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Enantioselective α-alkylation of unsaturated carboxylic acids using a chiral lithium amide

Eva M. Brun, Salvador Gil and Margarita Parra*

Departament de Química Orgánica, Universitat de València, C/Dr. Moliner 50, 46100 Burjassot, Spain

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Abstract—The regio- and stereochemistry of the alkylation of dienediolates from unsaturated carboxylic acids with benzylic halides, which often results in mixtures of isomers, can be controlled by means of changes in the lithium amide, allowing the α-regioisomer to be obtained as the major diastereoisomer. In addition, when chiral amines are used, moderate enantiomeric excesses can be attained. © 2001 Published by Elsevier Science Ltd.

1. Introduction

Unsaturated carboxylic acids are synthetically useful building blocks[1] because on deprotonation by two equivalents of lithium dialkylamides they afford dienediolates that react as ambident nucleophiles through their α or γ carbon atoms leading to single or clearly predominant compounds when allowed to react with electrophiles under appropriate conditions.[2] Regioselectivity depends both on the electrophile and the reaction conditions employed. Thus, α attack predominates in the irreversible reactions with primary alkyl halides[3] and secondary tosyl derivatives.[4] Higher levels of γ-adduct form with benzylic, allylic or secondary halides. Katzenellenbogen et al.[5] have reported the γ-allylated adducts as major products by use of counter ion interchange with copper(I) ions.

Control of the stereochemistry of these alkylation reactions is very important. It is well known that asymmetric catalytic C–C formation is a fundamental process in organic synthesis, and although new procedures are continuously being developed, enantioselective C–C bond formation is still difficult to achieve.[6]

It is well established that lithium enolates exist as complex ion pair aggregates whose metal center may be coordinated to solvent molecules or other chelating ligands. Recent attention has been directed toward the possibility that aggregates are involved in controlling reaction stereochemistry.[7] From the relatively low number of structural and rate studies and the enormous amount of empirical observations, a series of *dictums* have emerged that describe organolithium reactivities. Three that have been reiterated frequently are: (1) strong donor solvents (ligands) promote conversion of aggregates to monomers or ion pairs; (2) monomers are more reactive than aggregates; and (3) strong donor solvents enhance reactivity.[8] However, factors governing the stereoselectivity of alkylation reactions with enolates are less well understood. Herein, we report the effect of several lithium amide bases on the stereoselectivity of the alkylation of dienediolates of unsaturated carboxylic acids.

The use of chiral bases which function both as a strong base and a chiral auxiliary in the reaction has attracted considerable attention in asymmetric synthesis through enolates,[6b,9] but only three references have been found on the enantioselective alkylation of achiral lithium dienediolates with achiral halides in the presence of chiral amines as ligand. Several years ago, Ando and Shioiri[10] reported e.e. values of products ranging from 2 to 24% for the asymmetric alkylation of phenylacetic acid with ethyl iodide as electrophile and an amino ether with one stereogenic center as the chiral ligand. Higher e.e. values of 2–46% were obtained by Jiang et al.[11] in the alkylation of *p*-chlorophenylacetic acid with *iso*-propyl iodide and an amino alcohol with two stereogenic centers as the chiral induction agent. Surprisingly, both enantiomers of the chiral amine induced the same enantiomer of the alkylated product. Recently, Koga et al.[12] examined the alkylation of

* Corresponding author. Fax: +34 963983152; e-mail: margarita.parra@uv.es

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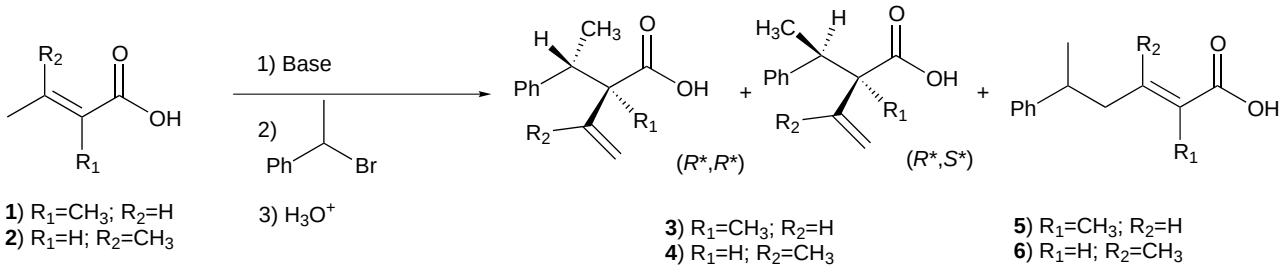

Scheme 1. Alkylation of dienediolates of α,β-unsaturated acids with 1-bromophenylethane.

phenylacetic acid with some halides, under several conditions, using a diamine as a chiral auxiliary and attaining e.e.s in the range of 1–68%. However, poor yields were reported under the conditions leading to the best selectivity. No reports of enantiomeric studies for π-extended enolates of carboxylic acids have been found.

From these results it is clear that chiral lithium amides promote intermolecular chirality transfer; there is not enough knowledge of the transition state involved in these stereoselective alkylations to allow, a priori, an accurate prediction of the required amine structure. Additionally, the ideal number of chelating centers, the use of nitrogen atoms exclusively or in combination with other heteroatoms and the question of whether lithium amides are better than the corresponding amines for chelation with lithium enolates need to be established.

2. Results and discussion

2.1. Modification of the amine structure

We decided to study the alkylation of 2-methylbutenoic **1** and 3-methylbutenoic **2** acids with 1-bromophenylethane (Scheme 1). The α-alkylation product is a mixture of two diasteroisomers. We studied a wide range of lithium amide bases (Fig. 1: **7**–**20**), either commercially available or easily accessible, in order to find the best base and conditions for regio- and enantioselectivity.

The standard conditions for the alkylation reactions[2] used 2.25 mmol of both the dienediolate and the halide; the base was generated from 2 equivalents of *n*-BuLi and a number of equivalents of amine that was optimized for each one (see Table 1). After work-up, the amine was extracted from the basic aqueous phase, dried and re-used. After acidification of the aqueous layer a clean mixture of acids was obtained in every case. The resulting α/γ ratios along with diastereoselectivity for α-products are summarized in Table 1. Previously reported results under standard conditions[13] (entries 1 and 2) are also included for comparison.

Because the simple amine 1,3,3-trimethyl-6-azabicyclo-[3.2.1]-octane **8** promoted good diastereoselectivity for 2-methylbutenoic acid **1** under standard conditions (entry 4), we tested the effect of temperature in order to find the optimum conditions for maximum stereoselectivity. Unfortunately, 100% diastereoselectivity was only obtained at −78°C (entry 3) with low yield. Raising the temperature (entry 5) gave an improved yield but the diastereoselectivity was no better than that achieved under standard conditions. With longer reaction times (entry 6) diastereoselectivity was lost without an increase in the yield and 2-hydroxy-2-methyl-3-butenoic acid was isolated. It is well known that lithium dienolates slowly react with trace oxygen leading to hydroperoxides, which on work-up lead to the corresponding α-hydroxyacids. However, we have not been able to correlate the presence of this lithium salt with loss of diastereoselectivity.

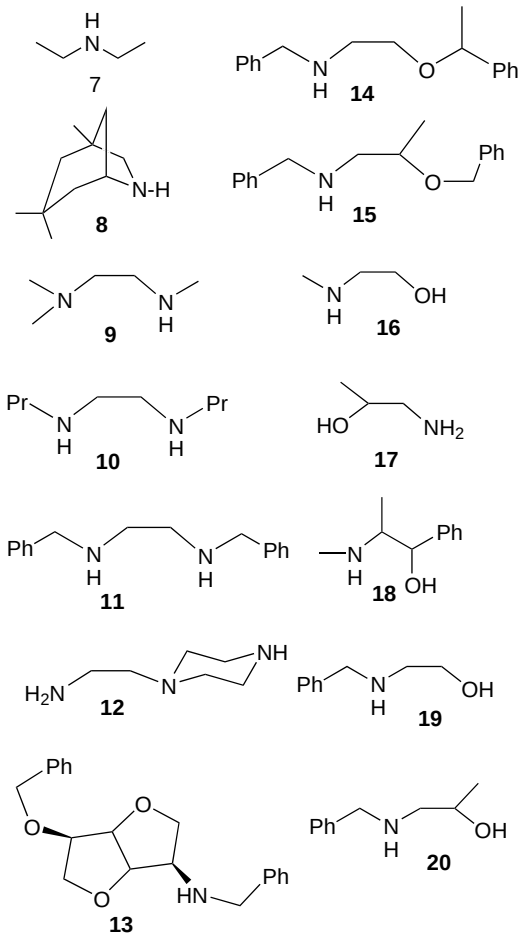

Figure 1. Amines used for amide generation.

Table 1. Diastereoselectivity in the α-alkylation of dienediolates of unsaturated carboxylic acids: the effects of nature of lithium amide bases

Entry	Acid	Amine	No. equiv. (conditions)	Yield (%)	Recovered acid	α/γ ratio	(*R**,*R**)/(*R**,*S**) ratio
1	**1**	**7**	2 (5 h, rt)	77		47/53	69/31
2	**2**	**7**	2 (5 h, rt)	75		73/27	11/89
3	**1**	**8**	2 (2 h, −78°C)	44	67	33/67	100/0
4	**1**	**8**	2 (5 h, rt)	75		42/58	73/27
5	**1**	**8**	2 (24 h, −25°C)	80		49/44[a]	70/30
6	**1**	**8**	2 (24 h, −78°C)[b]	38	49	24/24[a]	50/50
7	**1**	**8**	2 (5 h, 0°C)[b]	55	10	50/50	55/45
8	**1**	**9**	2 (5 h, 0°C)	79	8	51/49	64/36
9	**1**	**10**	2 (5 h, rt)	61		61/39	70/30
10	**1**	**11**	2 (5 h, rt)	84		54/46	74/26
11	**1**	**12**	1/3 (5 h, rt)	53		40/60	67/33
12	**1**	**12**	1 (5 h, rt)	54		43/57	66/34
13	**1**	**12**	2 (5 h, rt)	62		100/0	57/43
14	**1**	**13**	1/2 (5 h, rt)	77		47/53	68/32
15	**1**	**14**	1 (5 h, rt)	80		49/51	75/25
16	**1**	**15**	2 (5 h, rt)	71	27	47/53	71/29
17	**2**	**15**	2 (5 h, rt)	77		77/23	8/92
18	**1**	**16**	2 (5 h, rt)	60		73/27	47/53
19	**1**	**17**	2 (5 h, rt)	48	17	64/36	64/36
20	**1**	**18**	2 (5 h, rt)	45		50/50	52/48
21	**1**	**19**	2 (5 h, rt)	74	12	74/26	47/53
22	**2**	**19**	2 (5 h, rt)	92		86/14	4/96
23	**1**	**20**	2 (5 h, rt)	57	50	74/26	50/50
24	**2**	**20**	2 (5 h, rt)	83		100/0	6/94

[a] α-Hydroxyacid formed as the remainder of the mixture.
[b] Toluene used as solvent.

Table 2. ^{13}C NMR data of dienediolates of unsaturated carboxylic acids

Entry	Dianion	Conditions	C-(1)	C-(2)	C-(3)	C-(4)
1	**Li_2-1**[14]	Et_2NLi	173.4	79.6	141.2	85.8
			170.0	73.4	138.4	86.0
2	**Li_2-1**	**Li_2-20**	174.3	77.2	143.0	89.0
			172.0	73.9	137.5	86.6
3	**Li_2-2**[14]	Et_2NLi	174.9	82.0	146.9	96.5
		DMSO		76.7	137.5	88–91
4	**Li_2-2**	Et_2NLi	174.7	83.0	139.5	96.2
		excess	173.8	77.0	137.1	95.9
5	**Li_2-2**	(*R*) **Li_2-20**	175.4	75.5	146.0	93.2
			173.5	71.1	144.5	90.8
6	**Li_2-2**	(*S*) **Li_2-20**	176.4	76.1	150.2	93.5
			175.0	71.5	144.9	91.4

2.2. Modification of the amount of amine

Another factor that can be easily controlled is the amount of amine. We have described that it is possible to use a catalytic amount of amine for the generation of dianions from carboxylic acids without promoting Michael addition.[2] The amount of amine may be critical to the diasteroselectivity ratio if its structure controls aggregation states as expected. We have studied this with *N*-(2-aminoethyl)piperazine **12**, which has two potential deprotonation sites and three nitrogen atoms that may coordinate with lithium ions, either as amine or amide. It is clear from entries 11, 12 and 13 that the amount of this amine influences the regioselectivity of the process, but does not have a marked effect on the diastereoselectivity.

2.3. ^{13}C NMR study of lithium dienediolates

With alkoxyamide bases derived from **19** and **20** we obtained the best regioselectivity in the alkylation of the dienediolate of 3-methyl-2-butenoic acid **2** and only α-products were obtained. In order to determine if the regioselectivity is influenced by electronic effects, we recorded the ^{13}C NMR spectra of the dienediolates in different conditions. These spectra can be reliably analyzed only at low field for δ values above 68 ppm, as at higher fields signals due to THF, diethylamine and eventually DMSO shroud the spectra. The results are shown in Table 2, where known results under standard conditions are included.[14] Chemical shifts in ^{13}C NMR have been related with the π-electron density deduced from theoretical studies (where it was clearly shown

that C-(2) and C-(4) bear the highest π-electron density in these systems).[14b] Signals corresponding to the dianion of 2-methyl-2-butenoic acid **1** generated with amide **20** (Table 2, entry 2) are similar to those of the dianion generated under standard conditions (entry 1), showing that no electronic effects are promoted by the change of base, indicating that the regio- and diastereoselectivity change is due to steric effects. This is not so clear for 3-methyl-2-butenoic acid **2**, which has similar spectra for its dianion formed both under standard conditions and with excess lithium diethylamide (entries 3 and 4), but both enantiomers of lithium amide **20** promote a displacement to higher field, meaning increasing electronic density for both C-(2) and C-(4) (the effect at C-(2) is slightly greater). For 3-methyl-2-butenoic acid **2**, additional steric factors may also be responsible for the increase in α-regioisomer levels with amine **20**.

2.4. Discussion on the stereochemical outcome

In general alkoxyamines led to an increase of the (*R**,*S**)-diastereoisomer. This led to a clear increase (90% d.e.) for 3-methyl-2-butenoic acid **2**, but a lower diastereoselectivity for 2-methyl-2-butenoic acid **1** (its (*R**,*R**)-α-adduct is the major diasteroisomer using the standard conditions). The regio- and diastereoselectivity

Table 3. Enantioselectivity of α-alkylation products of dienediolate of 3-methyl-2-butenoic acid **2** with 1-bromophenylethane using 2-benzylaminepropanol as a chiral auxiliary

Entry	Amine	*T* (°C), *t* (h)	Yield (%)	α/γ ratio	d.e. (%)	e.e.$_{(R^*,R^*)}$ (%)	e.e.$_{(R^*,S^*)}$ (%)
1	*S*	25, 5	88	90/10	80	24	18
2	*S*	25, 5[a]	69	72/28	86	6	16
3	*S*	25, 5[b]	78	87/13	84	16	16
4	*S*	0, 15	77	84/16	90	20	28[c]
5	*S*	−20, 16	70	87/13	86	50	64
6	*S*	−35, 48	57	86/14	88	14	52
7	*S*	−50, 72	0	–	–	–	–
8	*R*	25, 5	79	100/0	84	10	16
9	*R*	0, 16	74	81/19	90	10	22

[a] 2 equivalents of LiBr were added.
[b] 1 equivalent of DMI was added.
[c] $[\alpha]_D^{25}=+20$ ($c=0.25$ g/100 mL, $CHCl_3$).

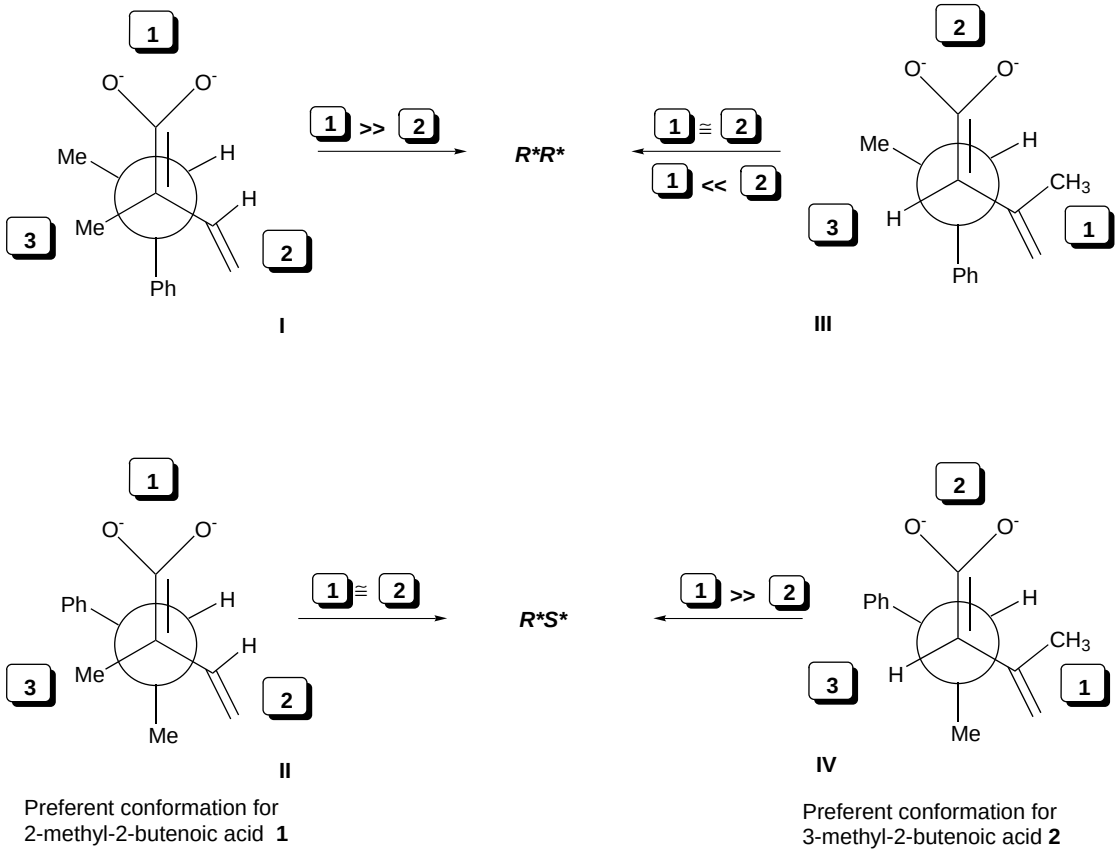

Figure 2. Steric factors governing the preferred approach of 1-bromophenylethane to each dienediolate.

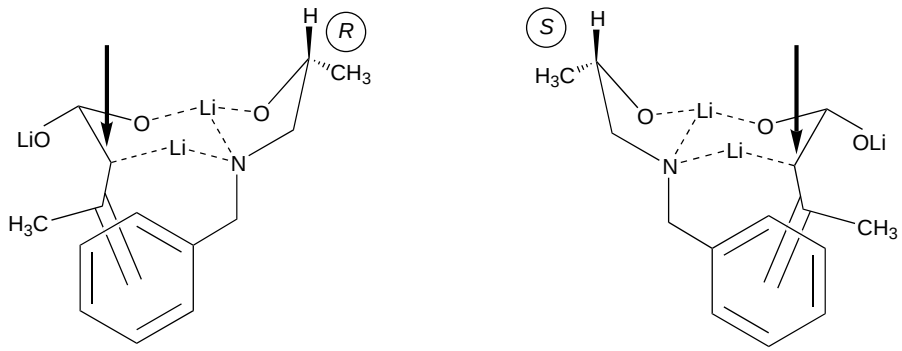

Figure 3. Transition states for enantioselective alkylation.

results, shown in Table 1, can be explained by means of the approach preference models shown in Fig. 2.

Steric effects of the bulkier groups 1 and 2 are critical to the stereochemical outcome. Thus, for 2-methyl-2-butenoic acid **1** under standard conditions, a heavily solvated diolate group is the bulkiest, and case **I** should be preferred. In the presence of alkoxyamines, solvent molecules are excluded and the diolate group is no longer the biggest when compared to the vinyl group; as a result both **I** and **II** compete. Extending this approach to the transition states, an increase in the amount of (*R**,*S**)-diastereoisomer is expected and experimentally a low (*R**,*R**)/(*R**,*S**) ratio is observed. For 3-methyl-2-butenoic acid **2** the *iso*-propylidene group should be the bulkiest under the standard conditions (approach **IV** is now favored over **III**). Hydroxylamines also displace solvent molecules from the solvation sphere rendering the diolate group smaller and situation **IV** becomes clearly predominant. Experimentally this leads to a higher rate of (*R**,*S**)-diastereoisomer formation along with an increase in the levels of the α-regioisomer because a smaller diolate group renders the α-position more accessible.

2.5. Chiral induction study

The above results encouraged us to start a study for promoting chiral induction on the alkylation of 3-methyl-2-butenoic acid **2** using both enantiomers of lithium *N*-benzyl-2-hydroxypropanamide as chiral auxiliaries. The results are summarized in Table 3. Enantiomeric excesses were determined by ^{1}H NMR after addition of (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine as a chiral solvating agent[15] (methyl ester derivatives failed to give any resolution by chiral GC analysis on a *Cyclodex-b* column). Under identical standard conditions to those used for the racemic amides, a 24% e.e. was obtained for the (*R**,*R**)-diastereoisomer and an 18% e.e. for the major (*R**,*S**)-diastereoisomer. We examined the temperature dependence of the enantioselectivity, and it was found that completing the reaction at −20°C over 16 hours led to a 64% e.e. of the (*R**,*S**)-diastereoisomer (entry 5). At the lower temperature of −35°C, prolonged reaction time was required and the reaction gave lower yield and selectivity (entry 6). Only the starting acid was recovered when the reaction was completed at −50°C (entry 7).

The high yield and e.e. attained in entry 5 compared to the moderate result from entry 6 led us to propose racemization of the bromide under the reaction conditions. Using a higher proportion of bromide is not feasible because it leads to a sharp fall in yield and e.e. Examples are known in which lithium enolates prepared from carbonyl compounds and lithium amides react less stereoselectively at the early stage of the reaction, becoming more stereoselective as alkylation proceeds.[16] This phenomenon is explained by the parallel presence of LiBr whose concentration is low at the early stage of the reaction, but increases as the reaction progresses. Accordingly, we tried adding 2 equivalents of LiBr to the reaction to replicate the good results observed with lithium enolates from carbonyl compounds,[16] but a decrease in enantioselectivity and yield was seen similar to that described by Koga[12] (entry 2). It seems that the effect of LiBr slowly released in situ cannot be reproduced by its external addition. On the other hand, we expected that 1,3-dimethyl-2-imidazolidinone (DMI), described as a safe substitute for HMPA which[17] favors solvent separated ion pairs, should lead to higher levels of α-alkylation. Unfortunately, when combined with amine **20** no change in regio- nor enantioselectivity was observed (entry 3).

Similar results were obtained when (*R*)-*N*-benzyl-2-hydroxypropanamine was used, but in this case the major enantiomer obtained was antipodal for both diastereoisomers (entries 8 and 9). Extending the chelated structure proposed by Shioiri[10] for saturated carboxylic acids, we propose structures in Fig. 3 for π-extended dienediolates where the more stable transition state can be fixed by a π-stacking effect[18] for both enantiomers of the amine. This leads to preferred attack compatible with electrophillic assistance by the lithium ions, as shown in Fig. 3.

3. Conclusion

A degree of asymmetric induction was observed in the chiral base mediated α-alkylation of 3-methyl-2-butenoic acid dienediolate, using a method which offers

the following advantages: (1) it is a simple operation; (2) chiral compounds can be obtained in a single step; and (3) the chiral bases used are easily recovered during work-up in a re-usable form. Hence this reaction provides a new method for moderately enantioselective carbon–carbon bond formation.

4. Experimental

4.1. General procedure for alkylation of carboxylic acids

The corresponding amine **20** (2.5 mmol) in THF (1 mL) was added to a solution of *n*-BuLi (5 mmol) in THF (1 mL) and the mixture was stirred under an Ar atmosphere at −78°C (CO_2/acetone bath) and then allowed to warm to 0°C, stirred for 0.5 h, and cooled to −78°C. The carboxylic acid (1.13 mmol) in THF (2 mL) was slowly added at −78°C. The solution was stirred for 0.5 h at 0°C and cooled again to −78°C. A solution of the halide (1.13 mmol) in THF (2 mL) was added dropwise and the reaction mixture was stirred at the temperature and for the period of time which is reported in Tables 1 and 3. Water (15 mL) was added to the mixture and the aqueous layer was extracted with diethyl ether (3×15 mL). The ethereal extracts were combined, dried ($MgSO_4$) and evaporated to afford the recovered amine. The aqueous layer was acidified under ice-cooling by careful addition of conc. HCl and then extracted with ethyl acetate (3×15 mL). The organic layer was washed with water, aqueous NaCl, further water and dried ($MgSO_4$). Evaporation of the solvent gave the crude acid reaction mixture which was analyzed.

4.2. (*R**,*S**)-3-Methyl-2-(1-phenylethyl)-3-butenoic acid 4

White solid; mp 64–66°C (by column chromatography). IR (KBr): ν_{max} = 3200–2700, 1680, 1380, 890 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.14 (d, J = 6.9 Hz, 3H, C$\underline{H}_3$-CH), 1.82 (s, 3H, C$\underline{H}_3$-C=), 3.12–3.22 (m, 1H, C$\underline{H}$Ph), 3.24 (d, J = 12 Hz, 1H, C$\underline{H}CO_2H$), 5.03 (s, 1H, 1C$\underline{H}_2$=), 5.07 (s, 1H, 1C$\underline{H}_2$=), 7.17–7.26 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 400 MHz) δ = 19.8 (C$\underline{H}_3$-CH), 20.0 (C$\underline{H}_3$C=), 39.7 (C$\underline{H}$Ph), 61.0 (C$\underline{H}CO_2H$), 116.8 (C$\underline{H}_2$=), 126.7 (C4Ar), 127.6 and 128.6 (4CHAr), 141.0 (C1Ar), 144.8 (C=), 177.7 (CO_2H). MS (EI): m/z (%) = 204 (M^+, 64), 186 (M−H_2O, 5), 159 (M−CO_2H, 6), 129 (M−CO_2H−2CH_3, 20), 106 (M−CH_3CH_2Ph, 100). HRMS: m/z calcd for $C_{13}H_{16}O_2$: 204.1150; found: 204.1144.

4.3. Determination of relative configuration of (*R**,*S**)-3-methyl-2-(1-phenylethyl)-3-butenoic acid 4

The major diastereoisomer was identified by means of the $J_{2\text{-}1'}$ coupling constant = 12 Hz, which indicates an *anti*-periplanar arrangement for the major conformation. Irradiation of the C-(3) methyl group resonance (δ = 1.82 ppm) induced a positive NOE on the methyl group at C-(1′) and no NOE was observed on the phenyl proton signals at δ = 7.17–7.26 ppm. Irradiation of the vinyl group (δ = 5.07–5.03 ppm) induced a positive NOE on the methyl group at C-(1′).

The minor diastereoisomer (*R**,*R**) was identified by means of the $J_{2\text{-}1'}$ coupling constant = 11.6 Hz, which indicates an *anti*-periplanar arrangement for the major conformation. Irradiation of the methyl group at C-(3) (δ = 1.60 ppm) induced a positive NOE on the phenyl proton signals (δ = 7.20 ppm) and no NOE was observed on the methyl group at C-(1′) (δ = 1.30 ppm). Similar conclusions can be drawn from the amide derivatives of both diastereoisomers.

Acknowledgements

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