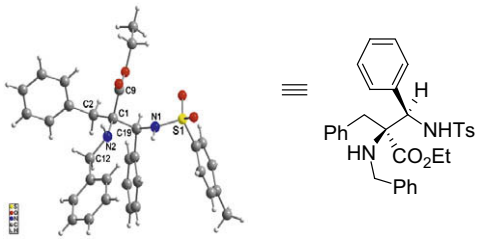
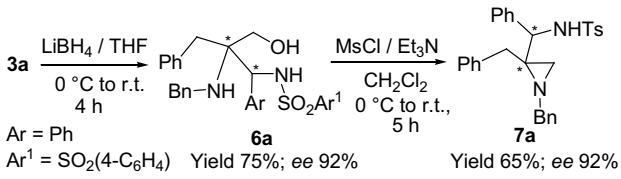


Figure 2. Crystal structure of **3a**.



Scheme 5. Synthesis of non-racemic aziridine **7a**.

N,N-diprotected amino acid esters with N-activated imines utilizing the MOC concept. We believe that this strategy will contribute significantly toward the enantioselective synthesis of α,β-diamino acid derivatives and aziridines as well. The determination of the absolute configuration of compounds **2** and **3** followed by mechanistic study, further modulation of the reaction conditions to get a single diastereomer, and the use of nonactivated imines which would lead to nonracemic β-lactams in a single step are under active study in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.050.

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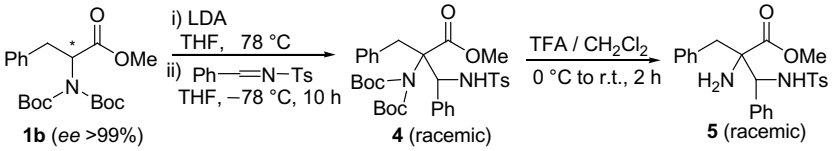

Scheme 4. Synthesis of racemic α,β-diamino ester derivative **5**.

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9. (a) *General experimental procedure for the imino-aldol reaction of N-benzyl-N-tert-butoxycarbonylamino acid ester* ***1a*** *with various imines*: To a solution of diisopropylamine (0.12 mL, 0.848 mmol) in 2 mL dry THF was added *n*-BuLi (1.6 M in hexane) (0.53 mL, 0.848 mmol) at 0 °C and stirred for 20 min. It was cooled to −78 °C and a solution of *N*-benzyl-*N*-*tert*-butoxycarbonyl amino acid ester **1a** (0.848 mmol) in 1.0 mL dry THF was added to it and allowed to stir for 1 h. *N*-Sulfonylimine (0.385 mmol) dissolved in 1.0 mL dry THF was slowly added into the reaction mixture and stirring was continued at the same temperature for 10 h. After completion of the reaction (monitored with TLC), it was quenched with a saturated aqueous ammonium chloride solution and extracted with 5 mL of ethyl acetate in two portions. The combined organic extract was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified on a silica gel column by flash column chromatography using ethyl acetate in petroleum ether as the eluent to afford the pure products **2a-f**.
Characterization data for compound **2a**: white solid; yield 84%; eluent: EtOAc/petroleum ether 10/90; R_f 0.45 (ethyl acetate/petroleum ether: 20/80); $[\alpha]_D^{25}$ +10.76 (*c* 0.415, $CHCl_3$); IR ν_{max} (KBr, cm^{-1}): 3334, 2978, 2927, 1738, 1696, 1389, 1160, 1090; ^{13}C NMR for the mixture of stereoisomers (100 MHz, $CDCl_3$): δ 13.4, 21.0, 21.3, 27.9, 29.6, 37.1, 40.6, 49.5, 61.2, 61.4, 61.9, 71.0, 80.9, 81.1, 81.5, 125.5, 125.8, 126.2, 127.0, 127.2, 127.80, 127.86, 128.0, 128.1, 128.5, 128.7, 128.8, 129.4, 129.9, 130.8, 131.2, 134.6, 135.7, 136.8, 138.1, 139.6, 139.9, 141.9, 142.3, 156.1, 157.1, 169.5; HRMS (ESI) *m/z* Calcd for $C_{37}H_{43}N_2O_6S$ (M^++H): 643.2841, found: 643.2834.
(b) The reaction is highly dependent on temperature, solvent, bases, and most importantly on time, and the corresponding de/ee of the product may change with slight changes in any of these conditions.
10. (a) Combined yields of two diastereomers of **3a–f** obtained as a mixture from the corresponding crude reaction mixture after passing through a small silica gel column.
(b) *General method for Boc deprotection of imino-aldol products* **2a–f**: To a stirring solution of substrates **2a–f** (0.10 mmol) in dry dichloromethane (1 mL) was added trifluoroacetic acid (0.5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. It was neutralized with aq saturated $NaHCO_3$ solution and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extract was washed with brine and dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel to provide **3a–f**.
Characterization data for **3a**: The general procedure described above was followed to afford **3a** as a white solid in 88% overall yield (combined yield of both the diastereomers). It was obtained as a mixture of diastereomers in 83:17 ratio (based on ^1H NMR analysis of crude reaction mixture), where the diastereomers were separated through flash column chromatography (eluent: EtOAc/petroleum ether 10/90).
For the major diastereomer of **3a**: IR ν_{max} (KBr, cm^{-1}): 3344, 2925, 2854, 2354, 1732, 1600, 1454, 1263, 1161, 1091, 1019; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.03 (t, *J* = 7.2 Hz, 3H), 2.20 (s, 3H), 3.04 (d, *J* = 14.7 Hz, 1H), 3.33 (d, *J* = 14.8 Hz, 1H), 3.51 (d, *J* = 12.4 Hz, 1H), 3.66 (d, *J* = 12.4 Hz, 1H), 3.95 (q, *J* = 7.1 Hz, 2H), 4.83 (d, *J* = 6.6 Hz, 1H), 6.2 (br s, 1H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.97–7.06 (m, 4H), 7.08–7.23 (m, 11H), 7.31 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 13.7, 21.2, 38.7, 46.9, 61.6, 61.7, 68.8, 126.8, 127.0, 127.6, 127.7, 128.26, 128.28, 128.3, 128.4, 128.9, 129.8, 130.4, 135.9, 136.3, 137.9, 139.5, 142.5, 173.1; HRMS (ESI) *m/z* Calcd for $C_{32}H_{34}N_2O_4S$ (M^++H): 543.2329, found: 543.2311; R_f 0.45 (ethyl acetate/petroleum ether: 20/80); mp: 158–160 °C; Optical rotation: $[\alpha]_D^{25}$ +10.25 (*c* 0.335, $CHCl_3$) for a 92% ee sample; Optical purity was determined by chiral HPLC analysis (Chiralpak AD-H column) using 95/5 hexane/isopropanol, flow rate = 1.0 mL/min, T_R 1: 72.6 min (major), T_R 2: 97.3 min (minor).
For the minor diastereomer of **3a**: IR ν_{max} (KBr, cm^{-1}): 3347, 3296, 2959, 2924, 2853, 1730, 1661, 1600, 1454, 1264, 1161, 1090, 1019; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.08 (t, *J* = 7.1 Hz, 3H), 2.25 (s, 3H), 3.02 (d, *J* = 15.2 Hz, 1H), 3.34 (d, *J* = 15.2 Hz, 1H), 3.74 (d, *J* = 11.8 Hz, 1H), 3.81 (d, *J* = 11.8 Hz, 1H), 3.98 (q, *J* = 7.1 Hz, 2H), 4.22 (d, *J* = 6.6 Hz, 1H), 4.73 (d, *J* = 7.7 Hz, 1H), 6.10 (d, *J* = 7.7 Hz, 1H), 6.85–6.88 (m, 2H), 6.98–7.09 (m, 4H), 7.22–7.33 (m, 11H), 7.70 (d, *J* = 8.3 Hz, 2H); HRMS (ESI) *m/z* Calcd for $C_{32}H_{34}N_2O_4S$ (M^++H): 543.2329, found: 543.2315; R_f 0.44 (ethyl acetate/petroleum ether: 20/80); optical rotation $[\alpha]_D^{25}$ −10.77 (*c* 0.65, $CHCl_3$) for a 80% ee sample; optical purity was determined by chiral HPLC analysis (Chiralpak AD-H column) using 95/5 hexane/isopropanol, flow rate = 1.0 mL/min, T_R 1: 35.1 min (major), T_R 2: 43.2 min (minor).
11. The crystals were obtained as a racemate hence the absolute configuration could not be assigned. After crystallization of **3a,** the mother liquor contained the pure enantiomer which could not be crystallized. CCDC No. of **3a**: 693721.
12. *Synthesis of [(2-benzyl, N-benzylaziridin-2-yl)-phenylmethyl]-4-methylbenzene sulfonamide* (**7a**): To a solution of alcohol **6a** (30 mg, 0.059 mmol) (single diastereomer) in dry CH_2Cl_2 (0.5 mL) were added mesyl chloride (2 mmol) and triethylamine (2.5 mmol). The reaction mixture was stirred at room temperature for 5 h. It was poured into water and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extract was washed with brine and dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography over silica gel (eluent: EtOAc/petroleum ether 10/90) to provide **7a** as a white solid in 65% yield. IR ν_{max} (KBr, cm^{-1}): 3286, 3060, 3029, 2923, 2854, 1600, 1495, 1454, 1426, 1324, 1286, 1163, 1089, 1062, 1044, 1030; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.21 (s, 3H), 2.27 (s, 2H), 2.47 (d, *J* = 14.9 Hz, 1H), 2.67 (d, *J* = 14.9 Hz, 1H), 3.46 (d, *J* = 13.4 Hz, 1H), 3.85 (d, *J* = 13.4 Hz, 1H), 4.23 (d, *J* = 7.6 Hz, 1H), 5.52 (d, *J* = 7.8 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 2H), 6.87–7.04 (m, 6H), 7.18–7.34 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.3, 29.7, 34.0, 35.7, 44.1, 56.5, 126.7, 126.8, 127.3, 127.4, 127.9, 128.1, 128.4, 128.5, 128.6, 129.0, 129.2, 137.2, 139.2, 139.3, 142.3, 142.4; HRMS (ESI) *m/z*: Calcd for $C_{30}H_{31}N_2O_2S$ (M^++H): 483.2106, found: 483.2106; R_f 0.33 (ethyl acetate/petroleum ether: 15/85); mp: 140–142 °C; optical rotation: $[\alpha]_D^{25}$ +31.80 (*c* 0.22, $CHCl_3$) for a 92% ee sample; optical purity was determined by chiral HPLC analysis (Chiralpak AD-H column); 95/5 hexane/isopropanol, flow rate = 1.0 mL/min. T_R 1: 28.3 min (major), T_R 2: 35.3 min (minor). (eluent: EtOAc/petroleum ether 10/90).