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An Approach to Enantioselective 5-*endo* Halo-Lactonization Reactions

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Enantioselective lactonization of 4-substituted but-3-enoic acids using iodobis(*N*-methylephedrine) hexafluoroantimonate in dichloromethane at low temperatures is reported. The presence of bis(*N*-methylephedrine)silver(I) hexafluoroantimonate, derived from the excess amounts of *N*-methylephedrine and silver hexafluoroantimonate that were necessary for the generation of the iodo complex in the reaction mixture, is crucial for the success of this reaction. The different parameters of these cyclization reactions have been examined.

Introduction

Halo-promoted cyclization reactions of functionalized ω-substituted carboxylic acids and amides are useful methods for the construction of lactones or other heterocyclic compounds.[1] The stereoselectivity of these reactions has been extensively studied and is now well understood in the case of substrate-controlled cyclization reactions (diastereoselective cyclizations). However, although enantioselective cyclization reactions have been reported, the results have been moderate. The most obvious method involves the intervention of chiral halo reagents. By using this approach, different results have been reported. Low enantioselectivities (*ee* < 10%) have been obtained using iodine complexes of dihydroquinidine[2] or chiral pyridines.[3,4] Improved results (*ee* < 45%) have been reported in reactions with ICl complexed by chiral amines such as (*R*)-1-phenylethylamine or (*R*)-1,2,3,4-tetrahydronaphthylamine.[4] Enantioselective cyclization reactions of (*E*)-5-arylpent-4-enoic acids are reported to be possible using catalytic amounts (30 mol-%) of cinchonidine derivatives in the presence of iodine (*ee* < 42%).[5] Enantioselective iodolactonization of an α-hydroxy unsaturated acid has also been reported to be effective by complexation of the acid with a chiral titanium reagent.[6]

Results and Discussion

Our previous studies on the reactivity of halo-bis(collidine) derivatives in cyclization reactions[7] have led us to look at a chiral version of these reactions. We examined first the halo-lactonization of pent-4-enoic acid derivatives. For this study we needed chiral halonium salts. These compounds were prepared as shown in Scheme 1 by using two different approaches. The first one involves the direct formation of these salts by the reaction of a silver salt with 2 equivalents of the desired chiral amines and 1 equivalent of halogen. The proof of their synthesis was confirmed by iodine or bromine discoloration and the formation of silver halide. The second method involves the exchange of the collidines in halo-bis(collidine) hexafluorophosphates for more basic amines. In these cases, when the reaction mixtures were warmed to room temperature, a black tar was formed. Attempts to characterize the complexes formed by low-temperature NMR spectroscopy were unsuccessful and the only proof of their formation is based on their reactivity and their thermal instability. These reagents were thus prepared between –40 and –78 °C and used in situ in the subsequent halo-lactonization reactions.

The halo-lactonization reactions were carried out by addition at low temperature of the pent-4-enoic acids **12**–**14** to the preformed halo reagents. After 2 h at a low temperature, the acid was totally consumed and the iodolactones were formed; the reaction mixture was then warmed to room temperature and the lactones isolated (Scheme 2). GC analysis using a cyclodextrin column gave the enantiomeric excesses of the lactones **15** and **16**. Our results are reported in Table 1. With pent-4-enoic acid (**12**), whatever the chiral reagent (entries a–g), no enantioselectivity was observed in the formation of the halo-lactones **15a**,**b**. With 4-phenylpent-4-enoic acid (**13**), very low enantioselectivities were obtained (entries h–l). No reaction was observed with the acid **14**. Under the conditions reported for the iodolactonization of 5-arylpent-4-enoic acids,[4] acid **12** led to the iodolactone **15a** with an *ee* of only 6%. In all these reactions, the chiral ligands were quantitatively recovered and reused.

These modest results led us to examine 5-*endo* halo-lactonization reactions. This type of cyclization reaction has never been examined in detail[1] even though the first exam-

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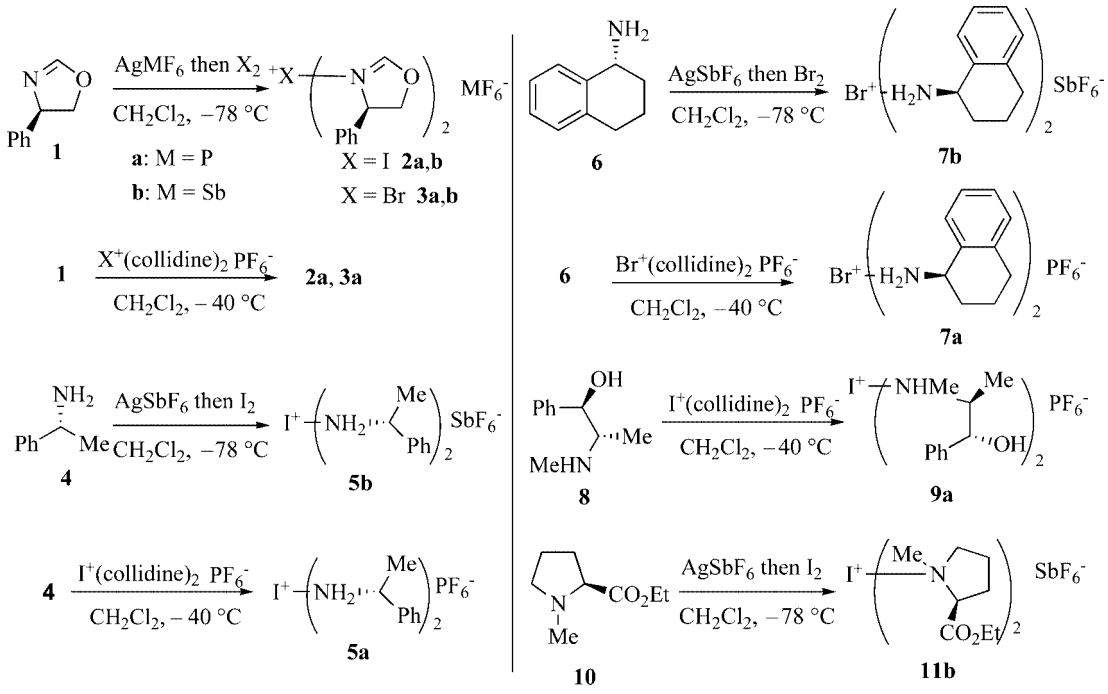
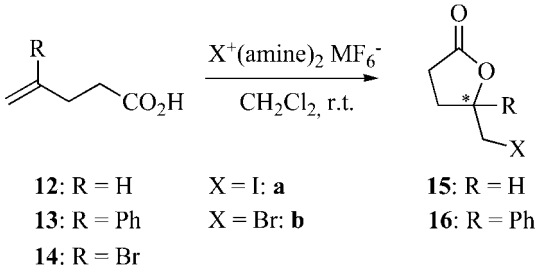


Scheme 1. Preparation of halo-bis(amine) salts.



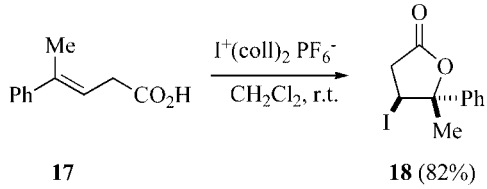
Scheme 2. Preparation of halo-lactones **15** and **16**.

Table 1. Halo-lactonization reactions of pent-4-enoic acids **12**–**14** using chiral halonium salts.

Entry	Acid	Halonium reagent	Lactone	Yield (%)	*ee* (%)
a	**12**	**2a**	**15a**	83	0[a]
b	**12**	**2a**	**15a**	73	0[b]
c	**12**	**2a**	**15a**	12	0[c]
d	**12**	**3b**	**15b**	86	0[b]
e	**12**	**5a**	**15a**	83	0[b]
f	**12**	**9a**	**15a**	78	0[b]
g	**12**	**11b**	**15b**	70	0[b]
h	**13**	**2b**	**16a**	72	5[a]
i	**13**	**5a**	**16a**	70	7[a]
j	**13**	**5b**	**16a**	20	2[a]
k	**13**	**7b**	**16b**	65	2[a]
l	**13**	**7a**	**16b**	60	3[a]
m	**14**	**5b**	–	–	–
n	**12**	[d]	**15a**	80	6[a]

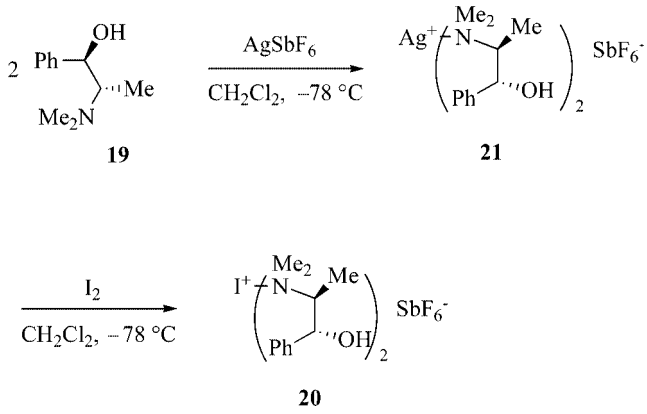
[a] Reaction carried out at –78 °C. [b] Reaction carried out at –40 °C. [c] Reaction carried out at –20 °C. [d] Reaction carried out with a mixture of ICl and (*R*)-1-phenylethylamine.[4]

ple was reported at the end of the nineteenth century.[8] We chose (*E*)-4-phenylpent-3-enoic acid (**17**) as the substrate.[9] Reaction with iodobis(collidine) hexafluorophosphate in dichloromethane at room temperature led to the formation of racemic iodolactone **18** in good yield (Scheme 3) whose stereochemistry was secured by X-ray crystallography.



Scheme 3. Iodolactonization of acid **17**.

To study the enantioselective version of this reaction, we chose (–)-*N*-methylephedrine (**19**) as the chiral amine. As described above for the preparation of the iodo complexes (Scheme 1), iodobis(*N*-methylephedrine) hexafluoroantimonate (**20**) was prepared by the reaction of 2 equivalents of *N*-methylephedrine (**19**) with 1 equivalent of iodine in the presence of 1 equivalent of silver hexafluoroantimonate (Scheme 4). Like the complexes in Scheme 1, complex **20** was unstable at room temperature and was thus prepared and used at a low temperature. In the absence of iodine, silver complex **21** was formed. Attempts to characterize these complexes using low-temperature NMR spectroscopy were unsuccessful. *N*-Methylephedrine was systematically recovered and reused.



Scheme 4. Preparation of complexes **20** and **21**.

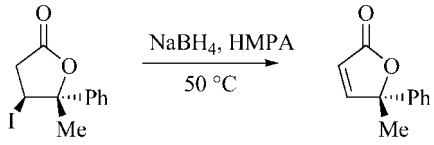
The acid **17** was then added at –78 °C to a mixture of complexes **20** and **21**. After 2 h at this temperature, the reaction mixture was analyzed. The iodolactone **18** was obtained in good yield and its enantiomeric excess was determined by GC analysis (cyclodextrin column). The same results were obtained when iodine was added to a mixture of the acid, silver hexafluoroantimonate and ephedrine. Our results are reported in Table 2. When the cyclization reaction was carried out with a stoichiometric $AgSbF_6$/ephedrine/I_2 ratio of 2:1:1, no enantioselectivity was observed (entries a and b). However, if the amount of iodine was less than this stoichiometry (that is, in the presence of the silver complex **21**), enantioselective cyclization reactions were observed. We noticed that the *ee* of this iodolactonization process increases in parallel with the increase in the amount of silver complex **21** present in the reaction mixture (see entries c–f). The best enantioselectivity (45%) was observed when the lactonization was carried out in the presence of 5 equivalents of the silver complex **21** relative to the iodine complex (entry g). Larger excesses of complex **21** (entries h and i) did not significantly modify the enantioselectivity of the lactonization reaction. No selectivity was observed (entries j and k) when the ratio of 2:1 amine/$AgSbF_6$ was not respected (excess of amine or excess of silver hexafluoroantimonate) and in the absence of the silver salt no reaction occurred at all (entry l). Thus, for the first time, we have been able to obtain an enantioselective 5-*endo* lactonization product with an enantiomeric excess of 45%. This result appears to be comparable to those already reported in the literature for 5-*exo* lactonization reactions under different conditions. Total consumption of the acid **17** was observed (same enantiomeric excess for the iodolactone **18**) by increasing the amount of iodine, *N*-methylephedrine and the silver salt by a factor of 2.5.

The absolute configuration of lactone **18** was determined after its transformation into the known α,β-ethylenic lactone **22**[10] (Scheme 5). The sign of the rotatory power of this lactone compared with that reported in the literature allowed us to assign the (*S*) configuration to the quaternary centre. The (*R*) configuration for the carbon atom bearing the iodine atom was then deduced from the mechanism of the iodolactonization reaction[1] and confirmed by the X-ray crystal structure.

Table 2. Enantioselective iodolactonization reactions of acid **17**.

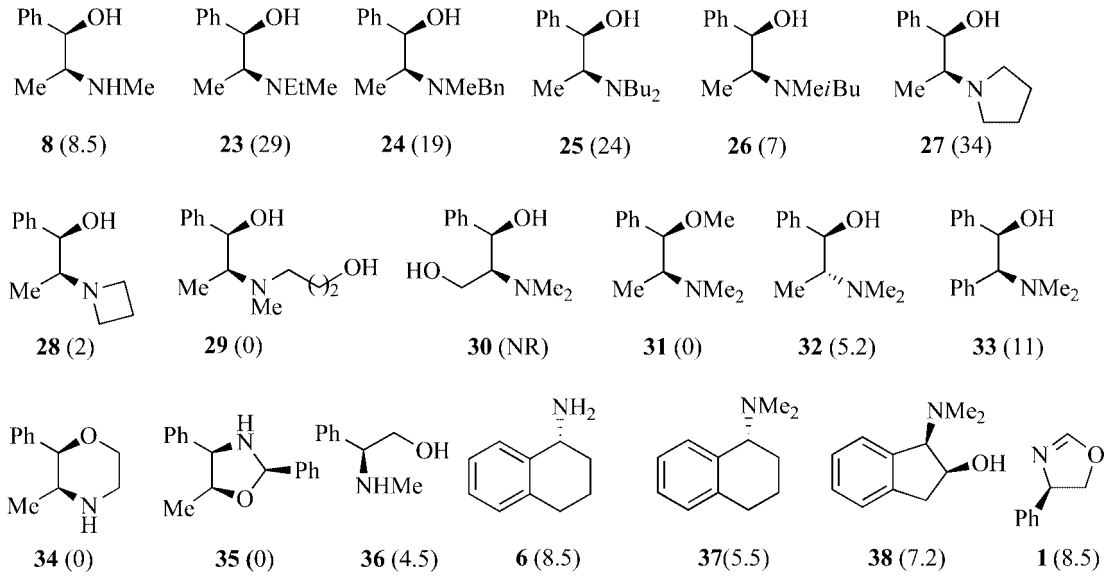
Entry	I_2 (equiv.)	*N*-Methylephedrine (equiv.)	$AgSbF_6$ (equiv.)	Yield[a] (%)	*ee*(%)
a	2.4	4.8	2.4	77	0
b	1	2	1	80	0
c	1	4.8	2.4	82	21
d	0.8	4.8	2.4	87	19
e	0.6	4.8	2.4	85	26
f	0.45	4.8	2.4	86	41
g	0.4	4.8	2.4	92	45
h	0.2	4.8	2.4	86	43
i	0.1	2.4	1.2	75	40[b]
j	0.4	4.8	1.2	51	0
k	0.4	2.4	2.4	85	0
l	0.4	4.8	0	NR	–

[a] All the reactions were carried out at –78 °C in the presence of 1 equiv. of acid **17**. Yields were calculated from the acid (entries a–c) or from the iodine (entries d–l). [b] The *ee* was 5% when the reaction was carried out at –20 °C.

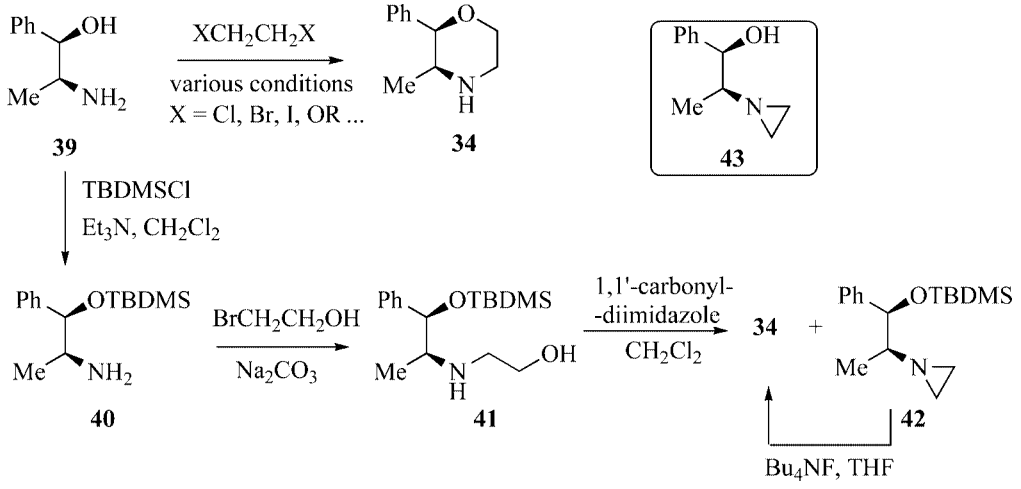


Scheme 5. Preparation of lactone **22**.

In a subsequent study we decided, using the previously determined optimum reaction conditions (Table 2, entry g), to examine various types of chiral amines. These amines were either commercially available or prepared using standard methods (see the Exptl. Sect.). We report in Scheme 6 the enantiomeric excesses obtained in the reactions of the iodobis(amine) reagents with acid **17**; iodolactones **18** were obtained with the same absolute configuration as that observed in the reaction with *N*-methylephedrine. Replacement of one or two of the methyl groups on the nitrogen atom of *N*-methylephedrine by other substituents (H, Et, Bu, *i*Bu and Bn) led to the formation of iodolactones **18** with lower enantiomeric excesses (amines **8** and **23**–**26**). This is also the case for the cyclopentanic amine **27**. Introduction of an additional alcohol function resulted in either a non-enantioselective cyclization (amine **29**) or no reaction at all (amine **30**). The diastereomer **32** of *N*-methylephedrine gave a lower enantiomeric excess. The other structures examined (compounds **1**, **6** and **33**–**38**) gave less interesting results. From these results it seems necessary to have a free hydroxy function (*ee* = 0 or no reaction with the amines **31**, **34** and **35**) and two alkyl groups fixed on the nitrogen atom, but these two groups should be small. However, the azetidine derivative **28** gave the almost racemic iodolactone. It would have been interesting to examine the case of the corresponding aziridine **43**, however, we were not able to obtain it from norephedrine **39**; all our attempts led to the exclusive formation of the cyclic amine **34**.[11] In the same way, although protection of the alcohol function



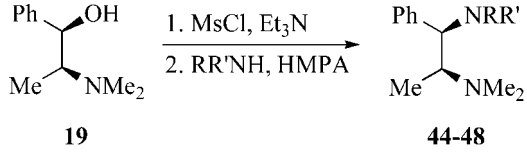
Scheme 6. *ee* values (%) measured for iodolactones **18** of (4*R*,5*S*) absolute configuration obtained by the iodolactonization of acid **17** with various amines.



Scheme 7. Attempts at the preparation of aziridine compound **43**.

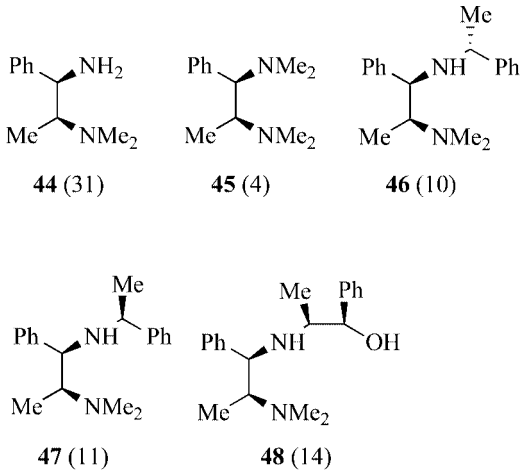
as a silyl ether led to the desired *N*-alkylated product **41**, subsequent attempts to form the aziridine ring gave rise to an inseparable mixture of compounds **34** and **42**. Treatment of this mixture with fluoride reagents mainly caused ring-opening of the aziridine and the six-membered heterocyclic compound **34** was mainly isolated (Scheme 7).

We report in Scheme 8 the case of diamines, which led to the iodolactone **18** with the opposite (4*S*,5*R*) absolute configuration. These compounds **44**–**48**, analogues of *N*-methylephedrine in which the hydroxy group is replaced by amino groups, were obtained from *N*-methylephedrine in two steps by double inversion reactions[12] (Scheme 9). The best enantioselectivity was obtained with diamine **44** possessing an NH_2 group. No iodolactonization was observed from the iodonium reagents formed from sparteine or Jacobsen ligands.



Scheme 8. Preparation of diamines **44**–**48**.

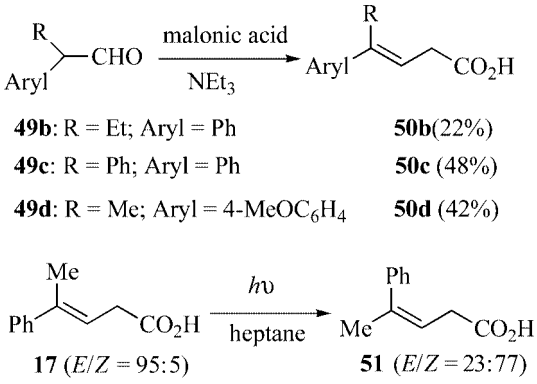
To improve the enantioselectivity of this iodolactonization reaction, we also examined other parameters of this reaction. The nature of the silver salt was found to be critical. Lower enantioselectivity was obtained when the iodobis(*N*-methylephedrine) salt was prepared from $AgPF_6$ (*ee* = 25%), whereas with $AgBF_4$ a low enantioselectivity (*ee* = 10%) in favour of the opposite enantiomer was obtained. The nature of the iodo reagent used for the formation of



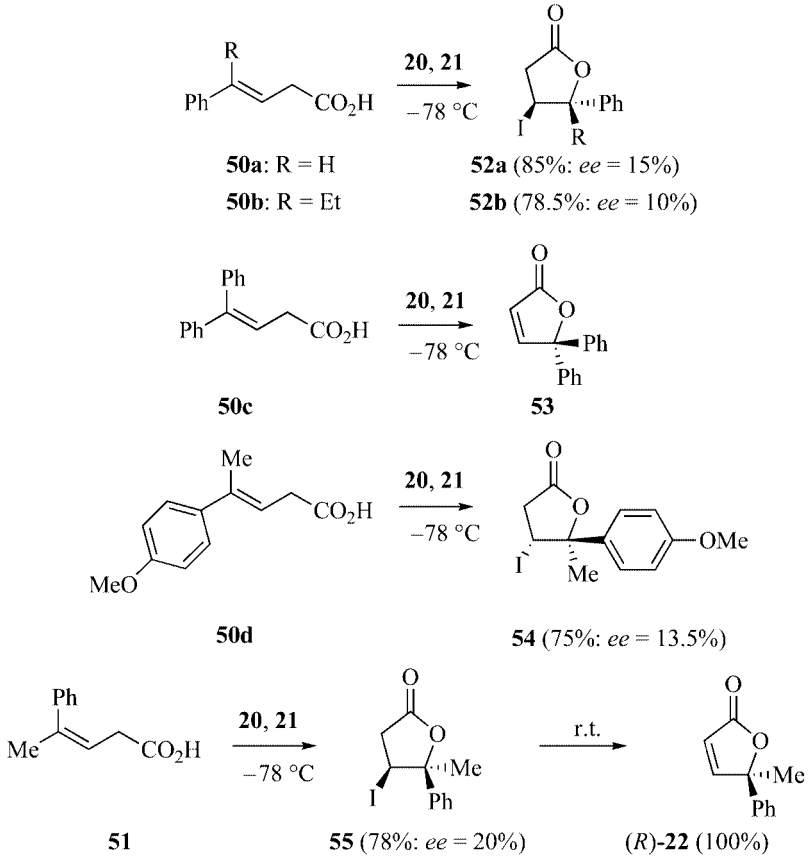
Scheme 9. *ee* values (%) measured for iodolactones **18** of (4*S*,5*R*) absolute configuration obtained by the iodolactonization of acid **17** with diamines **44**–**48**.

the complex is also very important. Instead of iodine, we investigated the use of other iodo reagents. With ICl we observed no reaction, whereas with $Me_3S^+I_3^-$, $Bu_4N^+I_3^-$ or iodobis(collidine) hexafluorophosphate we obtained the racemic iodolactone **18**. Only NIS, in addition to iodine, led to an enantioselective reaction (*ee* = 25%). The final parameters to be examined were the temperature and the presence of water. In general, the best results were obtained by reactions at –78 °C. The presence of water, probably introduced by hygroscopic silver salts, appears harmful for these reactions.

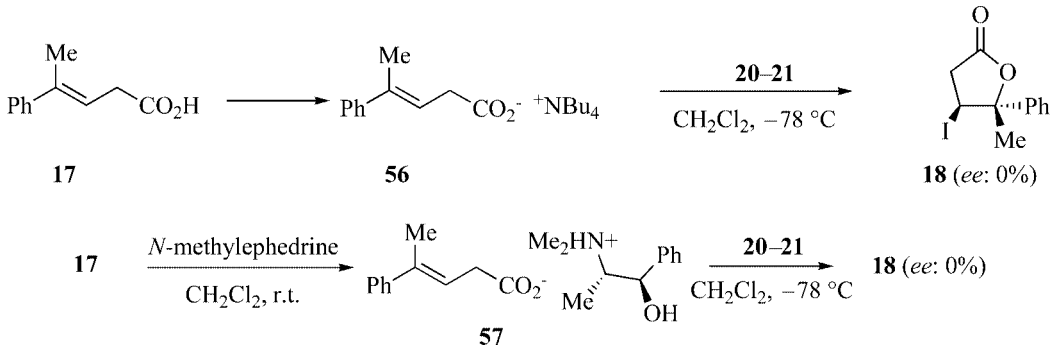
To examine the scope of this reaction, we checked the reactivity of some 4-arylalk-3-enoic acids. The acids **50b**–**d** were prepared by Knoevenagel condensation of aldehydes **49b**–**d** with malonic acid, followed by decarboxylation and isomerization of the carbon–carbon double bond. (*Z*)-4-Phenylpent-3-enoic acid (**51**) was obtained by photoisomerization of the corresponding (*E*) isomer **17**, followed by separation of the two isomers by liquid chromatography (Scheme 10). With these acids, as with acid **17**, only the 5-*endo* lactonization reactions were observed (Scheme 11).



Scheme 10. Preparation of 4-arylbut-3-enoic acids **50b**–**d** and **51**.



Scheme 11. Iodolactonization of acids **50a**–**d** and **51**.



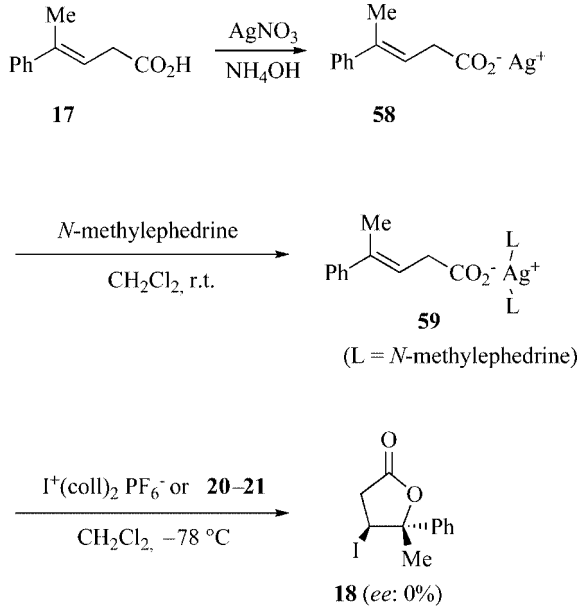
Scheme 12. Iodolactonization of salts **56** and **57**.

The iodolactones **52a**,**b** were obtained from the (*E*) acids **50a**,**b** by reaction with iodobis(*N*-methylephedrine) hexafluoroantimonate (**20**) in the presence of bis(*N*-methylephedrine)silver hexafluoroantimonate (**21**) and were identified by spectroscopic methods. In the two cases, the proportions of the two enantiomers were deduced from GC chromatograms. The absolute configuration (4*R*,5*S*) is identical to that of the lactone **18**. The unsaturated lactone **53** was isolated as the sole product from the acid **50c** (70% yield). The lactonization of acid **50d** led to iodolactone **54** with a (4*S*,5*R*) configuration. The iodolactone **55** with absolute configuration (4*R*,5*R*), obtained from the acid **51**, was unstable at room temperature, quantitatively transforming into the unsaturated lactone **22** with (*R*) configuration {$[a]_D^{20}$ = +42.0 (*c* = 0.8, CH_2Cl_2); *ee* = 20%} (Scheme 11).

Different hypotheses have been considered to explain the enantioselectivity observed in these reactions. The simplest explanation is the formation of ammonium carboxylates. We prepared the tetrabutylammonium carboxylate **56** to examine whether a simple ammonium salt could be involved in this kind of cyclization reaction. By reaction with iodobis(*N*-methylephedrine) hexafluoroantimonate (**20**) in the presence of the silver complex **21**, we obtained the racemic iodolactone **18** (90% yield). Similar results were obtained from the chiral ammonium salt **57** in its reaction with iodobis(collidine) hexafluorophosphonate or iodobis(*N*-methylephedrine) hexafluoroantimonate (**21**) (Scheme 12).

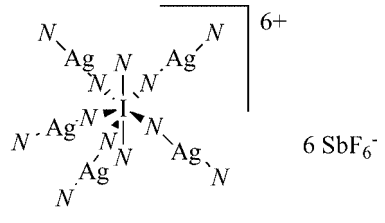
The formation of an ammonium carboxylate appearing improbable, we examined the possible formation of a chiral silver carboxylate intermediate. The reaction of 2 equivalents of *N*-methylephedrine with the insoluble silver carboxylate **58** led to a homogeneous solution of the corresponding salt (Scheme 13) which was characterized from its NMR spectra. After cooling to –78 °C, the complex **59** was treated with iodobis(collidine) hexafluorophosphate or a mixture of iodobis(*N*-methylephedrine) hexafluoroantimonate (**20**) and bis(*N*-methylephedrine)silver hexafluoroantimonate (**21**) to give in both cases the racemic lactone **18** in good yields.[13]

The possibility of complexation of the double bond of the acid with several molecules of silver complexes **21** can also probably be ruled out as the order of addition of the different reagents has no influence on the enantioselectivity



Scheme 13. Preparation and iodolactonization of the silver complex **59**.

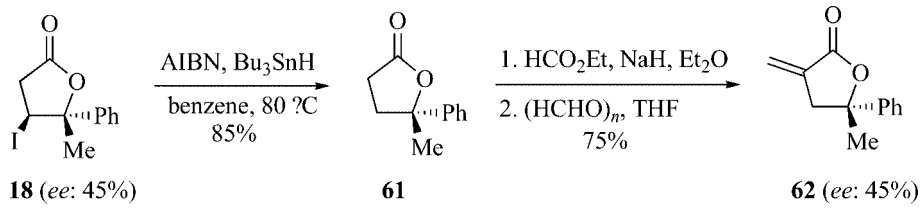
of the reactions. Another hypothesis to explain the enantioselectivity is that the iodolactonization reactions result from the reaction of the multicomponent complex **60** (Scheme 14). This complex could be obtained by an arrangement of five nitrogen ligands of complexes **21** around the iodine atom of complex **20**. This intermediate should have a pentagonal bipyramidal geometry according to the valence-shell electron-pair repulsion theory (VSEPR) and the geometry of seven-coordinate molecules.[14] The need



N = *N*-methylephedrine

60

Scheme 14. Postulated structure of complex **60**.



18 (*ee*: 45%) **61** **62** (*ee*: 45%)

Scheme 15. Preparation of lactone **62**.

for a free alcohol function on the ephedrine structure seems to imply the formation of hydrogen bonds between the different hydroxy functions. This architecture can be destabilized in the presence of counteranions other than the hexafluoroantimonate group as they should lead to closer approaches to the iodonium. Work is in progress to test these hypotheses. In addition, we observed that under the conditions used for the iodolactonization of acid **17**, no enantioselectivity could be obtained for substrates studied previously.[2–5] Equally, by using the conditions reported in the literature,[2–5] we observed no enantioselectivity for the halo-lactonization reactions of acid **17**. These observations lead us to conclude, for the moment, that it is difficult to find general conditions that are applicable to a variety of unsaturated acids.[15]

Optically active γ-butyrolactones and α-methylene-γ-butyrolactones are important compounds owing to their potential antibiotic, fungal, anthelmintic and antitumour activities.[16] Reaction of lactone **18** with tributyltin hydride in the presence of AIBN led to the deiodinated butyrolactone **61** (Scheme 15). This was easily transformed into the α-methylene-γ-butyrolactone **62** using a standard procedure. This method thus allows an easy access to this optically active lactone previously obtained by a different pathway.[17]

Experimental Section

NMR spectra were recorded in $CDCl_3$. GC was performed with a 40 m cyclodextrin DM column. The enantiomeric excesses of the different lactones were calculated by integration of the peaks of the two enantiomers in GC chromatograms. (*S*)-4,5-Dihydro-4-phenyloxazole (**1**) was prepared by reaction of (*S*)-2-amino-2-phenylethanol with ethyl orthoformate in the presence of trifluoroacetic acid in dichloromethane (55% yield).[18] (*R*)-1-Phenylethylamine (**4**), (*R*)-1,2,3,4-tetrahydronaphthalen-1-amine (**6**), (1*R*,2*S*)-ephedrine (**8**), (1*R*,2*S*)-2-dibutylamino-1-phenylpropan-1-ol (**25**), (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol (**27**) and (*S*)-2-(methylamino)-2-phenylethanol (**36**) are commercially available. Ethyl (*S*)-1-methylpyrrolidine-2-carboxylate (**10**) was obtained in three steps from L-proline by *N*-methylation using formaldehyde, followed by catalytic hydrogenation (99% yield)[19] and esterification (EtOH, cat. $SOCl_2$) (90% yield). 4-Phenylbut-3-enoic acid (**50a**) is commercially available. The products were purified by flash chromatography.

General Procedure for the Preparation of Halobis(amine) Salts. Method 1: Dichloromethane (16 mL) was added to a Schlenk flask containing dry $AgSbF_6$ (0.488, 1.42 mmol) maintained under argon. After cooling to –78 °C, a dichloromethane solution (2 mL) of the desired amine (2.84 mmol) was added dropwise. After 15 min at –78 °C, a dichloromethane solution (7.7 mL) of iodine (1.42 mmol) was added dropwise. We observed rapid iodine decolorization and the formation of a yellow solid (AgI). The same procedure was used for the formation of bromobis(amine) hexafluoroantimonate and other silver salts.

Method 2: Dichloromethane (10 mL) was added to a Schlenk flask containing iodobis(collidine) hexafluorophosphate[20] (0.73 g, 1.42 mmol) . After cooling to –40 °C, a dichloromethane solution (2 mL) of the desired amine (2.84 mmol) was added dropwise. After 1 h at this temperature, the iodobis(amine) hexafluorophosphate had formed and was used in subsequent reactions.

Preparation of Pent-4-enoic Acids 12–14: Pent-4-enoic acid (**12**) is commercially available. Acid **14** was prepared as previously reported.[21] Suzuki coupling of this acid with phenylboronic acid led to 4-phenylpent-4-enoic acid (**13**).[4]

General Procedure for the Iodolactonization of Acids 12–14: Acids **12**–**14** (1.42 mmol) were added to the halobis(amine) salts previously prepared at low temperatures. After 2 h at the desired temperature, the reaction mixture was warmed to room temp. and hydrolyzed with an aqueous 1 M HCl solution (10 mL). The solid was filtered. The aqueous phase was extracted with dichloromethane (3 × 10 mL). The organic phase was then washed with a sat. $Na_2S_2O_3$ solution (5 mL), brine (5 mL) and dried ($MgSO_4$). After concentration under vacuum, the residue was purified by liquid chromatography over silica gel (petroleum ether/diethyl ether, 90:10). Our results are reported in Table 1. 4,5-Dihydro-5-(iodomethyl)furan-2(3*H*)one (**15**)[2] and 4,5-dihydro-5-(iodomethyl)-5-phenylfuran-2(3*H*)one (**16**)[4] have been already described.

(*E*)-4-Phenylpent-3-enoic Acid (17):[9,22] A mixture of 2-phenylpropanal (10 g, 74.5 mmol), triethylamine (15.7 mL, 111.8 mmol, 1.5 equiv.) and malonic acid (7.75 g, 74.5 mmol) was refluxed overnight. After cooling to room temp. diethyl ether was added (30 mL) and the mixture was acidified by the addition of an aqueous 1 M HCl solution (pH 1). The aqueous phase was extracted with diethyl ether (30 mL) and then an aqueous 1 M NaOH solution (pH 10) was added. After extraction with diethyl ether (3 × 20 mL), this aqueous phase was acidified by addition of an aqueous 1 M HCl solution (pH 1) and extracted with diethyl ether (3 × 30 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by liquid chromatography over silica gel (CH_2Cl_2/Et_2O, 90:10) to give 5.90 g of (*E*)-4-phenylpent-3-enoic acid (5.90 g, 45%) and (*Z*)-4-phenylpent-3-enoic acid (0.66 g, 5%). (*E*) isomer: m.p. 78–79 °C. ^1H NMR ($CDCl_3$, 360 MHz): δ = 11.60 (br. s), 7.40–7.24 (m, 5 H), 5.93 (t, J = 6.1 Hz, 1 H), 3.30 (d, J = 7.2 Hz, 2 H), 2.07 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 178.4, 142.8, 138.7, 128.7, 127.7, 125.7, 118.3, 34.1, 16.2 ppm. IR (film): $\tilde{\nu}$ = 3022, 1710 cm^{-1}.

4,5-Dihydro-4-iodo-5-methyl-5-phenylfuran-2(3*H*)one (18): A dichloromethane solution (20 mL) of iodobis(collidine) hexafluorophosphate[20] (0.617 g, 12 mmol, 1.2 equiv.) was added to a dichloromethane solution (10 mL) of acid **17** (0.162 g, 10 mmol) during

0.5 h. After 1 h at room temp. the solvent was removed under vacuum and the residue purified by liquid chromatography over silica gel to give iodolactone **18** (0.241 g, 82% yield). White solid: m.p. 89.5–90 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.45–7.26 (m, 5 H), 4.65 (t, J = 6.4 Hz, 1 H), 3.00 (dd, J = 6.2 and 18.2 Hz, 1 H), 3.21 (dd, J = 7.2 and 16.8 Hz, 1 H), 1.94 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 183.6, 140.8, 128.9, 128.5, 124.3, 88.1, 42.2, 30.5, 27.7 ppm. IR (film): $\tilde{\nu}$ = 2984, 1784 cm^{-1}. $C_{11}H_{11}IO_2$ (302.18): calcd. C 43.73, H 3.67; found C 43.66, H 3.61. The crystal structure of **18** was established by single-crystal X-ray diffraction.

Representative Procedure for the Enantioselective Iodolactonization of Acid 17: At –78 °C under argon, a dichloromethane solution (2 mL) of (–)-(1*R*,2*S*)-*N*-methylephedrine (0.508 g, 2.84 mmol) was added dropwise to a Schlenk flask containing a dichloromethane solution (16 mL) of dry $AgSbF_6$ (0.488 g, 1.42 mmol). After 15 min at –78 °C, a dichloromethane solution of I_2 (1.28 mL of 0.18 M solution, 0.23 mmol) was added dropwise. After 15 min, a dichloromethane solution (2 mL) of (*E*)-4-phenylpent-3-enoic acid (**17**) (0.1 g, 0.568 mmol) was added dropwise. After 2 h at –78 °C, the reaction mixture was warmed to room temp. and an aqueous 1 M HCl solution (10 mL) was added. After filtration of the silver salts, the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by liquid chromatography over silica gel (petroleum ether/diethyl ether, 90:10) to give iodolactone **18** (86 mg). $[\alpha]_D^{20}$ = +22.1 (c = 1.2, $CHCl_3$). The aqueous phase was basified by addition of 1 N NaOH (pH 10) and extracted with dichloromethane (3 × 15 mL). After drying ($MgSO_4$), this organic phase was concentrated under vacuum to give (–)-(1*R*,2*S*)-*N*-methylephedrine (0.50 g, 98% yield).

Iodobis(*N*-methylephedrine) Hexafluoroantimonate (20): Iodo complex **20** was prepared at –78 °C following the procedure (method 1) reported for the preparation of the halobis(amine) salts. This salt was unstable at a temperature above –20 °C and could not be characterized.

Bis(*N*-methylephedrine)silver Hexafluoroantimonate (21): The silver salt **21** was prepared using the procedure used for the preparation of the iodo complex **20**. This salt was unstable at room temp. and could not be characterized. Its reaction at –78 °C with iodine gave rise to the formation of iodobis(*N*-methylephedrine) hexafluoroantimonate (**20**).

(*S*)-5-Methyl-5-phenylfuran-2(5*H*)-one (22): Iodolactone **18** (75 mg, 0.248 mmol) and $NaBH_4$ (12 mg, 0.496 mmol) were added to a flask containing HMPA (13 mL). The mixture was stirred for 3 h at room temp. and then for 1 h at 50 °C. After cooling, water was added (70 mL) and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL) and then dried ($MgSO_4$). After concentration under vacuum, the residue was purified by liquid chromatography over silica gel (pentane/CH_2Cl_2, 90:10 to 80:20) to give lactone **22** (30 mg, 70%) as a yellow oil. $[\alpha]_D^{20}$ = –92.0 (c = 1, $CHCl_3$; *ee* = 45%) {lit.:[10] $[\alpha]_D^{20}$ = –274.3 (c = 1.2, $CHCl_3$; *ee* > 98%)}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.58 (d, J = 5.5 Hz, 1 H), 7.30–7.27 (m, 5 H), 5.99 (d, J = 5.5 Hz, 1 H), 1.76 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 171.3, 159.4, 138.2, 127.8, 127.3, 123.7, 118.3, 87.9, 25.3 ppm.

General Method for the Methylation of Amines: A 39% aqueous formaldehyde solution (21 mmol) and a catalytic amount of 10% Pd/C were added to a methanol solution (5 mL) of the amine (10 mmol) . This mixture was stirred overnight under hydrogen (1 atm). After filtration, the filtrate was concentrated under vacuum and a mixture ethanol/toluene (1:1, 10 mL) was added. The solution was concentrated under vacuum to give quantitatively the *N*-methylamine, which was pure enough to be used without purification. This method was used for the preparation of amines **19**, **30**, **32**, **33**, **37**, and **38**. The same procedure was used with isobutyraldehyde for the preparation of *N*-isobutylephedrine (**26**).

***N*-Ethylephedrine (23):** Compound **23** was prepared in two steps from ephedrine by reaction with acetonitrile, followed by reaction with H_2 on Pd/C following a known procedure.[23]

***N*-Benzylephedrine (24):** Compound **24** was prepared in two steps from ephedrine by reaction with benzaldehyde (preparation of amine **35**), followed by reaction with sodium borocyanohydride/TMSCl in acetonitrile.[24]

(1*R*,2*S*)-2-(Azetidin-1-yl)-1-phenylpropan-1-ol (28): Compound **28** was obtained by reaction of norephedrine with 1,3-dibromopropane using a reported procedure.[25] ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.27–7.20 (m, 5 H), 4.65 (d, J = 2.7 Hz, 1 H), 3.26 (m, 2 H), 3.17 (m, 2 H), 2.36 (dq, J = 2.7 and 6.5 Hz, 1 H), 1.99 (m, 2 H), 0.56 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 141.4, 127.6, 126.4, 125.8, 125.6, 70.7, 69.0, 53.1 (2 C), 16.4, 8.5 ppm.

(1*R*,2*S*)-2-[(3-Hydroxypropyl)(methyl)amino]-1-phenylpropan-1-ol (29): Compound **29** was obtained in two steps by reaction of ephedrine **39** with 3-hydroxypropanenitrile, followed by hydrogenation on Pd/C.[23]

(1*R*,2*S*)-1-Methoxy-*N*,*N*-dimethyl-1-phenylpropan-2-amine (31): Compound **31** was prepared by *O*-methylation of *N*-methylephedrine following a reported procedure.[26]

(1*R*,2*S*)-[2-(*tert*-Butyldimethylsilyloxy)-1-methyl-2-phenylethyl]-amine (40): Compound **40** was prepared following a reported procedure.[27]

(1*R*,2*S*)-2-[2-(*tert*-Butyldimethylsilyloxy]-1-methyl-2-phenylethyl-amino]ethanol (41): A toluene solution (5 mL) of 2-bromoethanol (0.329 g, 2.71 mmol) was added to a toluene solution (5 mL) of amine **40** (0.72 g, 2.7 mmol) and the mixture was refluxed for 18 h. Na_2CO_3 (0.574 g, 5.42 mmol) was added and the mixture was refluxed again for 18 h. After cooling, the solid was filtered through Celite. The filtrate was dried ($MgSO_4$) and concentrated under vacuum. The residue was then purified by chromatography over silica gel to give the amino alcohol **41** (0. 48 g, 58%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.35–7. 26 (m, 5 H), 4.63 (d, J = 4.5 Hz, 1 H), 3.52 (t, J = 5.5 Hz, 2 H), 2.87 (m, 1 H), 2.75 (m, 2 H), 1.80 (br. s, 1 H), 1.00 (d, J = 6.2 Hz, 3 H), 0.91 (s, 9 H), 0.04 (s, 3 H), –0.18 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 142.7, 127.9, 127.1, 126.7, 77.7, 60.8, 59.3, 48.3, 25.8 (3 C), 18.2, 15.3, –4.5, –5.0 ppm. HRMS: calcd. for $C_{17}H_{21}NO_2Si$ 309.2124; found 309.2126.

Preparation of Compound 42: 1,1′-Carbonyldiimidazole (0.377 g, 2.3 mmol) was added to a dichloromethane solution (10 mL) of amino alcohol **41** (0.71 g, 2.3 mmol). After one night at room temp. water was added (5 mL) and the aqueous phase was extracted with dichloromethane (2 × 5 mL). The combined organic phases were dried (MgSO4) and concentrated under vacuum. The residue was then purified by liquid chromatography over silica gel to give (0.63 g) an inseparable mixture of compounds **42** and **34** (1:1.6). Compound **42**: ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.38–7.25 (m, 5 H), 5.03 (d, J = 5.5 Hz, 1 H), 3.86 (m, 1 H), 1.29–1.23 (m, 4 H), 1.19 (d, J = 7.0 Hz, 3 H), 0.95 (s, 9 H), 0.05 (s, 3 H), –0.24 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 143.0, 129.3, 128.9, 127.7, 77.9, 65.1, 27.0, 19.3, 19.2, 13.1, –3.5, –4.6 ppm. $C_{17}H_{29}NOSi$ (291.50): calcd. C 70.04, H 10.03; found C 70.21, H 10.12.

(1*R*,2*S*)-*N*′,*N*′-Dimethyl-1-phenylpropane-1,2-diamine (44): Triethylamine (2.35 mL, 16.7 mmol) and a THF solution (10 mL) of methanesulfonyl chloride (0.86 mL, 11.17 mmol) was added to a THF solution (22 mL) of (1*R*,2*S*)-*N*-methylephedrine. NaN_3 (1.085 g, 16.7 mmol) and HMPA (13 mL) were added to the chloramine thus formed at room temp.. After 30 min, a THF solution (8 mL) of $LiAlH_4$ (0.835 g, 22.2 mmol) was added and after a further 30 min, the mixture was hydrolyzed by successive addition of water (0.84 μL), an aqueous 1 M KOH solution (0.84 mL) and water (2.5 mL). The aqueous phase was extracted with diethyl ether (3 × 15 mL). The organic phases were washed with water (3 × 15 mL), dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by chromatography on silica gel (eluent CH_2Cl_2/MeOH/NH_4OH, 90:10:0.2) to give the product in 80% yield as a yellow oil. $[\alpha]_D^{20}$ = –10.3 (*c* = 2, CH_2Cl_2). ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.33–7.16 (m, 5 H), 4.18 (d, *J* = 4.5 Hz, 1 H), 2.48 (m, 1 H), 2.27 (s, 6 H), 1.65 (br. s, 2 H, NH_2), 0.88 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 144.4, 127.8, 126.5, 126.2, 65.6, 56.2, 42.6, 9.7 ppm. HRMS: calcd. for $C_{11}H_{18}N_2Na$ 201.1368; found 201.1369.

General Procedure for the Preparation of Diamines 45–48:[12] Triethylamine (4.18 mL, 0.03 mol) and then dropwise a THF solution (20 mL) of methanesulfonyl chloride (1.57 mL, 0.02 mol) were added to a solution of (1*R*,2*S*)-*N*-methylephedrine (**8**) in THF (40 mL) at 0 °C. After 1 h the solvent was removed under vacuum. The desired amine (0.09 mol, 3 equiv.) in THF/HMPA (1:3) solution (8 mL) was added, and the mixture was heated for 12 h at 80 °C. After cooling and addition of water (6 mL), the aqueous phase was extracted with Et_2O (3 × 15 mL). The organic phases were washed with water (3 × 15 mL), dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by chromatography on silica gel (eluent CH_2Cl_2/MeOH/NH_4OH, 90:10:0.2).

(1*R*,2*S*)-*N*,*N*,*N*′,*N*′-Tetramethyl-1-phenylpropane-1,2-diamine (45): Yield: 74%. White crystal: m.p. 52 °C. $[\alpha]_D^{20}$ = –25 (*c* = 1.0, CH_2Cl_2).^1H NMR ($CDCl_3$, 250 MHz): δ = 7.35–7.22 (m, 3 H), 7.12–7.08 (m, 2 H), 3.36 (d, *J* = 10.7 Hz, 1 H), 3.19 (m, 1 H), 2.10 (s, 6 H), 2.06 (s, 6 H), 1.11 (d, *J* = 6.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 135.5, 129.2, 127.2, 126.6, 72.2, 58.2, 41.1, 40.2, 8.6 ppm. ES-MS: *m*/*z* = 162.2 [M – $N(Me)_2$]$^+$. $C_{13}H_{22}N_2$ (206.32): calcd. C 75.68, H 10.75; found C 75.74, H 10.81.

(1*R*,2*S*)-*N*′,*N*′-Dimethyl-1-phenyl-*N*-[(*R*)-1-phenylethyl]propane-1,2-diamine (46): Yield: 94%. Yellow oil. $[\alpha]_D^{20}$ = –139.5 (*c* = 2.1, CH_2Cl_2). ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.36–7.15 (m, 10 H), 3.57 (d, *J* = 4.5 Hz, 1 H), 3.37 (q, *J* = 6.6 Hz, 1 H), 2.21 (m, 1 H), 2.02 (s, 6 H), 1.92 (br. s, 1 H), 1.35 (d, *J* = 7.0 Hz, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 145.6, 142.8, 128.0, 127.9, 126.8, 126.6, 126.3, 65.9, 60.3, 54.6, 42.9, 24.2, 11.0 ppm. ES-MS: *m*/*z* = 162.2 [M – N(Me)Ph]$^+$. $C_{19}H_{26}N_2$ (282.42): calcd. C 80.80, H 9.28; found C 80.82, H 9.33.

(1*R*,2*S*)-*N*′,*N*′-Dimethyl-1-phenyl-*N*-[(*S*)-1-phenylethyl]propane-1,2-diamine (47): Yield: 95%. Yellow oil. $[\alpha]_D^{20}$ = –142 (*c* = 1.05, CH_2Cl_2). ^1H NMR ($CDCl_3$, 63 MHz): δ = 7.33–7.18 (m, 10 H), 4.07 (d, *J* = 4.3 Hz, 1 H), 3.63 (q, *J* = 6.5 Hz, 1 H), 2.50 (m, 1 H), 2.30 (s, 6 H), 1.31 (d, *J* = 6.1 Hz, 3 H), 0.94 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 250 MHz): δ = 146.8, 142.7, 128.1, 127.8, 127.7, 126.5, 126.4, 126.3, 65.5, 61.4, 54.1, 42.8, 21.8, 10.5 ppm. $C_{19}H_{26}N_2$ (282.42): calcd. C 80.80, H 9.28; found C 80.75, H 9.34.

(1*R*,2*S*)-2-{[(1*R*,2*S*)-2-(Dimethylamino)-1-phenylpropyl]amino}-1-phenylpropan-1-ol (48): Yield: 48%. White crystal: m.p. 102 °C. $[\alpha]_D^{20}$ = –28 (*c* = 1.05, CH_2Cl_2). ^1H NMR ($CDCl_3$, 360 MHz): δ = 7.37–7.18 (m, 10 H), 4.86 (d, *J* = 3.2 Hz, 1 H), 4.02 (d, *J* = 4.7 Hz, 1 H), 2.78 (m, 1 H), 2.65 (m, 1 H), 2.30 (s, 6 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 0.68 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 142.8, 141.7, 128.1, 127.8, 127.3, 126.7, 126.5, 71.6, 65.5, 61.4, 55.9, 42.7, 15.1, 10.4 ppm. HRMS: calcd. for $C_{20}H_{28}ON_2Na$ 335.2099; found 335.2100.

Preparation of 2-Phenylbutanal (49b):[28] Dess–Martin periodinate (1.55 g, 3.66 mmol, 1.1 equiv.) was added to a dichloromethane solution (5 mL) of 2-phenylbutanol (0.5 g, 3.33 mmol). The mixture was stirred for 1 h at room temp. and then a saturated aqueous solution of $Na_2S_2O_3$ (10 mL) and a 10% aqueous solution of $NaHCO_3$ were added. After separation of the organic phase, the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under vacuum to give the aldehyde **49b** (0.48 g, 97% yield), which was pure enough for the next step. ^1H NMR ($CDCl_3$, 250 MHz): δ = 9.68 (s, 1 H), 7.38–7.18 (m, 5 H), 3.41 (t, *J* = 7.5 Hz, 1 H), 2.15 (m, 1 H), 1.74 (m, 1 H), 0.91 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 200.9, 136.2, 128.9, 128.7, 127.4, 60.8, 22.9, 11.6 ppm.

(*E*)-4-Phenylhex-3-enoic Acid (50b): Compound **50b** was prepared using the procedure described above for the preparation of acid **17**. The crude reaction mixture showed the formation of a mixture (80:20) of two diastereomers. The pure (*E*) isomer was obtained as an oil by liquid chromatography on silica gel (22% yield). ^1H NMR ($CDCl_3$, 360 MHz): δ = 11.70 (br. s, 1 H), 7.37–7.21 (m, 5 H), 5.79 (t, *J* = 7.2 Hz, 1 H), 3.29 (d, *J* = 7.0 Hz, 2 H), 2.50 (q, *J* = 7.2 Hz, 2 H), 0.99 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 178.7, 145.4, 139.1, 128.2, 127.0, 126.4, 117.9, 33.8, 23.3, 13.2 ppm. $C_{12}H_{14}O_2$ (190.24): calcd. C 75.76, H 7.42; found C 75.82, H 7.56.

4,4-Diphenylbut-3-enoic Acid (50c): Compound **50c** was prepared following the procedure described above for the preparation of acid **17** (48% yield). This compound has already been reported in the literature.[29]

(*E*)-4-(4-Methoxyphenyl)pent-3-enoic Acid (50d): Compound **50d** was prepared from aldehyde **49d** following the procedure described above for the preparation of acid **17**.[30] An 80:20 mixture of the two diastereomers was obtained. The pure (*E*) isomer was obtained as an oil by liquid chromatography on silica gel (CH_2Cl_2/Et_2O, 95:5). Yield: 42%. ^1H NMR ($CDCl_3$, 250 MHz): δ = 10.66 (br. s, 1 H), 7.36–7.32 (m, 2 H), 6.88–6.83 (m, 2 H), 5.85 (t, *J* = 7.2 Hz, 1 H), 3.81 (s, 3 H), 3.28 (d, *J* = 9.5 Hz, 2 H), 2.05 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 178.3, 158.8, 137.9, 135.4, 128.6, 116.7, 113.4, 55.2, 34.1, 16.2 ppm. $C_{12}H_{14}O_3$ (206.24): calcd. C 69.88, H 6.84; found C 69.91, H 6.93.

(*Z*)-4-Phenylpent-3-enoic Acid (51): (*E*)-4-Phenylpent-3-enoic acid (**17**) (0.5 g, 2.84 mmol) in heptane (180 mL) was placed in a Pyrex photochemical reactor and was irradiated for 5 h at 253.7 nm using a mercury lamp. The solution was concentrated under vacuum and the residue purified by liquid chromatography on silica gel to give the (*Z*) acid **51** (0.38 g, 77%) and the remaining (*E*) isomer **17** (0.12 g, 23%). ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.38–7.16 (m, 5 H), 5.63 (t, *J* = 7 Hz, 1 H), 3.05 (d, *J* = 7 Hz, 2 H), 2.09 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 178.9, 140.9, 140.7, 128.3, 127.7, 127.0, 117.6, 34.5, 25.6 ppm.

Iodolactonization of Acids 50a–d and 51: These iodolactonization reactions were carried out as reported for the iodolactonization of acid **17** using the conditions reported in Table 2, entry g. GC analysis (40 m cyclodextrin DM column) of the reaction mixtures allowed the *ee* of lactones **52a**,**b**, **54**, **55** to be calculated (Scheme 11). Their absolute configurations were deduced, by comparison with

lactone **18**, from the relative intensity of the two peaks of the enantiomers.

(4*R*,5*S*)-4,5-Dihydro-4-iodo-5-phenylfuran-2(3*H*)-one (52a): The racemic lactone has already been reported in the literature.[31] $[\alpha]_D^{20}$ = +5.3 (*c* = 1.25; CH_2Cl_2; *ee*: 15%).

(4*R*,5*S*)-5-Ethyl-4,5-dihydro-4-iodo-5-phenylfuran-2(3*H*)-one (52b): ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 7.40–7.26 (m, 5 H), 4.69 (dd, *J* = 5.0 Hz, *J* = 5.0 Hz, 1 H), 3.20 (dd, *J* = 18.4 and 7.6 Hz, 1 H), 3.00 (dd, *J* = 5.0 and 18.0 Hz, 1 H), 2.21 (q, *J* = 7.2 Hz, 2 H), 0.76 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 173.6, 138.9, 128.9, 128.3, 125.0, 90.1, 42.3, 36.6, 29.1, 9.0 ppm. HRMS: calcd. for $C_{12}H_{13}INaO_2$ 338.9858; found 338.9859.

5,5-Diphenylfuran-2(5*H*)-one (53): Compound **55** has already been reported in the literature.[32]

(4*S*,5*R*)-4,5-Dihydro-4-iodo-5-(4-methoxyphenyl)-5-methylfuran-2(3*H*)-one (54): $[\alpha]_D^{20}$ = –1.5 (*c* = 0.75, CH_2Cl_2; *ee*: 13.5%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.37–7.33 (m, 2 H), 6.95–6.88 (m, 2 H), 4.59 (t, *J* = 7.0 Hz, 1 H), 3.80 (s, 3 H), 3.20 (dd, *J* = 18.2 and 7.5 Hz, 1 H), 2.99 (dd, *J* = 18.0 and 6.5 Hz, 1 H), 1.91 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 173.6, 159.5, 132.6, 125.6, 114.1, 88.1, 55.3, 42.1, 30.2, 27.7 ppm. HRMS: calcd. for $C_{12}H_{13}INaO_3$ 354.9802; found 354.9805.

(4*R*,5*R*)-4,5-Dihydro-4-iodo-5-methyl-5-phenylfuran-2(3*H*)-one (55): ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 7.41–7.26 (m, 5 H), 4.70 (dd, *J* = 7.2 and 4.7 Hz, 1 H), 3.51 (dd, *J* = 18.4 and 7.0 Hz, 1 H), 3.12 (dd, *J* = 18.4 and 4.7 Hz, 1 H), 1.87 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 183.5, 143.2, 128.2, 128.1, 124.9, 89.1, 42.5, 28.4, 25.6 ppm. HRMS: calcd. for $C_{11}H_{11}IO_2$ 301.9804; found 301.9805.

Tetrabutylammonium (*E*)-4-Phenylpent-3-enoate (56): This salt was prepared following a known procedure.[33] A 25% MeOH solution of tetrabutylammonium hydroxide (0.571 mmol, 1.005 equiv.) was added to a dichloromethane solution (1 mL) of (*E*)-4-phenylpent-3-enoic acid (**17**) (0.1 g, 0.568 mmol). After stirring for 1 h at room temp. the solution was concentrated under vacuum. Toluene (2 × 1 mL) was added to the residue and the mixture was concentrated under vacuum to give salt **56** (0.235 g, 100% yield). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.44–7.14 (m, 5 H), 6.26 (t, *J* = 7.2 Hz, 1 H), 3.30 (m, 8 H), 3.15 (d, *J* = 7.0 Hz, 2 H), 2.03 (s, 3 H), 1.60 (m, 8 H), 1.42 (m, 8 H), 0.97 (t, *J* = 7.0 Hz, 12 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 176.7, 144.0, 132.9, 127.8, 126.0, 125.9, 125.2, 58.4, 38.9, 23.7, 19.5, 15.7, 13.4 ppm.

***N*-Methylephedrinium (*E*)-4-Phenylpent-3-enoate (57):** The procedure reported for the preparation of compound **56** was followed. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.38–7.14 (m, 10 H), 6.08 (t, *J* = 6.5 Hz, 1 H), 5.31 (m, 1 H), 3.11 (d, *J* = 6.5 Hz, 3 H), 3.04 (m, 1 H), 2.56 (s, 3 H), 1.97 (s, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 178.0, 143.1, 134.8, 127.7, 127.6, 126.7, 126.1, 125.4, 125.2, 122.7, 70.2, 65.7, 40.3, 36.7, 15.5, 5.9 ppm.

Silver 4-Phenylpent-3-enoate (58): 4-Phenylpent-3-enoic acid (**17**) (0.5 g) was added to a flask containing a 25% aqueous solution of NH_4OH (0.45 mL, 1 equiv.). After dissolution, $AgNO_3$ (0.58 g, 1.2 equiv.) was added and the mixture was stirred for 1 h at room temp. in the dark. The white solid was filtered, washed with water and dried under high vacuum (0.48 g, 60%). M.p. 154 °C (decomp.). ^{1}H NMR ([D$_6$]DMSO, 63 MHz): δ = 7.40–7.19 (m, 5 H), 6.00 (t, *J* = 7.5 Hz, 1 H), 3.06 (d, *J* = 7.2 Hz, 2 H), 1.98 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 63 MHz): δ = 175.0, 143.0, 134.0, 128.2, 126.6, 125.2, 124.1, 36.9, 15.6 ppm. $C_{11}H_{11}AgO_2$ (283.07): calcd. C 46.67, H 3.92; found C 46.27, H 3.91.

Silver Complex 59: Silver 4-phenylpent-3-enoate (**58**) (0.1, 0.353 mmol) was added to a flask containing dichloromethane (5 mL). (1*R*,2*S*)-*N*-Methylephedrine (0.126 g, 0.706 mmol, 2 equiv.) was added to this solid suspension. After stirring at room temp. for 1 h in the dark, the homogeneous solution was concentrated under vacuum to give the silver complex **59** (100% yield). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.33–7.14 (m, 15 H), 6.06 (t, *J* = 7.2 Hz, 1 H), 5.13 (m, 2 H), 3.16 (d, *J* = 7.2 Hz, 2 H), 2.56 (s, 12 H), 2.41 (m, 2 H), 1.97 (s, 3 H), 0.92 (d, *J* = 6.2 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 178.8, 143.4, 142.5, 135.4, 128.0, 126.8, 126.4, 125.8, 125.6, 123.3, 70.7, 67.8, 45.6, 37.2, 15.9, 10.8 ppm.

Iodolactonization of Silver Complex 59: (–)-*N*-Methylephedrine (50.6 mg, 0.282 mmol, 2 equiv.) was added to a dichloromethane solution (2 mL) of silver complex **59** (40 mg, 0.141 mmol, 1 equiv.). After 30 min at room temp. the flask was cooled to –78 °C. (–)-*N*-Methylephedrine (70.8 mg, 0.396 mmol, 2.8 equiv.) was added to a second flask containing a dichloromethane solution (5 mL) of $AgSbF_6$ (68 mg, 0.198 mmol, 1.4 equiv.) cooled to –78 °C. After 15 min a dichloromethane solution of iodine (0.314 mL of a 0.18 M solution, 0.4 equiv.) was added. After 15 min at –78 °C the content of the first flask was added through a cannula to the second flask. The reaction mixture was maintained for 2 h at –78 °C and then work up was carried out as previously reported. The racemic iodolactone **18** was obtained (32 mg, 76%)

(*S*)-4,5-Dihydro-5-methyl-5-phenylfuran-2(3*H*)-one (61): AIBN (3.5 mg) and Bu_3SnH (0.110 g, 0.381 mmol) were added to a benzene solution (4 mL) of iodolactone **18** (0.115 g, 0.381 mmol). The solution was refluxed overnight. After cooling, the solution was concentrated under vacuum. Acetonitrile (6 mL) was added and the solution was washed with pentane (3 × 10 mL). The acetonitrile solution was concentrated under vacuum and the residue purified by liquid chromatography on silica gel (pentane/diethyl ether, 80:20) to give lactone **61** as an oil (57 mg, 85% yield). $[\alpha]_D^{20}$ = –29.5 (*c* = 0.95, CH_2Cl_2; *ee*: 45%) {ref.[34] $[\alpha]_D^{20}$ = –34.1 (MeOH; *ee*: 90%)}.

(*S*)-4,5-Dihydro-5-methyl-3-methylene-5-phenylfuran-2(3*H*)-one (62): An ethereal solution (1 mL) of ethyl formate (13 mg, 0.176 mmol) and lactone **61** (31 mg, 0.176 mmol) was added during 1 h to a suspension of NaH (7 mg, 0.176 mmol) in diethyl ether (1 mL) maintained under argon. After 15 h at room temp. the solvent was removed under vacuum. THF (2 mL) and paraformaldehyde (27 mg, 0.88 mmol) were successively added. The mixture was refluxed for 3 h and after cooling an aqueous 6 M HCl solution (2 mL) was added. The aqueous phase was extracted with diethyl ether (3 × 3 mL). The organic phases were then washed with an aqueous saturated $NaHCO_3$ solution (3 mL), dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by liquid chromatography on silica gel (pentane/diethyl ether, 80:20) to give lactone **62** (25 mg, 75%). $[\alpha]_D^{20}$ = –2.2 (*c* = 0.25, CH_2Cl_2) {ref.[16] $[\alpha]_D^{20}$ = –11.3 (*c* = 1.2, $CHCl_3$)}.

Crystallographic Data: CCDC-626505 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

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[1] a) S. Robin, G. Rousseau, *Tetrahedron* **1998**, *54*, 13681–13736; b) S. Ranganathan, K. M. Muraleedharan, N. K. Vaish, N. Jayaraman, *Tetrahedron* **2004**, *60*, 5273–5308; c) K. E. Harding, T. H. Tiner, *Comprehensive Organic Synthesis* (Eds.: B. M.Trost, I. Fleming), Pergamon Press, Oxford, **1991**, vol. 4, p. 463; d) G. Cardillo, M. Orena, *Tetrahedron* **1990**, *46*, 3321–3408.
[2] R. B. Grossman, R. J. Trupp, *Can. J. Chem.* **1998**, *76*, 1233–1237.
[3] X.-L. Cui, R. S. Brown, *J. Org. Chem.* **2000**, *65*, 5653–5658.
[4] J. Haas, S. Piguel, T. Wirth, *Org. Lett.* **2002**, *4*, 297–300.
[5] M. Wang, L. X. Gao, W. P. Mai, A. X. Xia, F. Wang, S. B. Zhang, *J. Org. Chem.* **2004**, *69*, 2874–2876.
[6] O. Kitagawa, T. Hanano, K. Tanabe, M. Shiro, T. Taguchi, *J. Chem. Soc., Chem. Commun.* **1992**, 1005–1007.
[7] a) G. Rousseau, T. Strzalko, M.-C. Roux, *Tetrahedron Lett.* **2004**, *45*, 4503–4505; b) C. Mendés, S. Renard, M. Rofoo, M.-C. Roux, G. Rousseau, *Eur. J. Org. Chem.* **2003**, 472–476, and references cited therein.
[8] a) R. Fittig, B. Frost, *Justus Liebigs Ann. Chem.* **1884**, *226*, 363–376. For recent utilizations of this reaction, see, for example: b) S. Ma, L. Lu, *J. Org. Chem.* **2005**, *70*, 7629–7633; c) D. J. Hart, D. A. Ellis, *Heterocycles* **1998**, *49*, 117–120.
[9] S. H. M. Kumar, S. B. V. Reddy, J. E. Reddy, J. S. Yadav, *Tetrahedron Lett.* **1999**, *40*, 2401–2404.
[10] K. Susuki, K. Inomata, *Tetrahedron Lett.* **2003**, *44*, 745–749.
[11] M. J. Kalm, *J. Med. Chem.* **1964**, *7*, 427–433.
[12] R. K. Dieter, N. Deo, B. Lagu, J. W. Dieter, *J. Org. Chem.* **1992**, *57*, 1663–1671.
[13] Complexation of the silver carboxylate **58** by three molecules of *N*-methylephedrine is also possible. This complex also reacted with iodobis(collidine) hexafluorophosphate or iodobis(*N*-methylephedrine) hexafluoroantimonate to give the racemic lactone **18**.
[14] Z. Lin, I. Bytheway, *Inorg. Chem.* **1996**, *35*, 594–603.
[15] When the iodolactonization of acid **17** was carried out with *N*-methylephedrine (78% *ee*), we obtained under our optimum conditions, the iodolactone **18** with an *ee* of 35%, which corresponds to the expected value. Thus, no non-linear effect was observed in these cyclization reactions.
[16] See, for example: a) R. Bandichhor, B. Nosse, O. Reiser, *Top. Curr. Chem.* **2004**, *243*, 43–72; b) A. Hashem, A. Senning, *Adv. Heterocycl. Chem.* **1999**, *73*, 275–293; c) S. S. C. Koch, A. R. Chamberlin, *Studies in Natural Products Chemistry* (Ed.: Atta-ur-Rahman), Elsevier Science, Amstredam, **1995**, vol. 16, p. 687.
[17] E. I. Eliel, X. Bai, M. Ohwa, *J. Chin. Chem. Soc.* **2000**, *47*, 63–70.
[18] K. Kamata, I. Agata, A. I. Meyers, *J. Org. Chem.* **1998**, *63*, 3113–3116.
[19] L. Aurelio, J. S. Box, R. T. C. Brownlee, A. B. Hughes, M. M. Sleebs, *J. Org. Chem.* **2003**, *68*, 2652–2667.
[20] F. Homsi, S. Robin, G. Rousseau, *Org. Synth.* **2000**, *77*, 206–215.
[21] T. L. Gilchrist, P. D. Kemmitt, A. L. Germain, *Tetrahedron* **1997**, *53*, 4447–4456.
[22] P. Bulugahapitiya, Y. Landais, L. Parra-Papado, D. Planchenault, V. Weber, *J. Org. Chem.* **1997**, *62*, 1630–1641.
[23] F. Henin, S. Letinois, J. Muzart, *Tetrahedron Lett.* **1997**, *38*, 7187–7190.
[24] P. C. B. Page, H. Heany, S. Reigner, G. A. Rassias, *Synlett* **2003**, 22–28.
[25] D. Zhao, C.-y. Chen, F. Xu, L. Tan, R. Tillyer, M. E. Pierce, J. R. Moore, *Org. Synth.* **2000**, *77*, 12–21.
[26] S. Arrasate, E. Lete, N. Sotomayor, *Tetrahedron: Asymmetry* **2001**, *12*, 2077–2082.
[27] J. Spieler, O. Huttenloch, H. Waldmann, *Eur. J. Org. Chem.* **2000**, 391–399.
[28] K. Narasaka, A. Morikawa, K. Saigo, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2773–2776.
[29] A. R. Katritzky, J. Jiang, *J. Org. Chem.* **1995**, *60*, 7597–7604.
[30] M. Curini, F. Epifano, M. C. Marcotullio, F. Montanari, *Synlett* **2004**, 368–370.
[31] A. Kumar, R. Singh, A. K. Mandal, *Synth. Commun.* **1982**, *12*, 613–619.
[32] P. Canonne, M. Akssira, G. Fytas, *Tetrahedron* **1984**, *40*, 1809–1815.
[33] S. Knapp, Z. Dalian, *Org. Lett.* **2000**, *2*, 4037–4040.
[34] S.-i. Fukuzawa, K. Seki, M. Tatzuzawa, K. Mutoh, *J. Am. Chem. Soc.* **1997**, *119*, 1482–1483.

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