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Asymmetric synthesis of (*S*)-ibuprofen by esterification with amides of (*S*)-lactic acid as chiral auxiliaries: experimental and theoretical results

Alessandra Ammazzalorso,[a] Rosa Amoroso,[a,*] Giancarlo Bettoni,[a] Barbara De Filippis,[a] Letizia Giampietro,[a] Marco Pierini[b] and Maria Luisa Tricca[a]

[a]*Dipartimento di Scienze del Farmaco, Università "G. D'Annunzio", Via dei Vestini, 66100 Chieti, Italy*
[b]*Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università "La Sapienza", P. le A. Moro, 00185 Rome, Italy*

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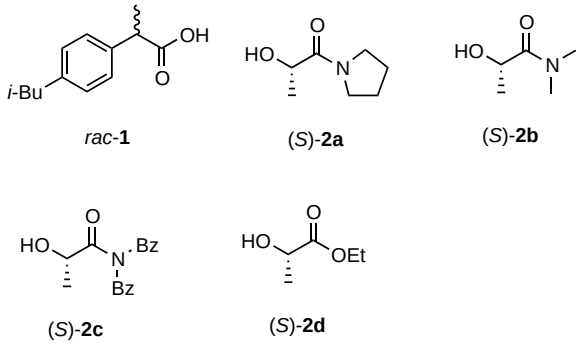
Abstract—A novel synthesis of chiral ibuprofen by a dynamic kinetic resolution process is described. The racemic ibuprofen was converted into the corresponding diastereomeric mixtures of esters with amides of (*S*)-lactic acid as chiral auxiliaries, using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) as condensation agents. The reactions afforded predominantly one of the two diastereomers with good diastereomeric ratios. The reasons of the stereoselectivity were also investigated by molecular mechanic calculations, using MM2 force fields.

The ibuprofen (*rac*-**1**) is an arylpropionic acid related to the class of non-steroidal, anti-inflammatory drugs.[1] It was shown that only the (*S*)-enantiomer is responsible for the desired therapeutic effects,[2] while the (*R*)-ibuprofen displays toxicity due to its storage in fatty tissue as a glycerol ester, whose long-term effects are not known;[3] despite this fact, the ibuprofen is currently administered as racemate. A number of approaches to prepare it in optically pure form, including resolution of diastereomeric salts, resolution of racemates, and asymmetric syntheses using chiral auxiliaries and chiral catalysts have been proposed.[4]

In this paper we describe an application of the dynamic kinetic resolution (DKR)[5] methodology to the asymmetric synthesis of chiral ibuprofen; our strategy is based on a stereoselective esterification with amides derived from (*S*)-lactic acid.

DKR is a synthetic process in which the starting isomers of a mixture have a chirally labile stereogenic center and are capable of epimerization in situ during a reaction. So, different rates of reaction between the two substrates allow the predominant formation of a single isomer of product, in agreement with the Curtin–Hammett principle.[6] One of the approaches to DKR is the simple asymmetric esterification of racemic carboxylic acids using homochiral aliphatic alcohols, in the presence of the dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) as condensation agents.[7] Recently, this strategy was applied to N-protected-amino acids that were esterificated with the chiral auxiliary (*S*)-α-methylpantolactone;[8] the good diastereoselectivity achieved in this reaction could be attributed to the easy racemization of the pyridinium salts deriving from starting aminoacids.



rac-**1** (*S*)-**2a** (*S*)-**2b** (*S*)-**2c** (*S*)-**2d**

Figure 1.

Keywords: (*S*)-ibuprofen; dynamic kinetic resolution; lactamides; molecular mechanic calculations.

* Corresponding author. Fax: 0039-0871-3555267; e-mail: ramoroso@unich.it

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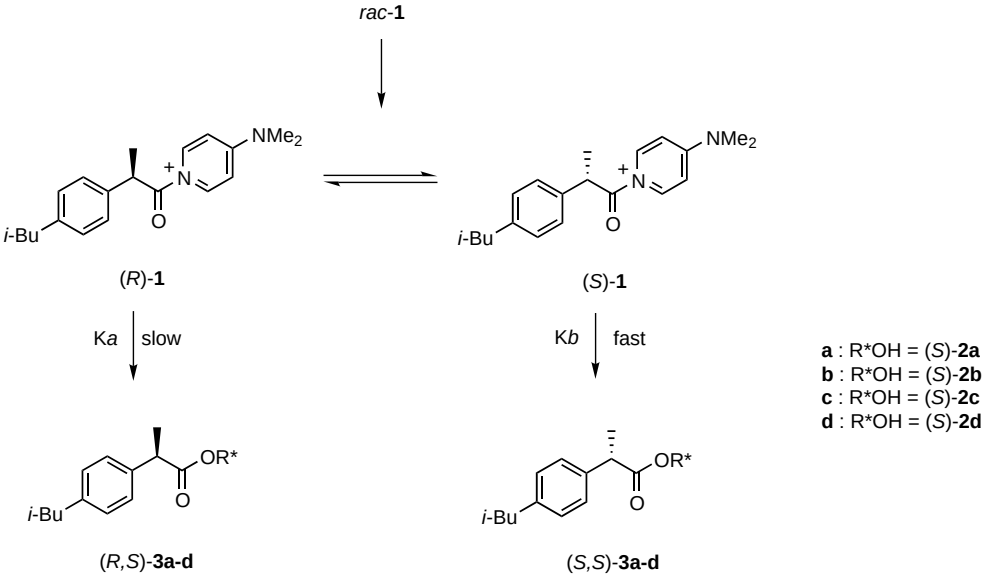
Amides or esters derived of lactic acid were found to be very efficient in a variety of asymmetric syntheses;[9] thus, we employed the (*S*)-**2a**–**d** alcohols in esterification reactions of racemic ibuprofen (*rac*-**1**) (Fig. 1), performed in the presence of 1 equiv. each of DCC and DMAP, in toluene or CH_2Cl_2.[10] The diastereomeric mixtures of esters (*R*,*S*)-**3a**–**d** and (*S*,*S*)-**3a**–**d** were obtained in good yields. As illustrated above, in the first step of these esterification reactions the formation of the pyridinium salt intermediate **I** takes place;[7] this compound, presumably capable of racemization, increases the reactivity of carbonyl group towards the nucleophilic attack of the alcohol (Scheme 1).

Table 1 summarizes the most significant results obtained in these esterification reactions under various conditions of solvent, temperature and amounts of chiral auxiliary. With pyrrolidine derived (*S*)-lactamide auxiliary (*S*)-**2a**, the diastereoselectivity was affected by the solvent, with the toluene giving the best results respect to the more polar solvent CH_2Cl_2. The effect of the temperature was evaluated only in CH_2Cl_2 and it was found to be negligible, with similar results obtained at −20, 0 and 40°C (entries 1–3). In toluene, the highest diastereomeric ratio of 85:15 was obtained at 0°C, using 1 equiv. each of acid and alcohol (entry 5); the use of 0.8 (entry 4) and 1.2 equiv. (entry 6) of lactamide provided a decrease in diastereoselectivity. The use of other amide auxiliaries like dimethyllactamide (*S*)-**2b** and dibenzyllactamide (*S*)-**2c** gave inferior results (entries 7–8). At last, ethyl lactate (*S*)-**2d** provided very low product diastereoselectivity (entry 9).

In all cases, the (*S*,*S*)-configuration predominates. Worth noting, the diastereomers of the mixtures **3** were easily separated on silica gel (eluent cyclohexane/ethyl acetate 70:30), furnishing the main compounds (*S*,*S*)-**3** in optically pure form. The absolute configuration was elucidated using the 85:15 diastereomeric mixture of **3** (Table 1, entry 5) chosen as a representative case: the hydrolysis with CH_3COOH/HCl[11] gave the known (*S*)-(+)-ibuprofen[12] in 80% isolated yield, having 82% of enantiomeric excess, determined by comparison with the known literature value ($[\alpha]_D$ +51.0 (*c* 1.0, $CHCl_3$)[4d]). The (*S*)-**2** chiral auxiliary was recovered with no detectable racemization.



Scheme 1. *Reagents and conditions* (see also Table 1): (*S*)-**2a**–**d**, DCC, DMAP, CH_2Cl_2 or toluene.

Table 1. Diastereoselective esterification of *rac*-**1**

Entry	Auxiliary	Solvent	Temperature (°C)	Time (h)	Yield (%)	d.r.[a] (*S*,*S*)-**3**/(*R*,*S*)-**3**
1	(*S*)-**2a** (1.0 equiv.)	CH_2Cl_2	−20	21	72	70:30
2	(*S*)-**2a** (1.0 equiv.)	CH_2Cl_2	0	2	70	65:35
3	(*S*)-**2a** (1.0 equiv.)	CH_2Cl_2	40	1	83	68:32
4	(*S*)-**2a** (0.8 equiv.)	Toluene	0	2	90	75:25
5	(*S*)-**2a** (1.0 equiv.)	Toluene	0	1	71	85:15
6	(*S*)-**2a** (1.2 equiv.)	Toluene	0	5	75	75:25
7	(*S*)-**2b** (1.0 equiv.)	Toluene	0	4	75	73:27
8	(*S*)-**2c** (1.0 equiv.)	Toluene	0	4	85	67:33
9	(*S*)-**2d** (1.0 equiv.)	Toluene	0	4	71	65:35

[a] The diastereomeric ratios were determined by gas chromatography and ^1H NMR analyses of the crude reaction mixtures, utilizing the signals of the methyl groups and of the protons at the stereogenic centers.

Considering the valuable aid that the modern calculation methods give to synthetic chemist, also in the prediction of stereochemistry,[13] some molecular mechanic calculations using MM2* force field were performed to qualitatively explore diastereoselectivity in the DKR process. The analysis concerned the study of differential stability, $\Delta\Delta E$, of four diastereomeric intermediates **IIa** and **IId**. These species originate in the second step of reaction, of optically active alcohols (*S*)-**2a** and (*S*)-**2d** to acyl pyridinium ion **I**, supposed in fast stereomutation (Fig. 2). The stability difference $\Delta\Delta E$ was compared, approximately, with that which exists among real transition states, $\Delta\Delta G^{\neq}$, responsible for different values of k_a and k_b rate constants. A conformational search was carried out and the steric energy was evaluated as mean of Boltzmann's probabilities of every conformation of **IIa** and **IId**:[14] the configurations (*S*,*R*,*S*) are more stable than (*R*,*R*,*S*) (Table 2). The subsequent loss of chirality at the carbon, center of reaction, as a result of DMAP elimination, requires that **3a** and **3d** esters, with configuration (*R*,*S*) and (*S*,*S*), are formed with the same order of selectivity, in agreement with the experimental trend. The calculation's results also indicate that the substitution on chiral auxiliary of ester by an amide function favors a diastereoselectivity increase. Similar results, but with quantitatively overevaluated predictions compared to experimental data, are achieved by performing $\Delta\Delta E$ calculation only on stability difference of (*S*,*R*,*S*)-**IIa–d** and (*R*,*S*,*S*)-**IIa–d** intermediates.[15]

The subsequent analysis of pyridium ions conformations showed that geometries having a *syn*periplanar torsional angle *T* are significantly the most populated (96.5%) (Fig. 3); on these geometries, the nucleophilic attack from the less hindered hydrogen side (*Si* face) should form a new chiral center, whose configuration is necessarily opposite to that of the asymmetric carbon, giving the (*S*,*R*,*S*)-**IIa–d** and (*R*,*S*,*S*)-**IIa–d** intermediate states. This assumption is also coherent with the simple Karabatsos model for nucleophilic attack on acyclic ketones.[16] A compared analysis of all the different energetic contributions, presumably responsible for differential observed stability, was next performed. For simplicity, the analysis was restricted to conformations of absolute minimum energy for (*S*,*R*,*S*)-**IIa–d** and (*R*,*S*,*S*)-**IIa–d** (Table 3). It can be seen that, in the case of **IIa**, the diastereoselection mechanism is mainly driven by favorable intramolecular non-bonded electrostatic and of Van der Waals interactions, which are

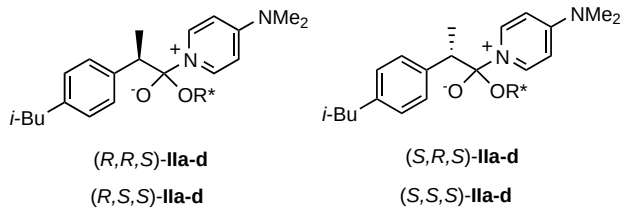


Figure 2.

Table 2. Calculated steric energy of intermediate diastereomers **IIa** and **IId**

Configuration	Energy of **IIa** (kcal/mol)	Energy of **IId** (kcal/mol)
(*S*,*R*,*S*)	−3.4	−11.9
(*S*,*S*,*S*)	3.4	−8.6
(*R*,*R*,*S*)	−2.5	−11.1
(*R*,*S*,*S*)	3.2	−9.7

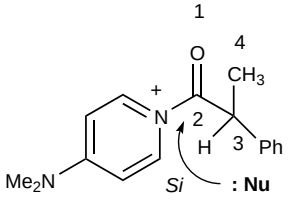


Figure 3. Nucleophilic attack on *Si* face of (*R*)-I intermediate in the conformation with *syn*periplanar angle T(1,2,3,4). Similarly, for (*S*)-I isomer, the attack takes place on *Re* face.

stronger in intermediates having the (*S*,*R*,*S*) configuration. Moreover, steric hindrance effects seem to cause a bigger distortion of bond and torsional angles in (*R*,*S*,*S*) isomer. These results are in agreement with: (i) the selectivity increase observed by using a less polar solvent of reaction, in which differences among intramolecular electrostatic interactions can be maximized; and (ii) the proximity of methyl groups bound to chiral carbons in the final esters, found only in the low energy conformations and having the (*R*,*S*,*S*) configuration.[15] In the case of **IId**, the smallest selectivity differences seem to be due to steric effects, with the biggest distortion of the geometries, associated to bond and torsional angles, while the electrostatic contribution is unfavorable to the formation of (*S*,*R*,*S*) conformations.

Table 3. Energetic contributions in the diastereoselectivity process

	$\Delta\Delta E$ **IIa** (*S*,*R*,*S*)–(*R*,*S*,*S*) (kcal/mol)	%	$\Delta\Delta E$ **IId** (*S*,*R*,*S*)–(*R*,*S*,*S*) (kcal/mol)	%	$\Delta\Delta E$ **IIa**–$\Delta\Delta E$ **IId** (kcal/mol)	%
Total energy	−6.41	100.0	−2.14	100.0	−4.27	100.0
Stretch	−0.20	3.1	−0.02	0.9	−0.18	4.2
Bend	−2.99	46.6	−1.79	83.6	−1.2	28.1
Torsion	−0.73	11.4	−0.69	32.2	−0.04	0.9
VDW	−2.29	35.7	−0.07	3.32	−2.22	52.0
Electrostatic	−0.20	3.1	0.43	−20.1	−0.63	14.8

Finally, the greatest diastereoselectivity observed with the chiral amide (*S*)-**2a** with respect to ester (*S*)-**2d** appears to be driven by either steric or electronic factors. The latter contribution can be reasonably attributed to the great polarizability of amide over that of ester groups.

In conclusion, a simple procedure for the stereoselective synthesis of ibuprofen was developed, through the intermediacy of lactamide auxiliaries; the advantages derived from the use of this synthetic strategy are the potential extension to a variety of α-arylcarboxylic acids and the recovery of the chiral auxiliaries without racemization.

Acknowledgements

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10. Typical esterification procedure: to a solution of *rac*-**1** (1 equiv.), DCC (1.0 equiv.) and DMAP (1.0 equiv.) in the appropriate solvent (10 ml/mmol), (*S*)-**2a–d** (1.0 equiv.) in the same solvent (2 ml/mmol) was added. The mixture was stirred at 0°C until completion of the esterification, following the reaction by TLC. The mixture was carefully filtered and the filtrate diluted with CH_2Cl_2 (10 ml/mmol). The organic phase was washed with HCl 0.5N (20 ml/mmol), a saturated aqueous solution of $NaHCO_3$ (20 ml/mmol) and H_2O (20 ml/mmol), dried over Na_2SO_4 and concentrated at reduced pressure. The residue was purified by chromatography on silica gel with cyclohexane/ethyl acetate 7:3 as solvent to give the diastereomerically enriched mixture of esters (*R*,*S*)-**3a–d** and (*S*,*S*)-**3a–d**.
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