doi:10.2533/chimia.2006.566 CHIMIA **2006**, *60*, No. 9

Chimia 60 (2006) 566–573

ISSN 0009–4293

The Formation of a Crystalline Oxazolidin-5-one from (L)-Alanine and its Use as a Chiral Template in the Practical Synthesis of α-Substituted Alanine Esters

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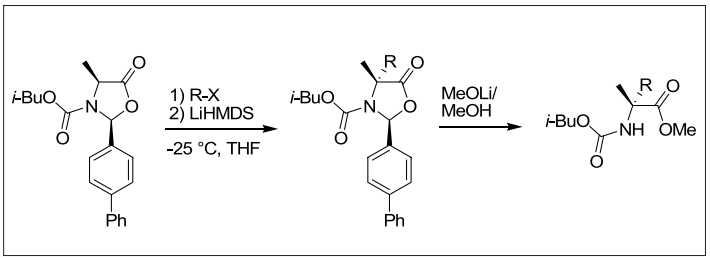
Abstract: Three different protocols to synthesize oxazolidin-5-ones have been studied with the goal to develop a method to synthesize a diastereomerically pure oxazolidin-5-one. A novel method is reported that uses a dynamic crystallization-induced asymmetric transformation to isolate a single diastereomer of an oxazolidin-5-one in 92% yield on kilogram scale. Alkylation of the oxazolidin-5-one template leads to good-to-excellent yields of N-protected α-substituted alanine esters in >98–99% ee.



Keywords: Crystallization-induced asymmetric transformation · Diastereoselective alkylation · α,α'-Disubstituted amino acid · Oxazolidin-5-one

Introduction

The subject of nonproteinogenic α-amino acids has been an area of growing interest in recent years. Substituted α-amino acids have been used in research in several areas, notably peptidomimetics, protein synthesis, natural products synthesis and in the synthesis of pharmaceutically interesting compounds [1].

Our interest in the synthesis of α,α'-disubstituted amino acids stems from a research program on protein–protein interactions [2] and more specifically on small-molecule inhibitors of cell–cell interactions between leukocyte function-assisted antigen (LFA-1) and intercellular adhesion molecule (ICAM-1). This research led to the discovery of a potent LFA-1 inhibitor, BIRT 377 (**1**) shown in Scheme 1 [3].

Retrosynthetically, **1** can be derived from the chiral α,α'-disubstituted amino acid **2**. There are a number of protocols available for synthesis of these compounds and these methods have been reviewed [4]. Of particular relevance to this work are methods based on alkylation of chiral templates, and examples can be found in the work by the groups of Schöllkopf [5], Williams [6], and Seebach [7] (Scheme 2).

The synthesis of **2** was envisioned *via* the procedure oftentimes referred to as Self-Reproduction of Chirality (SROC) which was initially developed by Seebach *et al.* [8]. Its key feature is the diastereoselective alkylation of stereochemically defined imidazolidinones or oxazolidinones. Thus, deprotonation at the α-position followed by alkylation gives α,α'-disubstituted imidazolidinones or oxazolidinones. Since the alkylation is highly stereospecific, one is able to isolate chiral α,α'-disubstituted amino acids of high enantiomeric purity after hydrolysis/deprotection of the imidazolidinone/oxazolidinone ring. The key to the success of this protocol is the ability to prepare 2-substituted imidazolidinones or oxazolidinones from chiral

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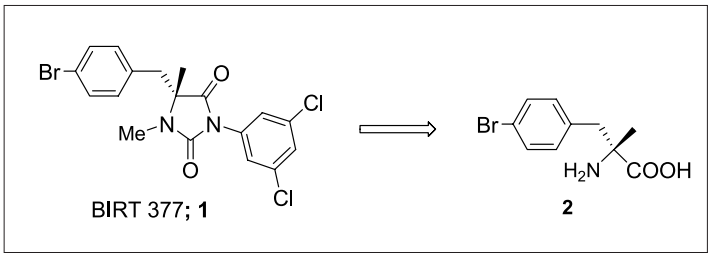
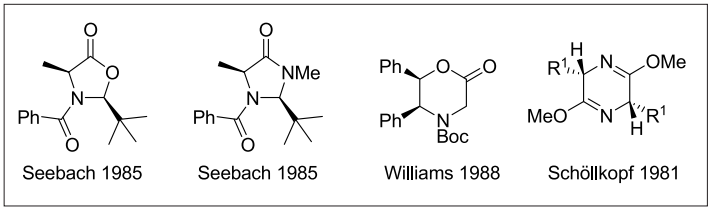


Scheme 1. Retrosynthetic analysis of BIRT-377



Scheme 2. Chiral templates used for the synthesis of α,α'-disubstituted amino acids

amino acids and to obtain these templates as pure diastereomers in high yield. Using the imidazolidinone approach, two routes to BIRT 377 starting from Boc-protected (D)-alanine were developed [9–11]. However, a route *via* a diastereomerically pure oxazolidinone seemed more attractive due to a potentially easier hydrolysis of the intermediate alkylated template and also the possibility of using cheap (L)-alanine as starting material for the synthesis of **1**, as opposed to its (D)-enantiomer, which is required in our previous approach [9]. To this end, we have communicated two protocols using oxazolidinones as templates for α-alkylation to make chiral quaternary amino acids [12][13]. In this paper, we report further details of our work and, more precisely, we describe our attempts at gaining some insight into the mechanisms of the different methods to make oxazolidinones.

Results and Discussion

Acylation of Imines

We were initially interested in applying the Seebach protocol for the generation of the oxazolidinone template. The generic Seebach protocol is shown in Table 1 and consists of acylation of an imine salt, such as **3**, made from an aromatic or aliphatic aldehyde and a sodium salt of an amino acid. Table 1 shows some examples from the literature based on (L)-alanine.

Evident from these results is the wide variation in *cis*:*trans* ratios and the sometimes low yield obtained. Particularly intriguing is the switch in diastereoselectivity of **4** in going from the alkylimine (**4a**, R = *t*-Bu) to the aryl imine (**4b**, R = Ph). It is also unclear from these results whether the reported *cis*:*trans* ratios reflect thermodynamic or kinetic compositions.

In our hands, treatment of **3a** (R = *t*-Bu) with benzoyl chloride at reflux gave **4a** in a 2:1 ratio of *cis* and *trans* oxazolidinones, lower than the 5:1 ratio reported by Seebach and Fadel [7a]. On the other hand, acylation of **3b** (R = Ph) gave **4b** in 1:7.3 ratio of *cis* and *trans* diastereomers, similar to the 1:7.5 reported by Fadel and Salaün [14].

During our studies we have found that N-acyloxazolidinones *cis*-**4a** and *trans*-**4b** easily undergo epimerization at C(2) when exposed to acidic reagents such as $ZnCl_2$ in dichloromethane to produce a 60:40 mixture of *cis* and *trans*-**4a** (22 h) or **4b** (2 h) when stirred at rt. The same ratios can be obtained starting from *trans*-**4a** and *cis*-**4b** diastereomers. These results clearly indicate the thermodynamically preferred composition for **4a** and **4b** and the ratios reported by Seebach and Fadel [7a] and Fadel and Salaün [14] therefore represent mixtures obtained under non-thermodynamic conditions (Scheme 3).

Unfortunately, this protocol turned out to be less suitable on larger scale due to operational difficulties. We found the Na-salt of (L)-alanine to be very hygroscopic and prone to forming a thick oil. Its conversion to the Schiff base under heterogeneous conditions in pentane or higher hydrocarbons was plagued by long reaction times and erratic results and the acylation of the imines gave products with variable *cis*:*trans* ratios. We therefore decided to search for alternative methods to prepare diastereomerically pure oxazolidinones.

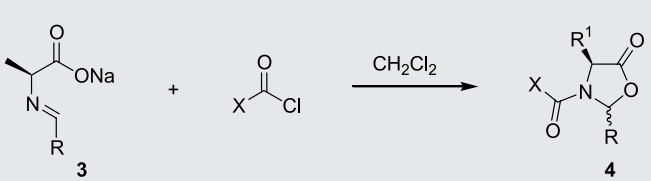
Cyclization Promoted by $SOCl_2$ and $ZnCl_2$

In our search of alternative condensation methods to make oxazolidinones, we attempted to use a one-step procedure by Karady *et al.* [18] In this protocol, N-Cbz-(L)-phenylalanine was condensed with 2 equiv. benzaldehyde in the presence of 1 equiv. *p*-TsOH to obtain a 9:1 *cis*:*trans* mixture of oxazolidinones in 40% yield. This procedure was later modified by Cheng *et al.* [19] and their approach was to react N-Cbz-(L)-phenylalanine (**5**) with benzaldehyde dimethyl acetal (**6**) in the presence of BF_3•Et_2O to afford oxazolidinone **7** (Scheme 4). A similar protocol was used by Schrader and Marlowe [20] using N-Cbz-(L)-alanine to obtain the *cis*-oxazolidinone in 75% yield after crystallization.

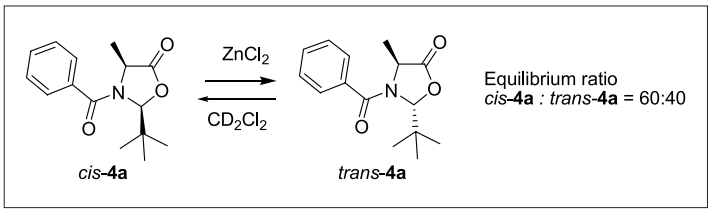
We sought alternative reaction conditions for this protocol because we eventually wanted to implement this on a larger scale and therefore wanted to avoid the use of corrosive BF_3•Et_2O and flammable diethyl ether as solvent. The low temperature condition was also a concern on large scale. Several Lewis acids were evaluated but neither gave any cyclized product. Only $ZnCl_2$, $ZnBr_2$ or $TiCl_4$ gave oxazolidinone **9** in appreciable yield (Table 2).

During this work, we became aware of

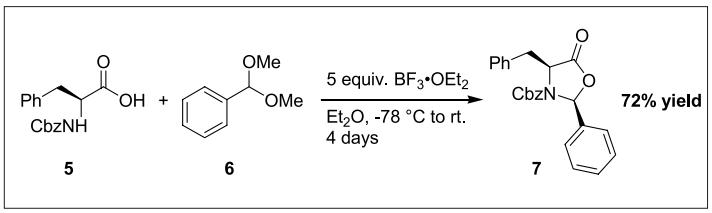
Table 1. Data collected from the literature for *cis:trans* ratios of oxazolidinones



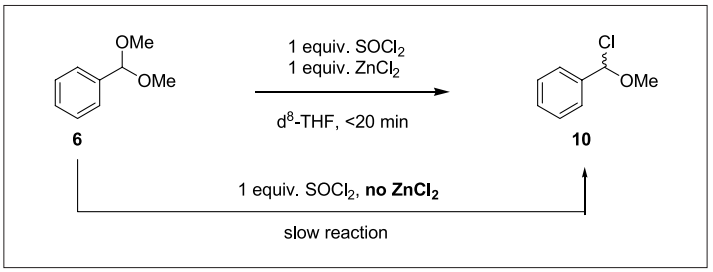
Entry	R	X	*Cis:Trans*	Yield of 4 [%]	Ref.
a	*t*-Bu	Ph	5:1	92	[7a]
b	Ph	Ph	1:7.5	94	[14]
c	Ph	BnO	1:2.5	31	[15]
d	Ph	Ph	*trans* only	50	[16]
e	Ferrocenyl	*t*-Bu	*cis* only	95	[17]



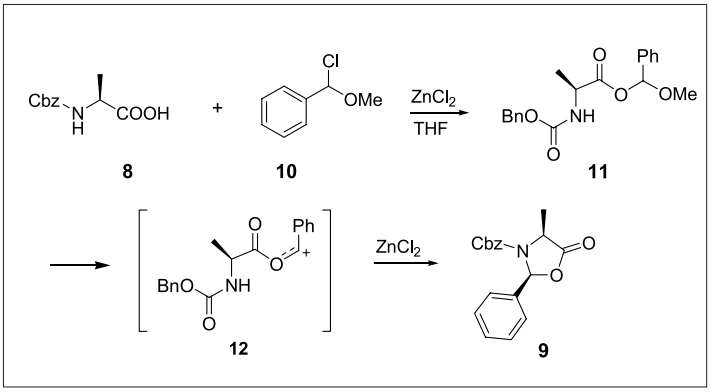
Scheme 3. Equilibration of *cis*- and *trans*-N-benzoyl oxazolidinone



Scheme 4. Protocol used by Cheng *et al*. [19]



Scheme 5. Activation of **6** with thionyl chloride



Scheme 6. Oxazolidinone *via* α-chloroether/$ZnCl_2$

a report by Micheel and Meckstroth [21] where catalytic amounts of $SOCl_2$ were used to affect the cyclization of glycine and aldehydes to oxazolidinones. In our case, addition of 1 equiv. $SOCl_2$ to the reaction increased the yield to 66% (entry 7). A limited solvent study of these conditions showed that THF gives the highest *cis*:*trans* ratio. The reaction proceeds also in EtOAc or CH_3CN. Furthermore, oxalyl chloride can be used in place of thionyl chloride. However, at least equiv. each of $ZnCl_2$ and $SOCl_2$ are necessary. With lower amounts, the reaction remained incomplete. The optimized reaction conditions give **9** in *ca.* 75% crude yield with 15:1 to 20:1 ratio. Recrystallization gives **9** in better than 50:1 *cis*:*trans* ratio and *ca.* 65% yield [12].

The use of at least 1 equiv. of $SOCl_2$ with N-Cbz-(L)-alanine initially led us to believe that the acid chloride of N-Cbz-(L)-alanine could be an intermediate. However, ^{1}H-NMR experiments in d_8-THF showed a fast reaction, <20 min at rt, between $SOCl_2$ and **6** in the presence of $ZnCl_2$ to yield α-chloro ether **10** (Scheme 5).

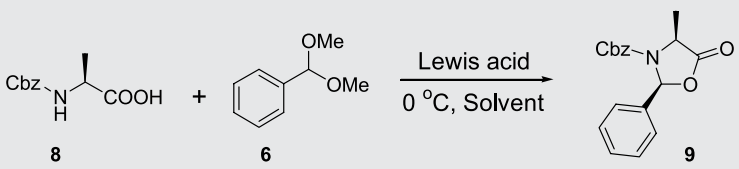
The corresponding formation of **10** in the absence of $ZnCl_2$ is very slow, *ca.* 40% after 18 h at room temperature. Furthermore, when $ZnCl_2$ is added to a mixture of N-Cbz-(L)-alanine, $SOCl_2$ and benzaldehyde dimethyl acetal, **10** is observed before the appearance of any oxazolidinone (**9**) as determined by ^{1}H-NMR. Thus, in the presence of $ZnCl_2$, **10** reacts with **8** to afford the cyclized product **9** (presumably through **11** and **12**) as shown in Scheme 6.

From our early studies of this reaction we noted that a *cis*:*trans* ratio of 5:1 was common. This ratio was also obtained if pure *cis*-**9** was treated with $ZnCl_2$ in CH_2Cl_2 suggesting that 5:1 is the thermodynamic composition. Interestingly, we found that a 3:1 *cis*:*trans* mixture of **9** could be enriched to 8:1 by stirring with $ZnCl_2$ in THF for 20 h at rt.

To clarify this behavior, we followed the reaction by ^{1}H-NMR. Surprisingly, the *trans*-**9** was formed selectively in the very early stages of the reaction as identified by the chemical shift of H(2). The selective formation of the *trans*-diastereomer in the early stages of the reaction is also observed by HPLC sampling of the reaction mixture. With time, however, the *cis*-diasteromer becomes the predominant species and by the end of the reaction the ratio of *cis*:*trans* is *ca.* 9:1. This indicates that *trans* is the kinetic diastereomer and the thermodynamic composition in THF is *ca.* 9:1 (*cis*:*trans*).

After work-up, **9** is isolated as a 15:1 to 20:1 mixture of *cis* and *trans* diastereomers. Apparently, there is some kind of enrichment taking place after the cyclization is completed. The exact ratio varies somewhat between runs and seems to depend also on the scale of the reaction and the reaction temperature during aqueous quench. We

Table 2. Cyclization experiments with different Lewis acids



Entry	Lewis acid	Solvent	Yield [%]	*Cis:Trans*
1	$ZnCl_2$	Et_2O	30	5:1
2	$ZnCl_2$	MTBE	–	–
3	$TiCl_4$	Et_2O	25	5:1
4	$ZnBr_2$(2 equiv.)	Bu_2O	35	5:1
5	$ZnBr_2$(1 equiv.)	Bu_2O	20	5:1
6	$ZnCl_2$(2 equiv.)	Bu_2O	30	5:1
7	$ZnCl_2/SOCl_2$	Bu_2O	66	5.5:1
8	**$ZnCl_2/SOCl_2$**	**THF**	**76**	**15:1 to 20:1**

reasoned that perhaps the minor diastereomer may be selectively hydrolyzed by acid released during the aqueous quench and that this could explain the improved ratios observed in the crude product. Therefore, a 5:1 *cis*:*trans* mixture of **9** was dissolved in THF and to this solution, a small amount of $ZnCl_2$ and $SOCl_2$ was added to mimic actual reaction conditions because these reagents are used in slight excess. This mixture was quenched with water slowly keeping the temperature below 10 °C. Samples for HPLC taken during the quench confirmed that the *trans* diastereomer is hydrolyzed more rapidly than the *cis*.

Although this protocol to make **9** was amenable to scale-up, it suffered from the use of more than stoichiometric amounts of $ZnCl_2$ and $SOCl_2$ and also the fact that the crude material needed recrystallization to reach high diastereomeric purity.

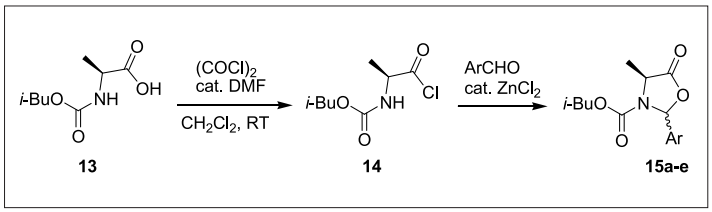
Cyclization Catalyzed by $ZnCl_2$ or $SnCl_4$

Our previous work on imidazolidinones [9–11] had demonstrated the possibility of a crystallization-driven asymmetric transformation [22] process to provide a pure diastereomer from a thermodynamic mixture of *cis*:*trans* isomers for use as a template for subsequent alkylation. Our intention was to take advantage of this reaction feature in the oxazolidinone synthesis as well. We also wanted to explore the use of acid chlorides as substrates for the oxazolidinone formation, based on the literature precedent that acetyl chloride reacts with aromatic aldehydes to form α-chlorobenzyl acetates in the presence of Lewis acids (*e.g.* $ZnCl_2$) [23]. Our hypothesis was that the *in situ* generation of an acid chloride from a carbamate-protected amino acid followed by reaction with an aromatic aldehyde would afford an oxazolidinone directly.

However, acid chlorides from N-acyl amino acids are difficult to prepare and are known to be unstable. Buckley *et al.* have shown that acid chlorides from N-amides of amino acids undergo racemization *via* azlactone formation [24]. This reaction is much slower with N-carbamates [25] and it is known [24] that N-ethoxycarbonyl alanine can be converted to the corresponding acid chloride using oxalyl chloride/DMF without racemization.

Thus, treatment of N-*i*-butyloxycarbonyl-(L)-alanine (**13**) in CH_2Cl_2 with catalytic DMF and 1 equiv. oxalyl chloride leads to the acid chloride **14** in quantitative yield. It can be isolated as a yellow oil or used directly in solution. Addition of benzaldehyde followed by a catalytic amount of solid $ZnCl_2$ leads to the formation of oxazolidinone **15c** in good yield as a thermodynamic mixture of *cis* and *trans* diastereomers in 85:15 ratio as outlined in Scheme 7.

We studied the formation of oxazolidinones from N-methoxy and N-*i*-butyloxy carbamates and different aldehydes. From our work on the corresponding N-amides, we knew that epimerization at the C(2) position readily takes place upon exposure to a variety of acidic reagents such as $ZnCl_2$ in CH_2Cl_2 or *p*-toluenesulfonic acid in refluxing benzene. Thus, formation of a variety of oxazolidinones with $ZnCl_2$ in CH_2Cl_2 established the equilibrium composition of *cis* and *trans* isomers and this is shown in Table 3.



Scheme 7. Novel synthesis of oxazolidinones

The preference for the *cis*-diastereomer in **15** is thought to arise from $A^{1,3}$-strain [26] with the N-acyl substituent pointing in the opposite direction from the substituents in the 2- and 4-positions, thus slightly lowering the energy of the *cis*-isomer. In entry 5, the ratio of *cis* and *trans* is almost equal and this is likely due to the steric bulk of the 9-anthranyl substituent leading to a very small energy difference between the two isomers.

The attempts to obtain a crystalline oxazolidinone were successful with N-*i*-butyloxy carbamate and 4'-biphenylcarboxaldehyde to give **15d**, Table 3, entry 4. In solution, the 85:15 ratio of *cis*- and *trans*-**15d** was observed. However, when the solvent was partially removed and the residue suspended in MTBE, an off-white solid could be filtered off which consisted of pure *cis*-**15d** in *ca.* 82% yield. Analysis of the mother liquors showed minor amounts of *cis* and *trans* product in a 85:15 ratio, along with some unreacted carbamate and α,α-dichloromethyl biphenyl. The presence of an 85:15 ratio of *cis*- and *trans*-**15d** in the mother liquor is clear evidence that a crystallization-induced asymmetric transformation operates to provide pure *cis*-diastereomer.

A small survey of Lewis acids showed that $SnCl_4$ gave the highest yield of **15d** (Table 4). Using the optimized conditions the oxazolidinone template was isolated in 92% yield on kilogram scale.

The structure of **15d** was confirmed by single crystal X-ray analysis and is shown in Fig. 1. The *cis* relationship of the 4-methyl and the 2-biphenyl substituents is therefore confirmed.

The reaction of N-*i*-butyloxycarbonyl-(L)-alanine and $(COCl)_2$ is rapid at room temperature and forms acid chloride **14** in quantitative yield as determined by ^{1}H-NMR in CD_2Cl_2. No changes occur when ^{13}C-labeled benzaldehyde (δ = 192.6 ppm for ^{13}C=O) is added to the acid chloride (Fig. 2, spectrum a). When 10 mol% $SnCl_4$ is added to this mixture, a major unknown peak is observed at 83.4 ppm as well as new peaks at 89.3 and 89.5 ppm corresponding to C(2) in *cis*-**15c** and *trans*-**15c**, respective-

Table 3. Equilibration ratios of different oxazolidinones

Entry	R	Aldehyde	*Cis*:*Trans*	Product
1	Me	Ph	85:15	**15a**
2	Me	4`-biphenyl	85:15	**15b**
3	*i*-Bu	Ph	85:15	**15c**
4	*i*-Bu	4`-biphenyl	85:15	**15d**
5	*i*-Bu	9-anthranyl	55:45	**15e**

Table 4. Influence of catalyst on the conversion to oxazolidinone **15d**

Catalyst	Conversion	*Cis*:*Trans*
$ZnCl_2$	87%	5:1
$SnCl_4$	94%	5:1
$TiCl_4$	<10%	3:1
Ti(*i*-PrO)$_4$	trace	–

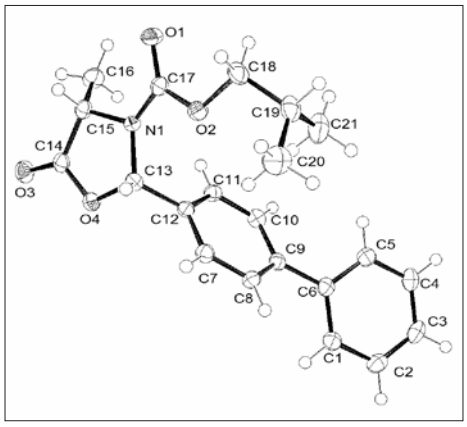
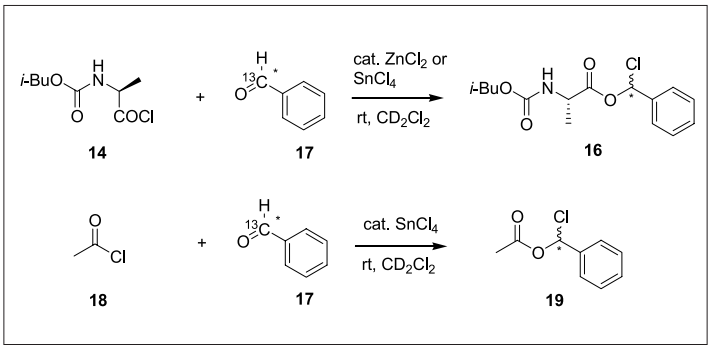
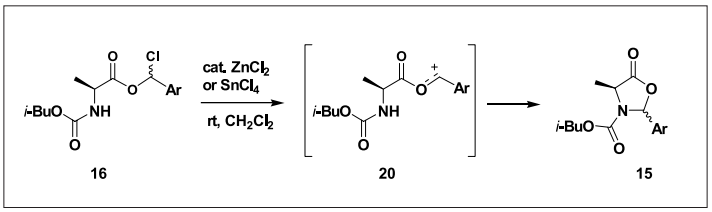


Fig. 1. Single crystal X-ray structure (ORTEP representation) for (L)-oxazolidinone (**15d**)



Scheme 8. Synthesis of ^{13}C-labeled α-chlorobenzyl esters



Scheme 9. Proposed mechanism for oxazolidinone formation

ly (Fig. 2, spectrum b). The peak at 83.4 ppm diminishes whereas the peaks at 89.3 and 89.5 from **15c** increase over time (Fig. 2, spectra c and d).

We propose that the unknown species observed at 83.4 ppm corresponds to an intermediate α-chloro benzyl ester **16** as shown in Scheme 8 [27].

The main support for intermediate **16** comes from correlation to the ^{13}C-NMR study of the analogous reaction with acetyl chloride (**18**) and ^{13}C-labeled benzaldehyde in the presence of catalytic $SnCl_4$ to give α-chlorobenzyl acetate (**19**), as laid out in Scheme 8. The signal for the benzylic carbon in **19** is readily observed at 82.9 ppm. This is very close to the signal at 83.4 ppm observed for the unknown intermediate (*vide supra*).

Unfortunately, the isolation of **16** is not possible since it undergoes rapid cyclization to the oxazolidinone. Additional qualitative evidence for an intermediate in the cyclization comes from ReactIR experiments. When benzaldehyde is added to a CH_2Cl_2 solution of the acid chloride in the presence of catalytic $SnCl_4$, a new carbonyl resonance at 1800 cm^{-1} is observed which is attributed to the oxazolidinone product. The benzaldehyde signal at 1702 cm^{-1} disappears at *ca.* 3 times faster rate than the appearance of the oxazolidinone signal suggesting the formation of an intermediate which is transformed into the oxazolidinone product at a slightly slower rate. Scheme 9 shows the proposed mechanism for oxazolidinone formation.

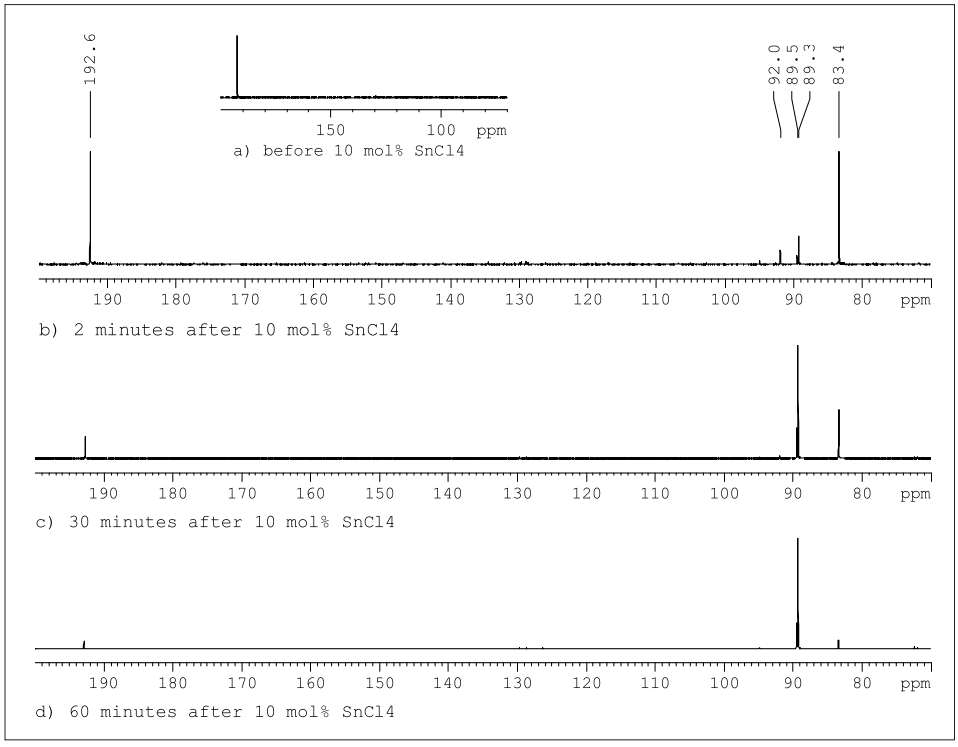


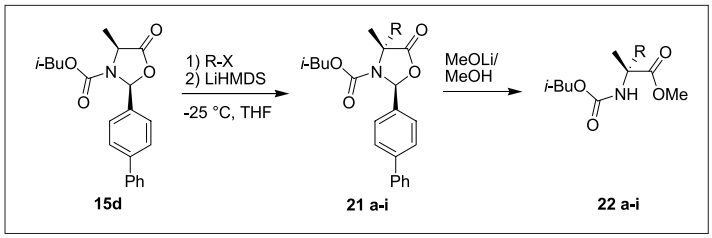
Fig. 2. Formation of oxazolidinone **15a** using ^{13}C-labelled PhCHO. ^{13}C-spectra; a) before 10 mol% $SnCl_4$. b) 2 min after 10 mol% $SnCl_4$. c) 30 min d) 60 min.

Alkylation of Oxazolidinones

Alkylation of **15d** is stereospecific and takes place from the face opposite the biphenyl moiety, leading *via* **21** to derivatives of **22** in >98% ee as determined by chiral-phase HPLC (Scheme 10). In the procedure, LiHMDS is added at –25 °C to a mixture of electrophile and **15d**. Alternatively, the enolate can be generated at –78 °C followed by addition of the electrophile. The results were poorer when the enolate was first generated at –25 °C followed by addition of electrophile, indicating that the enolate is stable at –78 °C but not at –25 °C.

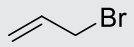
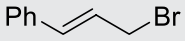
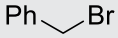
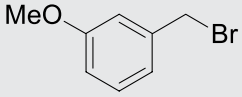
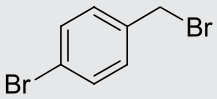
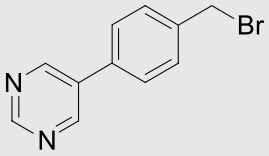
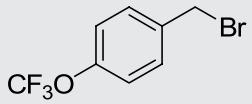
Crude oxazolidinone **21** is then treated with MeOLi in MeOH to make the methyl ester **22**. This liberates the 4'-biphenylcarboxaldehyde [28] which is isolated during workup as its sodium bisulfite adduct *via* filtration and can subsequently be regenerated [29] for use in the synthesis of **15d**.

The scope of the alkylation is shown in Table 5. Activated allylic-type electrophiles generally give excellent yield of derivatives of **22**. A non-activated alkyl electrophile



Scheme 10. Diastereoselective synthesis of α,α'-aminoesters

Table 5. Alkylation/Transesterification of **15d**

Entry	Electrophile, R-X	Yield of 22[a] [%]	Enantiomeric purity [% ee]
a		86%	>99
b		80%	98.9
c		93%	>99
d		70%	>99
e		97%	>99
f	*n*-BuBr[b]	70%	>99
g		67%	>99
h		90%	>99

[a] Isolated yields over two steps. [b] DMPU (1 equiv.) was added.

(*e.g.* butyl bromide) gave lower yield as can be expected. However, addition of 1 equiv. DMPU to the enolate before addition of the BuBr increased the isolated yield to 70% over two steps [30].

Summary

In summary, three methods to synthesize enantiomerically pure oxazolidinones from (L)-alanine have been evaluated and a novel synthesis of a chiral oxazolidinone using a dynamic asymmetric transformation has been demonstrated on kilogram scale. Alkylation of the oxazolidinone followed by hydrolysis leads to α-substituted esters of (L)-alanine in >98–99 % ee.

Experimental

General

All melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on Bruker spectrometers operating at 500/400 and 125/100 MHz, respectively. Elemental analysis were performed by QTI Analyses, NJ. Enantiomeric ratios were determined on a Chiralcel OD column using hexanes/isopropanol as eluent. Authentic samples of the opposite enantiomer were prepared in all cases. All chemicals were obtained from commercial sources and used as received unless otherwise noted. Anhydrous solvents from Aldrich were used directly.

(S)-2-Isobutoxycarbonylamino-propionic Acid (13c) [31]

(L)-Alanine (411 g, 4.61 mol, 1 equiv.) was added to a 12 l four-neck round bottom flask, fitted with mechanical stirrer, addition funnel and temperature probe. Water (3.42 l) was added and the resulting solution cooled to 10–15 °C with an ice/water bath. Solid NaOH (184.4 g, 4.61 mol, 1 equiv.) was added in portions to give a solution with pH 11–12. The temperature rose to *ca.* 20 °C with each portion of NaOH. Dimethylaminopyridine (DMAP, 23 g, 0.189 mol, 0.041 equiv.) was added and the reaction cooled back down to *ca.* 15 °C. To this solution was added *i*-butylchloroformate (688 ml, 5.30 mol, 1.15 equiv.) in one portion. The reaction was stirred vigorously and 30% aq. NaOH was added *via* the addition funnel at a rate to maintain the pH around 10–11. During the aq. NaOH addition the reaction temperature rose to 42 °C and was cooled down by addition of ice directly into the reaction mixture. A total of *ca.* 900 ml of 30% aq. NaOH was added. Once the pH had stabilized at pH 10–11, the reaction was cooled to room temperature and stirred overnight.

The reaction solution was cooled to 2–3 °C by addition of ice directly to the flask and the pH was then adjusted to 1–2 by addition of conc. HCl. The resulting turbid reaction mixture was extracted with CH_2Cl_2 (3 × 1.5 l) and the combined organic layer was concentrated on a rotavap and dried further under high vacuum to afford 843 g of a white, waxy solid (96% yield).

Anal. calc. for $C_8H_{15}NO_4$, C; 50.78, H; 7.99; N; 7.40: Found: C; 50.92, H; 8.29, N; 7.19.

^{1}H-NMR and ^{13}C-NMR data correlate well with published data [31].

(2S,4S)-2-Biphenyl-4-yl-4-methyl-5-oxo-oxazolidine-3-carboxylic Acid Isobutyl Ester (15d)

A 12 l four-neck round bottom flask, fitted with mechanical stirrer, addition funnel, reflux condenser, argon inlet and temperature probe, was purged with argon for 30 min. N-*i*-Butyloxycarbonyl-(L)-alanine (641 g, 3.39 mol, 1 equiv.) was added to the flask and dissolved in CH_2Cl_2 (3.3 l). Dimethylformamide (13.2 ml, 0.17 mol, 0.05 equiv.) was added, the mixture stirred at 200 rpm and cooled to 7–8 °C in an ice/water bath. Once at that temperature,

oxalyl chloride (301.7 ml, 3.46 mol, 1.02 equiv.) was added in one portion *via* the addition funnel. A 1–2 °C temperature rise was observed along with the release of gas (HCl, CO_2, CO) from the reaction. The ice/water bath was removed and the solution stirred at ambient temperature for 5 h until all gas bubbling had ceased. Biphenylcarboxaldehyde (661 g, 3.46 mol, 1.02 equiv.) was added as a solid in one portion to afford an orange solution. Within 5 min, a solution of $SnCl_4$ (170 ml, 1.0 M in CH_2Cl_2, 0.05 equiv.) was added, leading to a red solution and a rise in temperature from 13 to 26 °C over 5–10 min. The temperature stabilized and the solution was stirred at 25 °C for 20 h with a slow argon purge to remove HCl gas formed during the reaction. The reaction mixture was then concentrated under reduced pressure until *ca.* 1 l CH_2Cl_2 remained to afford a suspension. MTBE (1.9 l) was added and the suspension was stirred at ambient temperature for *ca.* 15 h. The thick suspension was cooled to 2–3 °C with ice/water bath, stirred at that temperature for 2.5 h and then filtered on a medium frit Büchner funnel to afford an off-white solid. The solid was washed with a 1 l portion of cold MTBE and dried on the frit under vacuum for 3 h to give 1.10 kg (92%) oxazolidinone product.

^{1}H-NMR, ^{13}C-NMR and combustion analysis data correlate well with those published [13].

General Procedure for Alkylation of 15d

The oxazolidinone template **15d** (4 mmol) and the corresponding alkyl halide (4.2 mmol) were suspended in THF (12 ml) under argon in a dry 50 ml flask. The mixture was cooled to –25 °C with a dry ice/acetone bath. LiHMDS (1.0 M in THF; 4.2 ml) was added slowly over 20 minutes *via* syringe. The mixture was stirred at –25 °C for 30 min and at room temperature for 3 h to afford an orange solution. Saturated NH_4Cl (15 ml) was added and the mixture was diluted with EtOAc (50 ml). The layers were separated and the aqueous layer was extracted with EtOAc (20 ml). The combined organic layer was washed with brine (30 ml) and dried over $MgSO_4$. Evaporation of the solvent afforded the crude alkylation product as an oil.

The crude alkylation product (~4 mmol) was dissolved in dry MeOH (16 ml) and MeOLi (4.4 ml, 1.0 M in MeOH) was added. The solution stirred at room temperature until TLC indicated disappearance of starting material (1–3 h). A mixture of saturated aqueous $NaHSO_3$ (30 ml) and CH_2Cl_2 (40 ml) was added. A white precipitate formed and the mixture was stirred at room temperature for *ca.* 1 h after which the solid was filtered off. The filtrate layers were separated and the aqueous phase extracted with CH_2Cl_2 (30 ml). The combined organic layer was washed with water (50 ml), brine (50 ml) and dried ($MgSO_4$) to afford the methyl ester as a yellow oil after evaporation of the solvent. The methyl esters were purified by flash chromatography on silica gel using EtOAc/hexanes.

(*R*)-2-Isobutoxycarbonylamino-2-methyl-pent-4-enoic Acid Methyl Ester (22a)

Flash chromatography on silica gel using 15% EtOAc/hexanes gave a light yellow oil (86% over two steps). ^{1}H-NMR (DMSO-d^6): 7.48 (br s, 1H), 5.65–5.74 (m, J = 7.5, 9.4, 18.0 Hz, 1H), 5.08 (dd, J = 9.4,18.0, 2H), 3.68–3.76 (m, 2H), 3.59 (s, 3H), 2.59 (dd, J = 7.0, 13.5 Hz, 1H), 2.39 (dd, J = 7.0, 13.5 Hz, 1H), 1.80–1.84 (m, 1H), 1.30 (s, 3H), 0.88 (d, J = 6.5 Hz, 6H). ^{13}C-NMR (DMSO-d^6): 173.04, 154.32, 131.90, 117.87, 68.72, 57.27, 50.91, 40.04, 26.77, 21.36, 17.92. LCMS: m/z = 244.1 $(M+H)^+$. Anal. calc. for $C_{12}H_{21}NO_4$, C; 59.24, H; 8.70; N; 5.76: Found: C; 59.19, H; 8.73, N; 5.72. Enantiomeric purity; >99 % ee.

(*E*)-(*R*)-2-Isobutoxycarbonylamino-2-methyl-5-phenyl-pent-4-enoic Acid Methyl Ester (22b)

Flash chromatography on silica gel using 15% EtOAc/hexanes gave a colorless oil (80% over two steps). ^{1}H-NMR ($CDCl_3$): 7.22–7.34 (m, 5H), 6.45 (d, J = 16 Hz, 1H), 6.04 (dt, J = 7, 16 Hz, 1H), 3.84 (m, 2H), 3.77 (s, 3H), 2.95 (br, 1H), 2.72–2.78 (dd, J = 7, 14 Hz, 1H), 1.90 (m, J = 7 Hz, 1H), 1.62 (s, 3H), 0.91 (d, J = 7 Hz, 6H). ^{13}C-NMR ($CDCl_3$): 174.3, 136.9, 134.3, 128.5, 127.5, 126.2, 123.6, 70.84, 59.74, 52.69, 40.47, 28.00, 23.35, 19.02. LCMS: m/z = 320.3 $(M+H)^+$. Anal. calc. for $C_{18}H_{25}NO_4$, C; 67.69, H; 7.89; N; 4.39: Found: C; 67.60, H; 7.90, N; 4.28. Enantiomeric purity; 98.9 % ee.

(*R*)-2-Isobutoxycarbonylamino-2-methyl-3-phenyl-propionic Acid Methyl Ester (22c)

Flash chromatography on silica gel using 10% EtOAc/hexanes gave a light yellow oil (93% over two steps). ^{1}H-NMR ($CDCl_3$): 7.22–7.26 (m, 3H), 7.03–7.06 (m, 2H), 5.36 (br, 1H), 3.84–3.93 (m, 2H), 3.73 (s, 3H), 3.93 (bd, 1H), 3.18 (d, J = 14 Hz, 1H), 1.89–1.96 (m, J = 7 Hz, 1H), 1.61 (s, 3H), 0.92–0.94 (d, J = 7 Hz, 6H). ^{13}C-NMR ($CDCl_3$): 174.18, 155.12, 136.21, 129.92, 128.22, 126.92, 70.83, 60.60, 52.56, 41.74, 28.01, 23.63, 19.02. LCMS: m/z = 294.1 $(M+H)^+$. Anal. calc. for $C_{16}H_{23}NO_4$, C; 65.51, H; 7.70; N; 4.77: Found, C; 65.52, H; 7.84, N; 4.72. Enantiomeric purity; >99 % ee.

(*R*)-2-Isobutoxycarbonylamino-3-(3-methoxy-phenyl)-2-methyl-propionic Acid Methyl Ester (22d)

Flash chromatography on silica gel using 10% EtOAc/hexanes gave a colorless oil (70% over two steps). ^{1}H-NMR ($CDCl_3$): 7.14–7.26 (m, 1H), 6.75–7.79 (m, 1H), 6.59–6.65 (m, 2H), 5.41 (br, 1H), 3.84–3.89 (m, 2H), 3.75 (s, 3H), 3.36 (bd, 1H), 3.16 (d, J = 14 Hz, 1H), 1.88–1.94 (m, J = 7 Hz, 1H), 1.62 (s, 3H), 0.93 (d, J = 7 Hz, 6H). ^{13}C-NMR ($CDCl_3$): 174.2, 159.4, 155.1, 137.7, 129.2, 122.2, 115.7, 112.3, 70.86, 60.57, 55.06, 52.62, 41.76, 27.98, 23.71, 19.03. LCMS: m/z = 324.3 $(M+H)^+$. Anal. calc. for $C_{17}H_{25}NO_5$, C; 63.14, H; 7.79; N; 4.33: Found, C; 63.12, H; 7.76, N; 4.29. Enantiomeric purity; >99% ee.

(*R*)-3-(4-Bromo-phenyl)-2-isobutoxycarbonylamino-2-methyl-propionic Acid Methyl Ester (22e)

Flash chromatography on silica gel using 20% EtOAc/hexanes gave 1.44 g (97% over two steps) slightly greenish oil. ^{1}H-NMR ($CDCl_3$): 7.37 (d, J = 8.3 Hz, 2H), 6.92 (d, J = 8.3 Hz, 2H), 5.35 (br, 1H), 3.89–3.92 (m, 1H), 3.82–3.86 (m, 1H), 3.75 (s, 3H), 3.40 (bd, J = 13 Hz, 1H), 3.15 (d, J = 13 Hz, 1H), 1.88–1.97 (m, 1H), 1.60 (s, 3H), 0.93 (d, J = 7 Hz, 6H). ^{13}C-NMR ($CDCl_3$): 171.84, 152.94, 133.24, 129.48, 129.23, 118.90, 68.85, 58.42, 50.57, 38.85, 25.93, 21.65, 16.92. LCMS: m/z = 372.8 $(M+H)^+$. Anal. calc. for $C_{16}H_{22}BrNO_4$, C; 51.62, H; 5.96; N; 3.76: Found, C; 51.57, H; 5.88, N; 3.70. Enantiomeric purity; >99% ee.

(*R*)-2-Isobutoxycarbonylamino-2-methyl-hexanoic Acid Methyl Ester (22f)

The oxazolidinone template (4 mmol) was suspended in THF (12 ml) under argon in a dry 50 ml flask. The mixture was cooled to –35 °C and LiHMDS (1.0 M in THF; 4.2 ml, 1.05 equiv.) was added slowly over 5 min *via* syringe to afford a yellow solution that was stirred for 30 min at –35 °C. DMPU (4 mmol, 1 equiv.) was added and the solution stirred another 30 min. *n*-BuBr (4.2 mmol, 1.05 equiv.) was added and the solution was allowed to reach rt over 4 h. See general experimental procedure for work-up and hydrolysis/esterification. Flash chromatography on silica gel using 10% EtOAc/hexanes gave 0.73 g light yellow oil (70% over two steps). ^{1}H-NMR ($CDCl_3$): 5.45 (br, 1H), 3.81(d, J = 6.6 Hz, 2H), 3.75 (s, 3H), 2.09 (br, 1H), 1.88 (m, J = 6.7 Hz, 1H), 1.70–1.81 (m, 1H), 1.56 (s, 3H), 1.17–1.34 (m, 3H), 0.98–1.12 (m, 1H), 0.91 (d, J = 6.7 Hz, 6H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C-NMR ($CDCl_3$): 175.17, 155.25, 70.90, 60.05, 52.76, 37.02, 28.20, 26.40, 23.57, 22.76, 19.21, 14.09. LCMS: m/z = 260.2 $(M+H)^+$. Anal. calc. for $C_{13}H_{25}NO_4$, C; 60.21, H; 9.72; N; 5.40: Found: C; 60.00,

H; 9.83, N; 5.17. Enantiomeric purity; >99% ee.

(R)-2-Isobutoxycarbonylamino-2-methyl-3-(4-pyrimidin-5-yl-phenyl)-propionic Acid Methyl Ester (22g)

The alkylation reaction was stirred at –25 °C for 16 h before warming to rt. Flash chromatography on silica gel using 35% EtOAc/hexanes gave a slightly greenish solid (67% over two steps). ^{1}H-NMR ($CDCl_3$): 9.11 (s, 1H), 8.86 (s, 2H), 7.42 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 8.3 Hz, 2H), 5.55 (br, 1H), 3.87–3.91 (m, 1H), 3.80–3.84 (m, 1H), 3.75 (s, 3H), 3.47 (bd, J = 12 Hz, 1H), 3.25 (d, J = 13 Hz, 1H), 1.85–1.94 (m, 1H), 1.60 (s, 3H), 0.90 (d, J = 7 Hz, 6H). ^{13}C-NMR ($CDCl_3$): 173.69, 157.04, 154.79, 154.36, 137.26, 133.55, 132.47, 130.70, 126.36, 70.58, 60.23, 52.33, 40.83, 27.70, 23.46, 18.67. LCMS: m/z = 372.8 $(M+H)^+$. Anal. calc. for $C_{20}H_{25}N_3O_4$, C; 64.67, H; 6.78; N; 11.31: Found: C; 64.49, H; 6.62, N; 11.18. Enantiomeric purity; >99% ee.

(R)-2-Isobutoxycarbonylamino-2-methyl-3-(4-trifluoromethoxy-phenyl)-propionic Acid Methyl Ester (22h)

Flash chromatography on silica gel using 10% EtOAc/hexanes gave 1.36 g (90% over two steps) slightly greenish oil. ^{1}H-NMR (DMSO-d^6): 7.44 (s, 1H), 7.27 (d, J = 7.6 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 3.82 (m, 1H), 3.74 (m, 1H), 3.61 (s, 3H), 3.31 (d, J = 13 Hz, 1H), 3.00 (d, J = 13.9 Hz, 1H), 1.86 (m, 1H), 1.21 (s, 3H), 0.90 (d, J = 6.7 Hz, 6H). ^{13}C-NMR (DMSO-d^6): 175.62, 156.93, 148.84, 137.45, 133.81, 121.96, 121.70 (JC-F = 254 Hz), 71.38, 60.29, 53.54, 41.54, 29.26, 23.92, 20.39. LCMS: m/z = 378.3 $(M+H)^+$. Anal. calc. for $C_{17}H_{22}F_3NO_5$, C; 54.11, H; 5.88; N; 3.71: Found: C; 54.25, H; 6.12, N; 3.70. Enantiomeric purity; >99% ee.

Acknowledgements

Assistance with the single-crystal X-ray determination from Dr. Andre White is much appreciated.

Received: June 20, 2006

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